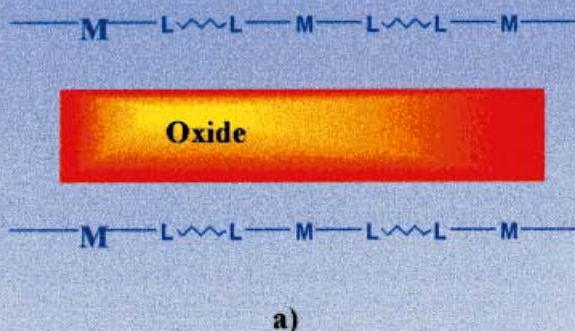
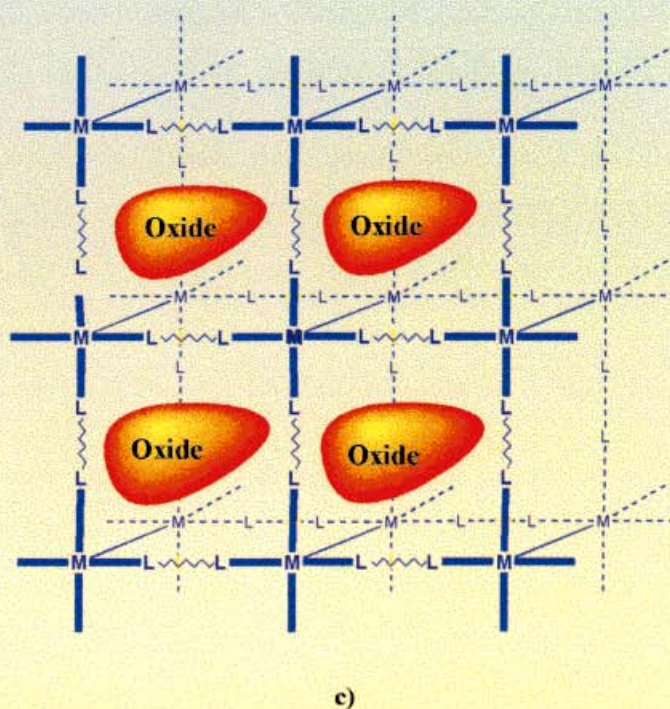
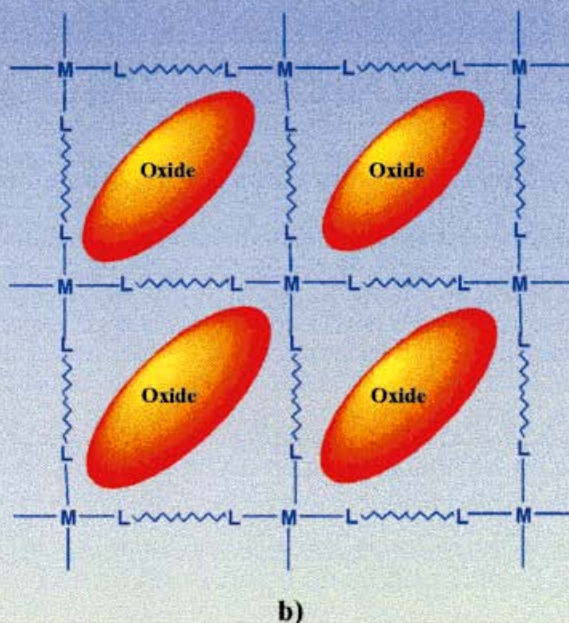


The Organic Component as a Ligand in a Polymeric Coordination Complex Cation



Ligand geometry and metal coordination preferences may provide a) one-, b) two-, or c) three-dimensional polymeric coordination complex cations as scaffolding for the manipulation of metal oxide substructures.



Organic – Inorganic Hybrid Materials: From “Simple” Coordination Polymers to Organodiamine-Templated Molybdenum Oxides

Pamela J. Hagrman, Douglas Hagrman, and Jon Zubieta*

Dedicated to Professor Achim Müller on the occasion of his 60th birthday

The vast range of solid-state properties exhibited by the oxides is a result of their diversity of chemical composition and structure type. However, while many naturally occurring oxides and minerals possess complex crystal structures, the majority are of simple composition and have highly symmetrical structures with rather small unit cells. Most silicates, important ores, gems, and many rocks and soils are examples of these materials. Although such simple oxides can possess unique and specific properties—such as piezoelectricity, ferromagnetism, or catalytic activity—as a general rule there is a correlation between the complexity of the structure of a material and its functionality. One approach to the design of novel oxide materials mimics nature's use of organic molecules to modify inorganic microstructures. In this instance, the inorganic oxide contributes to the increased functionality by assimilation as one component in a hierarchical structure where there is a synergistic interaction between organic material and the inorganic oxide. Synthetic studies of materials that possess

such an interface, coupled with the acquisition of the appropriate structural information, should contribute to the development of an increased understanding of methods to control the structure – property relationships within these hybrid materials. While the organic component may assume a variety of structural or functional roles in the design of novel oxide-based composite materials, the extensive contemporary interest in framework solids suggested their use as ligands in a polymeric coordination complex cation which provides not only charge compensation for the anionic oxide substructure but also a rigid framework for entraining and, to a degree, for controlling the surface of the growing oxide microstructure. These framework solids are particularly attractive from several perspectives: 1) They are accessible by self-assembly under exceedingly mild conditions which allows retention of the structural integrity of the starting materials and the isolation of kinetic, rather than exclusively thermodynamic, products; 2) they possess a remarkable chemical and structural

diversity; and 3) the numerous examples described in recent years demonstrate that some control is achievable in defining their architectures. Consequently, by appropriate selection of ligand types and through exploitation of the coordination preferences of the metal, one-, two-, or three-dimensional coordination complex cations may be constructed to provide a scaffolding for the entraining of the oxide substructure. Application of this strategy to the study of the molybdenum oxide/organodiamine – metal complex interface has produced a wealth of organic – inorganic hybrid materials of the MOXI family. These materials demonstrate not only the complexity of the organic – inorganic synthetic interface in the construction of such materials but also provide evidence of a powerful tool for the low-temperature synthesis of new materials endowed with structural complexity.

Keywords: coordination polymers • crystal engineering • hydrothermal synthesis • metal oxides • molybdenum

One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structures of even the simplest crystalline solids from a knowledge of their chemical compositions.

John Maddox

But in two or three dimensions, it's a synthetic wasteland. The methodology for exercising control so that one can make unstable but persistent extended structures on demand is nearly absent. Or to put it in a positive way—this is a certain growth point of the chemistry of the future.

Roald Hoffmann

[*] Prof. J. Zubieta, P. J. Hagrman, D. Hagrman
Department of Chemistry, Syracuse University
Syracuse, New York 13244 (USA)
Fax: (+1) 315-443-4070
E-mail: jazubiet@mailbox.syr.edu

1. Introduction

Oxygen is not only the most abundant terrestrial element, it is also highly reactive; consequently, oxides exist for most of

the elements with the exceptions of radon and the lighter noble gases,^[1] and inorganic oxides are ubiquitous in the geosphere and the biosphere.^[2] In addition to the hydrogen oxide that forms the basis of life, oxygen is found in combination with silicon and aluminum in the form of complex aluminosilicates which make up the vast proportion of solid-state oxides, but bones, shells, teeth, spicules, and petrified wood represent structurally complex oxides fashioned through biomineralization.^[4, 5]

The intense contemporary interest in solid-state oxides reflects their properties, which endow these materials with applications from heavy construction to microelectronic circuitry. The huge range of solid-state properties summarized in Table 1 is a result of the diversity of chemical compositions and structure type exhibited by the inorganic oxides.^[6]

However, while many naturally occurring oxides and minerals and even synthetic oxides possess complex crystal structures, the majority are of relatively simple composition and exhibit highly symmetrical structures with rather small unit cells. Although such simple oxides possess undeniably useful properties, there exists, in general, a correlation between the complexity of the structure of a material and the functionality which it displays.^[30] Thus, many of the remarkable materials fashioned by nature contain mixtures of inorganic oxides coexisting with organic molecules. For example, the calcite or aragonite forms of calcium carbonate can be specifically nucleated in molluscs by molecular manipulation induced by small amounts of an organic

component.^[31] It is now apparent that organic components can dramatically influence the microstructures of inorganic oxides, thus providing a method for the design of novel materials.

1.1. Organic–Inorganic Hybrid Materials

The control of inorganic structure by an organic component reveals an interactive structural hierarchy in materials.^[32] In such materials, the inorganic oxide contributes to the increased complexity and hence functionality through incorporation as one component in a multilevel-structured material where there is a synergistic interaction between the organic and inorganic components.^[30] Since this interaction within these organic–inorganic hybrid materials derives from the nature of the interface between the organic component and the inorganic oxide, synthetic and structural studies of materials that exhibit such an interface will contribute to the development of structure–function relationships for these hybrid materials.

There are now four major classes of materials in which organic components exert a significant structural role in the control of the inorganic oxide microstructure. These materials are zeolites,^[32, 33] mesoporous oxides of the MCM-41 class,^[34] biomineralized materials,^[2, 5, 35] and microporous octahedral–tetrahedral or square-pyramidal–tetrahedral framework transition metal phosphates (TMPO) with entrained organic cations.^[36, 37] While the dramatically expanding field of

Jon Zubieta, born and raised in New York City, received his B.S. degree from Fordham University in 1966 and his Ph.D. from Columbia University in 1971. After postdoctoral work at the University of Sussex (UK), he joined the chemistry faculty at the State University of New York at Albany. In 1990 he moved to Syracuse University. His research interests include the design and structural characterization of metal oxide clusters and solids,



J. Zubieta



P. Hargman



D. Hargman

applications of the coordination chemistry of technetium and rhenium to radiopharmaceuticals, and the development of drug delivery systems based on the organic–inorganic oxide interface.

Pamela Hargman, born in Syracuse, New York, received her B.S. degree from the State University of New York at Buffalo in 1994. She is currently pursuing her Ph.D. degree in inorganic chemistry at Syracuse University. Her research focuses on the applications of the techniques of solvothermal synthesis to the isolation of organically templated metal oxide materials.

Douglas Hargman, born in Salt Lake City, Utah, and raised in Idaho Falls, Idaho, received his B.S. degree in Chemical Engineering from the University of Nebraska-Lincoln. He is currently pursuing a Ph.D. in inorganic chemistry at Syracuse University, where he has been honored with the Outstanding Teaching Assistant Award and the William D. Johnson Award for teaching excellence. He is the recipient of the ACA Pauling Prize for the outstanding poster presentation at the ACA meeting in Buffalo in 1999. His research has focused on the hydrothermal synthesis and structural characterization of new oxide materials. His future plans include the elaboration of new synthetic methods in solid-state chemistry, including combinatorial synthesis and high throughput screens for property assessment.

Table 1. Some examples and applications of inorganic oxides

Class	Examples	Application	Ref.
magnetic oxides	CrO ₂	magnetic tapes	[7]
	ferrites of type Zn _{x+2} Fe _{1-x} [Mn _{1-x} Fe _x]O ₄ (Mn, Mg) spinels	transformer cores computer memories	[8] [8]
oxide sensors	BaTiO ₃	temperature sensor	[7]
	PbZrO ₃	acoustical pickup, piezo speakers	[10]
phosphors	Mn-doped Zn ₂ SiO ₄	green phosphor for oscilloscope tubes	[11]
	Eu-doped Y ₂ O ₃	red phosphor	
electronic materials	BaTiO ₃	surge protector	[9]
	ZnO	high-resistance semiconductor	[12]
	YBa ₂ Cu ₃ O _{7-x}	high-temperature superconductor	[13]
	Fe ₃ O ₄	black pigment	[8]
pigments	Fe ₂ O ₃	red pigment	[8]
	Al ₂ O ₃	refractory for fire brick	[14]
ceramics	PbZr _{1-x} Ti _x O ₃	ferroelectrics	[15]
	LiNbO ₃ , KTi(PO ₄)	harmonic generators, frequency mixers	[16]
optical materials catalysts	(VO) ₂ P ₂ O ₇	selective oxidation of <i>n</i> -butane to maleic anhydride	[17]
	Bi ₂ Mo ₂ O ₉	selective oxidation of propene to acrylonitrile	[18]
	V ₂ O ₅ /TiO ₂	selective oxidation of naphthalene to phthalic anhydride	[19]
	Cr ₂ O ₃ /Al ₂ O ₃	polymerization of alkenes	[20]
	Cu ₂ Al ₆ B ₄ O ₁₇	oxidative dehydrogenation	[20]
	SiO ₂ /MgO ₃	conversion of ethene into butadiene	[21]
	SO ₄ ²⁻ /ZrO ₂	cracking, isomerization, alkylation	[22]
	NASICON, Na _{1+x} Zr ₂ Si _x P _{3-x} O ₁₂	cation exchange, fast-ion conductor	[23]
	Mg ₆ Al ₂ (OH) ₁₆ CO ₃ ·4H ₂ O	anion exchange	[23]
	zeolites, M _{x/m} ^{m+} [Si _{1-x} Al _x O ₂]·H ₂ O	detergents	[24]
molecular sieves	zeolites	separating agents	[25, 26]
catalysts and molecular sieves	zeolites and ALPOs, [AlPO ₄] _y ·R· <i>n</i> H ₂ O, faujasite	catalytic cracking	[27]
	ALPO-5	hydrocracking	[28]
	silicalite	xylene isomerization	[29]
biomaterials	organoapatites	artificial bone	[30]

biomineralization will not be discussed in this review, two observations are relevant: 1) Complex inorganic materials may be prepared across a range of length scales by coding of precipitation reactions;^[38] 2) biologically-based organic materials interact with inorganic oxides primarily through O–H⋯O and N–H⋯O hydrogen-bonding interactions.^[39]

The pioneering work of Barrer on the synthetic zeolites^[40] represents the first systematic development of materials in which organic molecules were used to influence the growth of inorganic oxides. The incorporation of organic molecules, primarily amines and ammonium salts, into aluminosilicate frameworks has provided a dramatic expansion of this technologically important class of materials. The organic cation serves not only to provide charge compensation required by the substitution of Al³⁺ for Si⁴⁺ within the zeolite framework, but, by virtue of its size, shape, and polarity, also directs the crystallization of the silicate aggregates into the zeolitic framework. The basic conditions required for dissolution of SiO₂ dictate that quaternary ammonium salts be used as charge-compensating cations. Consequently, the template–framework interaction is primarily of the van der Waals type.

The rapidly expanding field of mesoporous oxides derives from the pioneering work on MCM-41 materials at Mobil Oil.^[34, 41] These hybrid materials are prepared by polymerization of soluble silica polyanions around a cationic template with a long hydrophobic tail. Since structural information from the amphiphilic organic template is imprinted on the oxide structure derived from silicate polymerization, variations in size, shape, and charge of the organic surfactant and in concentration, pH value, temperature, and shear forces allow

the realization of numerous morphologies which contain periodic arrays with adjustable channel diameters in the range of 16 to 100 Å, after removal of the organic components. Such large variable pore sizes render the materials of this class of interest as size- and shape-selective heterogeneous catalysts and as hosts for nanometer-scale electronic and optical devices.

The first example of a non-silicate, open-framework oxide with entrained organic cations, (Me₄N)(H₃O)[Mo₄O₄(PO₄)₃]_xH₂O, was reported in 1989^[42] and shown to contain an octahedral–tetrahedral framework constructed from Mo₄ oxoclusters connected by PO₄ tetrahedra into a three-dimensional covalent framework. Most significantly, the organic counterions could be thermally removed from the material to produce a microporous oxomolybdenum phosphate framework. Subsequently, not only were numerous MoPO materials synthesized, but a large and ever-expanding family of organically templated oxovanadium phosphate and phosphonate frameworks was described.^[36, 37, 43]

1.2. Design in Metal Oxide Synthesis

The common feature distilled from the four classes of inorganic oxide materials described above is the influence of the organic component in controlling the nucleation and growth of the inorganic oxide. Organic components alter the inorganic oxide microstructure. There is a synergism between the organic and inorganic components which allows the structural information from the organic molecule to imprint

onto the inorganic framework. Implicit in the evolution of these organic–inorganic hybrid materials is a shift from the thermodynamic to the kinetic domain, such that equilibrium phases are replaced by structurally more complex metastable phases. However, traditional solid-state syntheses produce thermodynamic products, often by solid–solid interactions at temperatures of about 1000 °C, conditions which will not retain the structural elements of the organic component. Consequently, low-temperature techniques must be adopted in an approach that resembles small-molecule chemistry. Hydrothermal synthesis has been found to provide a powerful technique for the preparation of organic–inorganic hybrid materials with retention of the structural elements of the reactants in the final products. Consequently, the general approach adopted for the preparation of new inorganic oxides employs organic molecules at low temperature to modify or control the surface of growing oxide crystals in a hydrothermal medium. Following these general guidelines, a fifth major class of organic–inorganic hybrid materials has been identified: dipodal organonitrogen-templated molybdenum oxides.

2. Synthesis

2.1. Hydrothermal Chemistry

While well established for the synthesis of zeolites, the hydrothermal method has more recently been adapted to the preparation of a wide variety of metastable materials, including the TMPO group and even complex polyoxoalkoxometalates.^[44] Hydrothermal reactions, typically carried out in the temperature range 120–260 °C under autogenous pressure, exploit the self-assembly of the product from soluble precursors.^[45] The reduced viscosity of water under these conditions enhances the diffusion processes so that solvent extraction of solids and crystal growth from solution are favored.^[46] Since differential solubility problems are minimized, a variety of simple precursors may be introduced, as well as a number of organic and/or inorganic structure-directing agents, from which those of appropriate size and shape may be selected for efficient crystal packing during the crystallization process. Under such nonequilibrium crystallization conditions, metastable kinetic phases rather than the thermodynamic phase are most likely to be isolated.^[47] While several pathways, including the one that results in the most stable phase, are available in such nonequilibrium mixtures, the kinetically favored structural evolution results from the smallest perturbations of atomic positions. Consequently, nucleation of a metastable phase may be favored.

The synthetic conditions employed to prepare the organodiamine molybdenum oxides (MOXI) of this study are relatively simple. An aqueous solution of the organic template, the molybdenum source, and in certain cases a heterometal source are heated to 120–220 °C for 12–72 h. In the majority of cases, crystals form at the reaction temperature and not upon cooling to room temperature. Since X-ray crystallography is the primary characterization

technique for these materials, suitable crystals are a prerequisite for the study.

It is also apparent that small changes in one or more of the reaction variables of the vast hydrothermal parameter space—such as time, temperature, pH value, stoichiometry, template identity, and duration—can have a profound influence on the reaction outcome. Consequently, quantitative predictions of reaction products are generally not possible, and one is often guided by analogy to previous results or by knowledge of the geometric constraints associated with a ligand type or of the coordination requirements of the heterometal.

2.2. Role of the Organic Component

The structure-directing organic molecules employed in the synthesis of the MOXI class of oxides are the dipodal organoamines, of the general types illustrated below (see Table 2 for abbreviations of the organic molecules). Such organoamines may adopt a variety of roles in these organic–inorganic hybrid materials: 1) charge-compensating cations, 2) ligands bonded directly to a molybdenum site of the molybdenum oxide skeletal backbone, and 3) ligands bonded to the heterometal site.

As charge-compensating cations, the organodiamines function in a role reminiscent of that adopted by the organic components of zeolites, mesoporous oxides, and TMPOs. The common features that link these structurally diverse materials are the critical phenomena which also influence biomineralization, namely, hydrogen-bonding and hydrophobic–hydrophilic interactions. As shown in Figure 1, the structure of $[\text{H}_3\text{N}(\text{CH}_2)_3\text{NH}_3][(\text{VO})_3(\text{OH})_2(\text{H}_2\text{O})_2(\text{PO}_4)_2]$ ^[48] reveals an open-framework vanadium phosphate with the organodiammonium cations occupying well-defined channels. The important structure-directing role of the entrained polar ammonium

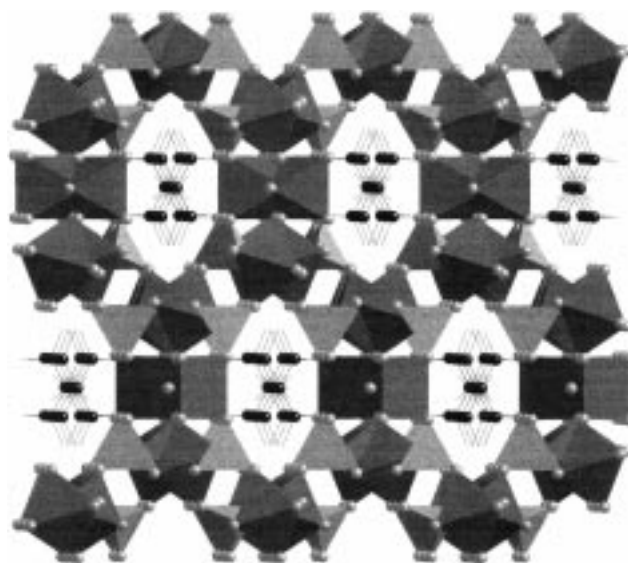


Figure 1. A polyhedral representation of the V-P-O framework of $[\text{H}_3\text{N}(\text{CH}_2)_3\text{NH}_3][(\text{VO})_3(\text{OH})_2(\text{H}_2\text{O})_2(\text{PO}_4)_2]$ down the crystallographic *a* axis. The channels are occupied by the templating $[\text{H}_3\text{N}(\text{CH}_2)_3\text{NH}_3]^{2+}$ cations, shown in ball-and-stick representation.

cation manifests itself in strong, geometrically specific hydrogen bonding between the NH groups of the cation and the oxygen atoms of the framework. It is likely that such multipoint hydrogen bonding, which constitutes the strongest interaction aside from the covalent bonds of the oxide framework, may render the material the kinetically least soluble species present in the hydrothermal reaction medium. The influences of hydrophobic–hydrophilic interactions are most evident in the structures of the vanadium organophosphonates, such as $[(\text{C}_2\text{H}_5)_4\text{N}][(\text{VO})_6(\text{OH})_2(\text{H}_2\text{O})_2(\text{O}_3\text{PC}_2\text{H}_5)_6]$ ^[49] (Figure 2). Two characteristics which influence structure are the association of organic groups from neighboring phosphonate units and the incorporation of hydrophobic $(\text{C}_2\text{H}_5)_4\text{N}^+$ cations. Consequently, two-dimensional materials are favored to reduce the interactions of the less polar organic moiety with the polar oxide network.

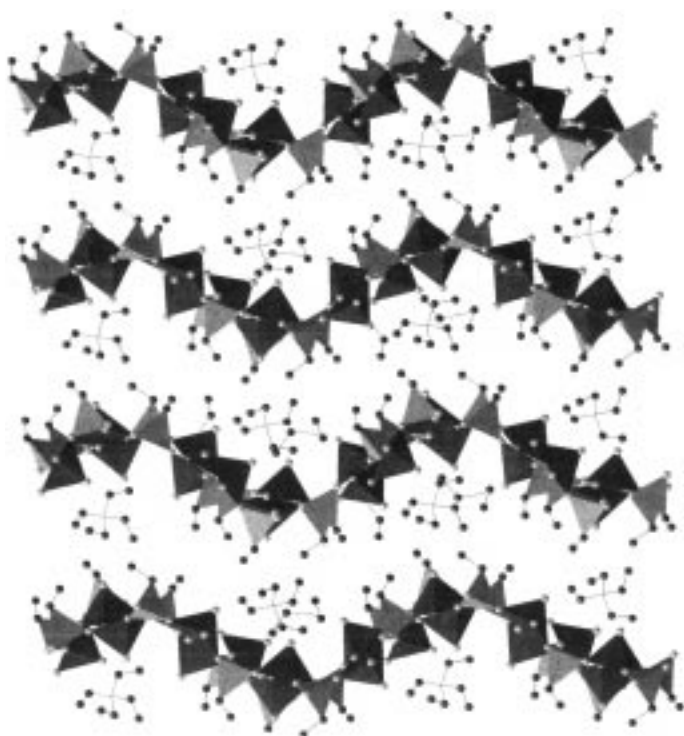


Figure 2. A polyhedral representation of the undulating V-P-O networks of $[(\text{C}_2\text{H}_5)_4\text{N}]_2[(\text{VO})_6(\text{OH})_2(\text{H}_2\text{O})_2(\text{O}_3\text{PC}_2\text{H}_5)_6]$, viewed along the *b* axis. The ethyl groups of the organophosphonate ligands project into the interlamellar regions above and below each layer. The organic cations occupy the interlamellar region, and divide the structure into polar and nonpolar domains.

Of course, organoamines may function as ligands in a variety of ligating modes. The material $[(\text{VO})(\text{PO}_4)(\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_3)]$ ^[50] (Figure 3) serves as an unusual example of an organic component that serves both as a monodentate ligand through an amine terminus and as a cation through protonation of the pendant nitrogen site. Strong multipoint hydrogen bonding between strands is also apparent in this structure.

In certain cases, it has proved advantageous to introduce a heterometallic component, either to provide charge compensation or as part of the inorganic bimetallic oxide framework itself. The structure of $[\text{Zn}(\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2)_2][\text{V}_6\text{O}_{14}]$ ^[51]

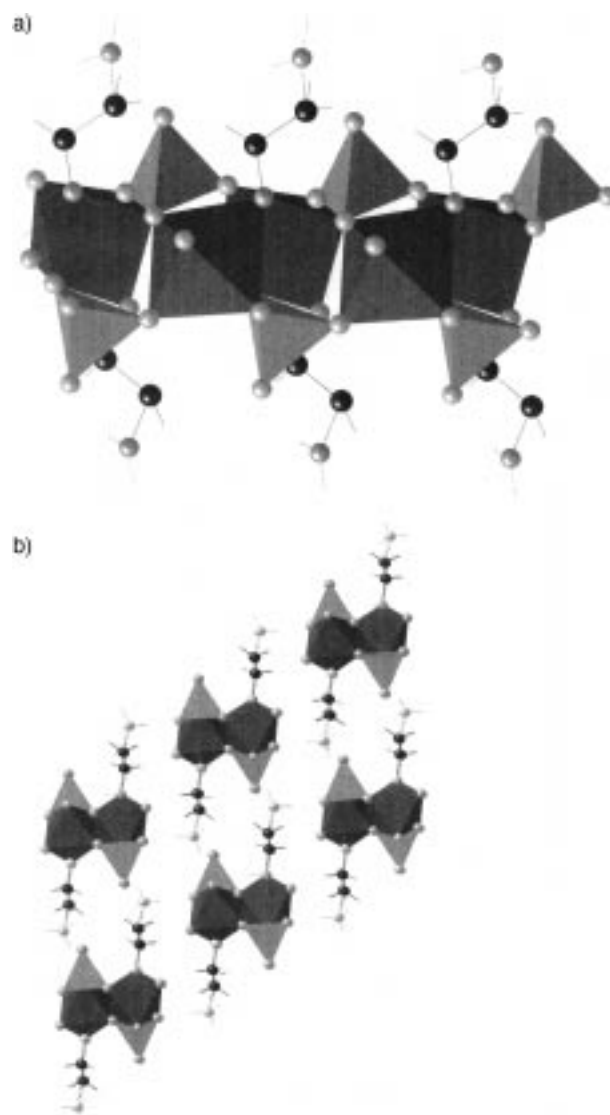


Figure 3. a) A polyhedral representation of the one-dimensional chains of $[(\text{VO})(\text{PO}_4)(\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_3)]$, to illustrate the role of the $\{\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_3\}^+$ group as ligand and charge-compensating cation. b) A view of the chain packing along the *b* axis and down the chain axes, showing the outward projection of the $\{\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_3\}^+$ groups which provides effective hydrogen bonding between adjacent chains.

(Figure 4) is an example of a simple coordination complex cation $[\text{Zn}(\text{en})_2]^{2+}$ entrained between vanadium oxide layers, which functions as an organic–inorganic counterpart in simple structural types. In contrast, the structure of $[\{\text{Zn}(4,4'\text{-bpy})_2\}_2\text{V}_6\text{O}_{17}]$ ^[51] (Figure 5) illustrates the incorporation of the heterometallic complex as a covalently attached unit of the metal oxide framework itself. These latter structures provided the impetus to investigate the role both of organodiamine groups and of organodiamine-ligated heterometals as ligands, counterions, space-filling units, and constituents of the metal oxide framework in molybdenum oxide phases.

It was also evident that ditopic organoamine ligands presented an unusual structural versatility. Such versatility has been exploited in recent years in the development of a vast structural chemistry based on cationic rods, square grids,

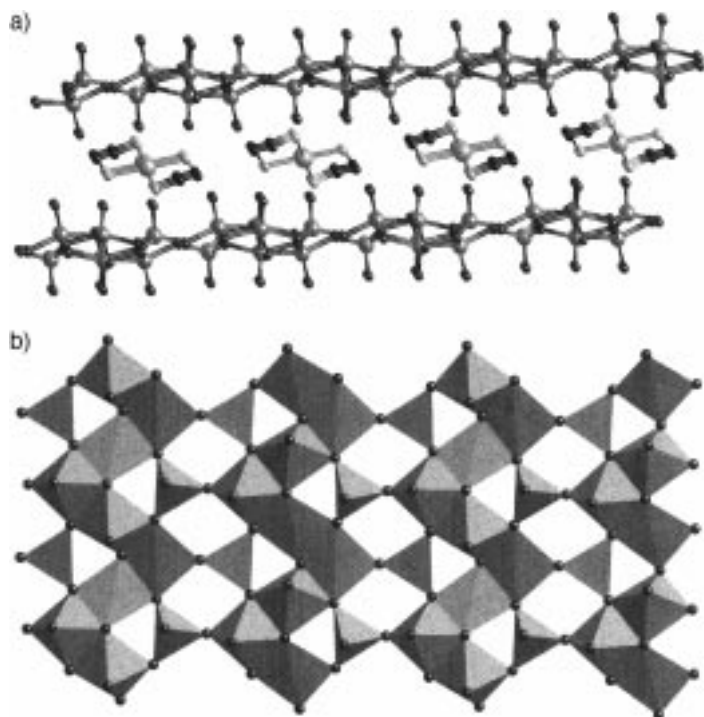


Figure 4. a) A view of the complex layer structure of $[\text{Zn}(\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2)_2][\text{V}_6\text{O}_{14}]$, to show the disposition of $[\text{Zn}(\text{en})_2]^{2+}$ groups in the interlamellar region between the $[\text{V}_6\text{O}_{14}]^{2-}$ layers. b) A polyhedral representation of the $[\text{V}_6\text{O}_{14}]^{2-}$ layer, showing the chains of edge-sharing V^{IV} square pyramids and bridging V^{V} tetrahedra.

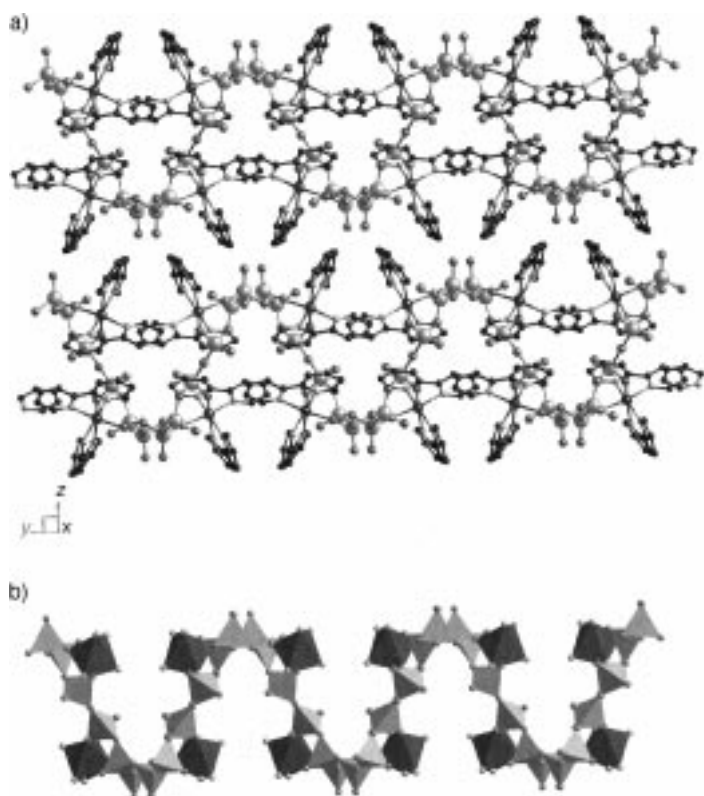


Figure 5. a) A view perpendicular to the vanadium oxide layers of the structure of $[(\text{Zn}(4,4'\text{-bpy})_2)_2\text{V}_6\text{O}_{17}]$. b) A polyhedral representation of the corner-sharing $[\text{VO}_4]$ tetrahedra (light polyhedra) and $[\text{ZnO}_2\text{N}_4]$ octahedra (dark polyhedra), to show the cavities occupied by the 4,4'-bpy ligands.

honeycomb grids, adamantoid frameworks, and interpenetrating networks.^[52, 188] Such assemblies seemed to offer novel coordination complex polymers and structural units for incorporation into molybdenum oxide frameworks to generate a new class of organic–heterometallic oxides. The structural diversity of these cationic building blocks is sufficiently complex and fascinating to merit a digression into their crystal architectures, a topic which has not been reviewed despite intense contemporary activity.

3. Structural Chemistry of Organodiamine Coordination Polymers

Crystal engineering of supramolecular architectures is of considerable contemporary interest by virtue of the potential applications of such materials to host–guest chemistry,^[53] catalysis,^[54] and the evolution of optical, magnetic and electronic properties.^[55, 56] Two types of interactions have been exploited in the construction of such supramolecular materials: 1) coordinate covalent bonds connecting metal centers and appropriate ligand types,^[57] and 2) hydrogen bonds in organic solids.^[58, 59] In the specific case of coordination polymers, the expectation is that the geometry of the metal will be propagated through the bridging ligands. The approach to the design of such coordination polymers has been to exploit organic ligands which, through their geometries and coordination preferences, impose a specific network topology.^[60] While organic building blocks of various connectivities and geometries have been used in the preparation of coordination polymers,^[57] this discussion will be limited to two- and three-connected units that employ organoamine donors. Although supramolecular cyanometalate systems possess an extensive and well-developed structural chemistry,^[61] such materials have yet to be employed in the preparation of molybdenum oxide phases; consequently, their chemistry will not be discussed here.

As summarized in Table 2, the structural versatility of even this limited subclass of coordination polymers is quite remarkable. This observation is less surprising if it is noted that the structural range reflects both metal and ligand properties: the oxidation state and coordination predisposition of the metal; 2) the ligand geometry, including relative orientation of the donor groups and the spacing between donor groups; and 3) the influence of the coordinating anions or ancillary ligands.

From the perspective of structural modification of molybdenum oxide phases, the cationic nature of the metal–organodiamine polymer subunits provides the significant unifying theme for the variety of coordination polymer structures presented in the subsequent sections. The coordination polymer structures are characterized by void volumes occupied by charge-compensating anions. Molybdenum oxides, whether present as polyanions, chains, two-dimensional networks, or three-dimensional frameworks, are in general negatively charged species. From this viewpoint, the cationic coordination polymers as subunits of molybdenum oxide phases can serve as charge-compensating and space-filling units, or they may bond directly to the molybdenum oxide

Table 2. Selected structural information for polymer structures formed from metal cations and ditopic nitrogen-donor ligands and related ligand types.^[a]

Compound	Metal–ligand skeletal structure	Metal coordination geometry	Structural description	Figure	Ref.
<i>A. 4,4'-bipyridine as bridge</i>					
[Cu(4,4'-bpy)(BF ₄) ₂ (H ₂ O) ₂] · (4,4'-bpy)	1D	{CuN ₂ O ₂ F ₂ }	linear [Cu(4,4'-bpy)(BF ₄) ₂ (H ₂ O) ₂] chains linked by hydrogen bonding of H ₂ O protons to uncoordinated 4,4'-bpy groups to form 2D sheets	6	[63]
[Mn(4,4'-bpy)(NCS) ₂ (H ₂ O) ₂] · (4,4'-bpy)	1D	{MnN ₄ O ₂ }	linear {Mn(4,4'-bpy)(NCS) ₂ (H ₂ O) ₂ } chains linked by hydrogen bonding of H ₂ O protons to uncoordinated 4,4'-bpy groups to form a 2D network	–	[64]
[Cu(4,4'-bpy)(ClO ₄) ₂ (H ₂ O) ₂] · (4,4'-bpy)	1D	{CuN ₂ O ₄ }	linear {Cu(4,4'-bpy)(ClO ₄) ₂ (H ₂ O) ₂ } chains linked by hydrogen bonding of H ₂ O protons to pendant perchlorate oxygen atoms of a neighboring strand to form a 2D network	–	[65]
[Zn(4,4'-bpy)(H ₂ O) ₄](NO ₃) ₂ · (4,4'-bpy)	1D	{ZnN ₂ O ₄ }	linear {Zn(4,4'-bpy)(H ₂ O) ₄ } chains linked by hydrogen bonding to the uncoordinated 4,4'-bpy into 2D sheets	–	[66]
[Zn(4,4'-bpy)(H ₂ O) ₄](NO ₃) ₂ · 2(4,4'-bpy) · 3 H ₂ O	1D	{ZnN ₂ O ₄ }	linear {Zn(4,4'-bpy)(H ₂ O) ₄ } chains linked by hydrogen bonding to pairs of uncoordinated 4,4'-bpy into 2D sheets	–	[66]
[Zn(4,4'-bpy)(H ₂ O) ₄](CF ₃ SO ₃) ₂	1D	{ZnN ₂ O ₄ }	linear {Zn(4,4'-bpy)(H ₂ O) ₄ } chains linked by hydrogen bonding to pairs of uncoordinated 4,4'-bpy into 2D sheets	–	[66]
[Fe(4,4'-bpy)(H ₂ O) ₃ (ClO ₄)](ClO ₄) · 1.5(4,4'-bpy) · H ₂ O	1D	{FeN ₂ O ₄ }	linear {Fe(4,4'-bpy)(ClO ₄)(H ₂ O) ₃ } ⁺ chains linked by hydrogen bonding to alternating single and paired uncoordinated 4,4'-bpy groups into 2D sheets	7	[66]
[Cu(4,4'-bpy)(MeCN) ₂](BF ₄)	1D	{CuN ₄ }	zigzag [Cu(4,4'-bpy)(MeCN) ₂] chains	8	[67]
[Co(4,4'-bpy) _{1.5} (NO ₃) ₂] · MeCN	1D	{CoN ₃ O ₄ }	linear {Co(4,4'-bpy)(NO ₃) ₂ } chains cross-linked by 4,4'-bpy groups into a ladder structure	9	[68]
[Ni(4,4'-bpy) _{2.5} (H ₂ O) ₂](ClO ₄) ₂ · 1.5(4,4'-bpy) · 2 H ₂ O	1D	{NiN ₄ O ₂ }	linear {Ni(4,4'-bpy)(H ₂ O) ₂ } ²⁺ chains cross-linked by 4,4'-bpy groups, with each Ni site additionally bonded to a monodentate, pendant 4,4'-bpy to form a 1D “railroad” assembly; π stacking of pendant groups results in a 2D sheet	10	[69]
[MX ₂ (4,4'-bpy)] (M = Ni, Cu; X = Cl, Br)	1D	{MX ₂ N ₂ }	mutually perpendicular [M(4,4'-bpy)] ²⁺ and [MX ₂] chains linked into a 2D network	11	[70]
[Ag(4,4'-bpy)](NO ₃)	1D	{AgN ₂ Ag}, T-shaped	[Ag(4,4'-bpy)] ⁺ linear chains linked through Ag–Ag bonds into a 3D structure; threefold interpenetration	12	[71]
[Cu(4,4'-bpy)(H ₂ O) ₃ (SO ₄)] · 2 H ₂ O (CUSO-1)	1D	{CuO ₄ N ₂ }	linear {Cu(4,4'-bpy)(H ₂ O) ₃ (SO ₄)} chains, stacked to produce a hexagonal motif	46	[72]
[Cu(dmp)(4,4'-bpy)](BF ₄) · MeCN	1D	{CuN ₄ }	zigzag chains of tetrahedral {CuN ₄ } sites linked by 4,4'-bpy tethers	–	[73]
[Cd(4,4'-bpy) ₂ (NO ₃) ₂] · 2 C ₆ H ₄ Br ₂	2D	{CdN ₄ O ₂ }	stacked cationic square-grid networks with no interpenetration	13	[74]
[Zn(4,4'-bpy) ₂ (H ₂ O) ₂](SiF ₆)	2D	{ZnN ₄ O ₂ }	stacked cationic square-grid networks with no interpenetration	–	[75]
[Zn(4,4'-bpy) ₂](SiF ₆) · DMF	2D	{ZnN ₄ F ₂ }	sheets of {Zn(4,4'-bpy) ₂ } square grids bridged through SiF ₆ ^{2–} groups into a 3D framework	–	[76]
[Cu ₂ (C ₃ H ₂ O ₄) ₂ (H ₂ O)(4,4'-bpy)] · H ₂ O	2D	{CuNO ₄ }	{Cu ₂ (C ₃ H ₂ O ₄)} squares linked through 4,4'-bpy groups into larger squares forming a 2D network, no interpenetration	14	[77]
[M ₂ (4,4'-bpy) ₃ (NO ₃) ₄] · x H ₂ O, M = Co, Ni, Zn	2D	{MN ₃ O ₄ }, pentagonal bipyramidal	[M(4,4'-bpy)(NO ₃) ₂] chains linked by 4,4'-bpy groups into double sheets; the sheets assemble into a tongue-and-groove 3D structure	15	[78]
[Cu(4,4'-bpy)Cl]	2D	{CuN ₂ Cl ₂ }	{Cu ₂ Cl ₂ } dimers linked through 4,4'-bpy groups into 2D sheets with large hexagonal grid pattern; twofold interpenetration of sheet arrays	16	[79]
[Cu(4,4'-bpy) ₂ (H ₂ O) ₂](ClO ₄) ₄ · (4,4'-H ₂ bpy)	2D	{CuN ₄ O ₂ }	2D square-grid network	–	[80]

Table 2. (Continued)

Compound	Metal – ligand skeletal structure	Metal coordination geometry	Structural description	Figure	Ref.
$[M(4,4'\text{-bpy})_2(\text{H}_2\text{O})_2](\text{ClO}_4)_2 \cdot (2,4'\text{-bpy})_2 \cdot \text{H}_2\text{O}$, $M = \text{Zn}, \text{Cd}$	2D	$\{\text{MN}_4\text{O}_2\}$	2D square-grid network	–	[80]
$[\text{Ag}(4,4'\text{-bpy})_2](\text{CF}_3\text{SO}_3)$	3D	$\{\text{AgN}_4\}$	diamondoid framework based on adamantoid cages; four independent diamondoid frameworks interpenetrate	17	[81]
$[\text{Cu}(4,4'\text{-bpy})_2](\text{PF}_6)$	3D	$\{\text{CuN}_4\}$	diamondoid framework based on adamantoid cages; four independent diamondoid frameworks interpenetrate	–	[82]
$[\text{Cu}(3,3'\text{-bpy})_2]\text{X}$, $\text{X} = \text{BF}_4^-, \text{PF}_6^-$	3D	$\{\text{CuN}_4\}$	diamondoid framework; two independent frameworks interpenetrate	–	[83]
$[\text{Cu}(4,4'\text{-bpy})_{1.5}](\text{NO}_3)(\text{H}_2\text{O})_{1.25}$	3D	$\{\text{CuN}_3\}$, trigonal planar	six porous and identical interpenetrating 3D frameworks	18	[84]
<i>B. tethered bipyridine bridges (py-X-py) and related types.</i>					
$[\text{Cu}_2(\text{bpbd})_3(\text{MeCN})_2](\text{PF}_6)_2$	1D	$\{\text{CuN}_4\}$, one CH_3CN nitrogen atom	$\{\text{Cu}(\text{bpbd})(\text{MeCN})\}$ undulating chains cross-linked by dpbd ligands into a ladder; each ladder is interpenetrated by four additional ladders into a polycatenated 2D sheet	19	[85]
$[\text{Cd}(\text{dpb})_{1.5}(\text{NO}_3)_2]$	1D	$\{\text{CdN}_3\text{O}_4\}$	$\{\text{Cd}(\text{dpb})(\text{NO}_3)_2\}$ linear chains cross-linked by dpb groups into a ladder; each ring is interpenetrated by rings of four different ladders	20	[86]
$[\text{Ag}(\text{bbp})](\text{CF}_3\text{SO}_3) \cdot \text{EtOH}$	1D	$\{\text{AgN}_2\}$	1D sinusoidal chains	22	[87]
$[\text{Ag}(\text{bbp})](\text{CF}_3\text{SO}_3)$	1D	$\{\text{AgN}_2\}$, weak additional Ag – Ag interaction to produce T-shaped site	1D helical chains; helices pair into double chains	22	[87]
$[\text{Ag}_2(\text{bbp})_4](\text{CF}_3\text{SO}_3)_2 \cdot \text{bbp}$	1D	$\{\text{AgN}_4\}$	$\{\text{Ag}_2(\text{bbp})_2\}$ 24-membered rings linked into tubular arrays	22	[87]
$[\text{Cu}(\text{dmp})(\text{dpe})](\text{BF}_4)$	1D	$\{\text{CuN}_4\}$	zigzag chains of tetrahedral $\{\text{CuN}_4\}$ sites linked by dpe tethers	–	[73]
$\alpha\text{-}[\text{Co}(\text{dpe})_{1.5}(\text{NO}_3)_2]$	1D	$\{\text{CoN}_3\text{O}_4\}$, pentagonal bipyramidal	$\{\text{Co}(\text{dpe})(\text{NO}_3)_2\}$ chains linked by dpe into a molecular bilayer	23	[88]
$[\text{Cd}(\text{dpe})_{1.5}(\text{NO}_3)_2]$	1D	$\{\text{CdN}_3\text{O}_4\}$	isostructural with $\alpha\text{-}[\text{Co}(\text{dpe})_{1.5}(\text{NO}_3)_2]$	–	[89]
$\gamma\text{-}[\text{Co}(\text{dpe})_{1.5}(\text{NO}_3)_2]$	1D	$\{\text{CoN}_3\text{O}_4\}$	$\{\text{Co}(\text{dpe})(\text{NO}_3)_2\}$ linear chains cross-linked by <i>anti</i> -dpe ligands into a ladder	–	[88]
$[\text{Cu}(\text{bpac})](\text{NO}_3)_2 \cdot 0.5 \text{EtOH}$	1D	$\{\text{CuN}_2\text{O}_4\}$, O donors from two bridging nitrate groups and one terminal bidentate nitrate group	$\{\text{Cu}(\text{bpac})\}$ linear chains linked by bridging nitrate ligands into a ladder	–	[90]
$[\text{Ag}(\text{pytz})(\text{NO}_3)]$	1D	$\{\text{AgN}_2\text{O}_2\}$ distorted square planar with two long Ag $\cdots$ O interactions	$\{\text{Ag}(\text{pytz})\}$ chains linked through $(\text{NO}_3)^-$ bridges into a 3D helical array	32	[91]
$[\text{Ag}_2(\text{bpy-4pz})_2](\text{PF}_6)_2$	1D	$\{\text{AgN}_3\text{S}\}$	binuclear $\{\text{Ag}_2(\text{bpy-4pz})_2\}$ boxes linked into a 1D chain	25	[92]
$[\text{Cu}_4(\text{bppy})(\text{CH}_3\text{CO}_2)_8]$	1D	$\{\text{CuO}_6\}$ and $\{\text{CuN}_2\text{O}_3\}$	binuclear $\{\text{Cu}_2(\text{CH}_3\text{CO}_2)_2\}$ units and linked by bppy groups into 1D $\{\text{CuN}_2\text{O}_3\}$ chains which are in turn linked through acetate bridges for $\{\text{Cu}_2(\text{CH}_3\text{CO}_2)_4\}$ units to form a 2D sheet	26	[93]
$[\text{Co}(\text{py}_2\text{S})(\text{NCS})_2] \cdot 2 \text{H}_2\text{O}$	1D	$\{\text{CoN}_4\text{N}'_2\}$ four pyridyl donors, two nitrogen donors from NCS^-	double-stranded 1D chain	–	[94]
$[\text{Cu}(\text{bpe})_2][\text{Cu}(\text{bpe})(\text{H}_2\text{O})_2(\text{SO}_4)_2] \cdot 2 \text{H}_2\text{O}$ (CUSO-2)	1D and 2D	$\{\text{CuN}_2\text{O}_4\}$ and $\{\text{CuN}_4\}$	2D sheets of $\{\text{Cu}(\text{bpe})_2\}^{2+}$ square grids; two independent sets of sheets interpenetrate; 1D $\{\text{Cu}(\text{bpe})(\text{H}_2\text{O})_2(\text{SO}_4)_2\}^{2-}$ chains are interwoven between the sheets	47	[72]
$[\text{Cu}(\text{bpe})(\text{H}_2\text{O})(\text{SO}_4)]$ (CUSO-3)	1D	$\{\text{CuN}_2\text{O}_3\}$, square pyramidal	1D $\{\text{Cu}(\text{bpe})\}^{2+}$ chains linked by SO_4^{2-} groups into a 3D covalent framework	48	[72]
$[\text{Ag}(\text{pytz})(\text{MeCN})](\text{PF}_6)$	1D	$\{\text{AgN}_3\}$ two pyridine donors, one methyl cyanide nitrogen donor	linear $\{\text{Ag}(\text{pytz})\}$ chains linked into double chains through long Ag $\cdots$ Ag interactions	33	[91]

Table 2. (Continued)

Compound	Metal–ligand skeletal structure	Metal coordination geometry	Structural description	Figure	Ref.
[Co(py ₂ S)Cl ₂]	2D	{CoN ₄ Cl ₂ }	{CoCl ₂ (py ₂ S) ₂ } units linked into 2D networks; interpenetration results in a two-layer interwoven network	–	[94]
β -[Co(dpe) _{1.5} (NO ₃) ₂] · CH ₃ CN	2D	{CoN ₃ O ₄ }	{Co(dpe)(NO ₃) ₂ } linear chains cross-linked by <i>gauche</i> -dpe ligands into a bilayer	24	[88]
[Cd(dpb-F ₄) _{1.5}](NO ₃) ₂	2D	{CdN ₃ O ₄ }	{Cd(dpb-F ₄)(NO ₃) ₃ } linear chains cross-linked by dpb-F ₄ ligands into a 2D brick motif; three independent sheets interpenetrate	21	[86]
[Ag(py ₂ urea) ₂](BF ₄)	2D	{AgN ₄ }	2D network based on ligand-bridged distorted tetrahedral Ag ^I sites, extended into three dimensions by hydrogen bonding	–	[95]
[Ag(py ₂ oxalamide) ₂](NO ₃)	2D	{AgN ₄ }	As above, but Ag...Ag distances are longer as controlled by the hydrogen bonding between the ligand backbones	–	[95]
[Cu(dpe) ₂](NO ₃) ₂ · 3 C ₆ H ₆ · 2 MeOH	3D	{CuN ₄ O ₂ }, long Cu...O distances	3D CdSO ₄ type framework; two independent frameworks interpenetrate to generate large channels occupied by C ₆ H ₆ and MeOH guest molecules	–	[96–98]
[Cu(bpe) ₂](PF ₆)	3D	{CuN ₄ }	tetrahedral {Cu(bpe)} sites each linked to four adjacent tetrahedral sites to form a 3D adamantoid structure; five such motifs interweave to form a polycatenated structure	–	[99]
[Cu(dzp) ₂](PF ₆)	3D	{CuN ₄ }	tetrahedral {CuN ₄ } sites linked through dzp ligands into a 3D adamantoid framework; three independent frameworks interpenetrate	–	[100]
[Ag(tpc)](BF ₄)	3D	{AgN ₄ }	tetrahedral {Ag(tpc)} sites linked through the fused ligands to four adjacent Ag centers to give a 3D motif; there is no interpenetration of motifs	29	[101]
[{Cu(bpac) ₂ (H ₂ O) ₂ }{Cu(bpac) ₂ (NO ₃)(H ₂ O) ₂ }] · (NO ₃) ₄ · bpac · 1.33 H ₂ O	3D	{CuN ₄ O ₂ }, two water molecules coordinated; {CuN ₄ OO'}, one water, one η^1 -nitrate	linear {Cu(bpac)} chains, parallel and perpendicular, linked at the {CuN ₄ } sites into a 3D framework; triply interpenetrated	–	[90]
<i>C. bisimidazole bridges</i>					
[Ag ₂ (bix) ₃](NO ₃) ₂	1D	{AgN ₃ }, trigonal planar	{Ag ₂ (bix) ₂ } rings linked by bix ligands into a 1D chain; chains interpenetrate to form a 2D polyrotaxane sheet	27	[102]
[Zn(bix) ₂](NO ₃) ₂ · 4.5 H ₂ O	2D	{ZnN ₄ }	tetrahedral {ZnN ₄ } sites linked through bix ligands into a 2D polymeric sheet; two independent sheets interpenetrate to form a 2D polyrotaxane	28	[103]
[Ni(bpa) ₂ (SO ₄)(H ₂ O)] · 4 H ₂ O	3D	{NiN ₄ O ₂ }, O donors from monodentate SO ₄ ²⁻ group and an aqua ligand	network of fused {Ni ₆ (bpa) ₆ } rings linked by bridging bpa groups into a 3D framework; two independent frameworks interpenetrate	—	[104]
[Cu(bim) _{2.5}](ClO ₄) ₂ · 2 MeOH	3D	{CuN ₅ }, intermediate between square pyramidal and trigonal bipyramidal	distorted {Cu(bim) _{1.5} } centers linked into hexagonal 2D sheets which are in turn linked above and below by bim groups to adjacent sheets to produce the 3D array	30	[105]
[Mn(bbi) ₃](BF ₄) ₂	3D	{MnN ₆ }	octahedral {Mn(bbi) ₃ } sites linked by bridging bbi ligands into a 3D framework; two frameworks interpenetrate	31	[106]
<i>D. 1,3,5-triazine, 2,4,6-tri(4-pyridyl)-1,3,5-triazine, and 1,2,4-triazole</i>					
[Ag(tz)](CF ₃ SO ₃)	3D	{AgN ₅ O}	three-connected triazine ligands linking Ag tetrahedra into a 3D framework	–	[107]
[Ag(tz)](CF ₃ SO ₃) · H ₂ O	3D	{AgN ₄ }, {AgN ₄ F}, {AgN ₃ F}, {AgN ₃ O}	exclusively triconnected tz ligands bridging distorted Ag tetrahedra into a complex 3D framework	–	[108]
[Cu(Htrz)Cl ₂]	1D	{CuCl ₄ N ₂ }	two-connected Htrz ligands bridging distorted octahedral Cu ^{II} sites	–	[109]

Table 2. (Continued)

Compound	Metal – ligand skeletal structure	Metal coordination geometry	Structural description	Figure	Ref.
[Cu ₃ (tpt) ₄](ClO ₄) ₃	3D	{CuN ₄ }	tetrahedral {CuN ₄ } sites linked into a 3D framework; two independent interpenetrating 3D frameworks	34	[110]
[Hg(tpt) ₂](ClO ₄) ₂ · 6 C ₂ H ₂ Cl ₄	3D	{HgN ₆ }	octahedral {Hg(tpt) ₃ } sites linked into a 3D framework; no interpenetration	–	[111]
[Zn(CN)(tpt) _{2/3} (NO ₃) _{1/3}] · 0.75 C ₂ H ₂ Cl ₄ · 0.75 CH ₃ OH	3D	{ZnN ₃ CO ₂ }, one N and one C from CN [–] ligands	{Zn ₄ (CN) ₄ (NO ₃) ₄ } square grids linked by tpt ligands into a 3D framework; two independent frameworks interpenetrate	35	[112]
[Cu ₂ Br ₂ (trz)]	3D	{CuN ₂ Br ₄ }, Cu ^{II} site; {CuNBr ₂ }, Cu ^I sites.	2,4-triazolate-and Br-bridged {CuN ₂ Br ₄ } chains linked by {CuBr ₂ N} sites into a 2D network, linking through the 1-triazolate site achieves the 3D framework	–	[115]
<i>E. pyridine, pyrazine, and pyrimidine</i>					
[Ag(pz)(NO ₃) ₂]	1D	{AgN ₂ O ₃ }	linear chain of distorted trigonal bipyramidal {AgN ₂ O ₃ } sites, linked by pz-bridging ligands; each Ag coordinates to a monodentate and a bidentate NO ₃ [–] ligand	–	[116]
[Ag(pz)](BF ₄)	1D	{AgN ₂ }	linear chains	–	[113]
[Ag(pz) ₃](BF ₄)	1D	{AgN ₄ }	zigzag chains of distorted tetrahedral {AgN ₄ } sites linked by two-connected pz bridges; each Ag bonds to two terminal, one-connected pz ligands	–	[116]
[Cu(pz)](CF ₃ SO ₃)	1D	{CuN ₃ O}	spiral chains of distorted tetrahedral Cu ^I sites bridged by pz ligands; each Cu ^I site bonds to a terminal pz and to an O donor of a CF ₃ SO ₃ [–] group	–	[117, 118]
[Cu(pz)X ₂] (X = Cl, Br)	1D	{CuN ₂ X ₂ }	linear chains cross-linked by long Cu ⋯ Br bonds into a 2D sheet	36	[119]
[Ag(pz)](PF ₆) _{0.5} (OH) _{0.5}	1D	{AgN ₂ }	linear chains of alternating pz bridging ligands and digonal Ag ^I sites	–	[107]
[Ag(pz) _{1.5}](CF ₃ SO ₃)	1D	{AgN ₃ O}	linear {Ag(pz)} chains linked to a neighboring chain by a bridging pz ligand to form a ladder motif	–	[107]
[Cd(pz)Cl ₂]	1D	{CdN ₂ Cl ₄ }	mutually perpendicular linear {Cd(pz)} chains and {CdCl ₂ } chains linked into planar 2D sheets	36	[120]
[Zn(pyrd)Cl ₂]	1D	{ZnN ₂ Cl ₄ }	mutually perpendicular undulating {Zn(pyrd)} chains and {ZnCl ₂ } chains, linked into undulating 2D sheets	–	[120]
[Cu(pz)(dmg) ₂]	1D	{CuN ₆ }	linear chains	–	[121]
[Cu(pzca)(Me ₂ CO) _{0.5}](BF ₄)	1D	{CuN ₂ O ₂ }, one oxygen from a μ ² -bridging acetone	1D {Cu(pzca)(Me ₂ CO)} chains linked by bridging pzca molecules into a 3D helical framework	37	[122]
[Cd(pyrd)(NO ₃) ₂] · 2 H ₂ O	1D	{CdN ₂ O ₄ }	1D {Cd(μ-pyrd)(NO ₃) ₂ (H ₂ O) ₂ } chains; hydrogen bonding between chains results in a 3D framework	–	[123]
[Cu ₂ Cl ₂ (pz)]	2D	{CuN ₂ Cl ₂ }	{Cu ₂ Cl ₂ } double chains linked through pz bridges into a 2D sheet	–	[124]
[Cu ₂ (pz) ₃](SiF ₆)	2D	{CuN ₃ }, trigonal planar	2D honeycomb networks constructed of {Cu ₆ (pz) ₆ } hexagons	38	[82]
α-[Ag ₂ (pz) ₃](BF ₄) ₂	2D	{AgN ₃ }	{Ag ₃ pz ₃ } rings fused into an undulating sheet	–	[113]
[Ag(pz) ₂](PF ₆)	2D	{AgN ₄ }, distorted tetrahedral geometry	2D pleated sheets constructed of fused {Ag ₆ (pz) ₇ } bicyclic folded rings	39	[125]
[Ag(pz) ₂][Ag ₂ (pz) ₅](PF ₆) ₃	2D	{AgN ₅ }, square pyramidal and {AgN ₄ }, square planar	Parallel sheets of fused {Ag ₄ (pz) ₄ } square grids, linked by pz bridges into a double layers; such double layers alternate with simple sheets of fused {Ag ₄ (pz) ₄ } square grids	41 b	[126]
[Ag _{2.5} (pyrd) ₃](ClO ₄) _{2.5}	1D	{AgN ₂ } and {AgN ₃ O}	{Ag ₄ (pyrd) ₄ } ⁴⁺ squares cross-linked by {Ag(pyrd) ₂ } ⁺ units into a 1D chain	–	[127]
[Cu ₂ (pzca) ₃](ClO ₄) ₂ · 2 Me ₂ CO	2D	{CuN ₃ O}, distorted trigonal pyramidal and {CuN ₃ O ₂ }, trigonal bipyramidal	{Cu ₆ (pzca) ₆ } rings fused into a 2D sheet with a hexagonal motif	40	[122]
[Ag _{2.5} (pyrd) ₃](ClO ₄) _{2.5}	1D	{AgN ₂ } and {AgN ₃ O}	{Ag ₄ (pyrd) ₄ } ⁴⁺ squares cross-linked by {Ag(pyrd) ₂ } ⁺ units into a 1D chain	–	[127]

Table 2. (Continued)

Compound	Metal–ligand skeletal structure	Metal coordination geometry	Structural description	Figure	Ref.
[Ag _{2.5} (pyrd) ₃](ClO ₄) _{2.5}	1D	{AgN ₂ } and {AgN ₃ O}	{Ag ₄ (pyrd) ₄ } ⁴⁺ squares cross-linked by {Ag(pyrd) ₂ } ⁺ units into a 1D chain	–	[127]
[Co(pz) ₂ (NCS) ₂]	2D	{CoN ₄ N ₂ }, 4 pyrazine, 2 thiocyanate nitrogen donors.	Octahedral {Co(NCS) ₂ (pz) ₄ } sites linked by pyrazine bridges into a layer	–	[128]
[Co(pyrd) ₂ (NCS) ₂]	2D	{CoN ₄ N ₂ }	As above	–	[128]
[Cd(pz) ₂ X ₂] (X = Cl, Br, I)	2D	{CdN ₄ X ₂ }	{CdX ₂ } chains linked by pyrazine bridges into a layer	–	[123]
[Cu(pz) ₂ (CH ₃ SO ₃) ₂]	2D	{CuN ₄ O ₂ }	{Cu ₄ (pz) ₄ } square grids fused into a sheet	–	[129]
[Cu(Me ₂ pz) ₃](PF ₆) ₂	2D	{CuN ₃ }, two weakly interacting F donors from neighboring PF ₆ [−] groups	puckered sheets of fused {Cu ₆ pz ₆ } rings	–	[130]
[Fe(pz) ₂ (NCS) ₂]	2D	{FeN ₆ }	2D sheet of fused square grids	–	[131]
[Cu(pz) ₂ Cl ₂]	2D	{CuN ₄ Cl ₂ }	2D square grid	–	[132]
[Ag(pz) ₃](SbF ₆)	3D	{AgN ₆ }	octahedral {AgN ₆ } sites linked into a cubic 3D framework	41 a	[126]
β-[Ag ₂ (pz) ₃](BF ₄) ₂	3D	{AgN ₃ }	three equivalent 3D three-connected frameworks interpenetrate; each framework topologically related to α-ThSi ₂	–	[113]
[Ag ₂ (2,3-Me ₂ pz) ₃](SbF ₆) ₂	3D	{AgN ₃ }, T-shaped	Zigzag {AgN ₂ } chains, cross-linked into a 3D framework; two independent frameworks interpenetrate	42	[133]
[Cu(Me ₂ pz) ₂](PF ₆)	3D	{CuN ₄ }	distorted tetrahedral {CuN ₄ } sites linked into a 3D framework	–	[130]
[Cu(pyrd) ₂](BF ₄)	3D	{CuN ₄ }	tetrahedral {CuN ₄ } sites linked by pyrimidine-bridging ligands into a 3D framework	43	[134]
<i>F. hexamethylenetetramine and piperazine</i>					
[Ag ₅ (hmta) ₆](PF ₆) ₅ · 3 CH ₂ Cl ₂	molecular	{AgN ₂ }, two additional weak Ag...F interactions	[Ag ₅ (hmta) ₆] ⁵⁺ clusters	–	[135]
[Ag(hmta)](SbF ₆) · H ₂ O	1D	{AgN ₃ O}, {AgN ₃ F}	ribbons of distorted Ag tetrahedra linked by three-connected hmta ligand	–	[108]
[Ag(hmta)](ClO ₄)	2D	{AgN ₃ }	hexagonal [Ag ₆ (hmta) ₆] rings fused into a 2D network	44	[136]
[Ag(hmta)](NO ₃)	2D	{AgN ₃ }	as for [Ag(hmta)](ClO ₄).	–	[137]
[Ag(pip) ₂](BF ₄)	2D	{AgN ₄ }	folded [Ag ₆ (pip) ₇] bicyclic rings fused into an undulating 2D motif	–	[125]
[Ag ₃ (hmta) ₂](ClO ₄) ₃ · 2 H ₂ O	3D	{AgN ₃ } and {AgN ₂ }	hexagonal [Ag ₆ (hmta) ₆] rings fused into 2D networks, which are in turn bridged by digonally coordinated {AgN ₂ } sites into a 3D framework	–	[136]
[Ag(hmta)](PF ₆) · H ₂ O	3D	{AgN ₃ }	trigonally flattened {AgN ₃ } sites linked into a 3D helical framework	–	[138]
[Ag ₄ (hmta) ₃ (H ₂ O)](PF ₆) ₄ · 3 EtOH	3D	{AgN ₂ } and {AgN ₃ }	hexagonal [Ag ₆ (hmta) ₆] ⁶⁺ rings linked through three-coordinate Ag sites into a 3D framework	45	[135]
[Ag ₁₁ (hmta) ₆](PF ₆) ₁₁	3D	{AgN ₂ }, {AgN ₃ O}, {AgN ₂ O ₂ }, {AgN ₂ O}, {AgN ₂ F}	2D networks of fused {Ag ₆ (hmta) ₆ } and {Ag ₃ (hmta) ₃ } rings linked by {AgN ₂ } bridges into a 3D framework	–	[108]
<i>G. hexakis(imidazol-1-ylmethyl)benzene</i>					
[Cd(hkimb) ₂](F ₂) ₂ · 14 H ₂ O	3D	{CdN ₆ }	3D NaCl-related covalent framework. Water molecules occupy the cavities	–	[139]
<i>H. mixed ligand bridges</i>					
[Cu(4,4'-bpy)(pz)(H ₂ O) ₂](PF ₆)	2D	{CuN ₄ O ₂ } 2 pyrazine and 2 4,4'-bpy donors	2D rectangular gridwork	–	[140]

[a] Abbreviations: bbi = N,N'-butylenebisimidazole; bbp = 1,3-bis(4-pyridyl)propane; bim = 1,2-bis(imidazolyl)ethane; bix = 1,4-bis(imidazol-1-ylmethyl)-benzene; bpa = 4,4'-bipyridylamine; bpac = 4,4'-bipyridylacetylene; bpb = 1,4-bis(4-pyridyl)butadiene; bpe = 1,2-*trans*-bis(4-pyridyl)ethene; bpp = 2,3-bipyridylpyrazine; bppy = 2,5-bis(2-pyridyl)pyrazine; 2,2'bpy = 2,2'-bipyridine; 4,4'bpy = 4,4'-bipyridine; bpy-4pz = 4-thiomethyl-6-(4-pyridyl)-2,2'-bipyridine; dmp = 2,9-dimethyl-1,10-phenanthroline; dpb = 1,4-bis(4-pyridyl)benzene; dpb-F₄ = 1,4-bis(4-pyridyl)tetrafluorobenzene; dpe = 1,2-bis(4-pyridyl)-ethane; dzp = 2,7-diazapyrene; en = ethylenediamine; hkimb = hexakis(imidazol-1-ylmethyl)benzene; hmta = hexamethylenetetramine; Htr = 1,2,4-triazole; Htz = 1,3,4-triazole; pip = piperazine; py₂S = 4,4'-dipyridyl sulfide; pyrd = pyrimidine; pytz = 3,6-bis(4-pyridyl)-1,2,4,5-tetrazine; pz = pyrazine; pzca = pyrazinecarboxamide; tpc = 1,2,3,4-tetrakis(4-pyridyl)cyclobutane; tpt = 2,4,6-tris(4-pyridyl)1,3,5-triazine; tz = 1,3,5-triazine.

skeletal core as terminating groups which passivate the growing oxide surface or as bridging units which can stitch separate molybdenum oxide units into larger assemblies. These arguments will be elaborated in Section 4.

3.1. Two- and Three-Connected Organoamine Ligands

The structures of the coordination polymers of interest are derived from metal-bridging ligand building blocks which contain nitrogen donors in simple geometric dispositions. The most extensively studied two-connected bridging ligand of this type is 4,4'-bipyridine (4,4'-bpy). While the dispositions of donor groups in the related 2,2'-bipyridine and *o*-phenanthroline preclude a metal-bridging role, it will be demonstrated that these ligands afford useful chelates for stabilization of peripheral heterometal sites on molybdenum oxide surfaces or for passivation of molybdenum oxide surfaces.

A degree of structural control may be introduced by manipulation of the disposition of 4-pyridyl groups of the parent 4,4'-bipyridine ligand through introduction of various tether groups. Linear rigid rods with varying spacer lengths are represented by 1,4-bis(4-pyridyl)benzene (dpb), 1,4-bis(4-pyridyl)butadiyne (bpbd), and diazapyrene (dzp). The relative orientations of the pyridyl donors can be modified by introduction of appropriate fixed spacers, as in 1,2-*trans*-bis(4-pyridyl)ethene (bpe) and bis(4-pyridyl)amine (bpa), or conformationally flexible tethers, as in 1,2-bis(4-pyridyl)ethane (dpe) and 1,3-bis(4-pyridyl)propane (bpp). The influence of donor-group identity may be addressed as well by the use of imidazole-bridged donors. Furthermore, the donor-group spacing can be dramatically shortened by adoption of pyrazine (pz) or piperazine (pip) as the bridging ligands, while the relative donor-group orientation may be altered as well by pyrimidine (pyrd). The trigonal three-connected ligand type is represented by 2,4,6-tris(4-pyridyl)-1,3,5-triazine (tpt). While square-planar four-connectors have been developed,^[62] these will not be discussed here.

3.2. Coordination Polymers Constructed from 4,4'-Bipyridine

The expansive chemistry of coordination polymers based on 4,4'-bipyridine includes one-, two-, and three-dimensional motifs exhibiting diamondoid, grid, ladder, brick, railroad, and octahedral building blocks. The dimensionality of the metal–bipyridyl skeletal unit provides a utilitarian framework for the description of the crystal chemistry of this subclass of coordination polymers.

3.2.1. One-Dimensional 4,4'-Bipyridyl-Based Coordination Polymers

Linear one-dimensional metal–4,4'-bipyridine subunit structures are the most common motif encountered. As shown in Figure 6, the structure of $[\text{Cu}(\text{4,4'-bpy})(\text{BF}_4)_2(\text{H}_2\text{O})_2] \cdot (\text{4,4'-bpy})$ ^[63] consists of octahedral Cu^{II} sites linked

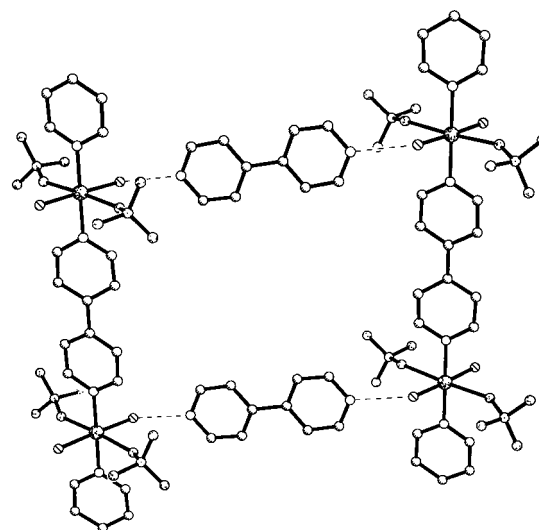


Figure 6. A view of the one-dimensional $[\text{Cu}(\text{4,4'-bpy})(\text{BF}_4)_2(\text{H}_2\text{O})_2]$ chains linked into a two-dimensional network through hydrogen bonding of the coordinated aquo ligands to the interstrand 4,4'-bipyridine groups in $[\text{Cu}(\text{4,4'-bpy})(\text{BF}_4)_2(\text{H}_2\text{O})_2] \cdot (\text{4,4'-bpy})$.

through 4,4'-bipyridine groups into a linear chain. The equatorial plane of the copper is occupied by fluorine atoms from each of two BF_4^- groups and two aquo ligands. The aquo groups participate in hydrogen bonding to the uncoordinated 4,4'-bipyridine to produce a two-dimensional hydrogen-bonded network. This is a common characteristic of these one-dimensional materials, shared by the first six entries of Table 2. However, the detailed architecture of the hydrogen-bonding interactions to produce the sheetlike structures may display considerable variations, as indicated by the first fifteen entries of Table 2. The structure of $[\text{Fe}(\text{4,4'-bpy})(\text{H}_2\text{O})_3(\text{ClO}_4)](\text{ClO}_4) \cdot 1.5(\text{4,4'-bpy}) \cdot \text{H}_2\text{O}$ ^[66] (Figure 7) illustrates this point. In this case, there are alternating single and double hydrogen-bonded 4,4'-bpy bridges between the $[\text{Fe}(\text{H}_2\text{O})_3(\text{ClO}_4)(\text{4,4'-bpy})]^+$ chains.

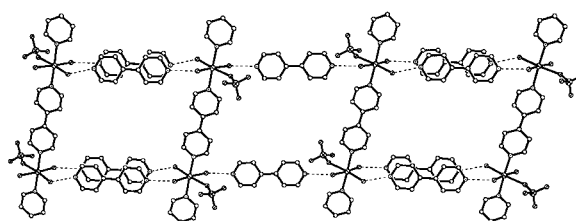


Figure 7. A view of the sheetlike structure adopted by $[\text{Fe}(\text{4,4'-bpy})(\text{H}_2\text{O})_3(\text{ClO}_4)](\text{ClO}_4) \cdot 1.5(\text{4,4'-bpy}) \cdot \text{H}_2\text{O}$, which is constructed from linear $[\text{Fe}(\text{4,4'-bpy})(\text{H}_2\text{O})_3(\text{ClO}_4)]^+$ chains linked by alternating single and double hydrogen-bonded 4,4'-bpy bridges.

The $\{\text{M}(\text{4,4'-bpy})\}$ motif is subject to considerable structural modification, which reflects the coordination preference of the metal and the nature of the coligands. For example, the Cu^{I} derivative $[\text{Cu}(\text{4,4'-bpy})(\text{MeCN})_2](\text{BF}_4)$ ^[67] exhibits zigzag chains (Figure 8), which reflects the preference of the metal for tetrahedral rather than tetragonal or octahedral geometry. Metal coordination and the metal–ligand stoichiometry are reflected in the structure of $[\text{Co}(\text{4,4'-bpy})_{1.5}(\text{NO}_3)_2] \cdot \text{MeCN}$ ^[68]

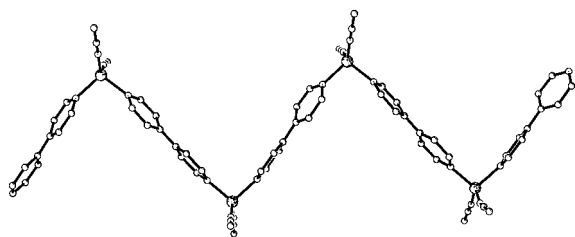


Figure 8. A view of the zigzag $\{Cu(4,4'\text{-bpy})(MeCN)_2\}^+$ cationic chains of $[Cu(4,4'\text{-bpy})(MeCN)_2](BF_4)$.

(Figure 9). The 4,4'-bpy ligands coordinate to the Co^{2+} ions to form the siderails and the rungs of a one-dimensional ladder. Alternatively, the structure may be described as a square motif, propagated in one dimension. The remaining coordination sites are occupied by bidentate NO_3^- groups. An

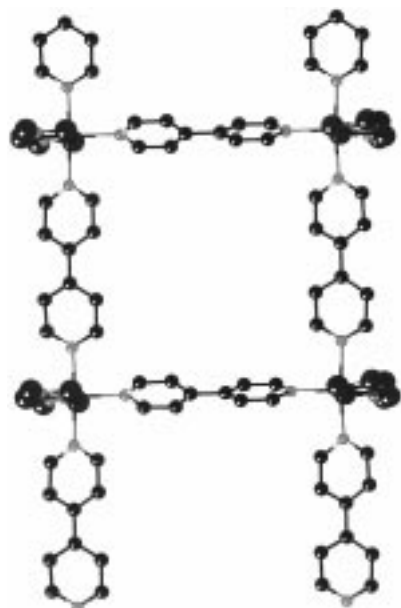


Figure 9. A view of the ladder structure adopted by $[Co(4,4'\text{-bpy})_{1.5}(NO_3)_2]$.

intriguing structural variant is presented by $[Ni(4,4'\text{-bpy})_{2.5}(H_2O)_2](ClO_4)_2 \cdot 1.5(4,4'\text{-bpy}) \cdot 2H_2O$ ^[69] (Figure 10). The ladder or square-grid motif of $[Co(4,4'\text{-bpy})_{1.5}(NO_3)_2]$ is maintained. However, an additional 4,4'-bpy moiety is coordinated to each Ni^{II} site as a monodentate ligand, which projects a pendant pyridyl group into the interstrand volume to produce

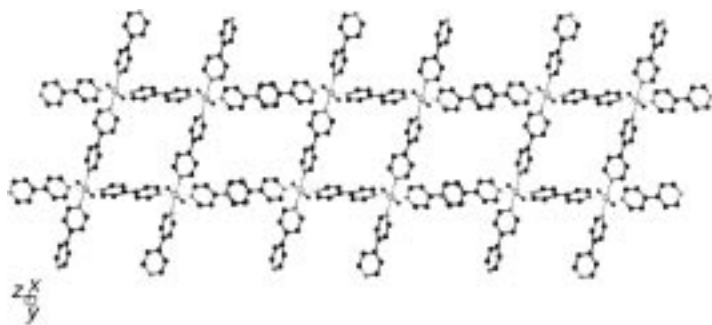


Figure 10. The railroad motif adopted by $[Ni(4,4'\text{-bpy})_{2.5}(H_2O)_2](ClO_4)_2 \cdot 1.5(4,4'\text{-bpy}) \cdot 2H_2O$ as a consequence of the monodentate coordination of one 4,4'-bpy ligand to each Ni^{II} site.

a railroadlike motif. Curiously, the pendant pyridyl groups π stack to form an extended two-dimensional network. The ClO_4^- and H_2O , and uncoordinated 4,4'-bpy units occupy the channels formed by the stacking of these sheets.

Coligand influences are demonstrated in the structure of $[CuBr_2(4,4'\text{-bpy})]$.^[70] As shown in Figure 11, the structure consists of linear $\{Cu(4,4'\text{-bpy})\}$ chains linked through bridging Br^- ions into a two-dimensional network. The structure reflects the preference of Cu^{II} for tetragonally distorted six-coordinate geometry and the bridging mode preferred by halides in Cu^{II} phases.

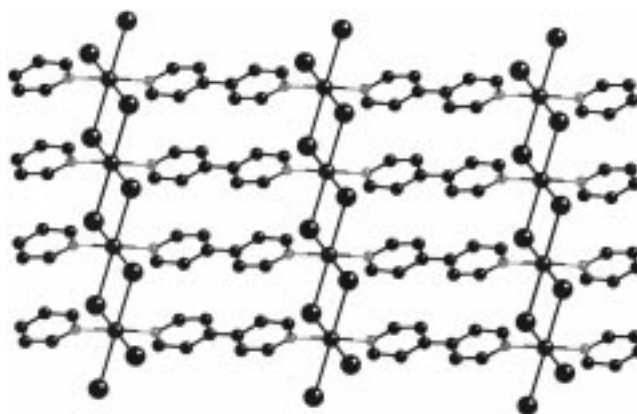


Figure 11. A view of the layer structure of $[CuBr_2(4,4'\text{-bpy})]$, which may be alternatively described as $\{CuBr_2\}$ chains linked by 4,4'-bpy bridges.

A particularly unusual example of the structural influence of the metal is provided by $[Ag(4,4'\text{-bpy})](NO_3)$ ^[71] As shown in Figure 12, the structure consists of linear $\{Ag(4,4'\text{-bpy})\}^+$ chains cross-linked by long $Ag\cdots Ag$ contacts into a three-dimensional framework based on T-shaped building blocks. In common with many coordination polymers of the two- or three-dimensional type, the void space is severely reduced by interpenetration, in this case of three independent frameworks. The NO_3^- counterions nestle in the restricted stairlike microchannels which are formed in this assembly. Interpenetration of two or more independent infinite substructures is a recurrent feature of framework solids. Entanglement based on polycatenane or polyrotaxane architecture appears as an inherent attribute of such structures. The excellent review by Batten and Robson^[188] discusses the phenomenon of ordered interpenetration in detail.

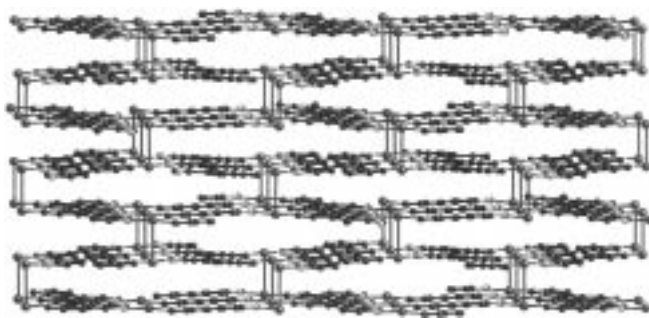


Figure 12. The three-dimensional structure of $[Ag(4,4'\text{-bpy})](NO_3)$, which consists of $\{Ag(4,4'\text{-bpy})\}^+$ chains linked through long $Ag\cdots Ag$ contacts, showing one of three independent frameworks.

3.2.2. Two-Dimensional 4,4'-Bipyridine-Based Coordination Polymers

The fundamental two-dimensional motif of fused square grids is represented in the structure of $[\text{Cd}(\text{4,4'-bpy})_2(\text{NO}_3)_2] \cdot 2\text{C}_6\text{H}_4\text{Br}_2$ ^[74] (Figure 13). The sheets are constructed from fused $\{\text{Cd}(\text{4,4'-bpy})_2\}^{2+}$ square grids, with each Cd^{II} site additionally coordinated in a monodentate fashion to two NO_3^- groups which project above and below this plane. The layers are stacked parallel and in registry with an interplane separation of 6.30 Å. Again, there is interpenetration of two independent stacks.

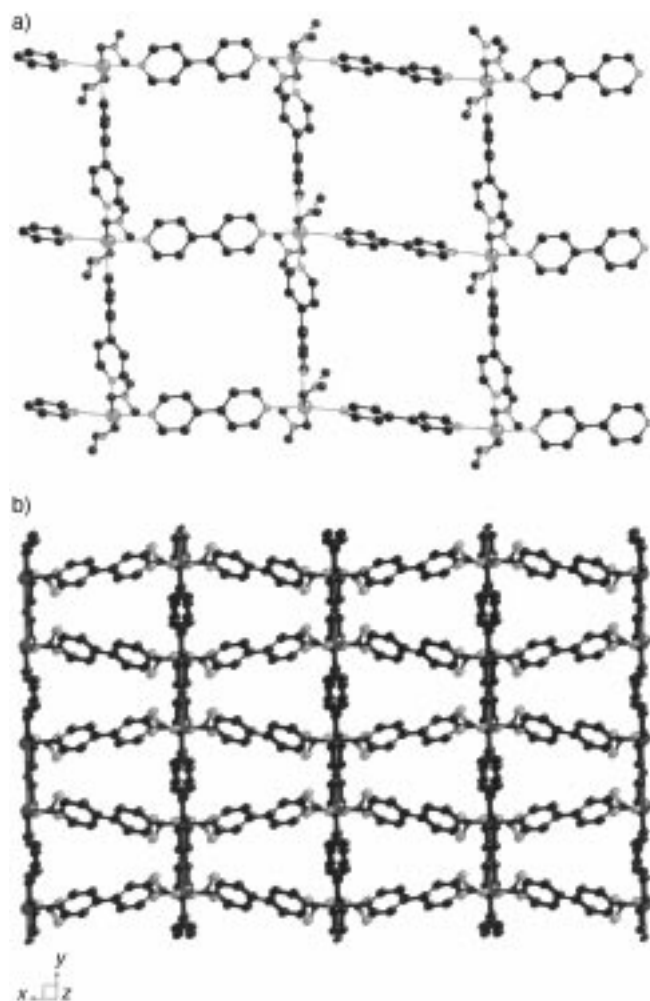


Figure 13. a) A view of the two-dimensional square grid pattern adopted by the layer networks of $[\text{Cd}(\text{4,4'-bpy})_2(\text{NO}_3)_2] \cdot 2\text{C}_6\text{H}_4\text{Br}_2$. b) A view along the crystallographic c axis of the two-dimensional networks stacked to form microchannels.

In an attempt to avoid interpenetration, $[\text{Zn}(\text{4,4'-bpy})_2(\text{SiF}_6)] \cdot \text{DMF}$ ^[76] was prepared and shown to consist of $\{\text{Zn}(\text{4,4'-bpy})_2\}^{2+}$ layers, constructed from the square-grid motif, and linked through bridging SiF_6^{2-} anions into a three-dimensional covalent framework. The resulting square channels are occupied by guest molecules.

Another strategy for modifying the architecture of the two-dimensional network relies on the introduction of a coligand, as demonstrated in $[\text{Cu}_2(\text{C}_3\text{H}_2\text{O}_4)_2(\text{H}_2\text{O})(\text{4,4'-bpy})] \cdot \text{H}_2\text{O}$ ^[77] (Figure 14). The structure consists of $\{\text{Cu}_4(\text{malonate})_4\}$

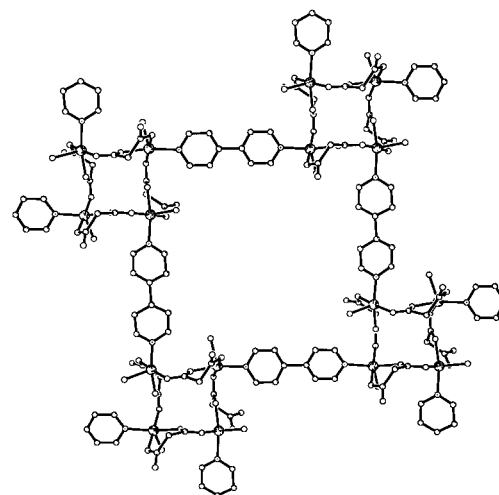


Figure 14. A view of the layer structure of $[\text{Cu}_2(\text{C}_3\text{H}_2\text{O}_4)_2(\text{H}_2\text{O})(\text{4,4'-bpy})] \cdot \text{H}_2\text{O}$ to show the $\{\text{Cu}_4(\text{malonate})_4\}$ squares linked by 4,4'-bpy bridges.

squares linked into a larger square grid through 4,4'-bpy groups. It is noteworthy that the Cu^{II} center adopts square pyramidal $\{\text{CuNO}_4\}$ geometry.

The structural versatility of these coordination polymers is once again dramatically illustrated by the structure of $[\text{Co}_2(\text{4,4'-bpy})_3(\text{NO}_3)_4] \cdot \text{H}_2\text{O}$ ^[78]. The pentagonal bipyramidal $\{\text{CoN}_3\text{O}_4\}$ sites are linked by 4,4'-bpy groups into one-dimensional chains. As shown in Figure 15, parallel chains are cross-linked through 4,4'-bpy bridges to an adjacent set of parallel chains to produce a double-sheet motif. The double sheets interlock by interdigitation of chains into a complex three-dimensional tongue-and-groove structure.

As illustrated in Figure 16, coligand influences are also manifest in the structure of $[\text{Cu}(\text{4,4'-bpy})\text{Cl}]$ ^[79]. The structure consists of binuclear Cu^{I} sites bridged by two chloride atoms $\{\text{Cu}_2\text{Cl}_2\}$ linked through 4,4'-bpy groups into layers with a large hexagonal grid pattern. Once again, there are two independent sets of interpenetrating two-dimensional motifs.

3.2.3. Three-Dimensional 4,4'-Bipyridine-Based Coordination Polymers

The structure of $[\text{Ag}(\text{4,4'-bpy})_2](\text{CF}_3\text{SO}_3)$ ^[81] (Figure 17) is prototypical of the diamondoid family^[52] of three-dimensional materials. The structure consists of tetrahedral $\{\text{AgN}_4\}$ sites linked through 4,4'-bpy ligands into a three-dimensional adamantoid framework; four independent frameworks interpenetrate so as to effect efficient packing.

The influence of metal coordination preference and ligand stoichiometry is evident in the structure of $[\text{Cu}(\text{4,4'-bpy})_{1.5}](\text{NO}_3) \cdot 1.25\text{H}_2\text{O}$ ^[84] (Figure 18). In this instance, the Cu^{I} sites, which adopt trigonal-planar $\{\text{CuN}_3\}$ coordination, are linked by the 4,4'-bpy ligands to form six interpenetrating three-dimensional frameworks. The trigonal geometry of the copper precludes the adamantoid unit as the building block for the framework.

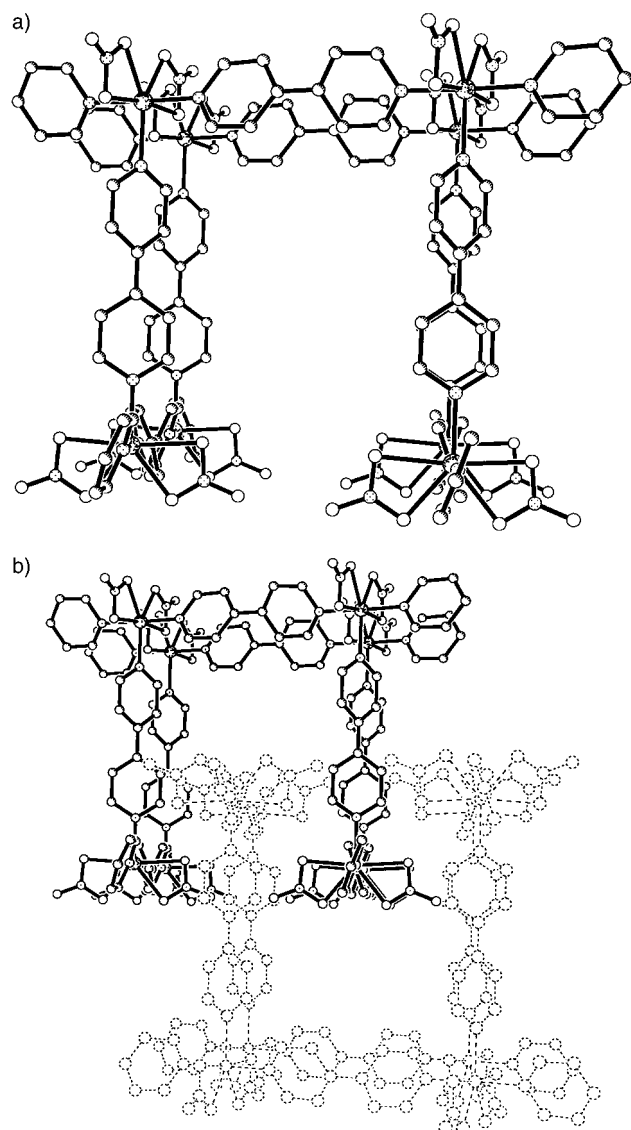


Figure 15. a) The double-sheet motif of $[\text{Co}_2(4,4'\text{-bpy})_3(\text{NO}_3)_4] \cdot \text{H}_2\text{O}$, constructed from $[\text{Co}(4,4'\text{-bpy})(\text{NO}_3)_2]$ linear chains linked by 4,4'-bpy bridges. One set of chains lies parallel to the plane of the page while the second set is normal to the page. b) A view of the interlocking of adjacent double sheets.

3.3. Coordination Polymers Constructed from Tethered Pyridine and Imidazole Groups

The structural consequences of introducing spacers between the nitrogen donor groups can be quite dramatic. Tethers may be introduced which simply add extension to the rodlike bipyridyl ligand, as for 1,4-bis(4-pyridyl)butadiyne, or which maintain a rigid backbone while reorienting the donor groups, as for 1,2-*trans*-bis(4-pyridyl)ethene or which allow conformational flexibility to the ligands, as for 1,2-bis(4-pyridyl)ethane.

3.3.1. One- and Two-Dimensional Coordination Polymers with Tethered Nitrogen Donors

The structural modifications consequent to extension of the donor-to-donor distance are manifested in the structure of

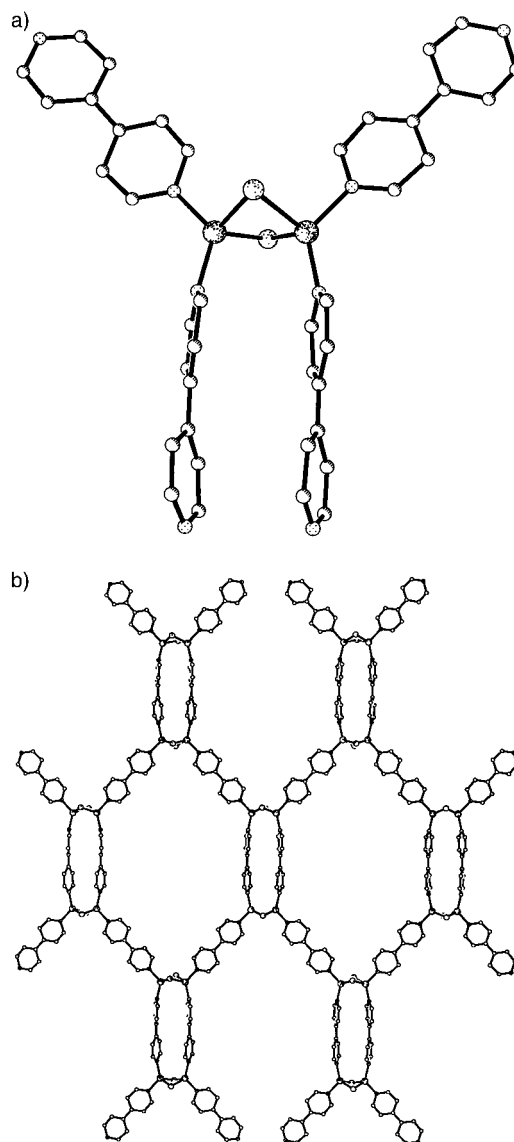


Figure 16. a) Structure of the binuclear $[\text{Cu}_2\text{Cl}_2(\text{bpy})_4]$ fundamental building block of $[\text{CuCl}(4,4'\text{-bpy})]$. b) The two-dimensional hexagonal grid pattern of one of the independent layers in $[\text{CuCl}(4,4'\text{-bpy})]$.

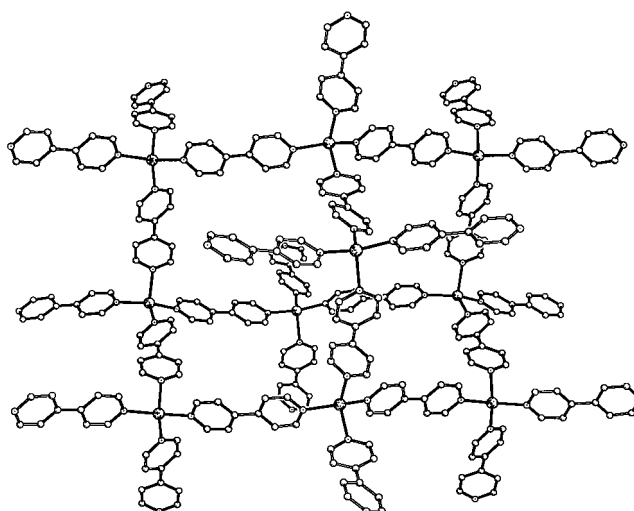


Figure 17. One adamantoid unit of the three-dimensional framework structure of $[\text{Ag}(4,4'\text{-bpy})_2](\text{CF}_3\text{SO}_3)$.

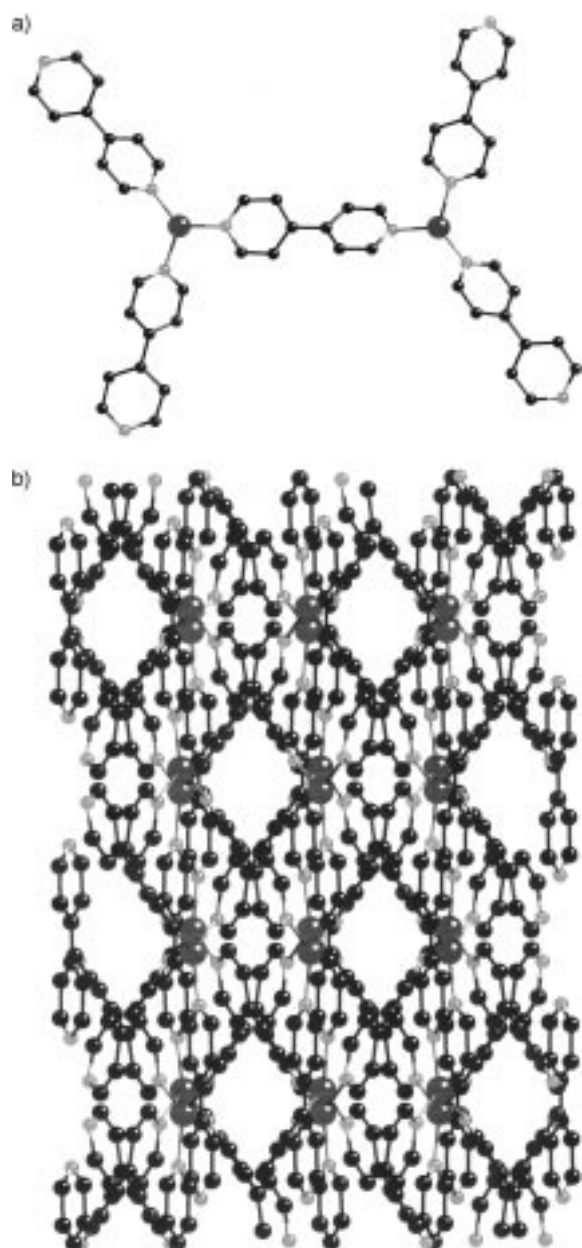


Figure 18. a) The fundamental building block of the three-dimensional structure of $[\text{Cu}(4,4'\text{-bpy})_{1.5}](\text{NO}_3) \cdot 1.25 \text{H}_2\text{O}$. b) A view down the crystallographic c axis illustrating the consequences of interpenetration of the independent three-dimensional frameworks to give channels occupied by the NO_3^- anions and water molecules.

$[\text{Cu}_2(\text{bpbd})_3(\text{MeCN})_2](\text{PF}_6)_2$.^[85] As illustrated in Figure 19, the structure consists of tetrahedral $\{\text{CuN}_4\}$ sites linked through bpbd ligands into an undulating ladder. This contrasts with the ladder structure of $[\text{Co}(4,4'\text{-bpy})_{1.5}](\text{NO}_3)_2$, which is flat with all linking ligands coplanar. Furthermore, while the Co^{2+} species exhibited no interpenetration, in this case each ladder is interpenetrated by four additional ladders to form a polycatenated braid which extends into a sheet.

The Cd^{II} compound $[\text{Cd}(\text{dpb})_{1.5}](\text{NO}_3)_2$ ^[86] also exhibits a ladder motif (Figure 20). In contrast to the structure of $[\text{Cu}_2(\text{bpbd})_3(\text{MeCN})_2](\text{PF}_6)_2$, the Cd material possesses a flat ladder motif but with bent rungs and siderails. Two inde-

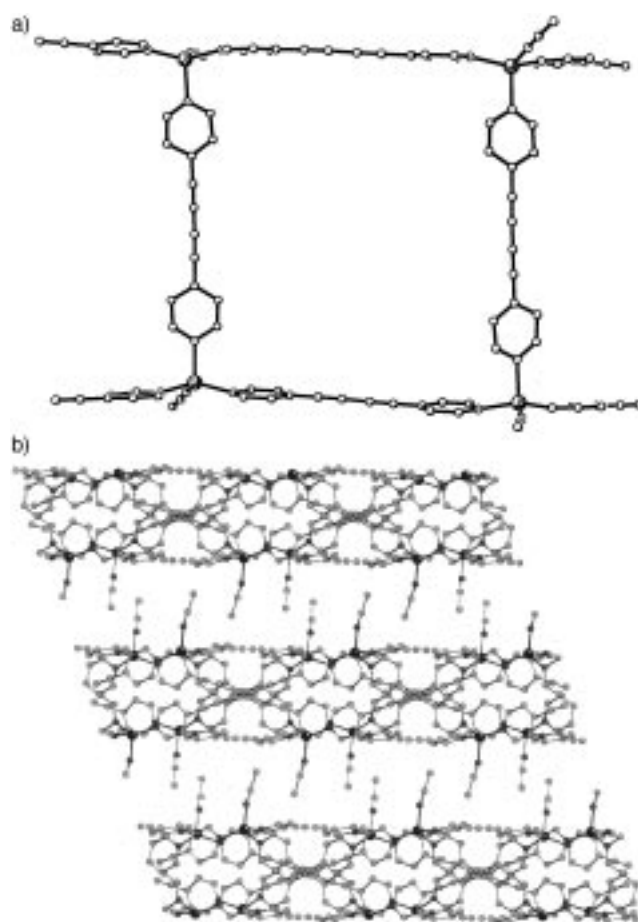


Figure 19. a) The ladder structure of $[\text{Cu}_2(\text{bpbd})_3(\text{MeCN})_2](\text{PF}_6)_2$. b) The results of interpenetration to form sheets of polycatenated braids parallel to the ac plane.

pendent sets of ladders interpenetrate such that a given ring interlocks with four rings of adjacent ladders. Curiously, substitution of dpb-F_4 , the tetrafluoro analogue of dpb, yields $[\text{Cd}(\text{dpb-F}_4)_{1.5}](\text{NO}_3)_2$, which, despite the similar formulation, exhibits the two-dimensional bricklike structure shown in Figure 21. Once again there is interpenetration with three independent brick motifs interwoven to produce a two-dimensional slab.

The structural chemistry of coordination polymers is significantly expanded by the introduction of conformationally flexible tethers between donor groups. This observation is nicely illustrated by the structures of $[\text{Ag}(\text{bbp})](\text{CF}_3\text{SO}_3) \cdot \text{EtOH}$, $[\text{Ag}(\text{bbp})](\text{CF}_3\text{SO}_3)$ and $[\text{Ag}_2(\text{bbp})_4](\text{CF}_3\text{SO}_3)_2 \cdot \text{bbp}$ ^[87] (Figure 22), which consist of sinusoidal chains, helical chains paired into double chains and binuclear $\{\text{Ag}_2(\text{bbp})_2\}$ rings fused into tubular motifs, respectively. The structures reveal the role of the variability of the metal coordination number in the determination of structure type. The Ag site of $[\text{Ag}(\text{bbp})](\text{CF}_3\text{SO}_3) \cdot \text{EtOH}$ exhibits the characteristic $\{\text{AgN}_2\}$ digonal geometry. In contrast, the Ag site of $[\text{Ag}(\text{bbp})](\text{CF}_3\text{SO}_3)$ is T-shaped, in a fashion reminiscent of $[\text{Ag}(4,4'\text{-bpy})](\text{NO}_3)$, with the long Ag–Ag interaction providing the connectivity between helical chains in the double chain. In $[\text{Ag}_2(\text{bbp})_4](\text{CF}_3\text{SO}_3)_2 \cdot \text{bbp}$, the Ag site enjoys

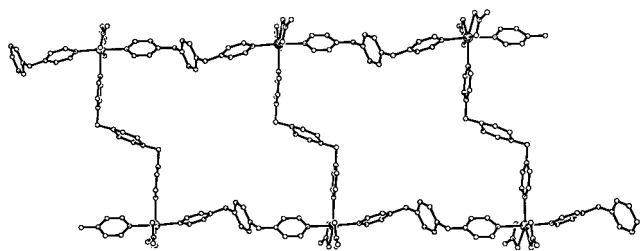


Figure 20. The ladder motif of $[\text{Cd}(\text{dpb})_{1.5}(\text{NO}_3)_2]$.

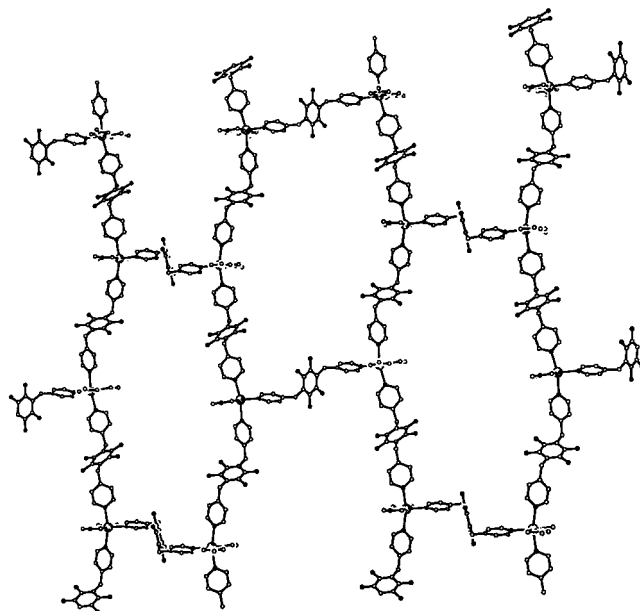


Figure 21. The two-dimensional brick motif of $[\text{Cd}(\text{dpb-F}_4)_{1.5}(\text{NO}_3)_2]$.

tetrahedral $\{\text{AgN}_4\}$ geometry. It is also noteworthy that in this latter structure, the uncoordinated bbp threads the $\{\text{Ag}_2(\text{bbp})_2\}$ rings of the tube.

Similarly, the α , β , and γ forms of $[\text{Co}(\text{dpe})_{1.5}(\text{NO}_3)_2] \cdot \text{Sol}$ ^[88] (Sol = solvent molecule) reflect the conformational flexibility of the ligand, which can adopt angular or linear orientations of the donor groups. The α isomer is isostructural with $[\text{Cd}(\text{dpe})_{1.5}(\text{NO}_3)_2]$ ^[89] and consists of two *gauche* spacers linking Co^{II} sites into a box, linked at the metal edges by *anti* spacers to give linear chains (Figure 23). In contrast, the β isomer contains two *anti* spacers for each *gauche* ligand to produce the bilayer structure shown in Figure 24. In the γ isomer, all spacer ligands adopt the *anti* conformation to produce a ladder structure similar to that described previously.

Coligand influences are evident in the structures of $[\text{Ag}_2(\text{bpy-4pz})_2](\text{PF}_6)_2$ ^[92] and $[\text{Cu}_4(\text{bppy})(\text{CH}_3\text{CO}_2)_8]$ ^[93]. Figure 25 shows the structure of $[\text{Ag}_2(\text{bpy-4pz})_2](\text{PF}_6)_2$ which exhibits a bridging ligand constructed from 2-pyridyl groups linked by a 4-thiomethylpyridine tether. The affinity of Ag^{I} for sulfur donors is evidenced by the introduction of the thioether donor into the metal $\{\text{AgN}_3\text{S}\}$ coordination sphere. The structure consists of $\{\text{Ag}_2(\text{bpy-4pz})_2\}$ binuclear rings linked through Ag–S bonds into a one-dimensional chain.

The structure of $[\text{Cu}_4(\text{bppy})(\text{CH}_3\text{CO}_2)_8]$ ^[93] is also based on tethered 2-pyridyl groups, with pyrazine as the linker in this

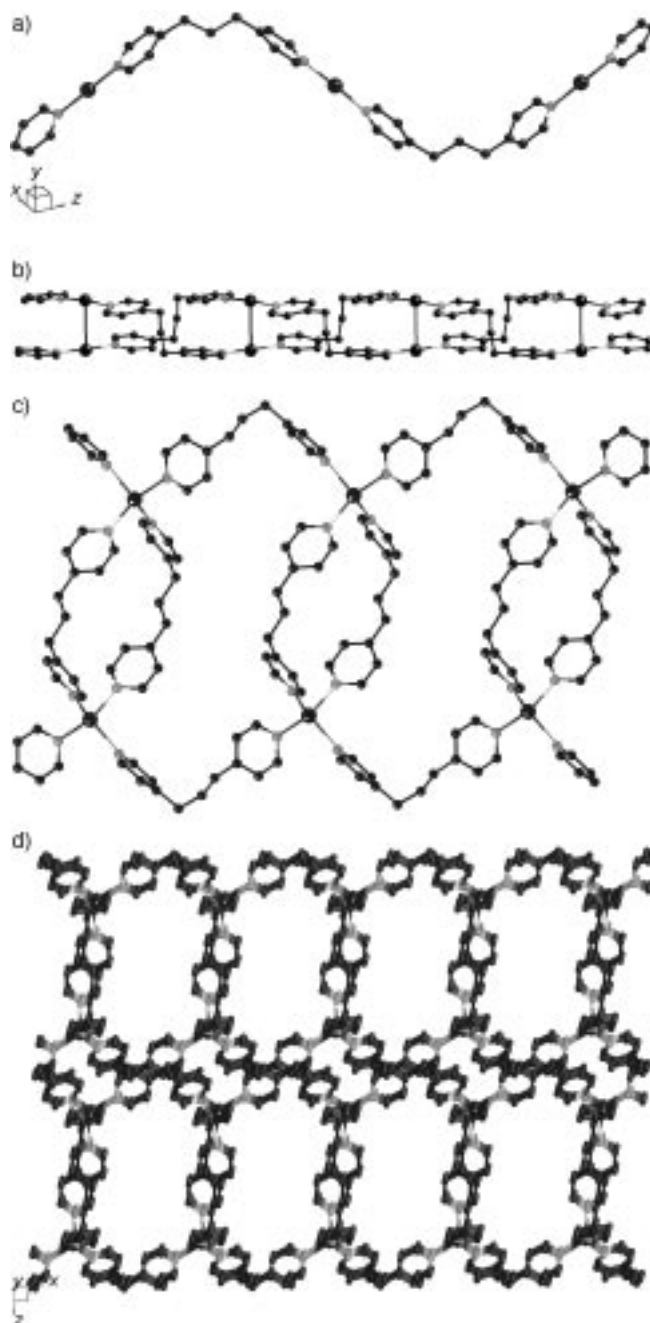
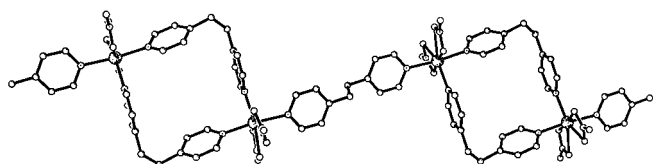
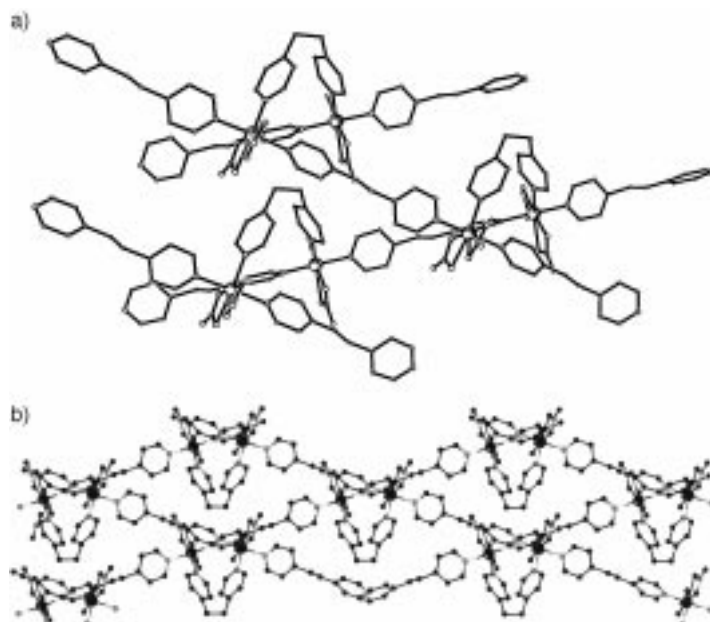
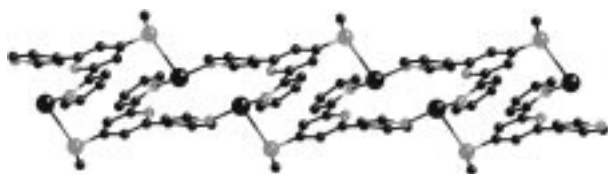
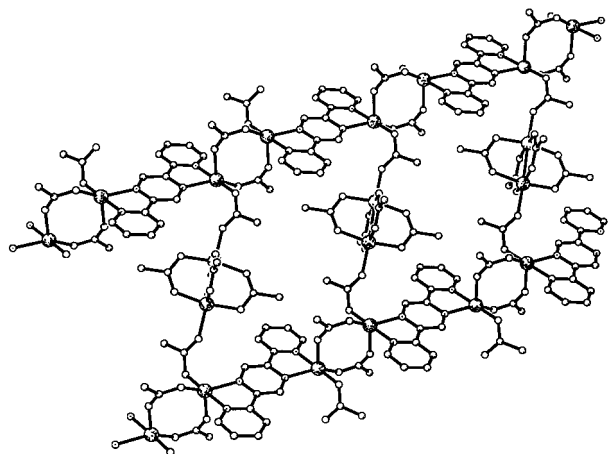


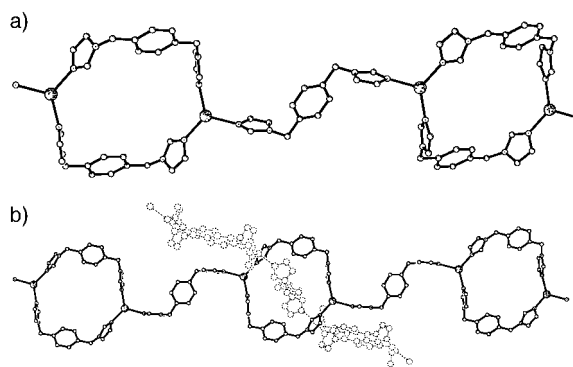
Figure 22. a) The sinusoidal chain of $[\text{Ag}(\text{bbp})](\text{CF}_3\text{SO}_3) \cdot \text{EtOH}$. b) A view of the helical chains linkage in $[\text{Ag}(\text{bbp})](\text{CF}_3\text{SO}_3)$. c) The linkage of $\{\text{Ag}_2(\text{bbp})_2\}$ rings into tubular channels in $[\text{Ag}_2(\text{bbp})_4](\text{CF}_3\text{SO}_3)_2 \cdot \text{bbp}$. d) The results of interpenetration of tubes in $[\text{Ag}_2(\text{bbp})_4](\text{CF}_3\text{SO}_3)_2 \cdot \text{bbp}$.

instance. The structure is constructed from $\{\text{Cu}_2(\text{acetate})_2\}$ dimers bridged by bppy ligands into a one-dimensional chain (Figure 26). Each Cu^{II} site of the chain exhibits square-pyramidal $\{\text{CuN}_2\text{O}_3\}$ geometry. In addition to the μ^2 -acetate of the $\{\text{Cu}_2(\text{acetate})_2\}$ grouping, each Cu site binds to a third acetate ligand which directs its second oxygen donor into the interstrand region. These donors are used to bond to $\{\text{Cu}_2(\text{acetate})_4\}$ binuclear units which serve to link the chains into a two-dimensional sheet.

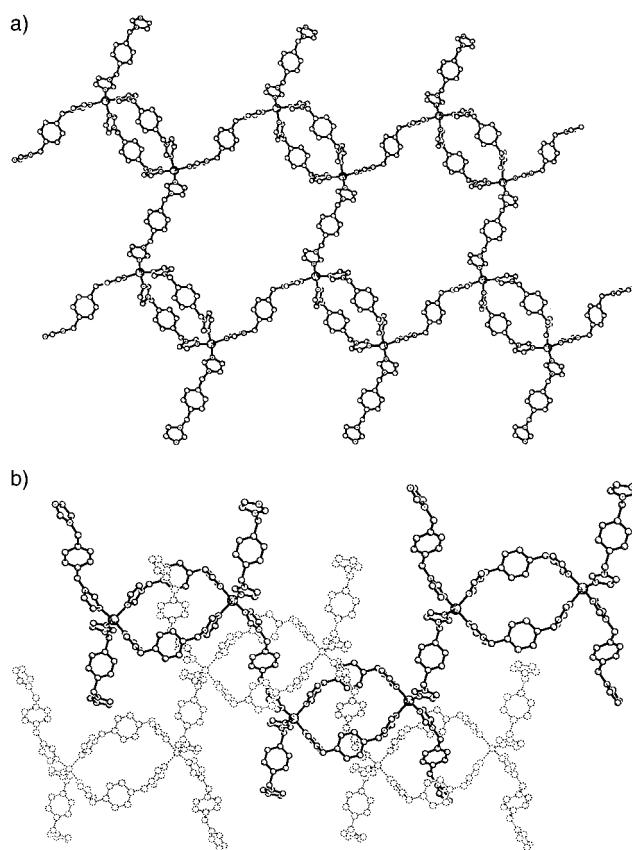
The consequences of donor-group modification may be perceived in the structure of $[\text{Ag}_2(\text{bix})_3](\text{NO}_3)_2$ ^[102] (Figure 27).


 Figure 23. The one-dimensional structure of α -[Co(dpe)_{1.5}(NO₃)₂].

 Figure 24. Two views of the bilayer formed by the linking of sets of parallel {Co(dpe)(NO₃)₂} chains by *gauche* dpe ligand bridges to provide the building block for the bilayer motif of β -[Co(dpe)_{1.5}(NO₃)₂].

 Figure 25. The one-dimensional chain of [Ag₂(bpy-4pz)₂](PF₆)₂.

 Figure 26. The structure of [Cu₄(bppy)(CH₃CO₂)₈].

The structure is constructed from {Ag₂(bix)₂} rings which are linked through a third bridging bix ligand into a one-dimensional chain of equispaced loops or rings. The chains interpenetrate with connector rods through the loops to form a polyrotaxane two-dimensional sheet.


 Figure 27. a) A view of a single chain motif of [Ag₂(bix)₃](NO₃)₂. b) The interpenetration of chains.

A polyrotaxane structure is also adopted by [Zn(bix)₂](NO₃)₂ · 4.5 H₂O,^[103] but with a distinct structure from that of [Ag₂(bix)₃](NO₃)₂ as a consequence of the coordination geometry at the Zn^{II} site. As shown in Figure 28, the structure is constructed of {Zn₂(bix)₂} rings linked by bix bridges into a two-dimensional sheet. Two independent sheets interpenetrate to form an extended two-dimensional rotaxane structure.


 Figure 28. a) A view of one two-dimensional motif of [Zn(bix)₂](NO₃)₂ · 4.5 H₂O. b) The interpenetration of two independent sheets.

3.3.2. Three-Dimensional Coordination Polymers with Tethered Nitrogen Donors

The structure of [Cu(bpe)₂](BF₄)^[99] illustrates the consequences of lengthening the bipyridyl ligand. The tetrahedral {Cu₄} sites are linked through bridging bpe ligands into a

three-dimensional framework of edge-sharing adamantoid units. It is noteworthy that five independent frameworks interpenetrate to produce channels occupied by BF_4^- counterions and solvent molecules. In contrast, $[\text{Cu}(4,4'\text{-bpy})_2](\text{PF}_6)$ and $[\text{Ag}(4,4'\text{-bpy})_2](\text{CF}_3\text{SO}_3)$ were seen to exhibit four interpenetrating motifs. Consequently, space extension results in larger cavities and inclusion of an additional framework. It is noteworthy that $[\text{Cu}(\text{dzp})_2](\text{PF}_6)^{[100]}$ also exhibits the adamantoid motif but with only three interpenetrating frameworks, an observation that suggests that the steric bulk of the ligand prevents interpenetration by a fourth framework.

An unusual structure is presented by $[\text{Ag}(\text{tpc})](\text{BF}_4)^{[101]}$ where reaction of AgBF_4 with 1,2-*trans*-bis(4-pyridyl)ethene in organic solvents in light results in the in situ cyclization of the ligand to a cyclobutane-linked tetrapyridyl ligand. The tetrahedral $\{\text{AgN}_4\}$ geometry at each Ag^+ site gives rise to the three-dimensional framework of Figure 29. Most significantly, there is no interpenetration.

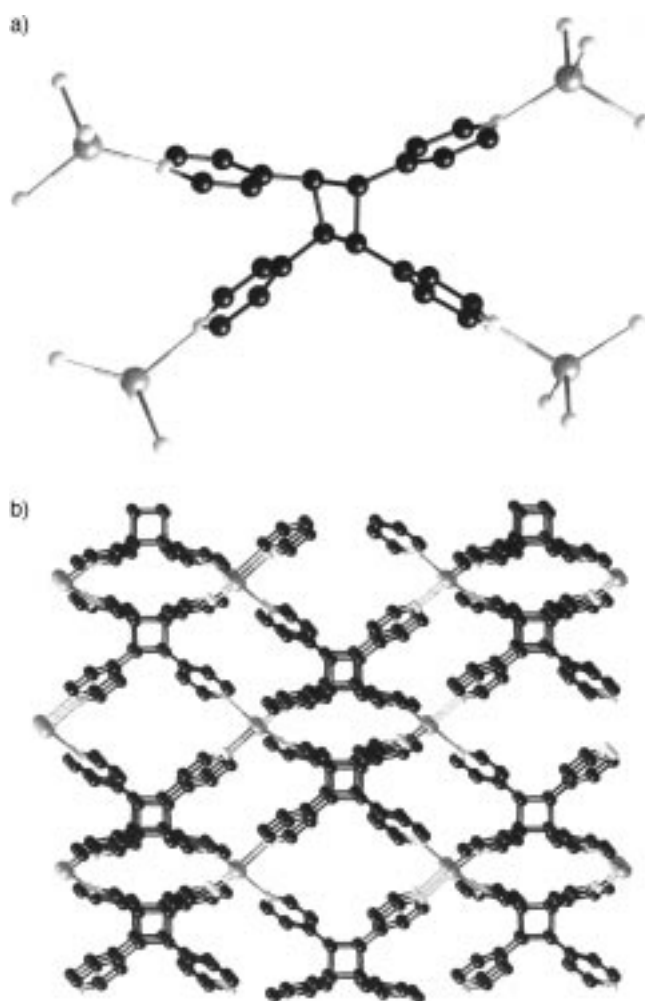


Figure 29. a) The tpc ligand of $[\text{Ag}(\text{tpc})](\text{BF}_4)$. b) A view of the channels formed by the covalently linked framework of $[\text{Ag}(\text{tpc})](\text{BF}_4)$.

Substitution of imidazole donors for pyridyl nitrogens again produces unique frameworks. The structure of $[\text{Cu}(\text{bim})_{2.5}](\text{ClO}_4)_2 \cdot 2\text{MeOH}^{[105]}$ is constructed from five-coordinate $\{\text{CuN}_5\}$ sites linked by bridging bim ligands into a three-dimensional framework. Three ligands on each Cu^{II} site are approximately planar and link to adjacent sites to form

hexagonal two-dimensional sheets, which are linked above and below by the remaining bim ligands to form the framework (Figure 30).

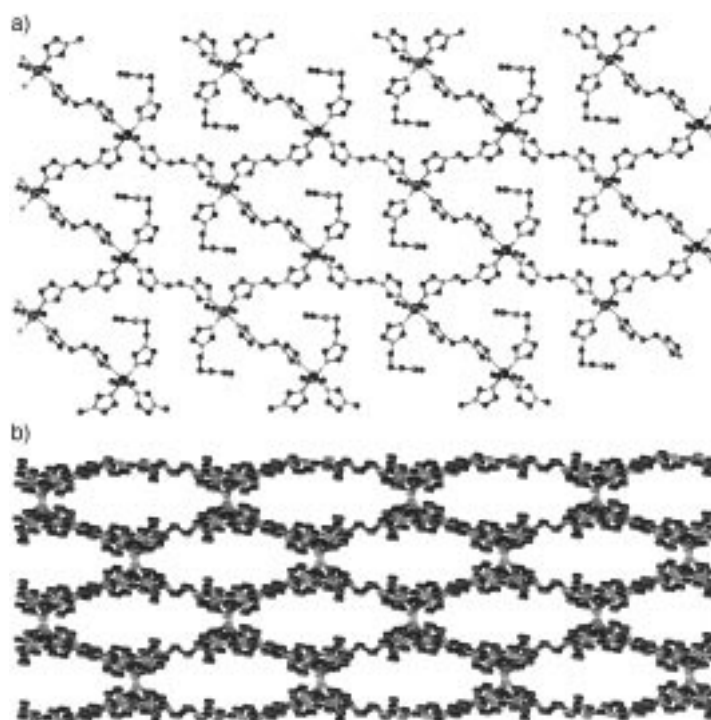


Figure 30. a) A view of the layer motif of $[\text{Cu}(\text{bim})_{2.5}](\text{ClO}_4)_2 \cdot 2\text{MeOH}$. $\{\text{Cu}(\text{bim})\}^{2+}$ chains are cross-linked in the *ac* plane to give a two-dimensional network. Each Cu^{II} site is coordinated to an additional bim ligand that projects above or below the plane and links each network to adjacent networks. (b) A view of the large cavities produced by the covalent linkage of the three-dimensional $\{\text{Cu}(\text{bim})_{2.5}\}^{2+}$ framework. The ClO_4^- anions and methanol molecules occupy these cavities.

The Mn^{II} site of $[\text{Mn}(\text{bbi})_3](\text{BF}_4)_2^{[106]}$ adopts octahedral $\{\text{MnN}_6\}$ geometry, which results in a three-dimensional framework constructed from linked $\{\text{Mn}_8(\text{bbi})_{12}\}$ rhombohedral boxes (Figure 31). In common with the majority of such structures, two independent arrays interpenetrate to form cavities occupied by the BF_4^- anions.

Not only are the coordination preferences of the metal center important determinants of structure, but anion coordination or geometry may also dramatically influence the geometry and dimensionality of such solids. An interesting example is provided by the structures of $[\text{Ag}(\text{pytz})(\text{NO}_3)]$ and $[\text{Ag}(\text{pytz})(\text{MeCN})](\text{PF}_6)$. The structure of $[\text{Ag}(\text{pytz})(\text{NO}_3)]^{[91]}$ (Figure 32) consists of one-dimensional $[\text{Ag}(\text{pytz})]^+$ chains linked by NO_3^- bridges into a three-dimensional framework with a helical motif along the 6_1 screw axis of the structure. In contrast, in the presence of a weakly coordinating anion in $[\text{Ag}(\text{pytz})(\text{MeCN})](\text{PF}_6)$, a one-dimensional structure, based on $[\text{Ag}(\text{pytz})]^+$ double chains linked by weak $\text{Ag} \cdots \text{Ag}$ interactions, is observed (Figure 33).

The structures of $[\text{Ag}(\text{py}_2\text{urea})_2](\text{BF}_4)$ and $[\text{Ag}(\text{py}_2\text{oxal-amide})_2](\text{NO}_3)^{[95]}$ provide examples of three-dimensional frameworks where the $\text{Ag} \cdots \text{Ag}$ distances are determined by the hydrogen-bonded frameworks of the ligand backbones. Both structures consist of tetrahedral Ag sites interconnected through the extended bipyridyl ligands. The most remarkable

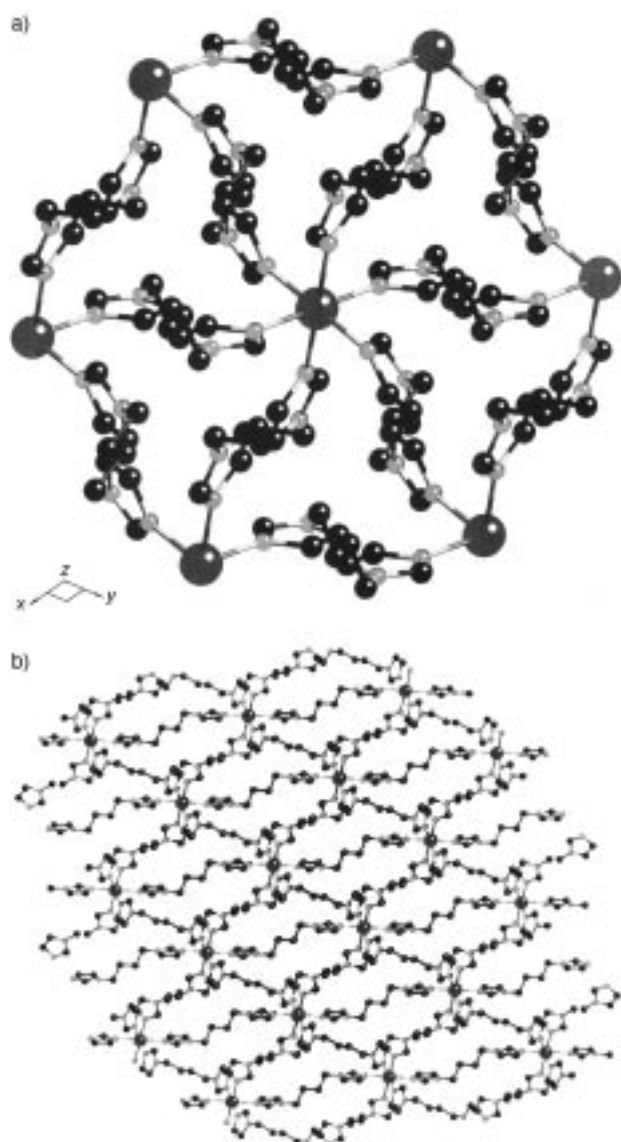


Figure 31. a) The rhombohedral array produced by the octahedral geometry at the $\{\text{MnN}_6\}$ site of $[\text{Mn}(\text{bbi})_3](\text{BF}_4)_2$. b) A view of the three-dimensional structure, to show the effects of interpenetration.

feature of the structures is the presence of one-dimensional α networks of pyridine-substituted ureas and oxalamides, respectively, whose hydrogen-bonding interactions determine the $\text{Ag} \cdots \text{Ag}$ spacings.

3.4. Coordination Polymers Constructed from Three-Connected Ligands

The structures based on the three-connected pyridyl donor ligand 2,4,6-tri(4-pyridyl)-1,3,5-triazine exhibit geometries that reflect metal coordination preference and influence of coligands. The structure of $[\text{Cu}_3(\text{tp})_4](\text{ClO}_4)_3$ ^[110] consists of $\{\text{CuN}_4\}$ sites linked into a three-dimensional framework. While there are two interpenetrating frameworks, neither intrudes into the large octahedral cavity of the other (Figure 34). Consequently, the structure exhibits considerable void volume.

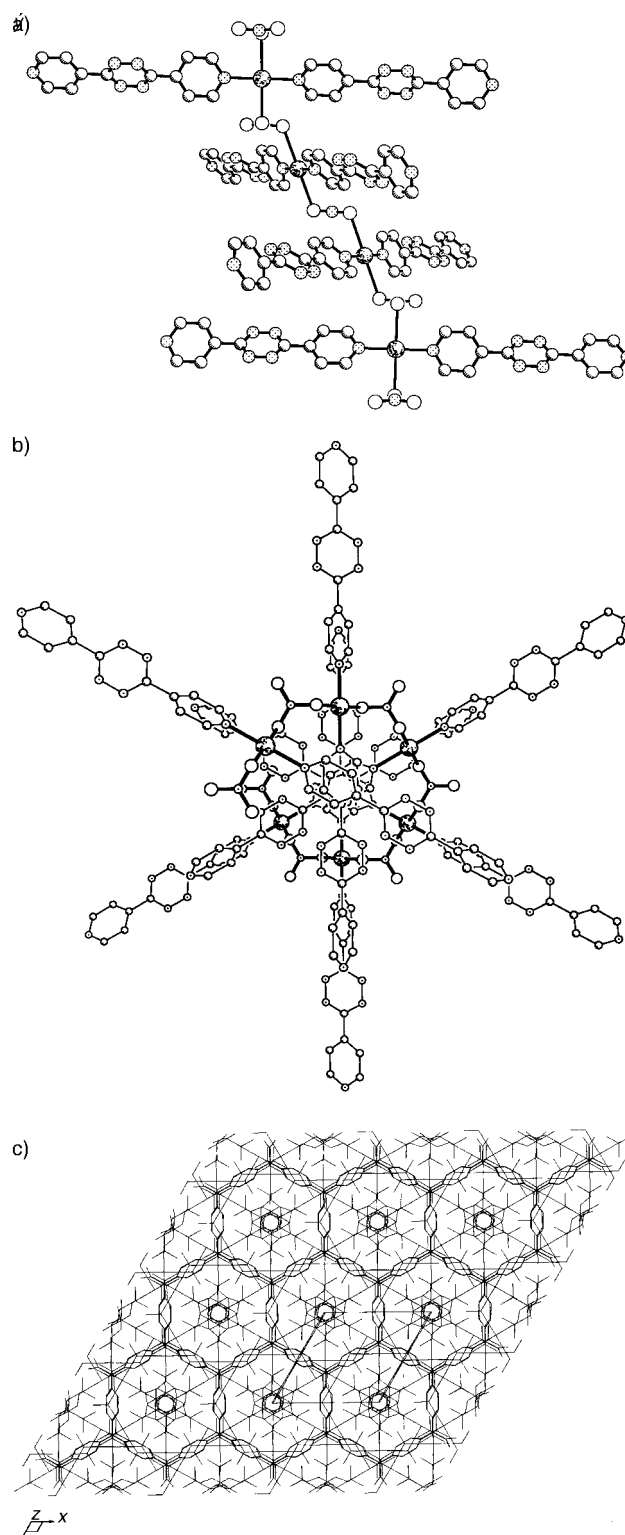


Figure 32. a) The linkage of $\{\text{Ag}(\text{pytz})\}^+$ chains by NO_3^- bridges in $[\text{Ag}(\text{pytz})(\text{NO}_3)]$. Each chain is rotated by 60° relative to its neighbors. b) A view down the helical axis with the $\text{Ag}-\text{NO}_3$ units highlighted to show the hexagonal channels. c) A view of the packing to illustrate the elegant symmetry of the structure.

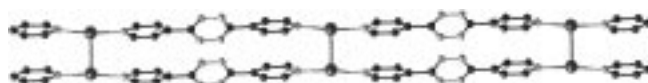


Figure 33. The double chain structure of $[\text{Ag}(\text{pytz})(\text{MeCN})](\text{PF}_6)$.

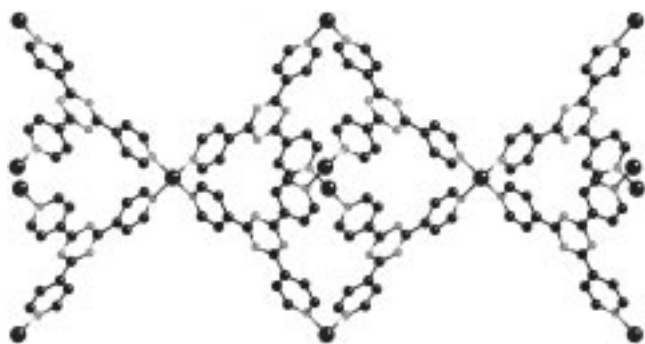


Figure 34. A view of one of the large chambers in $[\text{Cu}_3(\text{tpt})_4](\text{ClO}_4)_3$, formed by the linkage through tpt groups of six Cu^{I} centers at the vertices of a regular octahedron.

In contrast, the Hg^{II} site of $[\text{Hg}(\text{tpt})_2](\text{ClO}_4)_2 \cdot 6 \text{C}_2\text{H}_2\text{Cl}_4$ ^[111] exhibits octahedral $\{\text{HgN}_6\}$ coordination, to produce a three-dimensional framework with no interpenetration. These large intraframework cavities are occupied by $\text{C}_2\text{H}_2\text{Cl}_4$ molecules. The absence of interpenetration is reflected in the solvent molecule:Hg ratio of 6:1 and the spaciousness of the cavities.

The presence of CN^- coligands contributes to the unusual structure of $[\text{Zn}(\text{CN})(\text{NO}_3)(\text{tpt})_{2/3}] \cdot 0.75 \text{C}_2\text{H}_2\text{Cl}_4 \cdot 0.75 \text{CH}_3\text{OH}$ ^[112] (Figure 35). The structure is constructed from $\{\text{Zn}_4(\text{CN})_4(\text{NO}_3)_4\}$ squares linked through tpt ligands into a three-dimensional structure with two distinct cage types. There are two interpenetrating frameworks aligned such that the smaller cages are encapsulated within the larger cages, which results in large chambers surrounded by double shells. The cages are somewhat reminiscent of those observed in sodalite minerals but are considerably more spacious and accommodate approximately nine molecules each of $\text{C}_2\text{H}_2\text{Cl}_4$ and MeOH.

3.5. Coordination Polymers with Pyrazine and Pyrimidine as Ligands

Nitrogen heterocycles with two nitrogen donors, such as diazoles and diazines, often act as *exo*-bidentate ligands in the isolation of oligomeric and polymeric metal complexes.^[109, 114] Such systems have been extensively investigated for properties such as electrical conductivity, magnetism, and photochemistry.^[90] The complexes of pyrazine and pyrimidine reveal the representative structural patterns. With respect to the structural systematics of polymeric coordination complexes, pyrazine and pyrimidine contrast with the ligands of Sections 3.2–3.4: The distance between donor groups is contracted by the adoption of pyrazine as the linker ligand, while the donor group disposition is altered by the use of pyrimidine.

3.5.1. One-Dimensional Coordination Polymers of Pyrazine and Pyrimidine

A prototypical structure is adopted by $[\text{Cd}(\text{pz})\text{Cl}_2]$ ^[120] (Figure 36). Linear $\{\text{Cd}(\text{pz})\}^{2+}$ chains are linked by bridging chlorides into planar two-dimensional sheets. The influence of donor-group disposition is revealed in the structure of the

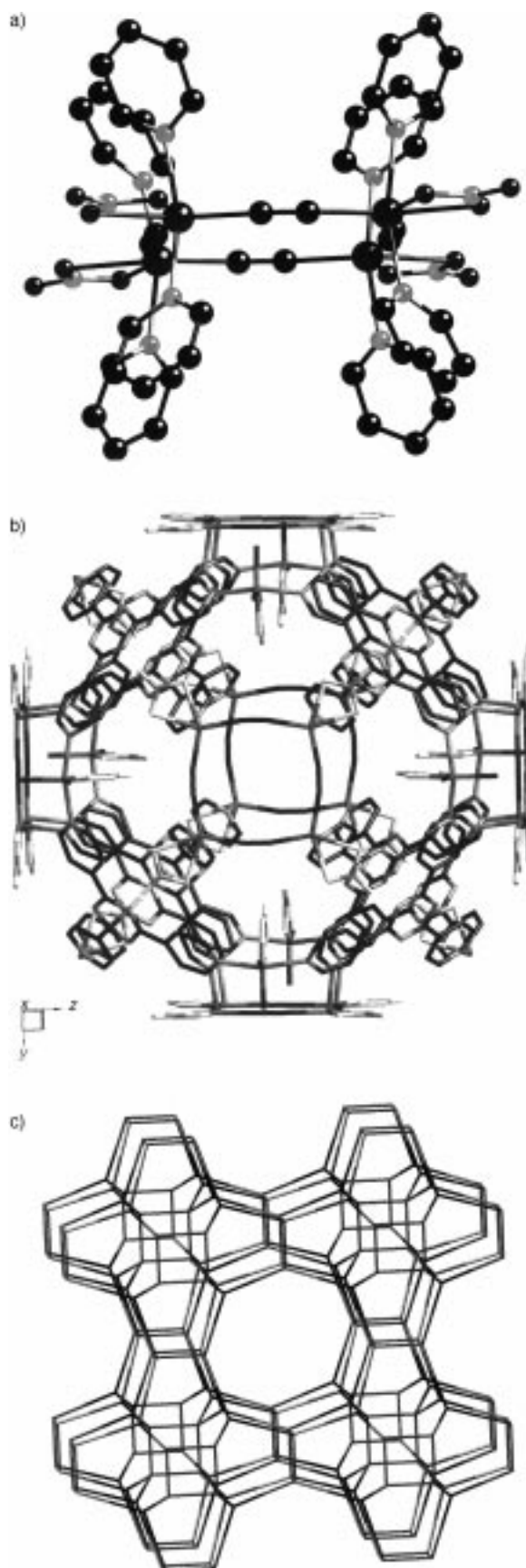


Figure 35. a) The $[\text{Zn}_4(\text{CN})_4(\text{NO}_3)_4(\text{tpt})_{8/3}]$ unit which provides the fundamental building block of $[\text{Zn}(\text{CN})(\text{NO}_3)(\text{tpt})_{2/3}]$. b) A view of the structure of one of the smaller A-type cages. c) Part of the infinite three-dimensional framework, showing eight A-type cages surrounding a central cavity.



Figure 36. The layer structure of $[\text{Cd}(\text{pz})\text{Cl}_2]$.

pyrimidine derivative $[\text{Zn}(\text{pyrd})\text{Cl}_2]^{[120]}$ where the $\{\text{Zn}(\text{pyrd})\}$ sheets are linked through Cl bridges into undulating sheets.

The structural influence of substituents is discerned in the structure of $[\text{Cu}(\text{pzca})(\text{Me}_2\text{CO})_{0.5}](\text{BF}_4)^{[122]}$ which consists of one-dimensional $\{\text{Cu}(\text{pzca})(\text{Me}_2\text{CO})\}^+$ chains linked by bridging pzca molecules into a three-dimensional helical framework (Figure 37). This arrangement generates a stacked two-dimensional hexagonal array with channels occupied by BF_4^- anions.

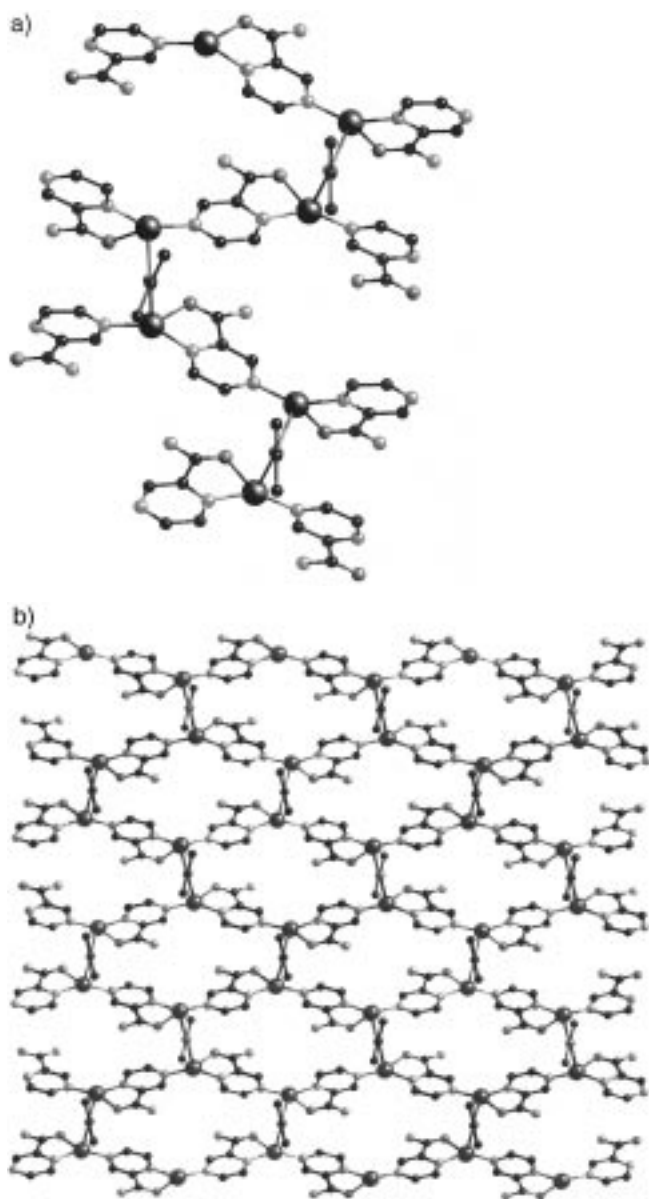


Figure 37. a) A portion of the helical $\{\text{Cu}(\text{pzca})(\text{Me}_2\text{CO})\}^+$ chains of $[\text{Cu}(\text{pzca})(\text{Me}_2\text{CO})_{0.5}](\text{BF}_4)$. b) The hexagonal channels formed by the three-dimensional covalently linked framework.

3.5.2. Two-Dimensional Coordination Polymers of Pyrazine

Once again, there are no obvious structural prototypes and the details of the networks reflect the metal coordination geometry or ligand influences. The structure of $[\text{Cu}_2(\text{pz})_3](\text{SiF}_6)^{[82]}$ consists of trigonal $\{\text{CuN}_3\}$ sites linked by pyrazines into a two-dimensional honeycomb grid of fused $\{\text{Cu}_6(\text{pz})_6\}$ rings (Figure 38). Two grids interpenetrate and SiF_6^{2-} anions

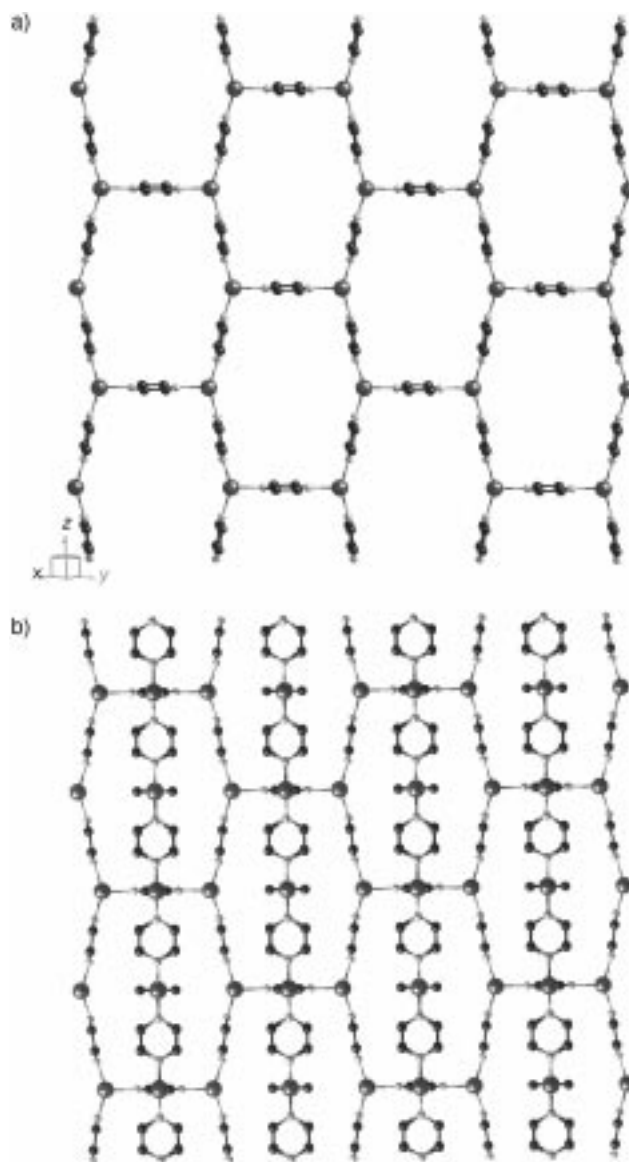


Figure 38. a) The two-dimensional honeycomb grid of $[\text{Cu}_2(\text{pz})_3](\text{SiF}_6)$. b) A view of the interpenetration of two independent grids.

occupy the generated cavities. In contrast, $[\text{Ag}(\text{pz})_2](\text{PF}_6)^{[125]}$ exhibits a structure constructed from $\{\text{Ag}_6(\text{pz})_7\}$ bicyclic folded rings fused into two-dimensional pleated sheets (Figure 39).

The structure of $[\text{Ag}(\text{pz})_2][\text{Ag}_2(\text{pz})_3](\text{PF}_6)_3^{[126]}$ may simply reflect changes in reaction conditions, a dramatic demonstration of the structural variability of these solids. The structure contains two distinct layer motifs. The first is the common square grid based on fused $\{\text{Ag}_4(\text{pz})_4\}$ rings; the second is

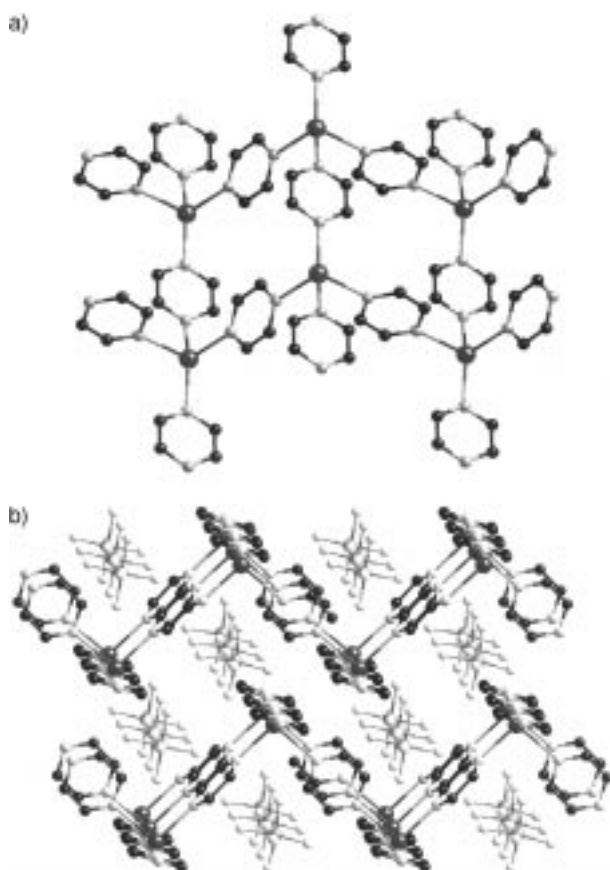


Figure 39. a) The building block for the sheet structure of $[\text{Ag}(\text{pz})_2](\text{PF}_6)$. b) A view along the a axis of the undulating sheets and of the PF_6^- anions that occupy the interlamellar regions.

constructed from two parallel sheets of such square grids linked by perpendicular pyrazine ligands into a double layer. The coordination geometries of the Ag sites are $\{\text{AgN}_4\}$ square planar for the former motif and $\{\text{AgN}_5\}$ square pyramidal for the second. Single and double layers are mutually parallel and alternate in an ABAB sequence.

The structure of $[\text{Cu}_2(\text{pzca})_3](\text{ClO}_4)_2 \cdot 2\text{Me}_2\text{CO}$ ^[122] exhibits a two-dimensional structure constructed from fused hexagonal rings of four- and five-coordinate Cu^+ sites bridged by tridentate pyrazinecarboxamide ligands (Figure 40).

3.5.3. Three-Dimensional Coordination Polymers of Pyrazine and Pyrimidine

It is curious that $[\text{Ag}(\text{pz})_3](\text{SbF}_6)$ ^[126] exhibits a simple structure based on $\{\text{AgN}_6\}$ octahedra linked into a cubic three-dimensional framework (Figure 41), topologically related to ReO_3 , while $[\text{Ag}(\text{pz})_2][\text{Ag}_2(\text{pz})_5](\text{PF}_6)_3 \cdot 2\text{Sol}$ exhibits a structure composed of alternating $\{\text{Ag}(\text{pz})_2\}^+$ single layers and $\{\text{Ag}_2(\text{pz})_5\}^{2+}$ double layers with PF_6^- anions occupying both interlayer regions and channels within the double layers (Figure 41 b). The topological relationship of this structure to those of α -polonium and ReO_3 have been discussed.^[126] The structural relationship of numerous frameworks of the types presented in this review to structural prototypes have been discussed extensively by Ciani and co-workers.^[108, 113] In

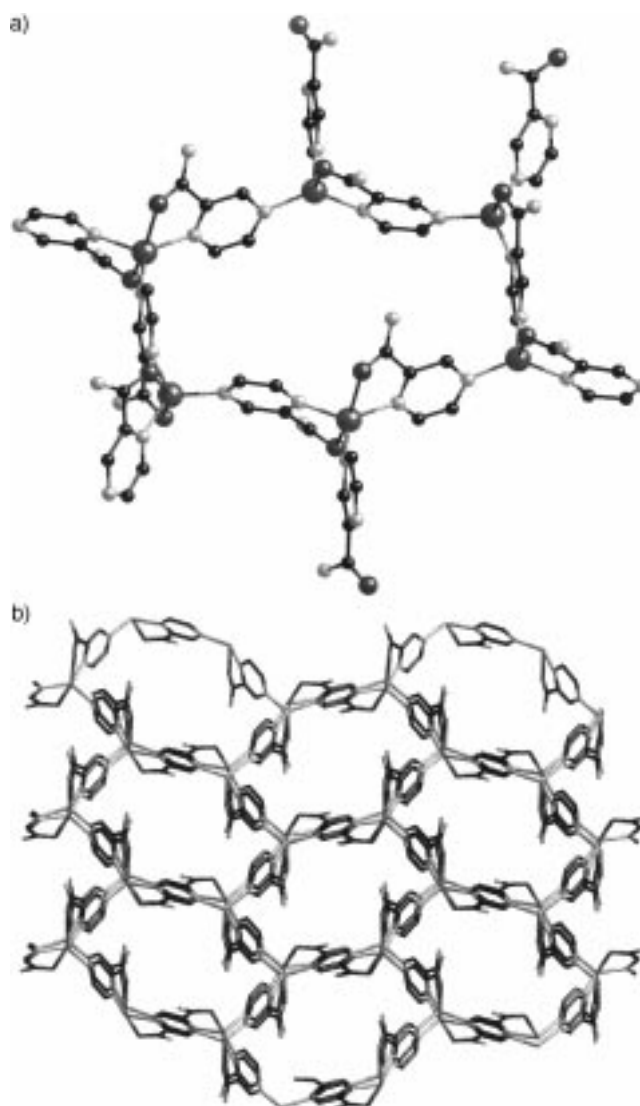


Figure 40. a) The hexagonal array of ligands at the copper centers. b) The layer structure of $[\text{Cu}_2(\text{pzca})_3](\text{ClO}_4)_2 \cdot 2\text{Me}_2\text{CO}$.

contrast to the Ag–pyrazine structures cited above, the structure $[\text{Ag}_2(2,3\text{-Me}_2\text{pz})_3](\text{SbF}_6)_2$ ^[133] (Figure 42) consists of zigzag $\{\text{AgN}_2\}$ chains cross-linked by bridging dimethylpyrazine ligands into an enantiomorphic three-dimensional framework.

The pyrimidine derivative $[\text{Cu}(\text{pyrd})_2](\text{BF}_4)$ ^[134] exhibits a noninterpenetrated structure constructed from tetrahedral $\{\text{CuN}_4\}$ sites linked by pyrimidine bridges. The distinctive channels which are characteristic of the structure are shown in Figure 43.

3.6. Coordination Polymers with Hexamethylenetetramine as Linker Ligand

Although hmta is potentially a tetradentate ligand, the structures reported to date exhibit both three- and four-connected geometries. Thus, the structure of $[\text{Ag}(\text{hmta})](\text{ClO}_4)$ ^[136] is constructed of three-connected Ag^I and hmta

sites resulting in $\{\text{Ag}_3(\text{hmta})_3\}$ rings fused into a two-dimensional sheet (Figure 44). The structure of $[\text{Ag}_3(\text{hmta})_2](\text{ClO}_4)_3 \cdot 2\text{H}_2\text{O}^{[136]}$ shares this trigonal sheet motif. However, the layers are linked by digonal Ag^+ cations, which are coordinated to the hmta nitrogen donors that project into the

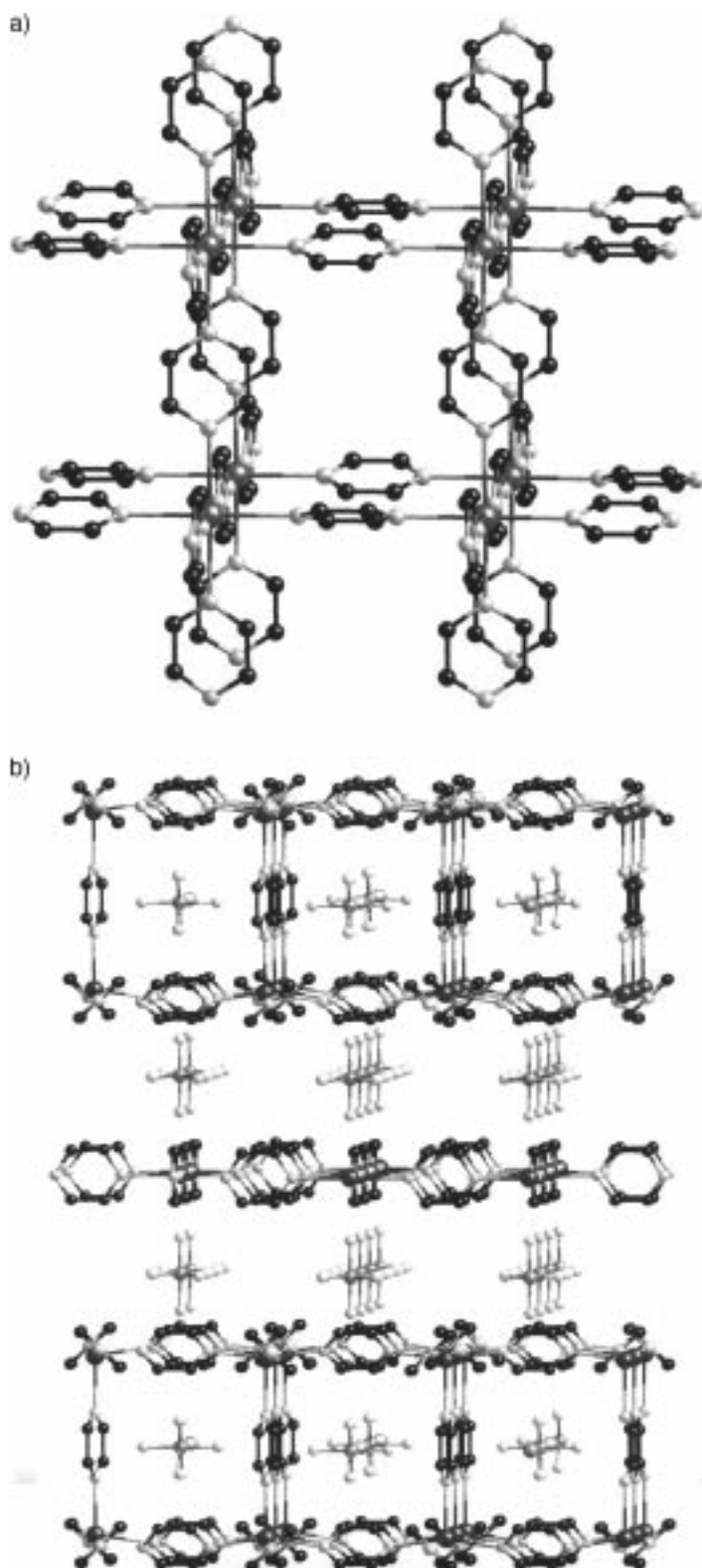


Figure 41. a) The simple cubic three-dimensional framework of $[\text{Ag}(\text{pz})_3](\text{SbF}_6)$. b) A view of the structure of $[\text{Ag}(\text{pz})_2][\text{Ag}_2(\text{pz})_3](\text{PF}_6)_3$.

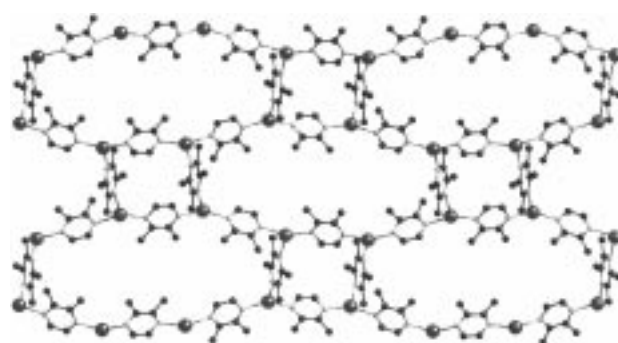


Figure 42. A view down the a axis of a single framework of $[\text{Ag}_2(2,3\text{-Me}_2\text{pz})_3](\text{SbF}_6)_2$.

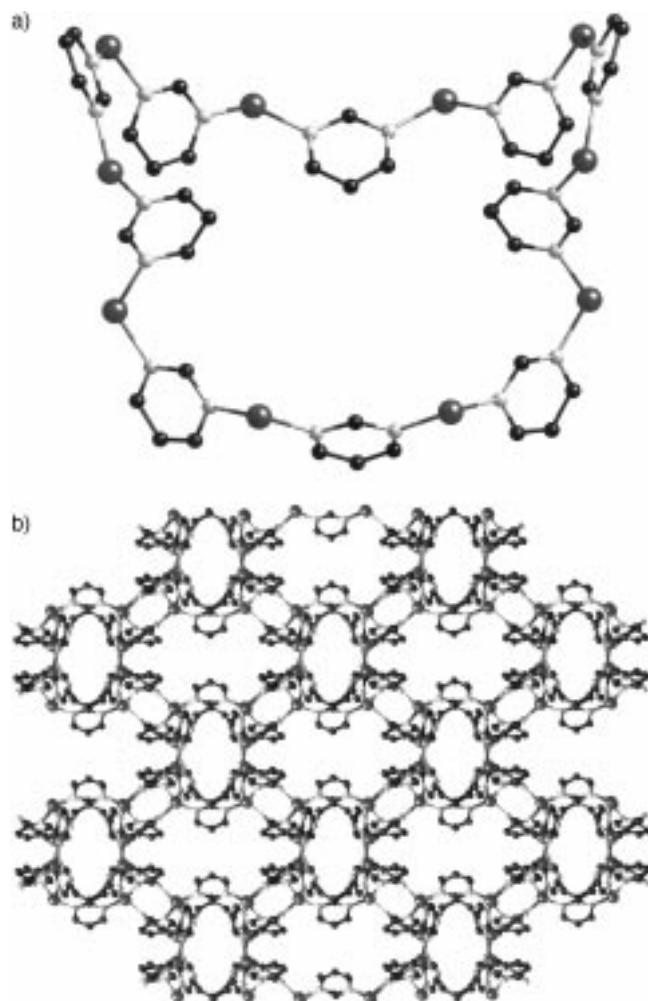


Figure 43. a) The cyclic building block for the structure of $[\text{Cu}(\text{pyrd})_2](\text{BF}_4)$. b) The channels produced by the framework structure of $[\text{Cu}(\text{pyrd})_2](\text{BF}_4)$.

interlamellar region. The anions and solvent molecules occupy the large hexagonal channels.

In contrast to the above, the structure of $[\text{Ag}(\text{hmta})](\text{PF}_6) \cdot \text{H}_2\text{O}^{[138]}$ consists of trigonally flattened $\{\text{AgN}_3\}$ sites linked into a three-dimensional helical framework. In contrast also to the structure of $[\text{Ag}_2(2,3\text{-Me}_2\text{pz})_3](\text{SbF}_6)$, which exhibits a similar framework, there is no interpenetration in $[\text{Ag}(\text{hmta})](\text{PF}_6) \cdot \text{H}_2\text{O}$; consequently, the framework is enantiomorphic.

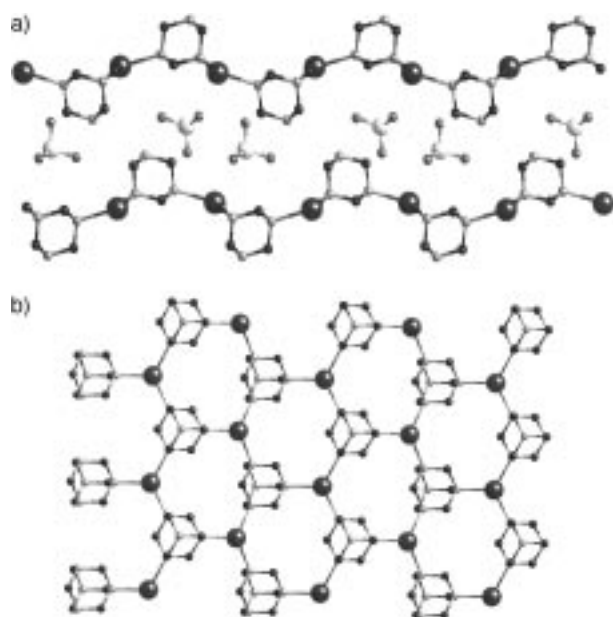


Figure 44. a) The stacking of two-dimensional $\{\text{Ag}(\text{hmta})\}_n^{4+}$ layers and interlamellar ClO_4^- anions in $[\text{Ag}(\text{hmta})](\text{ClO}_4)$. b) A view of a layer to show the three-connected geometries of the Ag^+ cations of the hmta ligands.

Finally, the structure of $[\text{Ag}_4(\text{hmta})_3(\text{H}_2\text{O})](\text{PF}_6)_4 \cdot 3\text{EtOH}$ ^[135] exhibits common geometric motifs in a unique structural type. The structure consists of hexagonal $\{\text{Ag}_6(\text{hmta})_6\}$ rings, reminiscent of the honeycomb motif of $[\text{Cu}_2(\text{pz})_3](\text{SiF}_6)$, linked by trigonal $\{\text{AgN}_3\}$ centers into a three-dimensional framework. This results in spacious cavities and channels (Figure 45).

3.7. Prelude to Oxides: The Copper Sulfate–Organodiamine Linker System

While the structural chemistry of these coordination polymers is complex and as yet lacking in a totally cohesive overview, certain general principles for guiding their applications to oxide synthesis may be elicited. Most obviously, the coordination polymers described above are cationic and consequently can serve as unique counterions for negatively charged oxide clusters and/or polymers. Depending on the coordination preferences of the metal constituent of the polymer, the polymer chain may also bond to the peripheral oxo groups of the oxide component to provide access to heterometallic oxide–organic hybrid materials. For example, while Cu^{I} might be expected to form linear polymeric cationic chains with little or no interaction with the oxide surface, the coordination requirements of Mn^{II} , Fe^{II} , Co^{II} , and Ni^{II} would encourage direct interaction with the oxide surface under appropriate conditions.

The architectures adopted by these coordination polymers are suitable both for charge compensation and for a structure-directing role, both for the determination of the oxide dimensionality and the development of the intimate details of connectivity within the oxide skeleton. Within a naive conceptual construct, linear cationic chains could, in principle, thread through the pores of a three-dimensional open frame-

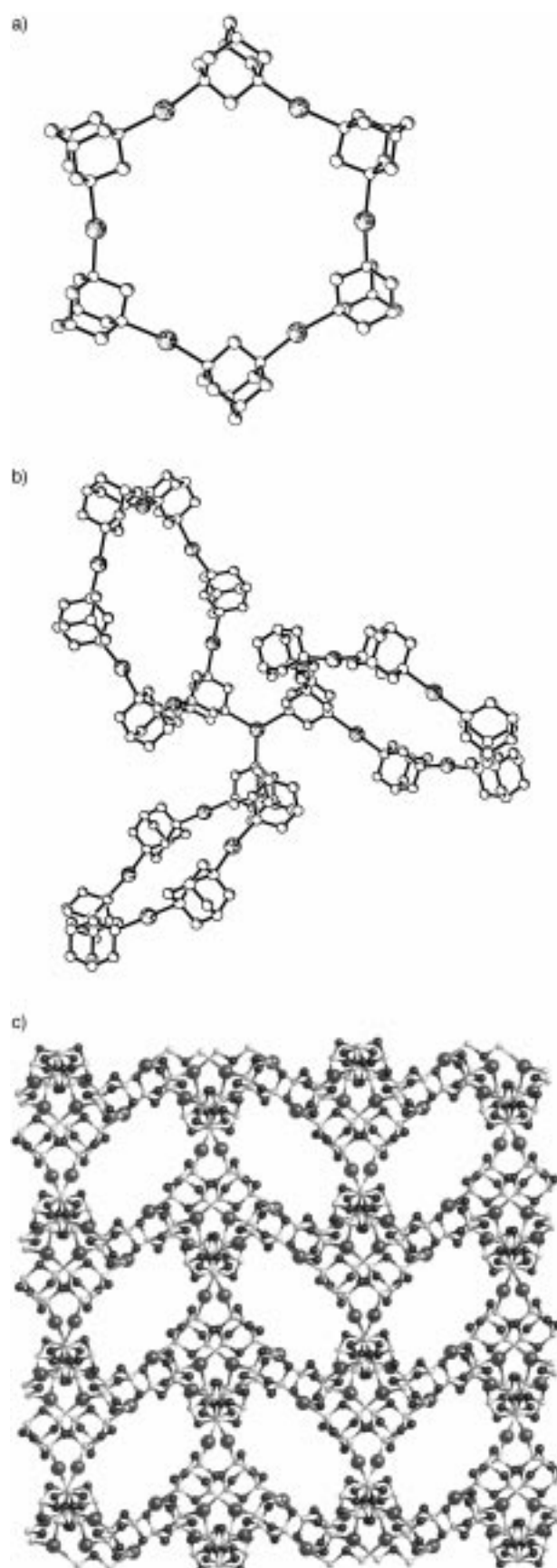


Figure 45. a) The cyclic building block of $[\text{Ag}_4(\text{hmta})_3(\text{H}_2\text{O})](\text{PF}_6)_4 \cdot 3\text{EtOH}$. b) The linking of three adjacent rings through the three-coordinate Ag site. c) A packing view along the c axis to show the rhombic channels which result from interpenetration.

work oxide or provide a cationic scaffolding to encapsulate clusters or one-dimensional structures. Alternatively, the linear polymeric cation may serve to stitch one- or two-dimensional oxide arrays into two- or three-dimensional covalently linked architectures. The two-dimensional square grid, honeycomb, double layer, or lattice-type polymeric cations may serve to sandwich alternating layers or strings of a negatively charged oxide component. The cavities and tunnels associated with the three-dimensional cationic structures of the adamantoid and other types might allow encryption of polyoxoanions or one-dimensional chains. Furthermore, from a simplistic geometric viewpoint, the introduction of spacers between donor groups of the bridging ligands of the polymeric cations provides spatial expansion and consequently may increase the void volume available to the anionic component. Moreover, expansion or contraction of metal–metal distances within the polymeric cationic moiety determines the periodicity of points of attachment between the heterometal sites of the polymeric cation and the surface of the oxide component in covalently linked composites. It is perhaps also significant that variable tethering of the metal sites of the polymeric cation results in variations in the charge/volume or charge/length ratio of the polymer, a characteristic which is necessarily reflected in the charge density of the oxide component. This observation raises the intriguing possibility of manipulation of the charge/volume ratios of oxides through the choice of cationic template.

However, it must be noted that the void volumes of the coordination polymer structures are often restricted by interpenetration. The interpenetration phenomenon reflects the efficient packing requirements of the crystalline state. Significantly, interpenetration is *not a universal phenomenon*. While there are, to date, insufficient examples to provide reliable guidelines for restricting interpenetration, several observations are relevant:

- 1) Appropriate coligand geometry can preclude interpenetration, as observed for $[\text{Zn}(4,4'\text{-bpy})_2(\text{SiF}_6)] \cdot x\text{H}_2\text{O}$.
- 2) Shortening of the donor–donor distance in the bridging ligand of the polymeric cation results in non-interpenetrating structures for $[\text{Cu}(\text{pyrd})_2](\text{BF}_4)$, $[\text{Ag}(\text{hmta})](\text{PF}_6) \cdot \text{H}_2\text{O}$, and $[\text{Ag}_4(\text{hmta})_3(\text{H}_2\text{O})](\text{PF}_6)_4 \cdot 3\text{EtOH}$.
- 3) Efficient occupancy of void space by anions and solvent molecules can alleviate the need for interpenetration, as observed for $[\text{Ag}(\text{hmta})](\text{PF}_6) \cdot \text{H}_2\text{O}$ and $[\text{Cu}(4,4'\text{-bpy})(\text{H}_2\text{O})_2(\text{BF}_4)_2] \cdot 4,4'\text{-bpy}$.

In this regard, hydrothermal synthesis offers several advantages. Enhancement of the solubility of both organic and inorganic components allows a variety of space-filling entities to be introduced, which are subsequently “selected” in the hydrothermal crystallization. Most specifically, the hydrothermal method favors the encapsulation of water molecules of crystallization which form complex microstructures within the channels or cavities of the oxide array through multipoint hydrogen bonding to the oxide surface and to the proton sites of the cationic component. Furthermore, incorporation of large polyoxoanion clusters or of one- or two-dimensional oxide arrays should provide efficient cation–anion packing to prevent interpenetration of the cationic polymers.

To address the feasibility of oxide incorporation into cationic polymer arrays, the oxoanion sulfate was chosen as a model for a coordinating tetrahedral EO_4^{n-} subunit. Variations of reaction conditions and ligand spacer lengths resulted in the facile preparation of one-, two-, and three-dimensional composite materials.

As shown in Figure 46, the structure of $[\text{Cu}(4,4'\text{-bpy})(\text{H}_2\text{O})_3(\text{SO}_4)] \cdot 2\text{H}_2\text{O}$ (**CUSO-1**) consists of $\{\text{Cu}(4,4'\text{-bpy})(\text{H}_2\text{O})_3\}_n^{+2n}$ chains running parallel to the *ab* plane. The sulfate anions are weakly coordinated to the copper sites of a chain, and occupy interchain positions to provide the appropriate charge balance. Parallel $\{\text{Cu}(4,4'\text{-bpy})(\text{H}_2\text{O})_3\}^{2+}$ chains form layers parallel to the *ab* plane and stack along the *c* axis. Adjacent layers are rotated by 60° to produce triangular cavities occupied by the sulfate anions or hexagonal cavities occupied by the ligand rings (Figure 46b).

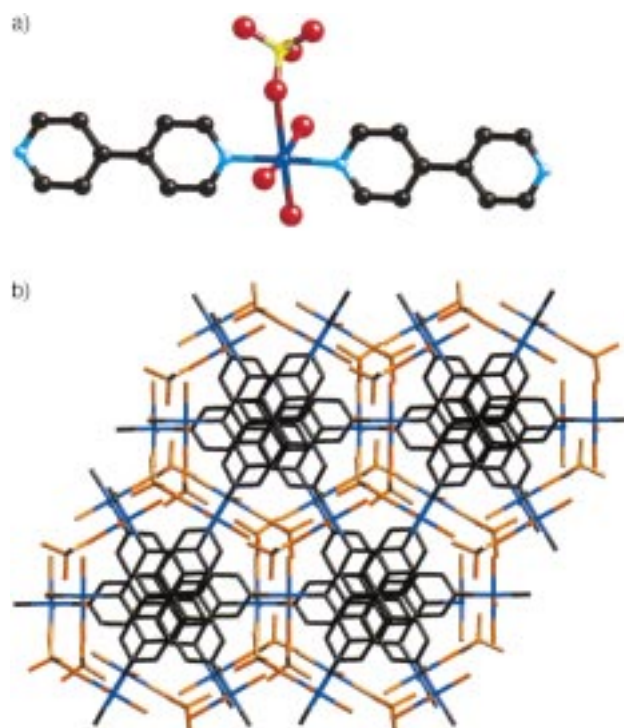


Figure 46. a) The Cu^{II} coordination geometry in $[\text{Cu}(4,4'\text{-bpy})(\text{H}_2\text{O})_3(\text{SO}_4)] \cdot 2\text{H}_2\text{O}$ (**CUSO-1**). b) A view of the structure down the *c* axis to show the stacking of chains which produces hexagonal cavities, occupied by the rings of the ligand.

One major determinant of structure is the Cu^{II} coordination geometry. The copper site of **CUSO-1** exhibits distorted 5+1 octahedral geometry. The coordination sphere is defined by two pyridyl nitrogen donors from two 4,4'-bpy ligands, three aquo oxygen donors, and the oxygen atom of a sulfate anion. The coordination geometry may be described as a basal plane consisting of the *trans* nitrogen donors and aquo ligands, with axial positions occupied by an aquo group and the oxygen atom of a weakly interacting sulfate.

In contrast, the structure of $[\text{Cu}(\text{bpe})_2][\text{Cu}(\text{bpe})(\text{H}_2\text{O})_2(\text{SO}_4)_2] \cdot 2\text{H}_2\text{O}$ (**CUSO-2**) is constructed from two motifs, a linear one-dimensional chain and a two-dimensional grid, which integrate to generate a unique three-dimensional framework. As shown in Figure 47, the one-dimensional chains consist of distorted octahedral copper sites bridged

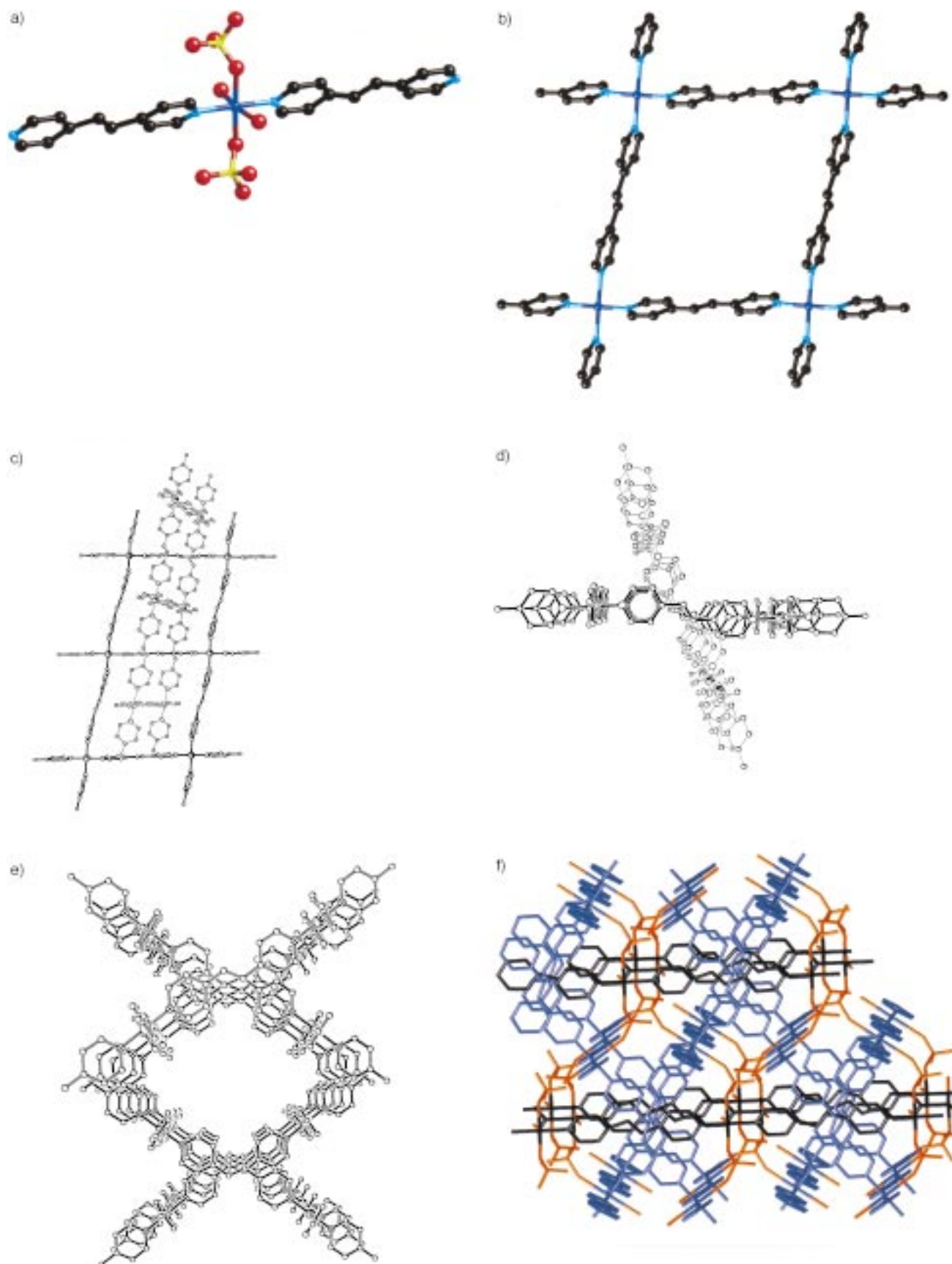


Figure 47. a) A view of one of the one-dimensional copper sites of **CUSO-2**. b) A view of the square grid associated with the second copper site. c), d) Two views of the interpenetration of grids in **CUSO-2**. e) A view parallel to the *c*-axis of the rhombic channels formed by the interpenetration of square grids. f) The threading of the one-dimensional chains through the network of square grids: the two-dimensional grids are in blue, the one dimensional chains in black, and the sulfate groups in orange.

by 4,4'-bpe ligands. Each Cu(1) center adopts $[\text{CuO}_4\text{N}_2]$ coordination geometry, defined by two *trans* pyridyl nitrogen donors from each of two bpe ligands, two aquo oxygen donors, and two oxygen donors from two sulfate groups. The sixfold coordination is best described as 4+2 distorted octahedral geometry. The equatorial plane is defined by two pyridyl nitrogen donors and two sulfate oxygen atoms. The weakly interacting axial positions are occupied by aquo ligands. Thus, in contrast to the structure of **CUSO-1**, the Cu–sulfate oxygen bonds are proximal while the Cu–aquo bonds are distal.

The second structural building block is the two-dimensional square grid pattern adopted by the $\{\text{Cu}(\text{bpe})\}^{2+}$ chains of the Cu(2) sites. The proximal coordination at the Cu(2) centers consists of square planar $\{\text{CuN}_4\}$ units, with each Cu(2) bonded to four nitrogen donors from four bpe ligands, to produce the grid work pattern of Figure 47b. These layers are propagated parallel to the crystallographic *ab* and *bc* planes to interweave as shown in Figure 47c. In addition to the four nitrogen donors from the bpe ligands, each Cu(2) center

participates in weak axial coordination to oxygen donors from sulfate groups of two adjacent one-dimensional chains associated with the Cu(1) sites. Consequently, the geometry of the Cu(2) centers is also best described as 4+2 distorted octahedral.

The one-dimensional chains are thus linked through weak sulfate bridges to the interpenetrating two-dimensional grids (Figure 47d). These chains thread through the two-dimensional networks to produce the unique and complicated three-dimensional framework shown in Figure 47e. The cross-linking of two-dimensional grids through interpenetrating one-dimensional chains is a unique feature of the structure.

The structure of $[\text{Cu}(\text{bpe})(\text{H}_2\text{O})(\text{SO}_4)]$ (**CUSO-3**) is constructed from one-dimensional $\{\text{Cu}(\text{bpe})(\text{H}_2\text{O})\}^{2+}$ chains linked through bridging sulfate groups into a three-dimensional framework. As shown in Figure 48, the chains consist of square-pyramidal Cu sites linked through bpe ligands. The geometry about the Cu sites is defined by *trans* nitrogen donors from two bpe ligands and two sulfate oxygen donors in

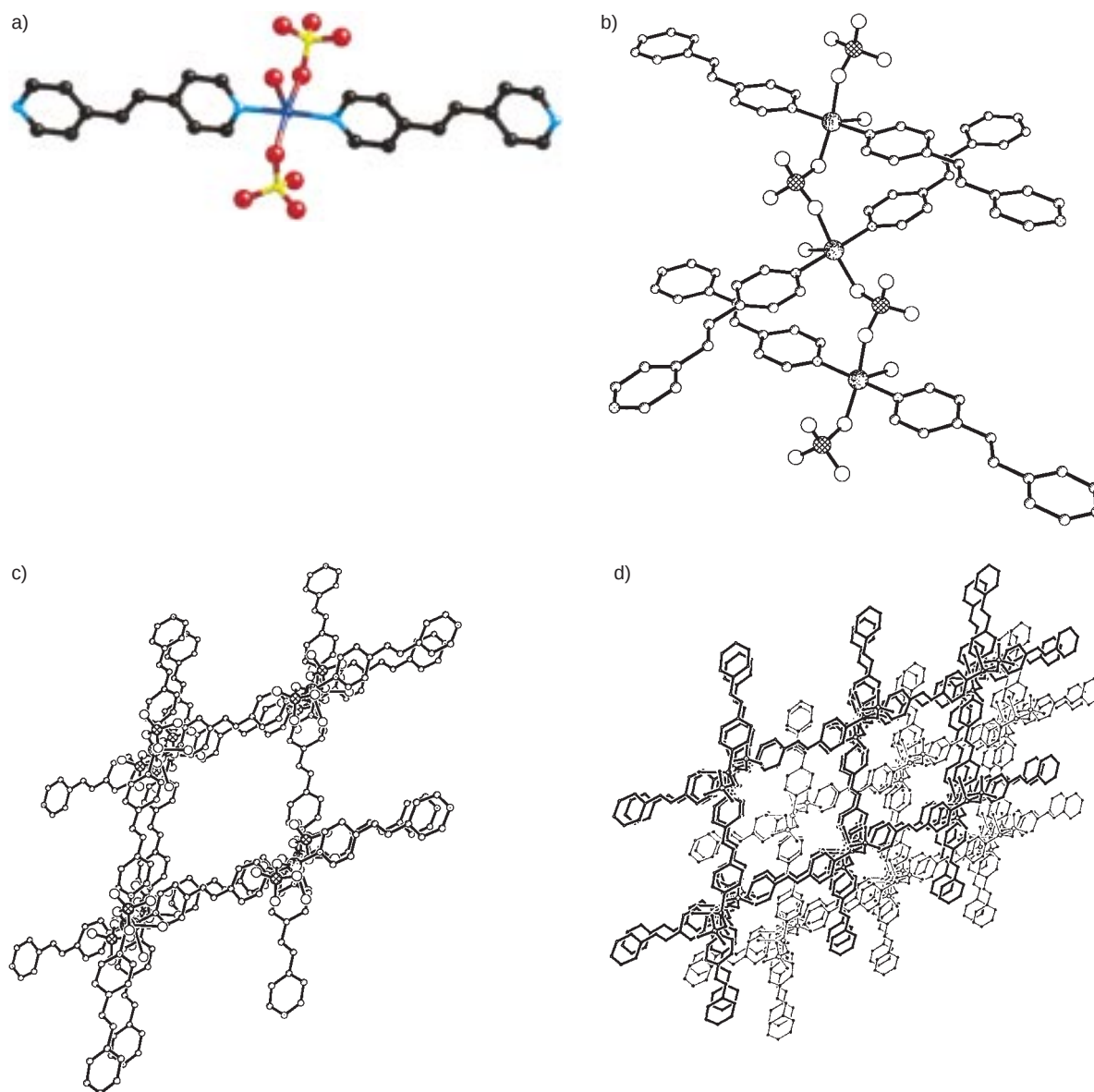


Figure 48. a) The Cu^{II} geometry in **CUSO-3**. b) A view of the undulating $\{\text{Cu}(\text{SO}_4)\}$ chain which links $\{\text{Cu}(\text{bpe})\}^{2+}$ linear chains. c) A view along the $[101]$ direction to show the rhombic grid of the three-dimensional framework. d) A view of the interpenetration of the two independent three-dimensional grids.

the equatorial plane, with an aquo ligand in the axial position. A copper center of a given chain is linked to copper sites from two adjacent chains through bridging sulfate groups. Each sulfate bridges copper centers from two neighboring chains by adoption of a μ^2 -bridging mode. This connectivity results in a three-dimensional framework of linked chains shown in Figure 48c. **CUSO-3** illustrates the diversity of coordination environments adopted by copper sites in copper-bridging diamine composite solids, which can exhibit coordination numbers ranging from 2 to 6.

The structural versatility of the composites constructed from cationic polymers and a simple oxoanion encouraged us to substitute molybdate for sulfate in the synthesis, which led to the isolation of the original member of the family of organoamine-heterometallic-molybdenum oxide composites $[\text{Cu}(\text{bpe})(\text{MoO}_4)]$ (**MOXI-1**).^[141]

The structure of **MOXI-1** is constructed from $\{\text{Cu}(\text{bpe})\}^{2+}$ linear chains bridged through $\{\text{MoO}_4\}^{2-}$ tetrahedra into a three-dimensional framework. The fundamental structural motif (Figure 49a) consists of distorted trigonal bipyramidal Cu^{II} centers coordinated to two bpe ligands and three molybdate tetrahedra. The geometry at the Cu sites is defined by three oxygen donors from three $\{\text{MoO}_4\}^{2-}$ groups in the equatorial plane and two bpe nitrogen donors that occupy the axial positions. Each molybdate group bridges three neighboring Cu sites to produce a bimetallic oxide layer motif $\{\text{CuMoO}_4\}$ (Figure 49b). Each molybdenum site thus possesses one pendant terminal oxo group, which is directed above or below the plane. The connectivity in the plane generates twelve-membered $\{\text{Cu}_3\text{Mo}_3\text{O}_6\}$ rings which fuse to propagate the layer structure. The bpe ligands extend from the metal oxide layers at an angle of ca. 35° and bridge adjacent layers to generate the overall three-dimensional covalent connectivity (Figure 49c). The structural changes engendered by the replacement of sulfate in **CUSO-3** with molybdate in **MOXI-1** are significant. The sulfate groups adopt μ^2 modality, while the molybdates act as μ^3 bridges. The sulfate covalent attachment restricts the $\{\text{CuSO}_4\}$ motif to chains, in contrast to the layer structure adopted by the $\{\text{CuMoO}_4\}$ moiety of **MOXI-1**. It is noteworthy that the molybdate component not only displays variable points of attachment to the cationic array but may also aggregate into polyanion clusters or chains, sheets and frameworks to generate an expansive structural chemistry.

4. Organodiamine–Molybdenum Oxide Composite Materials

The cationic coordination polymers described in Section 3 represent one approach, albeit the structurally most novel and unique, to composite oxide phases. However, the organic component may adopt other structure-directing roles, as noted in Section 2.2. For convenience of classification, the MOXI class of composite materials has been divided into three subclasses based on the role of the organodiamine as a protonated cation, as a ligand to a molybdenum site of the oxide array, or as a ligand to a heterometallic site which may be part of a cationic coordination polymer or simply a mononuclear site associated with the molybdenum oxide array (Table 3).

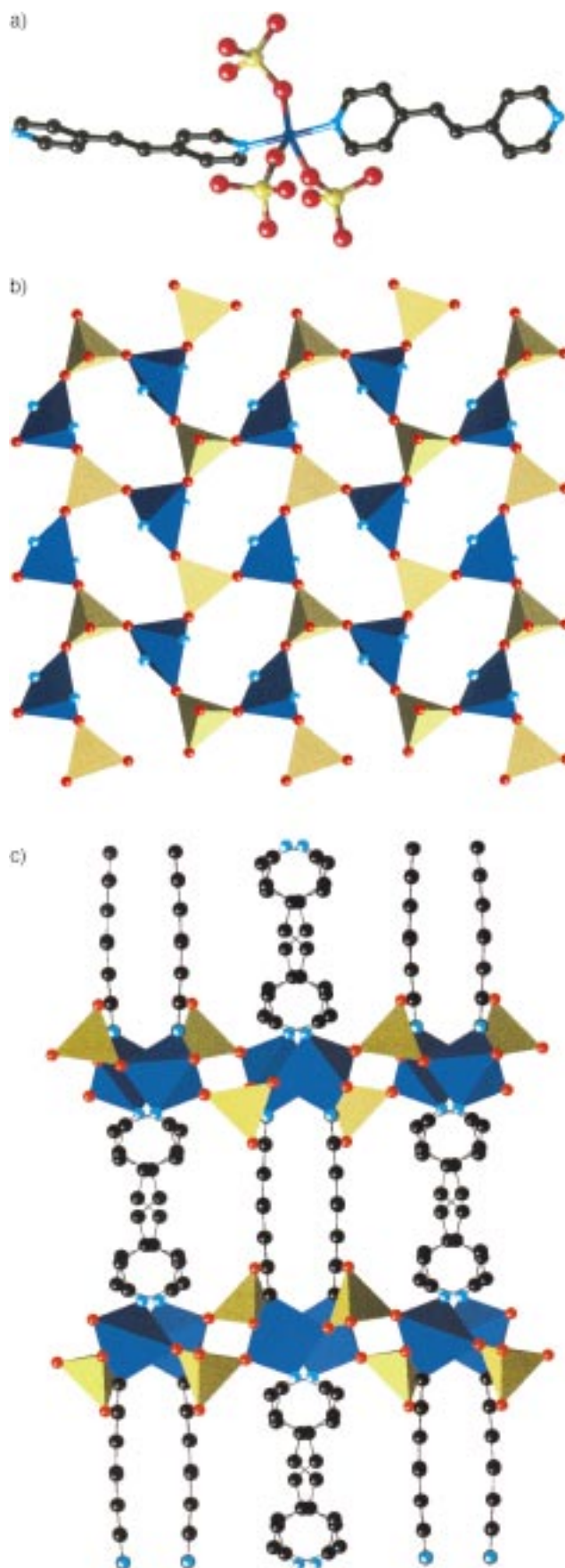


Figure 49. a) The Cu^{II} geometry in **MOXI-1**. b) The $\{\text{CuMoO}_4\}$ layer. c) A view of the alternating inorganic oxide layer–organic linker structure adopted by **MOXI-1**.

Table 3. Selected structural information for organic–inorganic hybrid materials of the organodiamine molybdenum oxide family.

Compound ^[a]	Mo oxide skeletal structure	metal coordination	Structure description	Figure	Ref.
<i>A. organic subunit incorporated as organoammonium cation</i>					
[H ₂ en][Mo ₃ O ₁₀] (MOXI-2)	1D	{MoO ₆ }	1D chains of edge-, corner-, and face-sharing octahedra	50	[142]
[H ₃ N(CH ₂) ₆ NH ₃][Mo ₄ O ₁₃]	1D	{MoO ₆ }	{Mo ₈ O ₂₆ } ⁴⁺ clusters constructed of edge-sharing octahedra, linked by corner-sharing into 1D chains	50	[143]
[4,4'-H ₂ bpy][Mo ₇ O ₂₂] · H ₂ O (MOXI-3)	2D	{MoO ₆ }	edge- and corner-sharing octahedra producing a stepped 2D motif	51	[146]
<i>B. organodiamine as ligand coordinated to Mo oxide skeleton</i>					
[MoO ₃ (2,2'-bpy)] (MOXI-4)	1D	{MoO ₄ N ₂ }	corner-sharing {MoO ₄ N ₂ } octahedra forming 1D chain	52	[148]
[Mo ₂ O ₆ (2,2'-bpy)] (MOXI-5)	1D	{MoO ₄ } and {MoO ₄ N ₂ }	alternating corner-sharing {MoO ₄ } tetrahedra and {MoO ₄ N ₂ } octahedra in 1D chain	52	[148]
[Mo ₃ O ₉ (2,2'-bpy) ₂] (MOXI-6)	1D	{MoO ₄ } and {MoO ₄ N ₂ }	corner-sharing repeat of two {MoO ₄ N ₂ } octahedra and one {MoO ₄ } tetrahedron	52	[148]
[Mo ₄ O ₁₃ (Hbpa) ₂] (MOXI-7)	{MoO ₅ N}	{MoO ₅ }	1D chain of edge- and corner-sharing {MoO ₅ N} octahedra and {MoO ₅ } distorted square pyramids; the pendant protonated pyridyl N groups hydrogen bond to adjacent chains to form a 2D sheet	53	[149]
[Mo ₂ O ₆ (bpy)] (MOXI-31)	1D	{MoO ₄ N ₂ }	1D chains of corner sharing Mo-octahedra linked by bpy ligands into a double chain	–	[150]
[MoO ₃ (4,4'-bpy) _{0.5}] (MOXI-8)	2D	{MoO ₅ N}	2D sheets constructed of fused {Mo ₄ O ₄ } square grids; the sheets are linked by 4,4'-bpy ligands into a 3D covalent framework	54	[151]
[HMo ₂ O ₆ (4,4'-bpy)] (MOXI-9)	2D	{MoO ₅ N}	as for [MoO ₃ (4,4'-bpy)]; one of four bridging oxo groups is protonated to render a mixed-valence material mixed	55	[151]
[Mo ₂ O ₆ (Htrz)] (MOXI-32)	2D	{MoO ₅ N}	2D sheets of corner-sharing Mo octahedra with two-connected bridging Htz ligands projecting into the interlamellar space	–	[150]
<i>C. organodiamines as ligands to heterometals</i>					
[{Ni(2,2'-bpy) ₂ Mo ₄ O ₁₄ }]	cluster	{MoO ₄ } and {NiO ₂ N ₄ }	Two {Mo ₂ O ₇ } ²⁻ units linked by two {Ni(4,4'-bpy) ₂ } ²⁺ groups into a {Mo ₄ Ni ₂ O ₆ } ring	–	[171]
[{Cu(<i>o</i> -phen) ₂ Mo ₈ O ₂₆ }] (MOXI-27)	cluster	{MoO ₄ }, {MoO ₆ }, {CuO ₄ N ₄ }	α-[Mo ₈ O ₂₆] cluster with peripheral corner-sharing {CuO ₄ N ₄ } square pyramids	56	[150]
[Ni(2,2'-bpy) ₂ Mo ₄ O ₁₃] (MOXI-10)	[Mo ₈ O ₂₆] ⁴⁻ cluster	{MoO ₆ } and {NiO ₂ N ₄ }	β-[Mo ₈ O ₂₆] ⁴⁻ clusters linked by {Ni(4,4'-bpy) ₂ } ²⁺ bridges into a 1D chain	57	[172]
[{Cu(en) ₂ Mo ₈ O ₂₆ }] (MOXI-11)	[Mo ₈ O ₂₆] ⁴⁻ cluster	{MoO ₅ }, {MoO ₆ }, and {CuO ₂ N ₄ }	γ-[Mo ₈ O ₂₆] clusters linked by {Cu(en) ₂ } ²⁺ groups into a 2D sheet	59	[170]
[{Cu(4,4'-bpy)} ₄ Mo ₈ O ₂₆] (MOXI-12)	[Mo ₈ O ₂₆] ⁴⁻ cluster	{MoO ₄ }, {MoO ₆ }, and {CuN ₂ } with two additional weak Cu...O interactions	δ-[Mo ₈ O ₂₆] ⁴⁻ clusters encapsulated in a matrix of linear {Cu(4,4'-bpy)} ⁺ polymeric rods	60	[177]
[{Cu(bpe)} ₄ Mo ₈ O ₂₆] (MOXI-13)	[Mo ₈ O ₂₆] ⁴⁻ cluster	{Mo ₄ }, {Mo ₆ }, and {CuN ₂ } with two additional weak Cu...O interactions	α-[Mo ₈ O ₂₆] ⁴⁻ clusters linked by {Cu(bpe)} ⁺ polymeric rods	–	[178]
[{Ni(4,4'-bpy) ₂ (H ₂ O) ₂ Mo ₈ O ₂₆ }] (MOXI-14)	[Mo ₈ O ₂₆] ⁴⁻ cluster	{MoO ₅ }, {MoO ₆ }, and {NiO ₃ N ₃ }	ε-[Mo ₈ O ₂₆] ⁴⁻ linked to 1D {Ni(4,4'-bpy) ₂ } ²⁺ chains to form a 2D network	62	[177]
[{Cu(pyrd)} ₄ Mo ₈ O ₂₆] (MOXI-34)	[Mo ₈ O ₂₆] ⁴⁻ cluster	{MoO ₆ }, {MoO ₅ }, {CuN ₂ O ₂ }	γ-[Mo ₈ O ₂₆] ⁴⁻ clusters bridged by {Cu ₄ (pyrd) ₄ O ₆ } units into a 2D sheet	61	[178]
[{Cu ₃ (4,7-phen) ₃ Mo ₁₄ O ₄₅ }] (MOXI-15)	[Mo ₈ O ₂₆] ⁴⁻ and [Mo ₆ O ₁₉] ²⁻ clusters	{MoO ₆ }, {CuN ₂ }, {CuN ₂ O}, {CuN ₂ O ₂ }	β-[Mo ₈ O ₂₆] ⁴⁻ and [Mo ₆ O ₁₉] ²⁻ linked clusters through {Cu ₃ (4,7-phen) ₃ } ³⁺ rings into a 2D network	63	[179]
[{Cu(4,4'-bpy)} ₄ Mo ₁₅ O ₄₇] · H ₂ O (MOXI-16)	1D	{MoO ₆ }, {CuN ₂ }	1D chains of edge- and corner-sharing Mo octahedra encapsulated in a matrix of linear {Cu(4,4'-bpy)} polymeric rods	64	[177]
[Cu(2,2'-bpy)Mo ₂ O ₇] (MOXI-17)	1D	{MoO ₅ }, {MoO ₆ }, {CuO ₄ N ₂ }	1D chain of edge-sharing octahedra and square pyramids with fused peripheral {Cu(2,2'-bpy)} ²⁺ groups	65	[172]
[Co(2,2'-bpy)Mo ₃ O ₁₀] (MOXI-18)	1D	{MoO ₄ }, {MoO ₆ }, {CoO ₄ N ₂ }	1D chains of Mo edge-sharing octahedra and corner-sharing tetrahedra linked by {Co(2,2'-bpy)} ²⁺ units into a 2D sheet	66	[172]

Table 3. (Continued)

Compound ^[a]	Mo oxide skeletal structure	metal coordination	Structure description	Figure	Ref.
[Cu ₂ (pyrd)Mo ₃ O ₁₀] (MOXI-19)	1D	{MoO ₆ } and {CuN ₃ O}	1D chains of edge-sharing Mo octahedra linked through {Cu ₂ (pyrd)} groups into a 3D covalent framework; the material is mixed valence	67	[182]
[Cu(2,2'-bpy)Mo ₄ O ₁₃] (MOXI-30)	1D	{MoO ₆ } and square-pyramidal {CuN ₂ O ₃ }	1D chain of edge- and corner-sharing {MoO ₆ } octahedra with fused peripheral {Cu(2,2'-bpy)} ²⁺ groups	–	[180]
[Cu(<i>o</i> -phen)MoO ₄] (MOXI-20)	[MoO ₄] ²⁻ units	{MoO ₄ } and {CuO ₃ N ₂ }	{Mo ₂ Cu ₂ O ₄ } rings fused into a 1D chain	70	[150]
[MoO ₄ {FeCl(2,2'-bpy)}] (MOXI-21)	[MoO ₄] ²⁻ units	{MoO ₄ }, {FeClO ₃ N ₂ }	corner-sharing {MoO ₄ } tetrahedra and {FeClO ₃ (2,2'-bpy)} octahedra linked into a 1D chain	71	[181]
[Mo ₃ O ₁₂ {Fe(2,2'-bpy)} ₂]·0.25 H ₂ O (MOXI-22)	[MoO ₄] ²⁻ units	{MoO ₄ }, {FeO ₄ N ₂ }	as for [MoO ₄ {FeCl(2,2'-bpy)}] with Cl on adjacent Fe sites replaced by O donor from {MoO ₄ } unit	71	[181]
[Mo ₄ O ₁₅ {Fe(2,2'-bpy)}] (MOXI-23)	[MoO ₄] ²⁻ and [Mo ₂ O ₇] ²⁻ units	{MoO ₄ }, {FeO ₄ N ₂ }	as for [Mo ₃ O ₁₂ {Fe(2,2'-bpy)} ₂] with bridging [MoO ₄] replaced by [Mo ₂ O ₇]	71	[181]
[Cu(bpa) _{0.5} (MoO ₄)] (MOXI-24)	[MoO ₄] ²⁻ units	{MoO ₄ } and {CuO ₃ N}	2D {CuMoO ₄ } sheets linked by bpa ligands into a 3D covalent framework	72	[182]
[Cu(pz) _{0.5} (MoO ₄)] (MOXI-25)	[MoO ₄] ²⁻ units	{MoO ₄ } and square-pyramidal {CuO ₄ N}	{Mo ₂ Cu ₂ O ₄ } rings fused into 1D tubes which are linked by bridging oxygen atoms and py ligands into a 3D covalent framework	73	[182]
[Cu(bpe)(MoO ₄)] (MOXI-1)	[MoO ₄] ²⁻ units	{MoO ₄ } and trigonal-bipyramidal {CuO ₃ N ₂ }	1D {Cu(bpe)} chains linked by {MoO ₄ } groups into a 3D covalent framework	49	[141]
[{Ni(dpa) ₂ }MoO ₄] (MOXI-26)	[MoO ₄] ²⁻ units	{MoO ₄ } and {NiN ₄ O ₂ }	2D networks of fused {Ni ₄ (dpa) ₄ } rings linked by η ² -{MoO ₄ } tetrahedra into a 3D framework	–	[183]
[{Zn(<i>o</i> -phen)}MoO ₄] (MOXI-29)	[MoO ₄] ²⁻ units	{MoO ₄ } and trigonal-bipyramidal {ZnN ₂ O ₃ }	1D chain of corner-sharing Mo tetrahedra and Cu square pyramids	–	[150]
[{Cu ₂ (trz) ₂ (H ₂ O) ₂ }Mo ₄ O ₁₃] (MOXI-33)	1D	{MoO ₆ }, {CuN ₄ O ₂ }, {CuN ₂ O ₄ }	1D chains of edge- and corner-sharing Mo octahedra entrained within a 3D {Cu ₂ (tz) ₂ } ²⁺ framework	68	[187]

[a] Compound identity number in boldface in parentheses.

4.1. Organoammonium – Molybdenum Oxide Phases

The use of organoammonium cations as structure-directing agents for oxide phases is well documented.^[51] The prototypical molybdenum oxide is (H₃NCH₂CH₂NH₃)[Mo₃O₁₀] (**MOXI-2**)^[142] (Figure 50a). The structure consists of a one-dimensional chain of edge-, corner-, and face-sharing molybdenum octahedra. The cation exhibits multipoint hydrogen bonding to the terminal and bridging oxo groups of the chain, and occupies channels formed by parallel stacking of three adjacent chains.

The significant structural role played by the organic cation is manifest in a comparison of the structure of **MOXI-2** with

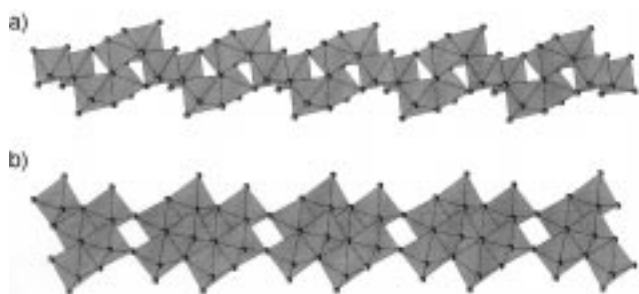


Figure 50. a) The structure of the one-dimensional chain of (H₃en)[Mo₃O₁₀] (**MOXI-2**). b) The structure of the anion of [H₃N(CH₂)₆NH₃][Mo₄O₁₃].

that of [H₃N(CH₂)₆NH₃][Mo₄O₁₃]^[143] (Figure 50b), which is constructed from {Mo₄O₁₃}²⁻ units composed of edge-sharing octahedra. Two {Mo₄O₁₃}²⁻ units fuse by edge sharing to form a compact {Mo₈O₂₆}⁴⁻ cluster; propagation is achieved by four corner-sharing interactions between adjacent {Mo₈O₂₆}⁴⁻ units. These organically templated structures may also be compared to the one-dimensional structures of K₂[Mo₃O₁₀]^[144] and (NH₄)₂[Mo₃O₁₀]^[145] which serve to illustrate the variable modes of polyhedral condensation which are generated by the introduction of cations with different charge and spatial requirements.

The only example of a two-dimensional organically templated molybdenum oxide of this subclass is provided by (4,4'-H₂bpy)[Mo₇O₂₂]·H₂O^[146] (**MOXI-3**), shown in Figure 51. The structure consists of molybdenum oxide layers, separated by an interlamellar region populated by (4,4'-H₂bpy)²⁺ cations and H₂O molecules of crystallization. The inorganic subunit of **MOXI-3** is both structurally and compositionally related to the layered oxide MoO₃.^[147] In a formal sense, **MOXI-3** may be considered to derive from MoO₃ through intercalation of (4,4'-H₂bpy)²⁺ cations and water, requiring the addition of an oxide anion to the inorganic framework to achieve charge compensation. Since charge/volume considerations result in one bipyridinium cation for seven molybdenum oxide sites, **MOXI-3** may be reformulated as (4,4'-H₂bpy)[(MoO₃)₇O]·H₂O to reflect its relationship to the MoO₃ parent.

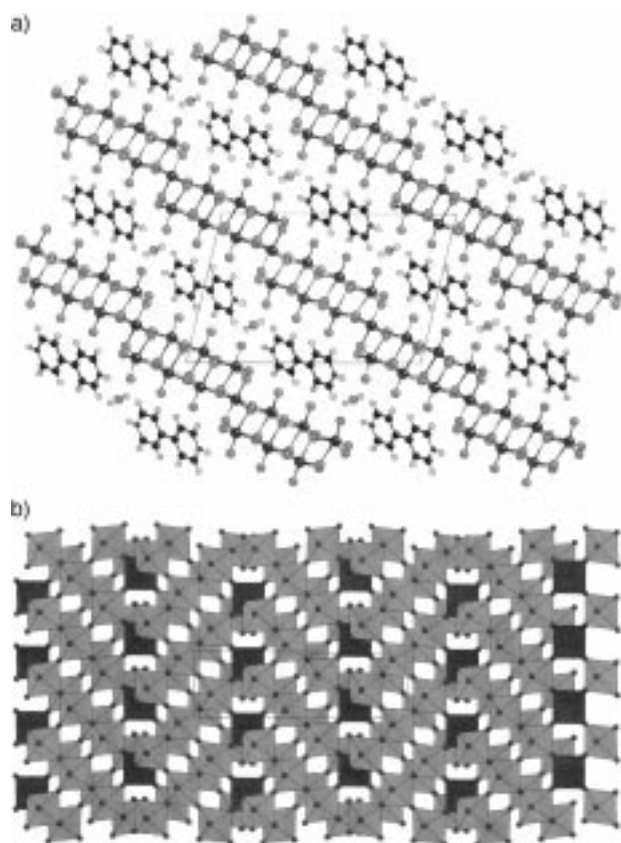


Figure 51. a) The stepped layer structure of **MOXI-3**. b) A view normal to the oxide layer. The darkened polyhedra indicate the positions of the dislocations that give rise to the “steps”.

However, the layer in MoO_3 is constructed from linear ribbons, two polyhedra thick, of edge-sharing $\{\text{MoO}_6\}$ octahedra; adjacent ribbons are linked through corner-sharing to produce the layer structure. Consequently, each Mo site in MoO_3 displays three triply bridging, two doubly bridging, and one terminal oxo group. In contrast, the oxide layers of **MOXI-3** are distinctly stepped. While the motif of ribbons of edge-sharing octahedra is present in both MoO_3 and **MOXI-3**, the ribbon in the latter executes a 90° turn and shifts one polyhedral length along the b direction at the “step” juncture at every seventh Mo site. Adjacent ribbons are again linked through corner-sharing interactions, but in such a fashion as to produce three distinct $\{\text{MoO}_6\}$ sites. The organic cations and the water molecules occupy the interlamellar region and participate in strong multipoint hydrogen bonding to each other and to the terminal oxo groups of the layer. The structure provides a dramatic demonstration of the role of organic cations in influencing oxide structure.

4.2. Organodiamines as Ligands to the Molybdenum Oxide Array

The compounds of the $[(\text{MoO}_3)_n(2,2'\text{-bpy})_m]$ family illustrate ligand control of stepwise growth of the polymer chain. As shown in Figure 52, the structures of $[\text{MoO}_3(2,2'\text{-bpy})]$ (**MOXI-4**), $[(\text{MoO}_3)_2(2,2'\text{-bpy})]$ (**MOXI-5**) and $[(\text{MoO}_3)_3(2,2'\text{-bpy})_2]$ (**MOXI-6**)^[148] are one-dimensional chains of fused

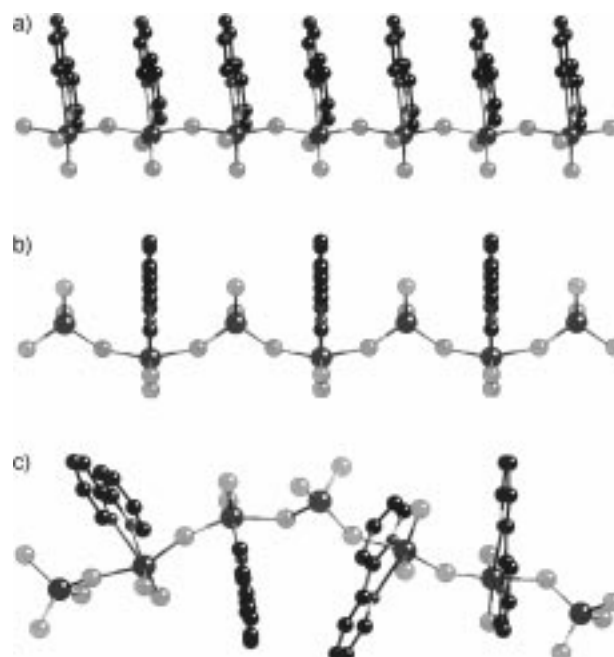


Figure 52. The structures of a) **MOXI-4**, b) **MOXI-5**, and c) **MOXI-6**.

molybdenum polyhedra. While the structure of **MOXI-4** consists of chains of corner-sharing $\{\text{MoO}_4\text{N}_2\}$ octahedra, that of **MOXI-5** is constructed from alternating corner-sharing $\{\text{MoO}_4\text{N}_2\}$ octahedra and $\{\text{MoO}_4\}$ tetrahedra. The structure of **MOXI-6** exhibits a repeat sequence of two corner-sharing $\{\text{MoO}_4\text{N}_2\}$ octahedra followed by a single $\{\text{MoO}_4\}$ tetrahedron. It is noteworthy that **MOXI-4–6** exhibit exclusively corner-sharing interactions while **MOXI-2**, $[\text{H}_3\text{N}(\text{CH}_2)_6\text{NH}_3]\text{-}[\text{Mo}_4\text{O}_{13}]$, $\text{K}_2[\text{Mo}_3\text{O}_{10}]$, and $(\text{NH}_4)_2[\text{Mo}_3\text{O}_{10}]$ exhibit edge sharing as one condensation mode. This suggests that the bipyridine ligand “passivates” the molybdenum oxide coordination sphere by blocking further Mo–oxo bond formation. This suggests a convenient route to low-dimensional metal oxides by exploitation of chelating amines as coligands.

Donor-group orientation has been seen in the case of the cationic coordination polymers of Section 3 to influence profoundly the structure of the array. Similarly, the structure of $[\text{Mo}_4\text{O}_{13}(\text{Hbpa})_2]$ (**MOXI-7**)^[149] is unique. The one-dimensional chain (Figure 53) is constructed from edge- and corner-sharing $\{\text{MoO}_5\text{N}\}$ octahedra and $\{\text{MoO}_5\}$ square pyramids. The Hbpa^+ group acts both as cation as a consequence of protonation of the nitrogen atom of the pendant arm and as a ligand covalently attached to the oxide chain. There is strong hydrogen bonding between the NH of the Hbpa^+ group and the oxo groups of an adjacent chain, to generate a two-dimensional rectangular grid motif, reminiscent of those observed for the one-dimensional coordination polymers, shown in Figure 6 for the prototypical $[\text{Cu}(4,4'\text{-bpy})\text{-(BF}_4)_2(\text{H}_2\text{O})_2] \cdot (4,4'\text{-bpy})$.

The rodlike 4,4'-bipyridine group can be used as a ligand, rather than as a cationic component as observed for **MOXI-3**. By raising the pH value of the reaction medium to prevent protonation of the pyridyl nitrogens, $[\text{MoO}_3(4,4'\text{-bpy})_{0.5}]$ (**MOXI-8**)^[151] was prepared. The structure of **MOXI-8** (Figure 54) consists of layers of corner-sharing $\{\text{MoO}_5\}$ square

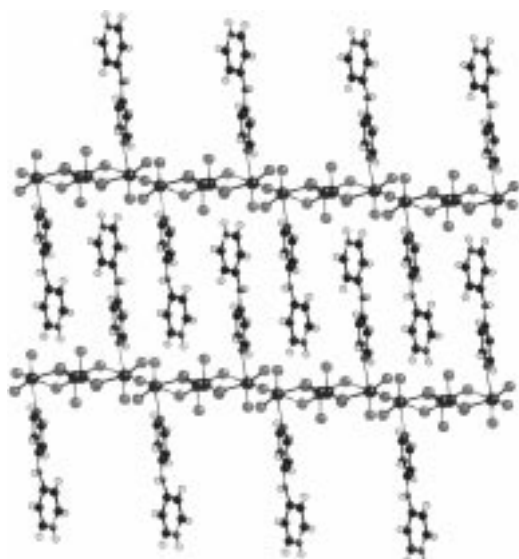


Figure 53. The structure of **MOXI-7**, which is constructed of one-dimensional chains hydrogen bonded into a rectangular grid motif.

pyramids linked through 4,4'-bipyridyl groups into a three-dimensional covalently bonded metal oxide/organic ligand framework. The overall structure of **MOXI-8** may be described in terms of alternating inorganic metal oxide layers and aromatic organic layers. The distorted $\{\text{MoO}_5\text{N}\}$ coordination geometry at each molybdenum site is defined by a terminal oxo group, four asymmetrically bridging oxo groups, and a pyridyl nitrogen donor, and has the typical “two short-two intermediate-two long” bond length geometry common to molybdenum oxides.

It should be pointed out that the structure of **MOXI-8** is quite distinct from the layered structure adopted by MoO_3 ,^[147] which exhibits both edge and corner sharing of $\{\text{MoO}_6\}$ octahedra. However, the structure of **MOXI-8** does have some features in common with the proposed structure of the pyridine intercalation phase $[\text{MoO}_3(\text{pyridine})]$.^[152]

A mixed valence analogue of **MOXI-8**, $[\text{HMo}_2\text{O}_6(4,4'\text{-bpy})]$ (**MOXI-9**) may be readily prepared by the introduction of a reducing agent into the synthesis. The structure of **MOXI-9** is similar to that of **MOXI-8**, except that the octahedra adopt a more regular 5+1 type coordination, rather than the 2+2+2 observed for **MOXI-8** (Figure 55). This structural trend is similar to that observed for MoO_3 and the mixed valence oxide hydroxides $[\text{MoO}_{3-x}(\text{OH})_x]$.^[153–156]

4.3. Molybdenum Oxide Phases Containing Organodiamine-Ligated Heterometals

The heterometal-containing molybdenum oxide compounds of this type fall into three general subgroups, classified according to the dimensionality of the molybdenum array and to the dimensionality of the $\text{M}'\text{-Mo-O}$ array. Three subgroups are identified:

- 1) Discrete molybdenum oxide polyanion clusters linked by heterometal–diamine coordination complexes or polymers into higher dimensional aggregates.

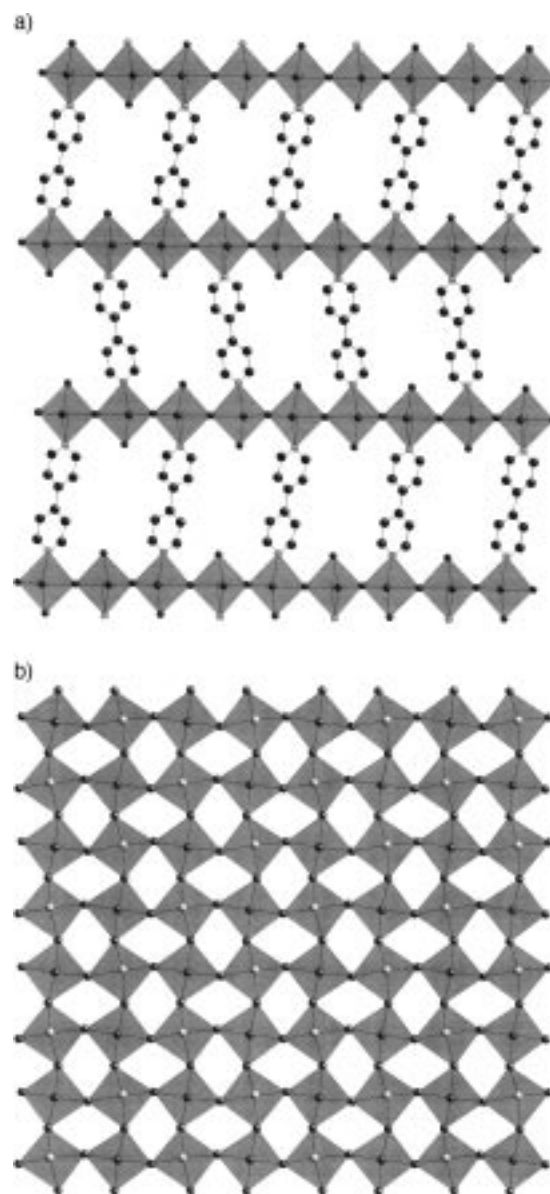


Figure 54. The structure of **MOXI-8** a) showing the linking of layers by 4,4'-bpy ligands; b) a view normal to the layer.

- 2) One-dimensional molybdenum oxide chains linked by heterometal–diamine coordination polymers into complex aggregates.
- 3) One-, two-, and three-dimensional arrays of mixed molybdenum oxide–heterometal–diamine fused polyhedra.

4.3.1. Solids Constructed from Discrete Molybdenum Oxide Clusters

There is significant contemporary interest in the solid-state chemistry of molecularly derived solids with extended linkages.^[157, 158] One-dimensional ensembles have been prepared from the $[\text{Mo}_6\text{Cl}_8(\text{O}_2\text{CR})_6]^{2-}$ cluster^[159] and three-dimensional assemblies for $[\text{Nb}_6\text{X}_3\text{Y}_6]^{4+}$.^[126, 127] Chain, layer, and three-dimensional frameworks based on polyoxometalate clusters, either directly fused through bridging oxo groups or linked through heterometallic sites, have also been described.^[160–170]

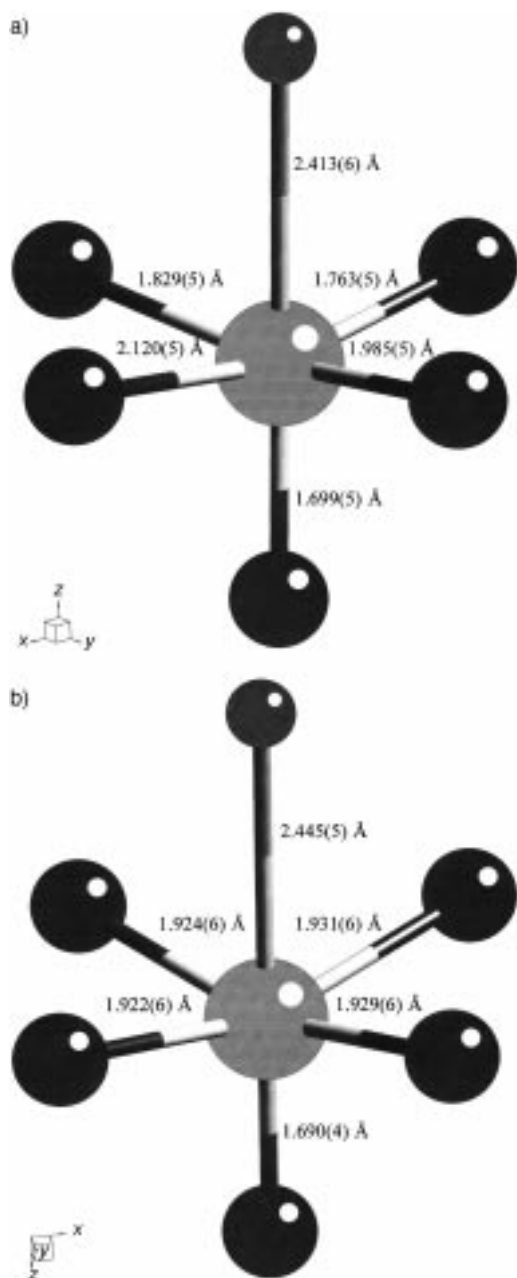


Figure 55. The contrasting geometries of the Mo sites of **MOXI-8** and **MOXI-9**.

Representative examples include the chain structure of $[\{\text{Co}(\text{H}_2\text{O})_4\}_2(\text{H}_2\text{W}_{12}\text{O}_{42})]^{6-}$,^[165] the two-dimensional network exhibited by $[\{\text{Ni}(\text{en})_2\}_3(\text{V}_{18}\text{O}_{42}\text{Cl})]^{-0.5}$,^[170] and the three-dimensional framework of $[\text{Na}_2\text{Co}_2\text{H}_2\text{W}_{12}\text{O}_{42}(\text{H}_2\text{O})_{12}]^{4-}$.^[169]

The primitive protostructure for this subgroup of the review is provided by $[\{\text{Ni}(2,2'\text{-bpy})_2\}_2\text{Mo}_4\text{O}_{14}]$,^[171] which displays a simple ring structure of two $\{\text{Mo}_2\text{O}_7\}^{2-}$ units linked by two $\{\text{Ni}(2,2'\text{-bpy})_2\}^{2+}$ groups into a cluster with a $\{\text{Mo}_4\text{Ni}_2\text{O}_6\}$ ring core. Similarly, the structure of $[\{\text{Cu}(o\text{-phen})_2\}_2\text{Mo}_8\text{O}_{26}]$ (**MOXI-27**) consists of an $\alpha\text{-}[\text{Mo}_8\text{O}_{26}]^{4-}$ cluster with two $[\text{Cu}(o\text{-phen})_2]^{2+}$ groups covalently attached to peripheral oxo groups (Figure 56). While these structures lack extension into the polymeric domain, the ease of attachment of heterometal–diamine complexes to the surface of such clusters is established.

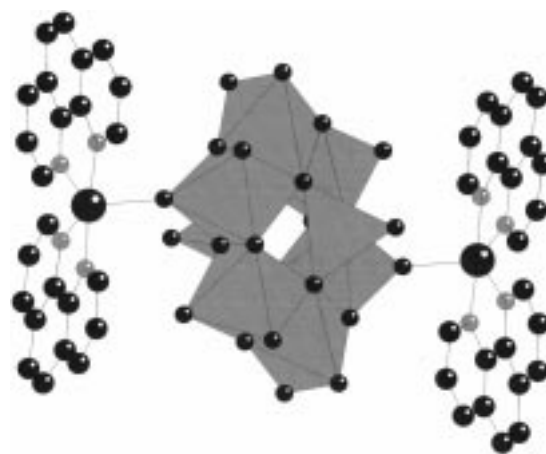


Figure 56. The structure of $[\{\text{Cu}(o\text{-phen})_2\}_2\text{Mo}_8\text{O}_{26}]$ (**MOXI-27**).

The prototypical solid-state structure is that of $[\text{Ni}(2,2'\text{-bpy})_2\text{Mo}_4\text{O}_{13}]$ (**MOXI-10**; Figure 57). The structure is constructed from $\beta\text{-}[\text{Mo}_8\text{O}_{26}]^{4-}$ clusters linked by $\{\text{Ni}(2,2'\text{-bpy})_2\}^{2+}$ bridges into a one-dimensional chain. It is instructive to note that the octamolybdate unit of **MOXI-10** is distinct from that observed for $[\{\text{Cu}(o\text{-phen})_2\}_2\text{Mo}_8\text{O}_{26}]$. Five isomers of $[\text{Mo}_8\text{O}_{26}]^{4-}$ have now been described. The α , β , and γ isomers

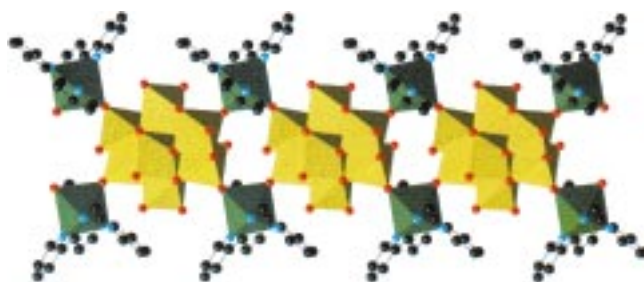


Figure 57. The structure of $[\text{Ni}(2,2'\text{-bpy})_2\text{Mo}_4\text{O}_{13}]$ (**MOXI-10**).

had been isolated in a number of salts,^[174, 175] while the δ form has been reported as the ($\alpha\text{-}\delta$) or ($\beta\text{-}\delta$) “intermediate” structure.^[176] The ϵ form is thus far unique to the heterometal–diamine molybdenum oxide materials. As shown in Figure 58, the isomer structures differ in number, type, and fusion mode of the molybdenum polyhedra. The five forms are conceptually and chemically interrelated by minimal bond breaking through lengthening of axial interactions and polyhedral rotations. The occurrence of a particular isomer in the hydrothermal product is not predictable, a not unreasonable observation given the lack of significant energy differences between the structure types.

The steric constraints imposed by the bulky *o*-phen ligands of $[\{\text{Cu}(o\text{-phen})_2\}_2\text{Mo}_8\text{O}_{26}]$ are evidently released in the ethylenediamine derivative $[\{\text{Cu}(\text{en})_2\}_2\text{Mo}_8\text{O}_{26}]$ (**MOXI-11**).^[170] The structure is constructed from $\delta\text{-}[\text{Mo}_8\text{O}_{26}]^{4-}$ clusters linked by $\{\text{Cu}(\text{en})_2\}^{2+}$ groups into the two-dimensional sheet shown in Figure 59.

As the structural complexity of the heterometal–diamine complex cation increases, more exotic composite arrays of linked clusters are observed. Thus, the structure of $[\{\text{Cu}(4,4'\text{-bpy})\}_4\text{Mo}_8\text{O}_{26}]$ (**MOXI-12**), as shown in Figure 60, consists of

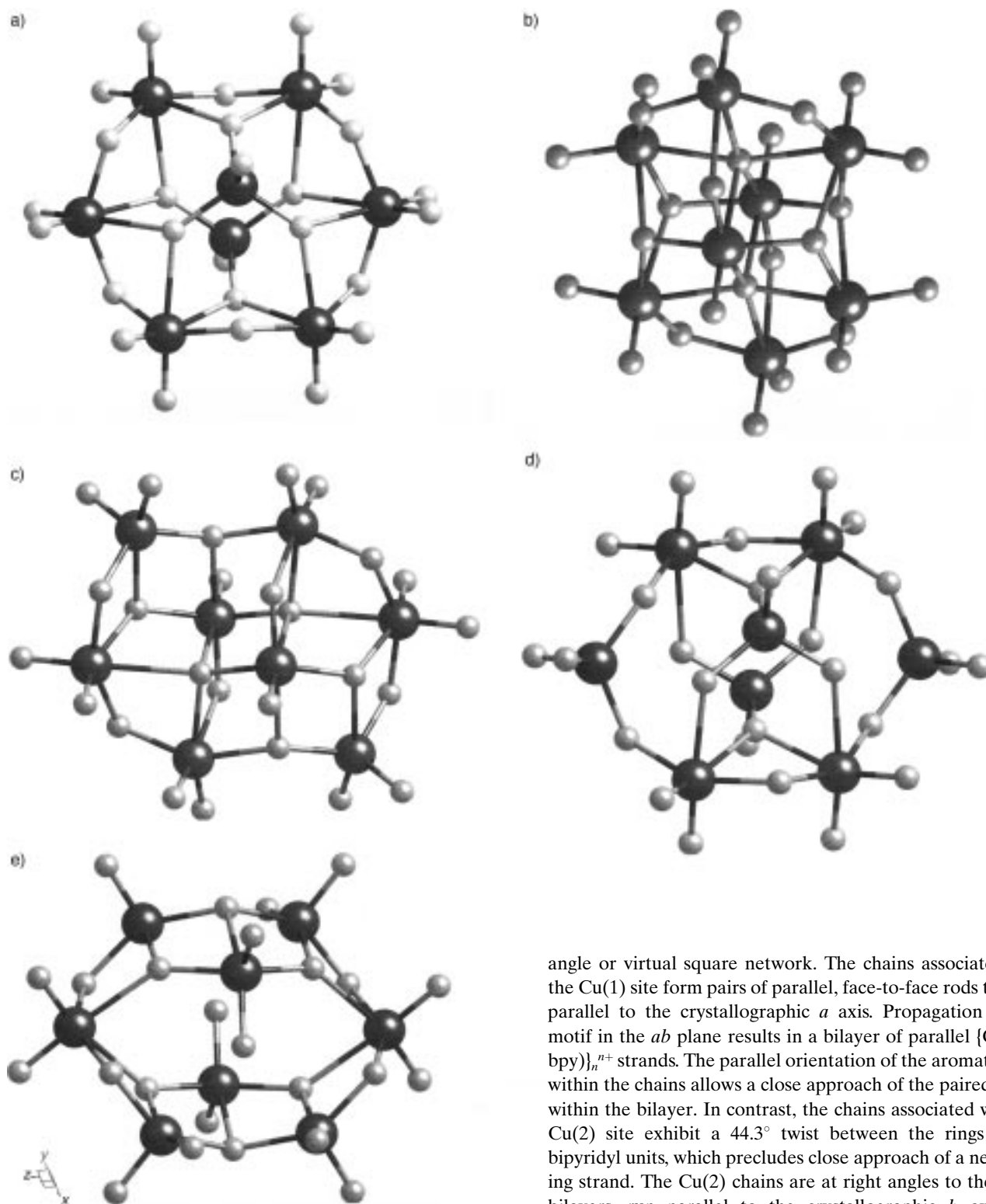
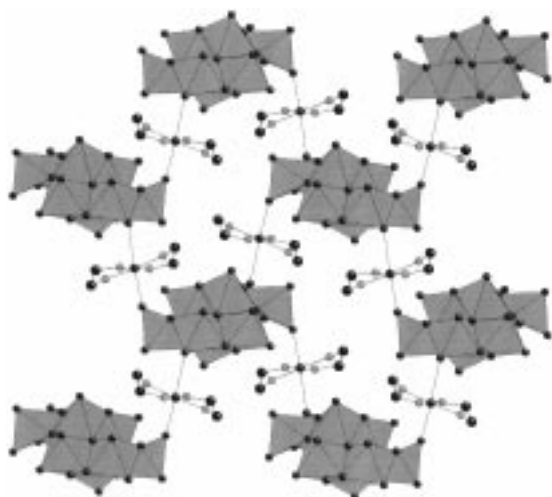
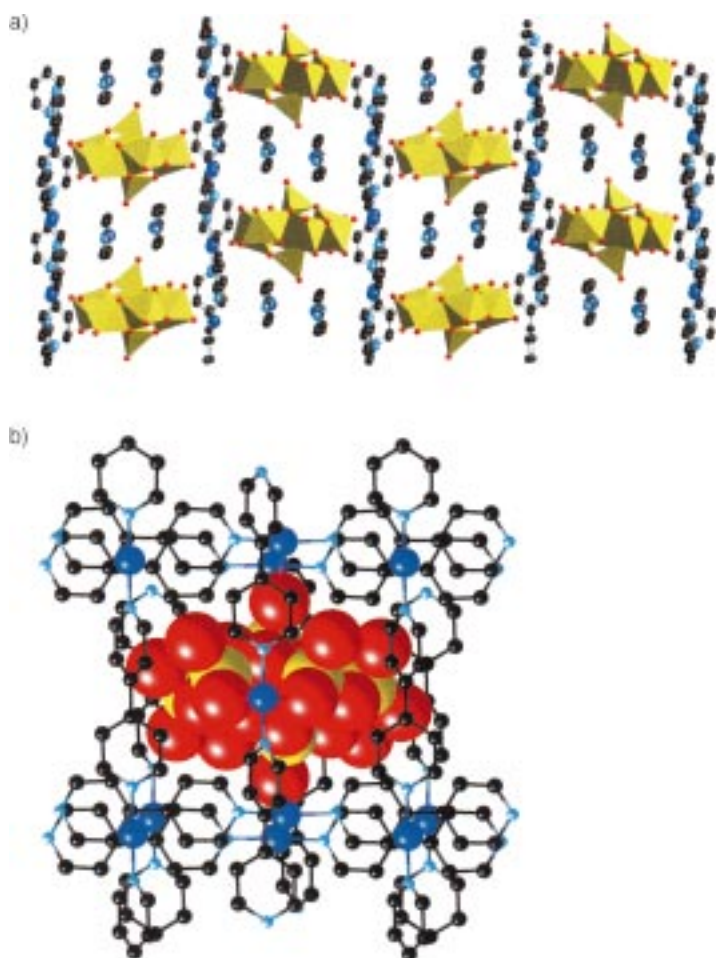


Figure 58. The structures of the a) α , b) β , c) γ , d) δ , and e) ϵ forms of $[\text{Mo}_8\text{O}_{26}]^{4-}$.

δ - $[\text{Mo}_8\text{O}_{26}]^{4-}$ clusters and $\{\text{Cu}(4,4'\text{-bpy})\}^+$ linear chains. The cation component, $\{\text{Cu}(4,4'\text{-bpy})\}^+$, provides the scaffolding as chains of digonally coordinated Cu^{I} centers. The relative orientation of the chains is unusual and results in cavities within the scaffolding that accommodate the $[\text{Mo}_8\text{O}_{26}]^{4-}$ units. There are two distinct chain environments that form a right

angle or virtual square network. The chains associated with the Cu(1) site form pairs of parallel, face-to-face rods that run parallel to the crystallographic a axis. Propagation of this motif in the ab plane results in a bilayer of parallel $\{\text{Cu}(4,4'\text{-bpy})\}_n^{n+}$ strands. The parallel orientation of the aromatic rings within the chains allows a close approach of the paired chains within the bilayer. In contrast, the chains associated with the Cu(2) site exhibit a 44.3° twist between the rings of the bipyridyl units, which precludes close approach of a neighboring strand. The Cu(2) chains are at right angles to the Cu(1) bilayers, run parallel to the crystallographic b axis, and propagate as parallel strands in the ab plane.

The $[\text{Mo}_8\text{O}_{26}]^{4-}$ clusters occupy cavities defined by two adjacent pairs of Cu(1) chains and one Cu(2) strand from each of two adjacent layers. The terminal oxo group of one tripodal Mo site exhibits weak long-range interactions of 2.555(5) and 2.691(4) Å with the Cu(1) sites, while oxo groups of tetrahedral and octahedral ring Mo sites display essentially non-bonding interactions with the Cu(2) sites. This long-range connectivity provides a virtual layer structure, in which the

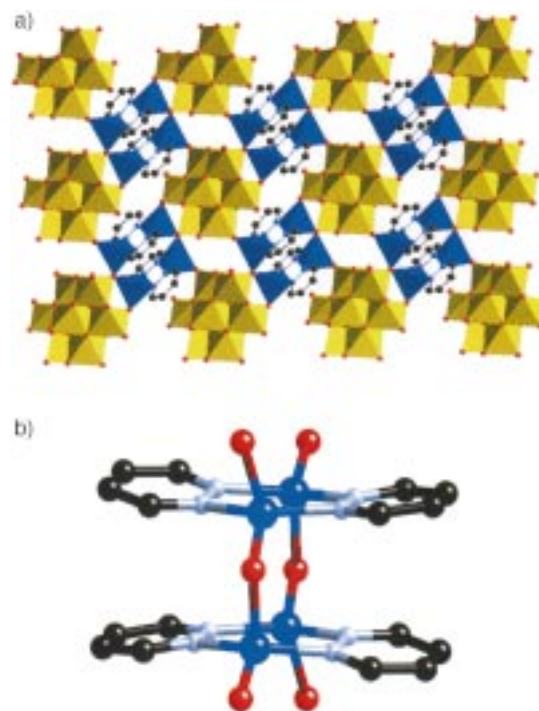
Figure 59. The structure of **MOXI-11**.Figure 60. a) The structure of **MOXI-12**. b) A view of the $[\text{Mo}_8\text{O}_{26}]^{4-}$ polyoxoanion entrained within the rigid polymeric cation network.

Cu(1) bilayers and $[\text{Mo}_8\text{O}_{26}]^{4-}$ subunits are sandwiched between the layers of parallel $\{\text{Cu}(2)(4,4'\text{-bpy})\}_n^{n+}$ strands. Adjacent layers are slotted together since alternate Cu(2) strands interact with $[\text{Mo}_8\text{O}_{26}]^{4-}$ clusters of an adjacent layer.

A related structure is exhibited by $[\{\text{Cu}(\text{bpe})\}_4\text{Mo}_8\text{O}_{26}]$ (**MOXI-13**). However, the α form of the octamolybdate is

observed with capping tetrahedral sites involved in the bonding to the parallel $\{\text{Cu}(\text{bpe})\}^+$ double chains. In contrast to the structure of **MOXI-11**, the interlamellar chains are parallel to the double chains.

An unusual structural variant of **MOXI-12** and **MOXI-13** results when pyridazine is introduced in place of the 4,4'-bipyridine of **MOXI-12** or the 4,4'-bipyridylethene of **MOXI-13**. In the case of $[\{\text{Cu}(\text{pyrd})\}_4\text{Mo}_8\text{O}_{26}]$ (**MOXI-34**),^[178] the γ - $[\text{Mo}_8\text{O}_{26}]^{4-}$ type is observed. Each molybdate cluster bonds to four $\{\text{Cu}_2(\text{pyrd})_2\}$ units, which are present in the form of the tetranuclear $\{\text{Cu}_4\text{O}_6(\text{pyrd})_4\}$ clusters (Figure 61). The copper

Figure 61. a) A view of the two-dimensional sheet of γ - $[\text{Mo}_8\text{O}_{26}]^{4-}$ clusters linked by $\{\text{Cu}_4\text{O}_6(\text{pyrd})_4\}$ clusters of **MOXI-34**. b) The $\{\text{Cu}_4\text{O}_6(\text{pyrd})_4\}$ cluster.

clusters consist of pairs of oxo-bridged copper tetrahedra which are linked through four pyridazine ligands in such a fashion as to generate a Cu_4 box of dimensions $3.25 \text{ \AA} \times 3.02 \text{ \AA}$ with π -stacked pyridazine rings. Each $\{\text{Cu}_4\text{O}_6(\text{pyrd})_4\}$ cluster links a molybdate cluster to three neighboring cluster units. The resultant two-dimensional sheet may be described in terms of corner-shared polyhedra from two distinct cluster types.

Modification of the coordination polymer scaffolding in these materials can be readily accomplished by the introduction of a d-block cation with coordination requirements different from those of Cu^{I} , such as Ni^{II} for which octahedral geometry is most common. The point is illustrated by the structure of $[\{\text{Ni}(4,4'\text{-bpy})_2(\text{H}_2\text{O})_2\}_2\text{Mo}_8\text{O}_{26}]$ (**MOXI-14**; Figure 62). The structure of **MOXI-14** is constructed from novel ε - $[\text{Mo}_8\text{O}_{26}]^{4-}$ clusters and $\{\text{Ni}(\text{H}_2\text{O})_2(4,4'\text{-bpy})_2\}_n^{2n+}$ one-dimensional zigzag chains. The molybdate cluster adopts an unprecedented structure consisting of six $\{\text{MoO}_5\}$ square pyramids and two $\{\text{MoO}_6\}$ octahedra that edge-share to form an ellipsoidal cluster, whose major axis is defined by the

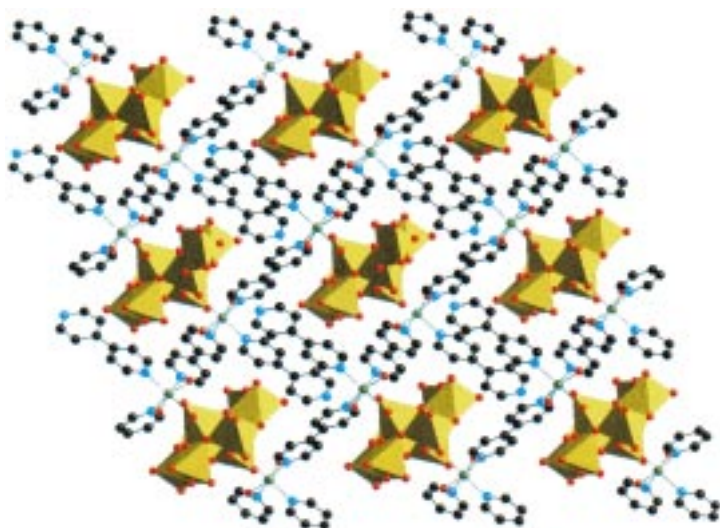


Figure 62. The structure of **MOXI-14**.

vector that joins the octahedral sites. The geometry adopted by this ϵ -[Mo₈O₂₆]^{4−} subunit reflects the steric constraints imposed by the polymer scaffolding of the {Ni(H₂O)₂(4,4′-bpy)₂}_n²ⁿ⁺ motif. The cationic component forms zigzag chains of *fac*-[NiO₃N₃] octahedra linked through bridging, bidentate 4,4′-bpy groups. Each Ni^{II} site of the chain is coordinated to nitrogen donors from three 4,4′-bpy ligands, two aqua ligands, and a terminal oxo group from the molybdate cluster subunit. Since the 4,4′-bpy groups occupy *cis* positions on the Ni^{II} sites, the {Ni(H₂O)₂(4,4′-bpy)₂}_n²ⁿ⁺ chain has a fold of about 90° at each Ni atom. It is noteworthy that the third 4,4′-bpy unit of each Ni center adopts monodentate coordination. The pendant 4,4′-bpy groups of adjacent {Ni(H₂O)₂(4,4′-bpy)₂}_n²ⁿ⁺ chains project into the interchain region to form π -stacked pairs, which define the boundaries of the interchain cavity.

The polymeric scaffolding of **MOXI-14** is connected to the polyoxoanion clusters by covalent bonding of the terminal oxo group of one Mo center to the Ni^{II} site. This produces a two-dimensional covalent framework with “chains” of [Mo₈O₂₆]^{4−} groups incorporated within the polymeric {Ni(H₂O)₂(4,4′-bpy)₂}_n²ⁿ⁺ backbone. The anionic subunits are confined within a rectangular channel defined by neighboring {Ni(H₂O)₂(4,4′-bpy)₂}_n²ⁿ⁺ strands and the pendant 4,4′-bpy groups that project from these strands. The ellipsoidal structure adopted by the [Mo₈O₂₆]^{4−} moiety in **MOXI-14** conforms to the shape constraints thus imposed.

The most unusual example of a solid constructed from linked clusters is provided by [(Cu₃(4,7-phen)₃)₂Mo₁₄O₄₅] (**MOXI-15**)^[179] which consists of β -[Mo₈O₂₆]^{4−} and [Mo₆O₁₉]^{2−} clusters interconnected by {Cu₃(4,7-phen)₃}³⁺ rings into a two-dimensional network (Figure 63). The hexamolybdate fragments appear to be stabilized by sandwiching between {Cu₃(4,7-phen)₃}³⁺ rings, an observation which illustrates the dramatic influence of cation geometry on the anion packing.

4.3.2. Solids Exhibiting One-Dimensional Molybdenum Oxide Arrays

An example of one-dimensional molybdenum oxide chains linked to polymeric coordination cations is provided by

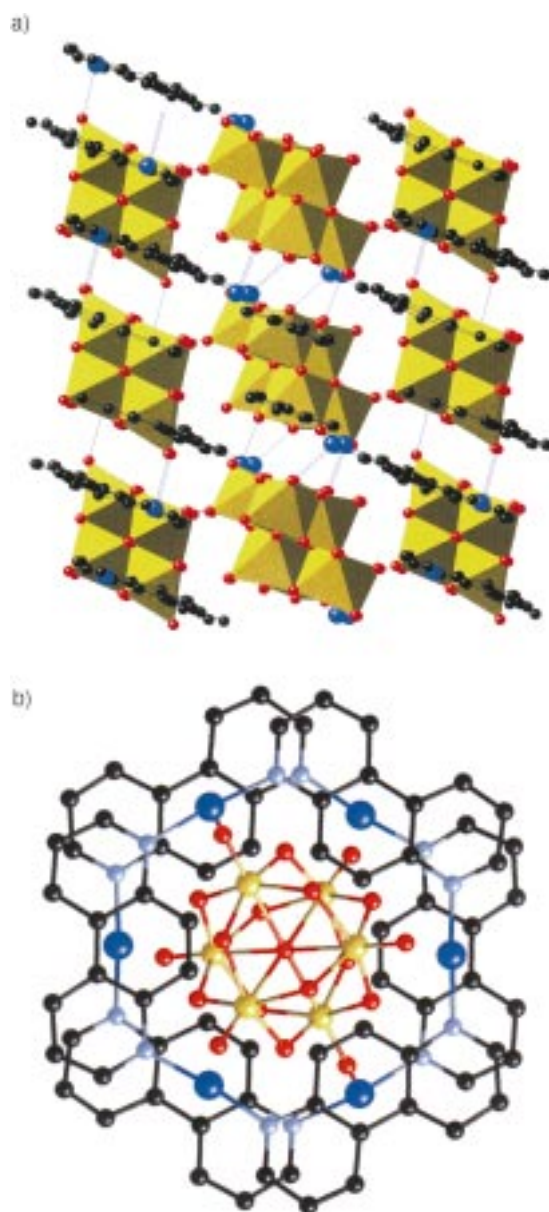


Figure 63. a) A polyhedral representation of the structure of **MOXI-15**. b) A view of the [Mo₆O₁₉]^{2−} clusters sandwiched between {Cu₃(4,7-phen)₃}³⁺ rings.

[(Cu(4,4′-bpy))₄Mo₁₅O₄₇] · H₂O (**MOXI-16**; Figure 64).^[177] The structure of **MOXI-16** is constructed from {Mo₁₅O₄₇}_n^{4n−} chains parallel to the crystallographic *a* axis and {Cu(4,4′-bpy)}_nⁿ⁺ rods parallel to the *b* axis. There are two distinct Mo environments. The Mo(1) sites form chains of *trans*, corner-sharing octahedra and have two terminal, one doubly bridging, and three triply bridging oxo groups. Two Mo(1) chains are linked by a double chain of Mo(2) centers, which is constructed from *cis*-planar, edge-sharing octahedra. Each Mo(2) site has a single terminal, one doubly bridging, and four triply bridging oxo groups. The terminal oxo group of each Mo(1) site is directed toward a Cu⁺ site of the {Cu(4,4′-bpy)}_nⁿ⁺ rods that extend at right angles to the {Mo₁₅O₄₇}_n^{4n−} chains. The result is an inorganic virtual layer of parallel molybdenum oxide chains that is sandwiched between

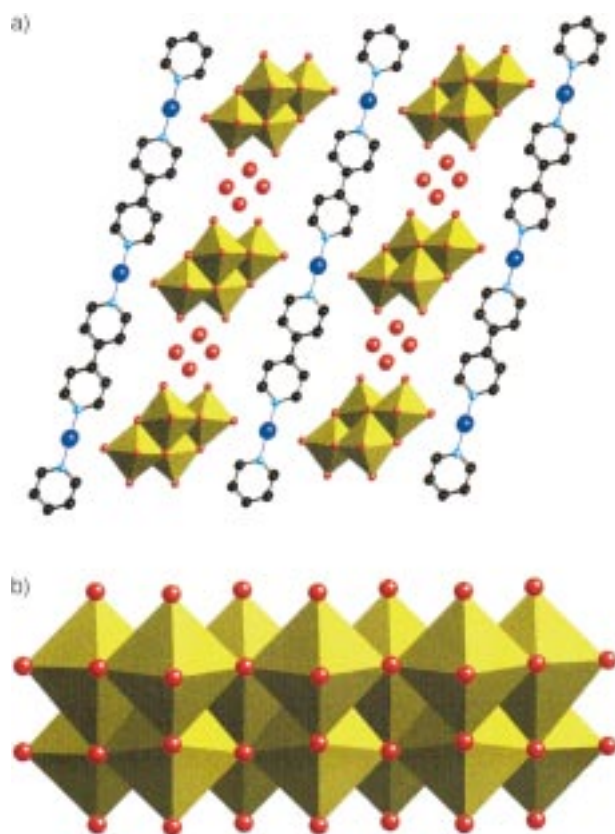


Figure 64. a) A view of the structure of **MOXI-16**, along the crystallographic *b* axis and parallel to the chain axis. b) A polyhedral view of the molybdenum oxide chain.

organic/inorganic composite layers; water molecules of crystallization occupy the interstrand region. It is noteworthy that the chain structure is not related to those previously described in Section 4.1.

An elaboration of structural types may be effected by modification of the nature of the organodiamine ligand. For example, exploitation of the chelating 2,2'-bipyridine in place of the bridging 4,4'-bipyridine resulted in the isolation of $[\text{Cu}(2,2'\text{-bpy})\text{Mo}_2\text{O}_7]$ (**MOXI-17**) and $[\text{Co}(2,2'\text{-bpy})\text{Mo}_3\text{O}_{10}]$ (**MOXI-18**).^[172] The structure of **MOXI-17** consists of a buckled one-dimensional molybdenum oxide chain linked to peripheral $\{\text{CuN}_2\text{O}_4\}$ octahedra (Figure 65). The $\{\text{Mo}_2\text{O}_7\}$ chain is constructed from edge-sharing $\{\text{MoO}_6\}$ octahedra and $\{\text{MoO}_5\}$ square pyramids. Each molybdenum octahedron shares common edges with a neighboring molybdenum octahedron, a molybdenum square pyramid, and two copper octahedra, and a common corner with one square-pyramidal unit. One square-pyramidal site engages in edge sharing with

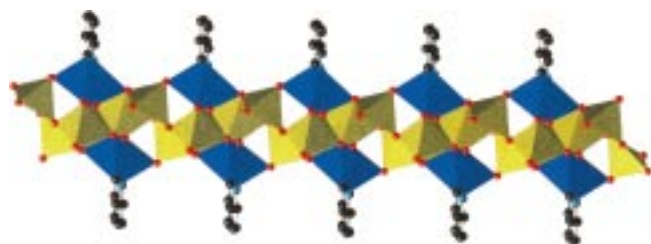


Figure 65. A view of the structure of **MOXI-17**.

an adjacent square pyramid and a molybdenum octahedron, and displays corner sharing with a second molybdenum octahedron and two $\{\text{CuN}_2\text{O}_4\}$ octahedra, while the second $\{\text{MoO}_5\}$ site exhibits edge sharing to a square-pyramidal and an octahedral molybdenum site, and corner-sharing to a $\{\text{MoO}_6\}$ site and a $\{\text{CuN}_2\text{O}_4\}$ octahedron. Consequently, each $\{\text{CuN}_2\text{O}_4\}$ unit links to four molybdenum polyhedra of the chain, to share four vertices in two edge and two corner interactions with the molybdenum sites. The folding of the molybdenum chain reflects the incorporation of the $\{\text{CuN}_2\text{O}_4\}$ units through four-point, two-edge attachments and illustrates the role of the M^{2+} site in defining chain geometry.

Since one-dimensional molybdenum oxide chains are a recurring theme in oxide structural chemistry, the incorporation of appropriate metal–ligand subunits should allow bridging in higher dimensional solids. The structure of **MOXI-18** (Figure 66) illustrates this point. The structure consists of one-dimensional molybdenum oxide chains, constructed of molybdenum tetrahedra, octahedra and square pyramids,

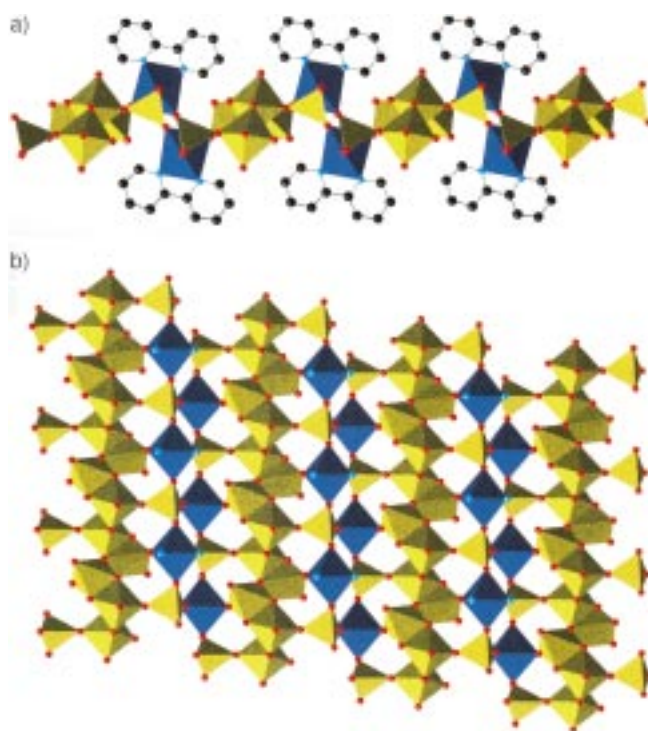


Figure 66. The structure of **MOXI-18** a) parallel to the two-dimensional net and b) normal to the layer. Co sites are blue; Mo sites are yellow.

linked through $\{\text{CoN}_2\text{O}_4\}$ octahedra into a two-dimensional covalent network. The oxide chain itself results from the edge-sharing of $\{\text{MoO}_6\}$ octahedra and $\{\text{MoO}_5\}$ square pyramids. The $\{\text{MoO}_4\}$ tetrahedra link to the chain through a single corner-sharing interaction, but bridge two $\{\text{CoN}_2\text{O}_4\}$ octahedra through two additional corner-sharing linkages. Each Co site is defined by the nitrogen donors of the 2,2'-bpy ligand and four oxygen donors from three $\{\text{MoO}_4\}$ groups and one $\{\text{MoO}_6\}$ octahedron. The overall structure may be described as folded chains of edge-sharing molybdenum polyhedra linked through double chains of alternating $\{\text{CoN}_2\text{O}_4\}$ octahedra and $\{\text{MoO}_4\}$ tetrahedra into a two-dimensional network.

Pyrimidine offers an intriguing ligand variant to the bridging bipyridine class of ligands in that the donor-to-donor distance is drastically reduced. The consequences of introducing pyrimidine into the Cu-molybdenum oxide chemistry are quite unanticipated. The structure of $[\text{Cu}_2(\text{pyrd})\text{Mo}_3\text{O}_{10}]$ (**MOXI-19**)^[182] is constructed from $\{\text{MoO}_6\}$ octahedra and $\{\text{CuO}_3\text{N}\}$ tetrahedra, which link to form a three-dimensional bimetallic oxide framework with channels occupied by the pyrimidine groups. As shown in Figure 67, the $\{\text{MoO}_6\}$ octahedra form a chain of edge-sharing polyhedra, structurally analogous to that observed for the one-dimensional

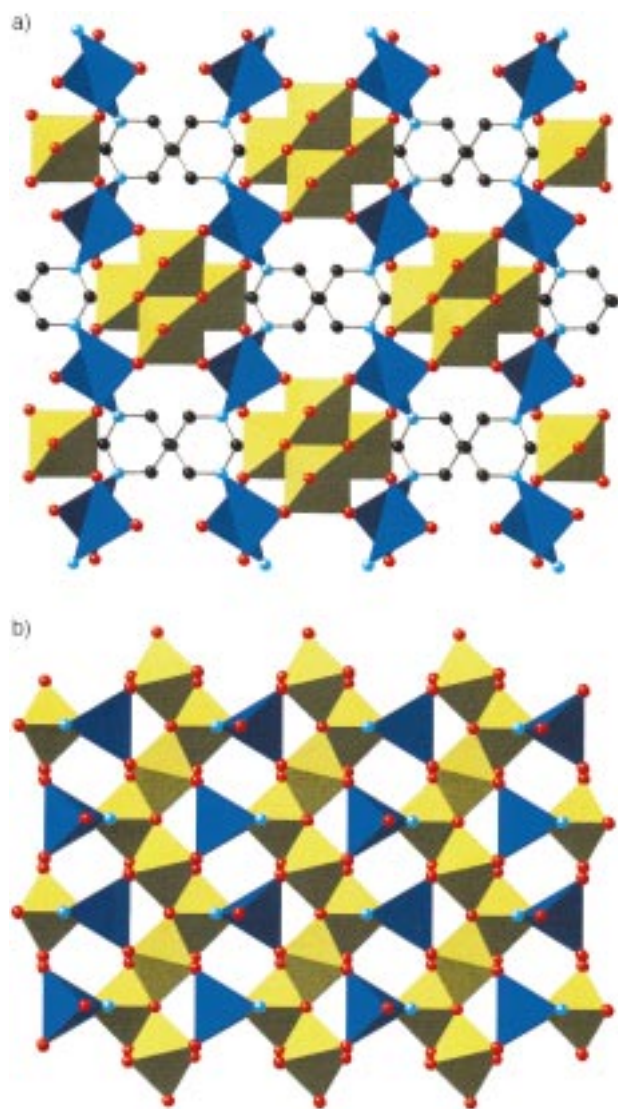


Figure 67. a) A view of the structure of **MOXI-19** to show the channels occupied by the pyrimidine groups. b) The linking of $\{\text{Mo}_3\text{O}_{10}\}^{2-}$ chains by $\{\text{Cu}(\text{pyrd})\}$ bridges.

$(\text{NH}_4)_2[\text{Mo}_3\text{O}_{10}]$. Each Cu site coordinates to two oxo groups of two Mo sites of one chain and bridges an adjacent chain by bonding to one oxo group. In addition, each Cu center coordinates to a nitrogen donor of a pyrimidine ligand, which serves to bridge to a second Cu site through its second nitrogen donor. When viewed along the crystallographic *a* axis, the Mo-oxide chains are linked through stacked $\{\text{CuO}_3\text{N}\}$

tetrahedra to produce channels of sufficient diameter to accommodate parallel stacks of pyrimidine groups.

It is noteworthy that crystals of **MOXI-19** are black, indicative of mixed valence; the only example to date for this class of materials. Valence sum calculations^[173, 184] provide an average oxidation state of +5.7 for the Mo sites; curiously, the Cu sites exhibit an average oxidation state of +1.5, which suggests extensive electronic delocalization.

A curious feature of the structural chemistry of molybdenum oxides with metal-dipodal organonitrogen ligand complex cations is the absence of three-dimensional cationic frameworks, despite the use of M^{II} sites with octahedral coordination preferences. One expedient for the construction of such three-dimensional cationic frameworks would appear to be the introduction of tripodal or higher denticity ligands with appropriate donor-group orientations. The expectation of a three-dimensional cationic framework has been realized by employing 1,2,4-triazole as the organic component in the isolation of $[\{\text{Cu}_2(\text{triazolate})_2(\text{H}_2\text{O})_2\}\text{Mo}_4\text{O}_{13}]$ (**MOXI-33**).^[187] As shown in Figure 68, the structure of **MOXI-33** consists of one-dimensional $\{\text{Mo}_4\text{O}_{13}\}_n^{2n-}$ chains entrained within the three-dimensional framework of the $\{\text{Cu}_2(\text{triazolate})_2(\text{H}_2\text{O})_2\}_n^{2n+}$ polymeric coordination cation. There are two unique copper sites in the cationic framework. One site, Cu(A), is effectively square pyramidal $\{\text{CuN}_4\text{O}\}$ through ligation to four triazolate nitrogen donors, one from each of four triazolate ligands and to a terminal oxo group of the molybdate chain. The second site, Cu(B), is octahedral $\{\text{CuN}_2\text{O}_4\}$, and exhibits coordination to two *trans* disposed triazolate nitrogen donors, two aqua ligands, and two terminal oxo groups of the molybdate chains. The organic moiety adopts the anionic triazolate form in a three-connected ligation mode. The resulting cationic framework is constructed from undulating chains of Cu(A) sites bridged through the 1,2-nitrogen donors of the triazolate ligands and linked to adjacent chains through the Cu(B) centers which coordinate to the remaining 4-position nitrogen donors of the triazolate ligands (Figure 68b). This connectivity pattern produces a honeycomb network when viewed along the crystallographic *c* axis. Furthermore, the disposition of bridging triazolate ligands about a chain results in linkage to four adjacent parallel chains giving rise to large tunnels which are occupied by the molybdate chains.

The undulating molybdate chain (Figure 68c) is constructed from edge-sharing molybdenum octahedra and tetrahedra. It is noteworthy that the polyhedral connectivity within these $\{\text{Mo}_4\text{O}_{13}\}_n^{2n-}$ chains is distinct from that reported for other one-dimensional molybdenum oxides: $\text{K}_2\text{Mo}_3\text{O}_{10}$, $(\text{NH}_4)_2\text{Mo}_3\text{O}_{10}$, $(\text{H}_3\text{NCH}_2\text{CH}_2\text{NH}_3)\text{Mo}_3\text{O}_{10}$, $[\text{H}_3\text{N}(\text{CH}_2)_6\text{NH}_3]\text{Mo}_3\text{O}_{10}$, $\text{Na}(\text{NH}_4)\text{Mo}_3\text{O}_{10}$, and $[\{\text{Cu}(4,4'\text{-bpy})\}_4\text{Mo}_{15}\text{O}_{47}]$.^[177] The chain structure conforms to the constraints imposed by the copper–triazolate framework and the coordination requirements of the Cu^{II} sites of the framework.

While it is tempting to classify the structural chemistry of **MOXI-33** in terms of “ship in the bottle” isolation of an oxide substructure within a rigid three-dimensional cationic framework, it is evident that this is a naive interpretation. Thus, $[\text{Cu}_2\text{Br}_2(\text{trz})]$,^[115] and $[\text{Cu}_3(\text{trz})_2\text{V}_4\text{O}_{12}]$ ^[150] exhibit distinctive coordination polymer substructures, as shown in Figure 69.

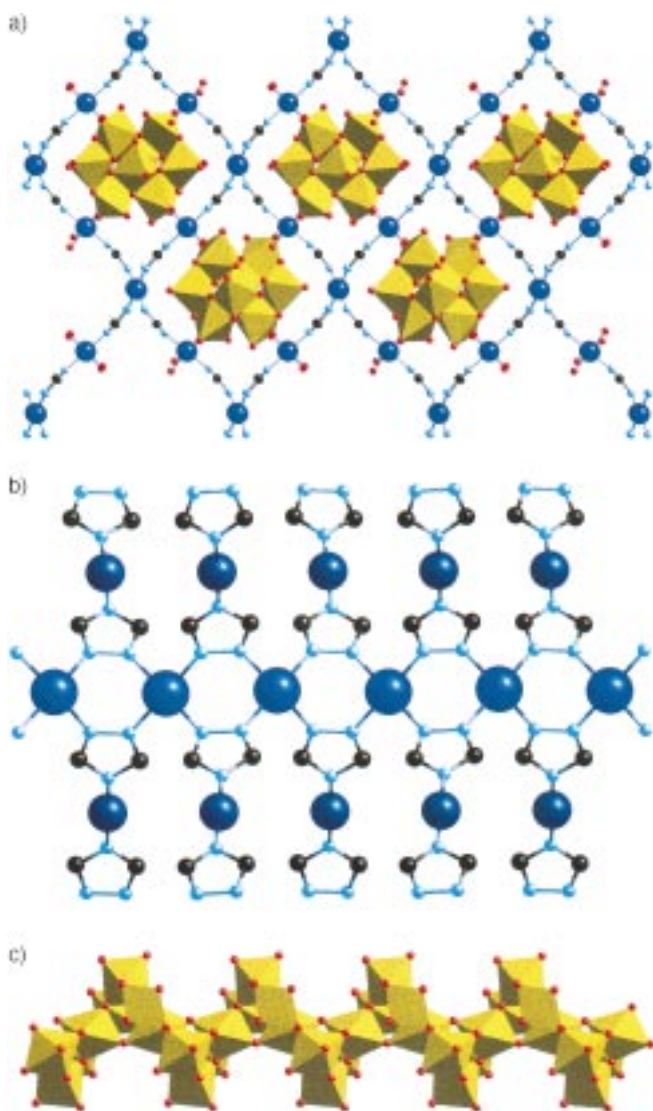


Figure 68. a) A view parallel to the molybdenum oxide chains of the structure of **MOXI-33**. b) A view of the $\{\text{Cu}_2(\text{triazolate})_2(\text{H}_2\text{O})_2\}_n^{2n+}$ substructure. c) A view of the molybdenum oxide chain.

This observation belies the construct in which the engineered polymeric coordination cation provides a rigid matrix for the manipulation of the metal oxide motif, but rather suggests a synergism between the oxide and cationic coordination complex polymer at the organic–inorganic interface.

4.3.3. Solids Constructed from “Isolated” $[\text{MoO}_4]^{2-}$ and $[\text{Mo}_2\text{O}_7]^{2-}$ Units Fused to Bridging Heterometal–Diamine Units

The solids of this subclass are distinguished by the absence of Mo–O–Mo bridging interactions or limitation to a single Mo–O–Mo bridge unit, requiring that structural propagation occur through $\text{M}'\text{–O–Mo}$ linkages. A simple prototype is provided by $[\text{Cu}(\text{o-phen})\text{MoO}_4]$ (**MOXI-20**; Figure 70). Two $[\text{MoO}_4]^{2-}$ tetrahedra and two $\{\text{CuO}_3\text{N}_2\}$ square pyramids form an eight-membered $\{\text{Mo}_2\text{Cu}_2\text{O}_4\}$ ring which propagates

through Cu–O–Mo linkages into a stepped one-dimensional chain.

The structural versatility of such one-dimensional motifs is illustrated by the structures of $[\text{MoO}_4\{\text{FeCl}(\text{2,2'}\text{-bpy})\}]$ (**MOXI-21**), $[\text{Mo}_3\text{O}_{12}\{\text{Fe}(\text{2,2'}\text{-bpy})\}_2] \cdot 0.25 \text{H}_2\text{O}$ (**MOXI-22**), and $[\text{Mo}_4\text{O}_{15}\{\text{Fe}(\text{2,2'}\text{-bpy})\}_2]$ (**MOXI-23**), which show the stepwise extension of chain repeat units by simple variations in reaction stoichiometries.

As shown in Figure 71, the structure of **MOXI-21** consists of one-dimensional chains comprised of $\{\text{FeClN}_2\text{O}_3\}$ octahedra and $\{\text{MoO}_4\}$ tetrahedra. Every iron octahedron corner shares through each of its oxygen atoms with an adjacent $\{\text{MoO}_4\}$ unit while each $\{\text{MoO}_4\}$ unit serves to bridge three iron octahedra. The terminal chlorides on the iron sites alternate such that two adjacent $\{\text{FeClN}_2\text{O}_3\}$ octahedra will have their chloride substituents oriented to opposite sides of the chain.

The structure of **MOXI-22** consists of chains constructed from $\{\text{FeN}_2\text{O}_4\}$ octahedra and $\{\text{MoO}_4\}$ tetrahedra. In the case of **MOXI-21**, all adjacent iron octahedra are linked through two $\{\text{MoO}_4\}$ tetrahedra. In contrast, in **MOXI-22** there are additional corner-sharing interactions between pairs of adjacent $\{\text{FeN}_2\text{O}_4\}$ octahedra and an additional $\{\text{MoO}_4\}$ tetrahedron. Consequently, adjacent pairs of $\{\text{FeN}_2\text{O}_4\}$ octahedra are linked through three $\{\text{MoO}_4\}$ tetrahedra. These units comprise two iron centers and three molybdenum centers and are then linked to a neighboring $\{\text{Fe}_2\text{Mo}_3\}$ unit by two corner-sharing interactions. Thus, the connectivity of adjacent iron sites in the chain alternates between linkage through three $\{\text{MoO}_4\}$ tetrahedra and linkage through two $\{\text{MoO}_4\}$ tetrahedra. The orientations of the additional $\{\text{MoO}_4\}$ units in **MOXI-22** with respect to the chain structure of **MOXI-21** alternate to occupy opposite sides of the chain.

MOXI-23 exhibits a one-dimensional structure very similar to that observed for **MOXI-22**. In the case of **MOXI-23**, however, the adjacent iron centers are bridged by two $\{\text{MoO}_4\}$ units and an $\{\text{Mo}_2\text{O}_7\}$ unit, while **MOXI-22** exhibits bridging through $\{\text{MoO}_4\}$ tetrahedra, exclusively. Adjacent $\{\text{Mo}_2\text{O}_7\}$ units in **MOXI-23** alternate to occupy opposite sides of the chain. The length of the $\{\text{Mo}_2\text{O}_7\}$ unit and the constraints thus imposed on the $\{\text{FeN}_2\text{O}_4\}$ units that it bridges perturb the structure of the one-dimensional chains with respect to the chains of **MOXI-22**.

As a common motif, **MOXI-21–23** all share a four-polyhedral ring which consists of two $\{\text{MoO}_4\}$ tetrahedra and two $\{\text{FeXN}_2\text{O}_3\}$ ($\text{X} = \text{Cl}$ for **MOXI-21**, O for **MOXI-22** and **MOXI-23**) octahedra. These polyhedra corner-share such that each molybdenum center serves to bridge two iron octahedra in the ring. Attachment to the next such four-ring is through the third corner-sharing interaction of each molybdenum tetrahedron. As the additional $\{\text{MoO}_4\}$ or $\{\text{Mo}_2\text{O}_7\}$ linkages are incorporated in **MOXI-22** and **MOXI-23**, the basic four-ring remains intact. However, the two iron centers in the four-polyhedra ring are now additionally linked through the aforementioned $\{\text{MoO}_4\}$ or $\{\text{Mo}_2\text{O}_7\}$ moieties. Thus, bridging of adjacent iron octahedra in **MOXI-22** and **MOXI-23** alternates between two molybdenum tetrahedra and either three molybdenum tetrahedra or two molybdenum tetrahedra and one dimolybdate bi-tetrahedral unit, respectively.

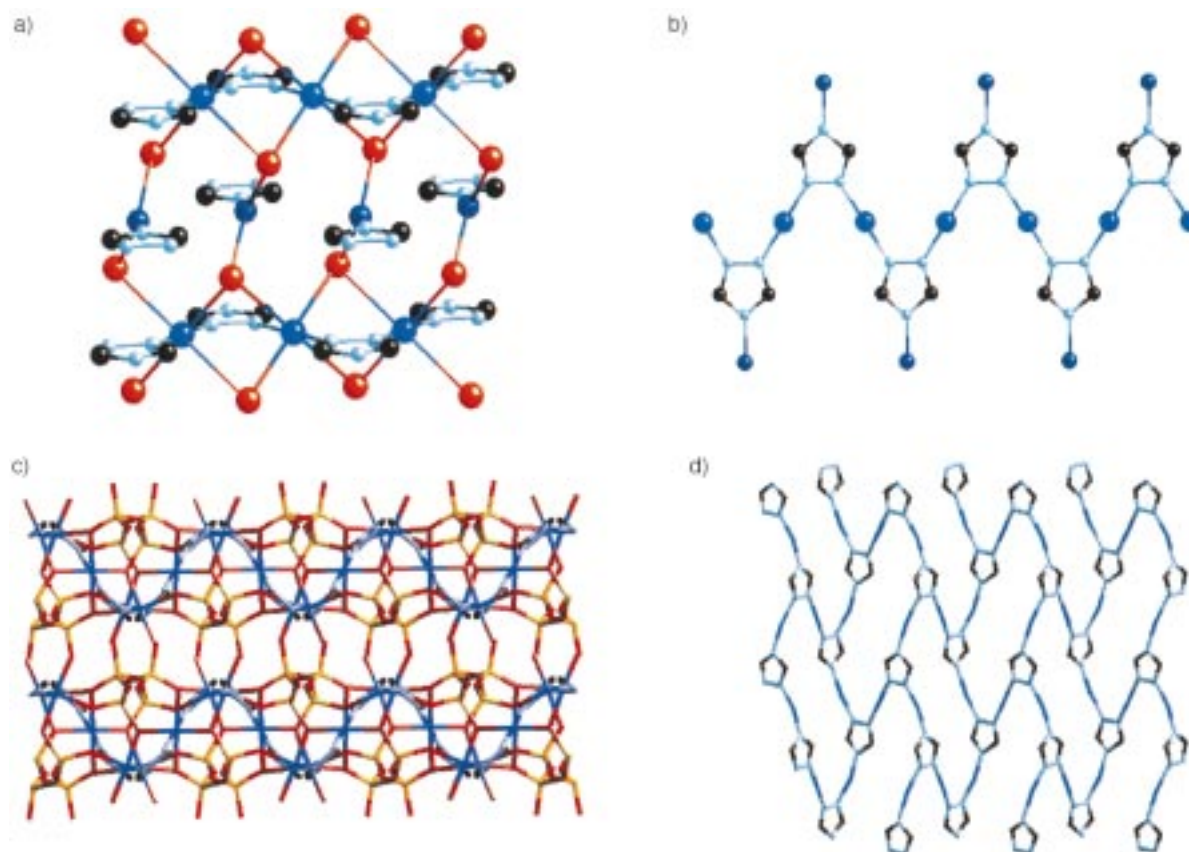


Figure 69. a) The structure of $[\text{Cu}_2\text{Br}_2(\text{trz})]$. b) The copper–triazolate one-dimensional substructure of $[\text{Cu}_2\text{Br}_2(\text{trz})]$. c) The structure of $[\text{Cu}_3(\text{trz})_2\text{V}_4\text{O}_{12}]$. d) The copper–triazolate two-dimensional substructure of $[\text{Cu}_3(\text{trz})_2\text{V}_4\text{O}_{12}]$.

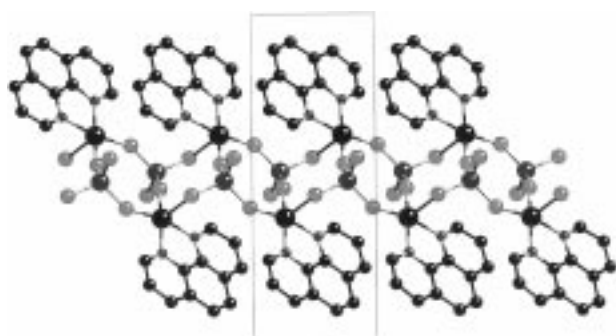


Figure 70. The structure of **MOXI-20**.

The final examples again illustrate the exploitation of bridging organodiamine ligands of significantly different donor-to-donor extension in providing structures with distinctive $\text{M}'\text{-O-Mo}$ arrays. As shown in Figure 72, the structure of $[\text{Cu}(\text{bpa})_{0.5}\text{MoO}_4]$ (**MOXI-24**) consists of $\{\text{CuMoO}_4\}$ bi-metallic oxide layers covalently linked through bpa ligands into a three-dimensional framework. The structure exhibits the pattern of alternating organic–inorganic regions characteristic of the metal–organophosphate phases.^[44] The inorganic layer is constructed from $\{\text{MoO}_4\}$ tetrahedra and $\{\text{CuO}_5\text{N}\}$ octahedra which form double chains linked through $\{\text{Cu-O-Mo}\}$ bridges into a two-dimensional network. One Cu site forms corner-sharing interactions with five adjacent Mo sites of the chain, while the second Cu site forms four corner-

sharing linkages to Mo chain sites and one to an Mo site of an adjacent chain. In addition, the two unique Cu sites form a binuclear edge-sharing unit through a $\{\text{Cu}_2\text{O}_2\}$ interaction. One Mo site bridges three Cu binuclear units of a given chain and provides linkage to an adjacent chain through its fourth oxo group. The second Mo site bridges three Cu binuclear units of the chain and projects a terminal oxo group into the interlamellar region.

In comparing **MOXI-24** to $[\text{Cu}(\text{bpe})\text{MoO}_4]$ (**MOXI-1**), the influence of ligand types on oxide structure is revealed. In contrast to **MOXI-1**, which contains $\{\text{Cu-bpe-Cu}\}$ chains with $\{\text{CuO}_4\text{N}_2\}$ coordination geometry, **MOXI-24** exhibits $\{\text{Cu-bpa-Cu}\}$ binuclear units; that is, there is no $\{\text{Cu-diamine-Cu}\}$ chain propagation and the coordination geometry is $\{\text{CuO}_5\text{N}\}$. As shown in Figure 49, the layer structure adopted by **MOXI-1** consists of simple $\{\text{Cu}_3\text{Mo}_3\text{O}_6\}$ fused rings rather than the more complex connectivity enjoyed by **MOXI-24**. The consequences of ligand geometry are also manifest in the packing diagrams for **MOXI-1** and **MOXI-24**, shown in Figures 49 and 72, respectively.

Two contrasting geometric features of the ligands bpa and bpe are evident: the angles between the donor groups and the Cu–Cu distances imposed by linker length, 11.74 Å and 13.56 Å for **MOXI-24** and **MOXI-1**, respectively. To assess the influence of donor-group separation on structure, the oxide $[\text{Cu}(\text{pz})_{0.5}\text{MoO}_4]$ (**MOXI-25**) was prepared. The structure consists of a complex three-dimensional bimetallic oxide with channels occupied by the pyrazine ligand (Figure 73). The

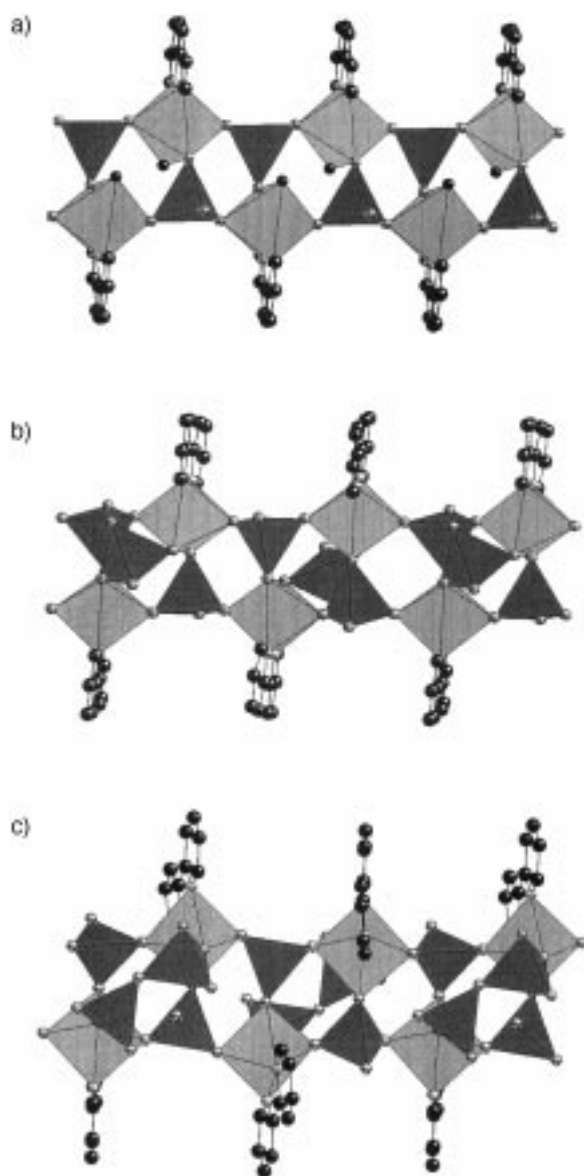


Figure 71. The chain structures of a) **MOXI-21**, b) **MOXI-22**, and c) **MOXI-23**.

structure is constructed from corner-sharing $\{\text{MoO}_4\}$ tetrahedra and $\{\text{CuO}_4\text{N}\}$ square pyramids, which form chains of stacked $\{\text{Cu}_2\text{Mo}_2\text{O}_4\}$ rings. Each Mo site links three adjacent Cu sites of a chain and employs the fourth oxo group to connect to an adjacent chain. Four adjacent chains are linked to form a cavity occupied by the pyrazines which serve to ligate to Cu sites of opposite chains.

5. Conclusions

Organodiamine-templated metal oxides represent a new class of materials in which an organic component exerts a crucial role in dictating the inorganic oxide microstructure. While in other examples of organic–inorganic hybrid materials, such as zeolites, MCM-41 type mesoporous materials, and TMPO's, the organic component adopts the role of charge-compensating and space-filling counterion for the negatively

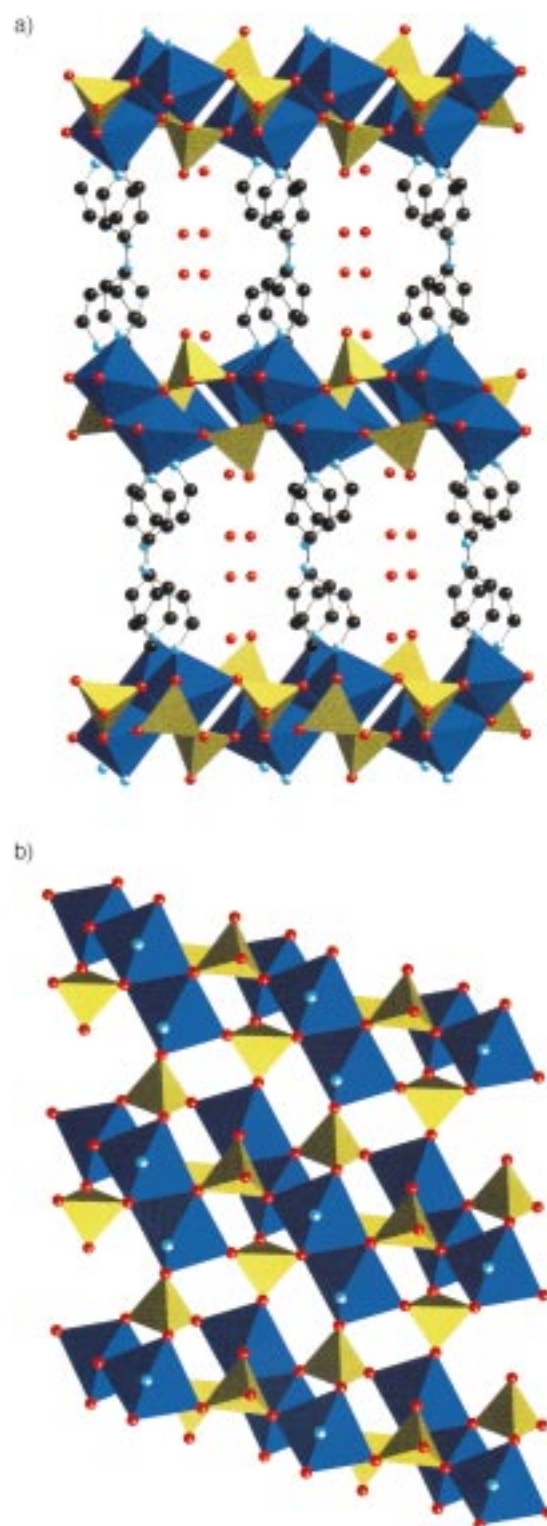


Figure 72. a) A view of the covalently linked three-dimensional structure of **MOXI-24**, showing the ligand bridging of $[\text{CuMoO}_4]$ layers. b) The $[\text{CuMoO}_4]$ layer structure of **MOXI-24**.

charged metal oxide skeleton, the organic components of the molybdenum oxide class manifest a variety of structural roles, including templating, tethering of functional groups, passivation of metal coordination spheres to produce low-dimensionality materials, and imprinting of structural information upon thermal removal.

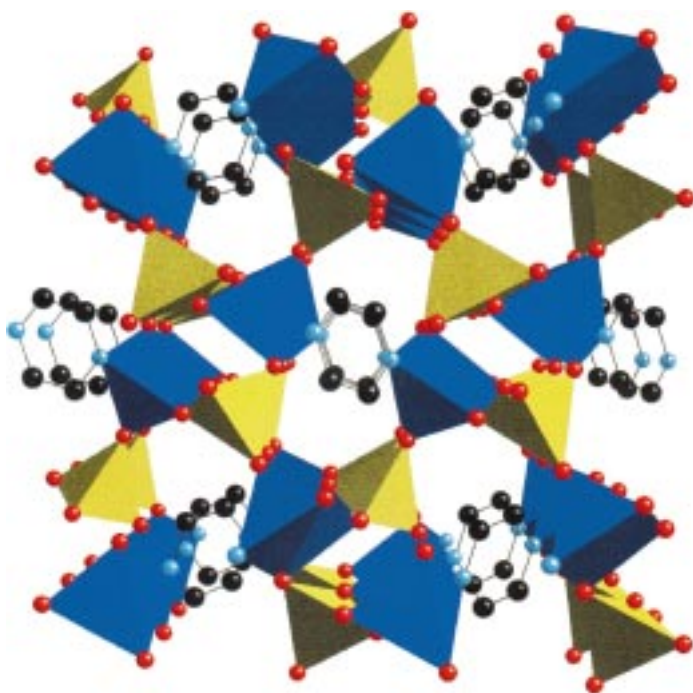


Figure 73. A view of the structure of **MOXI-25**, showing the channels occupied by the pyrazine ligands.

Of the three subclasses of organodiamine-molybdenum oxide solids, those based on the organodiamine as protonated cation and on direct ligation of the organodiamine to the oxide skeleton reflect the common modes of incorporation of organodiamines into coordination chemistry in general and are not unanticipated. The MOXI structures characterized by organodiammonium cations exhibit one- and two-dimensional structures, an observation consistent with the routine occurrence of low-dimensional structures in the inorganic molybdenum oxide chemistry. Such organic cation templated materials also reveal the structural role of multipoint hydrogen bonding and of the partitioning of the solid into polar and nonpolar domains. While the number of examples is too limited to draw general conclusions, it does appear that organodiammonium cations with alkyl backbones favor one-dimensional structures, while those with aromatic linkers provide layered network structures. This observation may reflect the greater facility for intercalation between oxide layers of flat aromatic residues which would favor two-dimensional structures, while the more effective multipoint hydrogen bonding propensities of the aliphatic NH_3^+ terminus, in contrast to the iminium $\text{RR}'\text{R}''\text{NH}^+$ terminus of the aromatic organoamines, might serve to disrupt propagation of oxide bridging interactions in more than one dimension.

The consequences of ligation of organodiamine groups directly to the molybdenum oxide skeleton are apparent in the passivation of the oxide surface, which again results in low-dimensionality oxide substructures. However, the influences of ligand geometry are also manifest in this small group of materials. Chelating bipyridyl ligands, such as 2,2'-bpy, by blocking two coordination sites on the same metal center and subtending a large volume of the coordination sphere with the organic residue passivate the metal toward oxide bridging in

more than one dimension. In contrast, when the ligand geometry enforces a bridging modality on the nitrogen donors, more complex structures are observed, such as the hydrogen-bonded sheetlike structure of $[\text{Mo}_4\text{O}_{13}(\text{Hbpa})_2]$ (**MOXI-7**) and the organically buttressed two-dimensional molybdenum oxide structure of $[\text{MoO}_3(4,4'\text{-bpy})_{0.5}]$ (**MOXI-8**).

The subclass of organodiamine-molybdenum oxides incorporating cationic coordination polymers is a natural evolution of the recent dramatic developments in the designed synthesis of coordination polymers through the propagation of structural characteristics by tethered donors of fixed geometries. The brief introduction to the organodiamine coordination polymers in Section 3 of this review reveals a remarkably diverse structural chemistry which reflects a number of characteristics including tether length and geometry, the disposition of the donor groups, the presence of additional functional groups, the coordination preferences of the metal and its oxidation state, and the role of the anion. While this latter influence has often been overlooked, it is manifest in the contrasting structures of $[\text{Ag}(\text{pytz})(\text{MeCN})](\text{PF}_6)$ and $[\text{Ag}(\text{pytz})(\text{NO}_3)]$ and in the structural role of the coordinating sulfate oxoanions in the structures of **CUSO 1–3**. Molybdate, whether as monomeric $[\text{MoO}_4]^{2-}$ or as oligomeric $[\text{Mo}_x\text{O}_y]^{2-}$ or as one- or two-dimensional networks, may be considered a charge-balancing anion for the cationic coordination polymer. The two component units would seem ideally suited for the preparation of new complex ionic materials.

A consistent feature of the MOXI materials of this subclass is the absence of interpenetration of coordination polymer frameworks, a characteristic attribute of coordination polymer structures with “innocent” anions. The exclusion of interpenetration of polymer units in the MOXI materials reflects both the effective space-filling role of the molybdenum oxide anion component and ligation of the oxide to the coordination polymer through bridging oxo group interactions. Such interactions can be relatively weak, as in the case of $[\text{Cu}(4,4'\text{-bpy})]_4[\text{Mo}_{15}\text{O}_{47}]$ where the distinctiveness of the coordination polymers and molybdenum oxide chains is evidently maintained, or quite strong as for $[\text{Cu}(\text{bpe})\text{MoO}_4]$, where the Cu^{II} centers have been intimately incorporated into the bimetallic oxide layer.

While both ligand geometry and the coordination preferences of the heterometal play a structural role, it is premature to offer more than a tentative analysis of their influences on the synthetic design. Extension of the spacer between nitrogen donors may favor layer structures. The structures of both $[\text{Cu}(\text{bpe})\text{MoO}_4]$ and $[\text{Cu}(\text{bpa})_{0.5}\text{MoO}_4]$ exhibit the characteristic pattern of metal oxide sheets alternating with organic tethers, a motif shared by metal organodiphosphonates, $[\text{M}_x(\text{O}_3\text{P-linker-PO}_3)_y]$.^[185] Such partitioning into polar and nonpolar domains appears to be a structural characteristic of such hybrid materials.

Of course, an obvious expedient is to minimize the distance between donors, as in pyrazine or pyrimidine. The structural chemistry is now quite different from that observed for copper-pyrazine and copper-pyrimidine with conventional anions, reviewed in Section 3.5. The structures of $[\text{Cu}(\text{pz})_{0.5}\text{MoO}_4]$ (**MOXI-25**) and $[\text{Cu}_2(\text{pyrd})\text{Mo}_3\text{O}_{10}]$ (**MOXI-19**) do

not possess cationic coordination polymer subunits but rather exhibit incorporation of the copper into the three-dimensional copper-molybdate framework with the organic component occupying well-defined channels in the framework. It may be that sterically less demanding organic components can be more readily accommodated in the void volumes of three-dimensional frameworks, whereas extended rodlike tethers dictate two dimensional networks or discrete coordination polymer substructures. As evidenced by the structures of $[\text{Cu}_2\text{Br}_2(\text{trz})]$, $[\text{Cu}_3(\text{trz})_2\text{V}_4\text{O}_{12}]$, and $[\{\text{Cu}_2(\text{trz})_2(\text{H}_2\text{O})_2\}\text{Mo}_4\text{O}_{13}]$, the anionic component of these materials is not simply a “clay” to be molded by the engineered polymer substructure, but rather exerts a pronounced influence on the cationic substructure. The synergistic relationship between the substructures of these composite oxide materials belies a simple “ship in the bottle” approach to their design and reveals a complex chemistry at the organic–inorganic interface. This observation suggests that predictability of detailed structural features in the designed synthesis of such materials will continue to prove problematic.

The current interest in inorganic solid-state materials reflects useful properties derived from molecular recognition which result in applications to sorption, catalysis, molecular electronics, and optical systems. Molecular recognition in the sense of appropriate juxtaposition of functional groups for reactivity and cooperative electronic effects is often related to the periodicity of the crystalline state. These considerations render the pursuits of designed synthesis and crystal engineering quite attractive. While completely predictable design remains elusive, the introduction of organodiamine components has allowed us to fashion a new class of composite materials with novel two- and three-dimensional bimetallic oxide structures with channels and cavities whose dimensions are dictated by the geometry of the organodiamine.

However, it is also evident that the synthesis of the MOXI family of materials has achieved at best a primitive degree of design and predictability. Such composite materials are complex, possessing an interactive structural hierarchy. Furthermore, in addition to this spatial hierarchy, such materials are generally metastable kinetic phases requiring a shift in paradigm from the thermodynamic to the kinetic domain. This intrinsic dynamic nature of such materials further enhances their essential complexity. Such complexity sets limits on the degree of predictability.^[186] Arguably, design does not require total predictability, but rather an appreciation of the reciprocity of structure–function relationships. This suggests that as the products of empirical development are unravelled, control of desired properties will be achieved.

The evolution of the MOXI family of materials will require continued definition of the chemical possibilities. These include not only the roles of ligand geometries and heterometal coordination preferences but a systematic investigation of the vast hydrothermal parameter space, which includes factors such as pH value, stoichiometries, temperature, fill volume, and sacrificial precursors. As the data base for these materials expands, the synthetic and structural patterns will emerge as well as an appreciation for the structure–function relationships of this family of oxides.

This work was supported by NSF Grant CHE9617232. We also thank the Keck Foundation for partial funding of the X-ray crystallographic laboratory.

Received: June 8, 1998

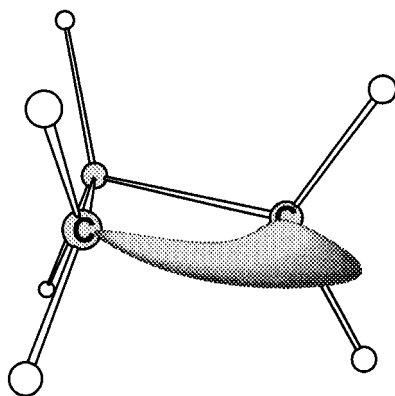
Supplemented version: October 19, 1998 [A285IE]

German version: *Angew. Chem.* **1999**, *111*, 2798–2848

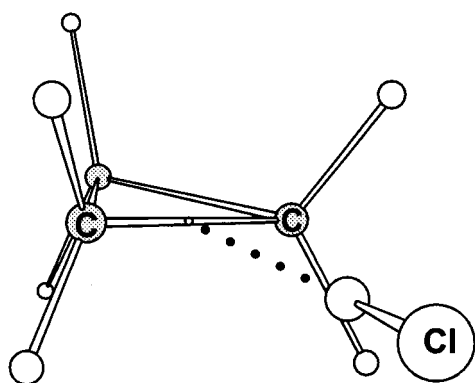
- [1] N. N. Greenwood, A. Earnshaw, *Chemistry of the Elements*, Pergamon Press, New York, **1984**.
- [2] “Inorganic Biomaterials”: L. L. Hench in *Materials Chemistry, An Emerging Discipline, Ser. 245* (Eds.: L. V. Interrante, L. A. Casper, A.-B. Ellis), American Chemical Society, **1995**, chap. 21, pp. 523–547.
- [3] B. Mason, *Principles of Geochemistry*, 3rd ed., Wiley, New York, **1966**.
- [4] S. Mann, *J. Chem. Soc. Dalton Trans.* **1993**, 1.
- [5] S. Mann, S. L. Burkett, S. A. Davis, C. E. Fowler, N. H. Mendelson, S. D. Sims, D. Walsh, N. T. Whilton, *Chem. Mater.* **1997**, *9*, 2300.
- [6] A. F. Wells, *Structural Inorganic Chemistry*, 4th ed., Oxford University Press, Oxford, **1975**.
- [7] T. G. Reynolds, R. C. Buchanan in *Ceramic Materials for Electronics* (Ed.: R. C. Buchanan), 2nd ed., Dekker, New York, **1991**, p. 207.
- [8] W. Büchner, R. Schliebs, G. Winter, K. H. Büchel, *Industrial Inorganic Chemistry*, VCH, New York, **1989**.
- [9] W. H. McCarroll in *Encyclopedia of Inorganic Chemistry*, Vol. 6 (Ed.: R. B. King), Wiley, New York, **1994**, p. 2903.
- [10] G. H. Hartling in *Ceramic Materials for Electronics* (Ed.: R. C. Buchanan), 2nd ed., Dekker, New York, **1991**, p. 129.
- [11] H. W. Leverenz, *Luminescence of Solids*, Wiley, New York, **1980**.
- [12] R. Einzinger, *Annu. Rev. Mater. Sci.* **1987**, *17*, 299.
- [13] J. M. Tarascon, P. Barboux, P. F. Miceli, L. H. Greene, G. W. Hull, M. Eibschutz, S. A. Sunshine, *Phys. Rev. B* **1988**, *37*, 7458.
- [14] D. I. Makin in *Modern Oxide Materials* (Eds.: B. Cockayne, D. W. Jones), Academic Press, New York, **1972**, p. 235.
- [15] C. N. R. Rao, K. J. Rao in *Solid State Compounds* (Eds.: A.-K. Cheetham, P. Day), Clarendon Press, Oxford, **1992**, p. 281.
- [16] J. D. Bierlein, C. B. Arweiler, *Appl. Phys. Lett.* **1987**, *49*, 917.
- [17] G. Centi, F. Trifuro, J. R. Ebner, V. M. Franchetti, *Chem. Rev.* **1988**, *88*, 55.
- [18] R. K. Grasselli, *Appl. Catal.* **1985**, *15*, 127.
- [19] M. Gasior, I. Gasior, B. Grzybowska, *Appl. Catal.* **1984**, *10*, 87.
- [20] T. Okuhara, M. Misono in *Encyclopedia of Inorganic Chemistry*, Vol. 6 (Ed.: R. B. King), Wiley, New York, **1994**, p. 2889.
- [21] H. Niiyama, E. Echigoya, *Bull. Chem. Soc. Jpn* **1972**, *45*, 655.
- [22] T. Yamaguchi, *Appl. Catal.* **1990**, *61*, 1.
- [23] A. Clearfield, *Chem. Rev.* **1988**, *88*, 125.
- [24] J. M. Newsam in *Solid State Compounds* (Eds.: A.-K. Cheetham, P. Day), Clarendon Press, Oxford, **1992**, p. 234.
- [25] D. M. Ruthven, *Principles of Absorption and Adsorption Processes*, Wiley-Interscience, New York, **1984**.
- [26] R. Szostak, *Molecular Sieves—Principles of Synthesis and Identification*, Van Nostrand Reinhold, New York, **1988**.
- [27] J. A. Raleo, *Zeolite Chemistry and Catalysis*, ACS Monograph (7), American Chemical Society, Washington, DC, **1976**.
- [28] *New Developments in Zeolite Science* (Eds.: Y. Murakami, A. Iijima, J. W. Ward), Elsevier, Amsterdam, **1986**.
- [29] D. E. W. Vaughan, *Properties and Applications of Zeolites*, (Ed.: R. P. Townsend), The Chemical Society, London, **1979**, p. 294 (Chem. Soc. Special Publ. No. 33).
- [30] S. I. Stupp, P. V. Braun, *Science* **1997**, *277*, 1242.
- [31] C. M. Zaremba, A. M. Belcher, M. Fritz, Y. Li, S. Mann, P. K. Mansma, D. E. Morse, J. S. Speck, G. D. Stucky, *Chem. Mater.* **1996**, *8*, 679.
- [32] J. V. Smith, *Chem. Rev.* **1988**, *88*, 149.
- [33] M. L. Occelli, H. C. Robson, *Zeolite Synthesis*, American Chemical Society, Washington, DC, **1989**.
- [34] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710.
- [35] S. Mann, *Nature* **1993**, *365*, 499.

- [36] R. C. Haushalter, L. A. Mundi, *Chem. Mater.* **1992**, *4*, 31.
- [37] M. I. Khan, L. M. Meyer, R. C. Haushalter, C. L. Schweitzer, J. Zubieta, J. L. Dye, *Chem. Mater.* **1996**, *8*, 43.
- [38] S. Mann, G. Ozin, *Nature* **1996**, 382, 313.
- [39] J. C. MacDonald, G. M. Whitesides, *Chem. Rev.* **1994**, *94*, 2383.
- [40] R. M. Barrer, *Hydrothermal Chemistry of Zeolites*, Academic Press, New York, **1982**.
- [41] J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, R. D. Schmitt, C. T.-W. Chen, D. H. Olson, E. W. Sheppard, S. B. McCullen, J. B. Higgins, J. L. Schlenker, *J. Am. Chem. Soc.* **1992**, *114*, 10834.
- [42] R. C. Haushalter, K. G. Strohmaier, F. W. Lai, *Science* **1989**, *246*, 1289.
- [43] C. Warren, R. C. Haushalter, J. Zubieta, unpublished results.
- [44] M. I. Khan, J. Zubieta, *Prog. Inorg. Chem.* **1995**, *43*, 1.
- [45] A. Rabenau, *Angew. Chem.* **1985**, *97*, 1017; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1026.
- [46] R. A. Laudise, *Chem. Eng. News* **1987**, 65(39), 30.
- [47] J. Gopalakrishnan, *Chem. Mater.* **1995**, *7*, 1265.
- [48] V. Soghomonian, Q. Chen, R. C. Haushalter, J. Zubieta, C. J. O'Connor, Y.-S. Lee, *Chem. Mater.* **1993**, *5*, 1690.
- [49] M. I. Khan, Y.-S. Lee, C. J. O'Connor, R. C. Haushalter, J. Zubieta, *Chem. Mater.* **1994**, *6*, 721.
- [50] M. I. Khan, R. C. Haushalter, C. J. O'Connor, J. Zubieta, *Chem. Mater.* **1995**, *7*, 593.
- [51] Y. Zhang, J. R. D. DeBord, C. J. O'Connor, R. C. Haushalter, G. Clearfield, J. Zubieta, *Angew. Chem.* **1996**, *108*, 1067; *Angew. Chem. Int. Ed. Engl.* **1996**, *33*, 989.
- [52] M. J. Zaworotko, *Chem. Soc. Rev.* **1994**, *23*, 283.
- [53] M. Fujita, Y. J. Kwon, S. Washizu, K. Ogura, *J. Am. Chem. Soc.* **1994**, *116*, 1151.
- [54] "Supramolecular Architecture" (Ed.: T. Bein): *ACS Symp. Ser.* **1992**, 499.
- [55] O. Ermer, *Adv. Mater.* **1991**, *3*, 608.
- [56] K. Inoue, T. Hayamizu, H. Iwamura, D. Hashizume, Y. Ohashi, *J. Am. Chem. Soc.* **1996**, *118*, 1803.
- [57] R. Robson in *Comprehensive Supramolecular Chemistry*, Vol. 6 (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, J.-M. Lehn), Pergamon, New York, **1996**, p. 733.
- [58] G. R. Desiraju, *Crystal Engineering. The Design of Organic Solids*, Elsevier, Amsterdam, **1989**.
- [59] M. C. Etler, *Acc. Chem. Res.* **1990**, *23*, 120.
- [60] J. M. Lehn, *Pure Appl. Chem.* **1994**, *66*, 1961.
- [61] T. Iwamoto in *Comprehensive Supramolecular Chemistry*, Vol. 6 (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, J.-M. Lehn), Pergamon, New York, **1996**, p. 643.
- [62] B. F. Abrahams, B. F. Hoskins, D. Michail, R. Robson, *Nature* **1994**, *369*, 727.
- [63] A. J. Blake, S. J. Hill, P. Hubberstey, W.-S. Li, *J. Chem. Soc. Dalton Trans.* **1997**, 913.
- [64] M.-X. Li, G.-Y. Xie, Y.-D. Gu, J. Chen, P.-J. Zheng, *Polyhedron* **1995**, *14*, 1235.
- [65] X.-M. Chen, M.-L. Tong, Y.-J. Luo, Z.-N. Chen, *Aust. J. Chem.* **1996**, *49*, 835.
- [66] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Chem. Soc. Dalton Trans.* **1997**, 1801.
- [67] A. S. Batsanov, M. J. Begley, P. Hubberstey, J. Stroud, *J. Chem. Soc. Dalton Trans.* **1996**, 1947.
- [68] P. Losier, M. J. Zaworotko, *Angew. Chem.* **1996**, *108*, 2957; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2779.
- [69] O. M. Yaghi, H. Li, T. L. Groy, *Inorg. Chem.* **1997**, *36*, 4292.
- [70] N. Masciocchi, P. Cairati, L. Carlucci, G. Mezza, G. Ciani, A. Sironi, *J. Chem. Soc. Dalton Trans.* **1996**, 2739.
- [71] a) F. Robinson, M. J. Zaworotko, *J. Chem. Soc. Chem. Commun.* **1995**, 2413; b) O. M. Yaghi, H. Li, *J. Am. Chem. Soc.* **1996**, *118*, 295.
- [72] D. Hargman, R. P. Hammond, R. C. Haushalter, J. Zubieta, *Chem. Mater.* **1998**, *10*, 2091.
- [73] A. J. Blake, S. J. Hill, P. Hubberstey, W.-S. Li, *J. Chem. Soc. Dalton Trans.* **1998**, 909.
- [74] M. Fujita, Y. J. Kwon, S. Washizu, K. Ogura, *J. Am. Chem. Soc.* **1994**, *116*, 1151.
- [75] R. W. Gable, B. F. Hoskins, R. Robson, *J. Chem. Soc. Chem. Commun.* **1990**, 1677.
- [76] S. Subramanian, M. J. Zaworotko, *Angew. Chem.* **1995**, *107*, 2295; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2127.
- [77] J. Li, H. Zeng, J. Chen, Q. Wang, X. Wu, *Chem. Commun.* **1997**, 1213.
- [78] M. Kondo, T. Yoshitomi, K. Seki, H. Matsuzaka, S. Kitagawa, *Angew. Chem.* **1997**, *109*, 1844; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1725.
- [79] O. M. Yaghi, G. Li, *Angew. Chem.* **1995**, *107*, 232; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 207.
- [80] M.-L. Tong, B.-H. Ye, J.-W. Cai, X.-M. Chen, S. W. Ng, *Inorg. Chem.* **1998**, *37*, 2645.
- [81] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Chem. Soc. Chem. Commun.* **1994**, 2755.
- [82] L. R. MacGillivray, S. Subramanian, M. J. Zaworotko, *J. Chem. Soc. Chem. Commun.* **1994**, 1325.
- [83] S. Lopez, M. Kahraman, M. Harmata, S. W. Keller, *Inorg. Chem.* **1997**, *36*, 6138.
- [84] O. M. Yaghi, H. Li, *J. Am. Chem. Soc.* **1995**, *117*, 10401.
- [85] A. J. Blake, N. R. Champness, A. Khlobystov, D. A. Lemenovskii, W.-S. Li, M. Schröder, *Chem. Commun.* **1997**, 2027.
- [86] M. Fujita, Y. J. Kwon, O. Sasaki, K. Yamaguchi, K. Ogura, *J. Am. Chem. Soc.* **1995**, *117*, 7287.
- [87] L. Carlucci, G. Ciani, D. W. v. Gudenberg, D. M. Proserpio, *Inorg. Chem.* **1997**, *36*, 3812.
- [88] T. L. Hennigar, D. C. MacQuarie, P. Losier, R. D. Rogers, M. J. Zaworotko, *Angew. Chem.* **1997**, *109*, 1044; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 972.
- [89] M. Fujita, Y. J. Kwon, M. Miyazawa, K. Ogura, *J. Chem. Soc. Chem. Commun.* **1994**, 1977.
- [90] L. Carlucci, G. Ciani, P. Macchi, D. M. Proserpio, *Chem. Commun.* **1998**, 1837.
- [91] M. A. Withersby, A. J. Blake, N. R. Champness, P. Hubberstey, W.-S. Li, M. Schröder, *Angew. Chem.* **1997**, *109*, 2421; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2327.
- [92] M. J. Hannon, C. L. Painting, W. Errington, *Chem. Commun.* **1997**, 1805.
- [93] A. Neels, H. Stoeckli-Evans, A. Escuer, R. Vicente, *Inorg. Chem.* **1995**, *34*, 1946.
- [94] O.-S. Jung, S. H. Park, D. C. Kim, K. M. Kim, *Inorg. Chem.* **1998**, *37*, 610.
- [95] C. L. Schauer, E. Matwey, F. W. Fowler, J. W. Lauher, *J. Am. Chem. Soc.* **1997**, *119*, 10245.
- [96] K. N. Power, T. L. Hennigar, M. J. Zaworotko, *Chem. Commun.* **1998**, 595.
- [97] M. O'Keeffe, *Z. Kristallogr.* **1991**, *196*, 21.
- [98] M. O'Keeffe, *Nature* **1998**, *392*, 879.
- [99] A. J. Blake, N. R. Champness, S. S. M. Chung, W.-S. Li, M. Schröder, *Chem. Commun.* **1997**, 1005.
- [100] A. J. Blake, N. R. Champness, A. N. Khlobystov, D. A. Lemenovskii, W.-S. Li, M. Schröder, *Chem. Commun.* **1997**, 1339.
- [101] A. J. Blake, N. R. Champness, S. S. M. Chung, W.-S. Li, M. Schröder, *Chem. Commun.* **1997**, 1675.
- [102] B. F. Hoskins, R. Robson, D. A. Slizys, *J. Am. Chem. Soc.* **1997**, *119*, 2952.
- [103] B. F. Hoskins, R. Robson, D. A. Slizys, *Angew. Chem.* **1997**, *109*, 2430; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2336.
- [104] R. LaDuca, Jr., J. Zubieta, unpublished results.
- [105] L. P. Wu, Y. Yamaguchi, T. Kuroda-Sowa, T. Kamikawa, M. Munakata, *Inorg. Chim. Acta.* **1997**, *256*, 155.
- [106] P. C. M. Duncan, D. M. L. Goodgame, S. Menzer, D. J. Williams, *Chem. Commun.* **1996**, 2127.
- [107] D. Venkataraman, S. Lee, J. S. Moore, P. Zhang, K. A. Hirsch, G. B. Gardner, A. C. Covey, C. L. Prentice, *Chem. Mater.* **1996**, *8*, 2030.
- [108] M. Bertelli, L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Mater. Chem.* **1997**, *7*, 1271.
- [109] J. G. J. Jarvis, *Acta Crystallogr.* **1962**, *15*, 964.
- [110] B. F. Abraham, S. R. Batten, H. Hamit, B. F. Hoskins, R. Robson, *Angew. Chem.* **1996**, *108*, 1794; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1690.
- [111] S. R. Batten, B. F. Hoskins, R. Robson, *Angew. Chem.* **1995**, *107*, 884; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 820;.

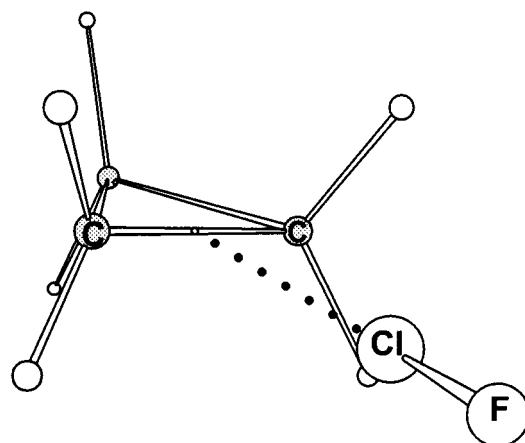
- [112] S. R. Batten, B. F. Hoskins, R. Robson, *J. Am. Chem. Soc.* **1995**, *117*, 5385.
- [113] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Am. Chem. Soc.* **1995**, *117*, 4562.
- [114] a) M. Inoue, M. Kubo, *Coord. Chem. Rev.* **1976**, *21*, 1; b) P. J. Steel, *Coord. Chem. Rev.* **1990**, *106*, 227.
- [115] R. Hammond, J. Zubieta, unpublished results.
- [116] R. G. Vranka, E. L. Amma, *Inorg. Chem.* **1966**, *5*, 1020.
- [117] T. Otieno, S. J. Retting, R. C. Thompson, J. Trotter, *Can. J. Chem.* **1989**, *67*, 1964.
- [118] T. Otieno, S. J. Retting, R. C. Thompson, J. Trotter, *Can. J. Chem.* **1990**, *68*, 1901.
- [119] T. Fetzer, A. Lentz, T. Debaerdemaeker, *Z. Naturforsch. B* **1989**, *44*, 553.
- [120] J. Pickardt, B. Staub, *Z. Naturforsch. B* **1996**, *51*, 947.
- [121] F. Kubel, J. Strahle, *Z. Naturforsch. B* **1981**, *36*, 441.
- [122] M. Munakata, L. P. Wu, T. Kuroda-Sowa, M. Maekawa, K. Moriwaki, S. Kitagawa, *Inorg. Chem.* **1997**, *36*, 5416.
- [123] J. Pickardt, B. Staub, *Z. Naturforsch. B* **1997**, *52*, 1456.
- [124] S. Kawata, S. Kitagawa, H. Kimagai, S. Iwabuchi, M. Katada, *Inorg. Chim. Acta* **1998**, *267*, 143.
- [125] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *Inorg. Chem.* **1995**, *34*, 5698.
- [126] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *Angew. Chem.* **1995**, *107*, 2037; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1895.
- [127] C. V. K. Sharma, S. T. Griffin, R. D. Rogers, *Chem. Commun.* **1998**, 215.
- [128] F. Lloret, G. DeMunno, M. Julve, J. Cano, R. Ruiz, A. Caneschi, *Angew. Chem.* **1998**, *110*, 143; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 135.
- [129] J. S. Haynes, S. J. Retting, J. R. Sams, R. C. Thompson, J. Trotter, *Can. J. Chem.* **1987**, *65*, 420.
- [130] T. Otieno, S. J. Retting, R. C. Thompson, J. Trotter, *Inorg. Chem.* **1993**, *32*, 1607.
- [131] J. A. Real, G. DeMunno, M. C. Munoz, M. Julve, *Inorg. Chem.* **1991**, *30*, 2701.
- [132] P. W. Carreck, M. Goldstein, E. M. McPartlin, W. D. Unsworth, *J. Chem. Soc. Chem. Commun.* **1971**, 1634.
- [133] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *Chem. Commun.* **1996**, 1393.
- [134] S. W. Keller, *Angew. Chem.* **1997**, *109*, 295; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 247.
- [135] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *Inorg. Chem.* **1997**, *36*, 1736.
- [136] L. Carlucci, G. Ciani, D. W. v. Gudenberg, D. M. Proserpio, A. Sironi, *Chem. Commun.* **1997**, 631.
- [137] A. Michelet, B. Voissat, P. Khodadad, N. Rodier, *Acta. Crystallogr. Sect. B* **1981**, *37*, 2171.
- [138] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Am. Chem. Soc.* **1995**, *117*, 12861.
- [139] B. F. Hoskins, R. Robson, D. A. Slizys, *Angew. Chem.* **1997**, *109*, 2861; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2752.
- [140] M.-L. Tong, X.-M. Chen, X.-L. Yu, T. C. W. Mak, *J. Chem. Soc. Dalton Trans.* **1998**, 5.
- [141] D. Hagrman, R. C. Haushalter, J. Zubieta, *Chem. Mater.* **1998**, *10*, 361.
- [142] M. I. Khan, J. Zubieta, *Inorg. Chim. Acta.* **1993**, *213*, 325.
- [143] Y. Xu, L.-H. An, L.-L. Koh, *Chem. Mater.* **1996**, *8*, 814.
- [144] K. Range, A. Fässler, *Acta Crystallogr. Sect. C* **1990**, *46*, 488.
- [145] B. M. Gatehouse, P. Leverett, *J. Chem. Soc. A* **1968**, 1398.
- [146] P. J. Zapf, R. C. Haushalter, J. Zubieta, *Chem. Commun.* **1997**, 321.
- [147] L. Kihlborg, *Ark. Kemi* **1963**, *21*, 357.
- [148] P. J. Zapf, R. C. Haushalter, J. Zubieta, *Chem. Mater.* **1997**, *9*, 2019.
- [149] P. J. Zapf, R. L. LaDuca, Jr., R. S. Rarig, Jr., K. M. Johnson III, J. Zubieta, *Inorg. Chem.* **1998**, *37*, 3411.
- [150] P. J. Zapf, J. Zubieta, unpublished results.
- [151] R. L. LaDuca, Jr., P. J. Zapf, C. J. Warren, R. C. Haushalter, J. Zubieta, unpublished results.
- [152] J. W. Johnson, A. J. Jacobson, S. M. Rich, J. F. Brody, *J. Am. Chem. Soc.* **1981**, *103*, 8246.
- [153] R. Rousseau, E. Canadell, P. Alemany, D. H. Galván, R. Hoffmann, *Inorg. Chem.* **1997**, *36*, 4627.
- [154] S. Adams, K.-H. Ehses, J. Spilker, *Acta Crystallogr. Sect. B* **1993**, *49*, 958.
- [155] P. G. Dickens, J. J. Birtill, C. J. Wright, *J. Solid State Chem.* **1979**, *28*, 185.
- [156] K.-A. Wilhelmi, *Acta Chem. Scand.* **1969**, *23*, 419.
- [157] S. L. Suib, *Chem. Rev.* **1993**, *93*, 803.
- [158] F. J. DiSalvo, *Science* **1990**, *247*, 649.
- [159] N. Prokopuk, D. F. Shriver, *Inorg. Chem.* **1997**, *36*, 5609.
- [160] O. Recheweg, H.-J. Meyer, *Z. Naturforsch. B* **1995**, *50*, 1377.
- [161] O. Recheweg, H.-J. Meyer, *Z. Anorg. Allg. Chem.* **1996**, *622*, 411.
- [162] V. N. Molchanov, I. V. Tatjanina, E. A. Torchenkova, *J. Chem. Soc. Chem. Commun.* **1981**, 93.
- [163] T. Yamase, H. Naruke, *J. Chem. Soc. Dalton. Trans.* **1991**, 285.
- [164] J. R. Galán-Mascarós, C. Giménez-Saiz, S. Triki, J. Gómez-García, E. Coronado, L. Ouahab, *Angew. Chem.* **1995**, *107*, 1601; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1460.
- [165] H. T. Evans, Jr., T. J. R. Weakley, G. B. Jameson, *J. Chem. Soc. Dalton Trans.* **1996**, 2537.
- [166] C. Giménez-Saiz, J. R. Galán-Mascarós, S. Triki, E. Coronado, L. Ouahab, *Inorg. Chem.* **1995**, *34*, 524.
- [167] E. K. Anderson, J. Villadsen, *Acta Chem. Scand.* **1993**, *47*, 748.
- [168] A. Kitamura, T. Ozaki, A. Yagasaki, *Inorg. Chem.* **1997**, *36*, 4275.
- [169] I. Loose, M. Bösing, R. Klein, B. Krebs, R. P. Schulz, B. Scharbert, *Inorg. Chim. Acta.* **1997**, *263*, 99.
- [170] J. R. D. DeBord, R. C. Haushalter, L. M. Meyer, D. J. Rose, P. J. Zapf, J. Zubieta, *Inorg. Chim. Acta* **1997**, *256*, 165.
- [171] Y. Zhang, P. J. Zapf, L. M. Meyer, R. C. Haushalter, J. Zubieta, *Inorg. Chem.* **1997**, *36*, 2159.
- [172] P. J. Zapf, C. J. Warren, R. C. Haushalter, J. Zubieta, *Chem. Commun.* **1997**, 1543.
- [173] I. D. Brown in *Structure and Bonding in Crystals, Vol. II* (Eds.: M. O'Keefe, A. Navrotsky), Academic Press, New York, **1981**, p. 1.
- [174] M. T. Pope, *Heteropoly and Isopoly Oxometalates*, Springer, New York, **1983**.
- [175] M. Inoue, T. Yamase, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3055.
- [176] R. Xi, B. Wang, K. Isobe, T. Nishioka, K. Toriumi, Y. Ozawa, *Inorg. Chem.* **1994**, *33*, 833.
- [177] D. Hagrman, C. Zubieta, D. J. Rose, J. Zubieta, R. C. Haushalter, *Angew. Chem.* **1997**, *109*, 904; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 795.
- [178] D. Hagrman, C. Sangregorio, C. J. O'Connor, J. Zubieta, *Chem. Commun.* **1998**, 1283.
- [179] D. Hagrman, P. J. Zapf, J. Zubieta, *Chem. Commun.* **1998**, 1283.
- [180] P. J. Zapf, D. Hagrman, J. Zubieta, unpublished results.
- [181] P. J. Zapf, R. P. Hammond, R. C. Haushalter, J. Zubieta, *Chem. Mater.* **1998**, *10*, 1336.
- [182] D. Hagrman, C. J. Warren, R. C. Haushalter, R. S. Rarig, Jr., K. M. Johnson III, R. L. LaDuca, Jr., J. Zubieta, *Chem. Mater.* **1998**, *10*, 3294.
- [183] R. L. LaDuca, Jr., R. Finn, J. Zubieta, unpublished results.
- [184] I. D. Brown, K. K. Wu, *Acta. Crystallogr. Sect. B* **1976**, *32*, 1957.
- [185] D. M. Poojary, B. Zhang, A. Clearfield, *J. Am. Chem. Soc.* **1997**, *119*, 12550, and references therein.
- [186] G. B. Olson, *Science* **1997**, *277*, 1237.
- [187] D. Hagrman, J. Zubieta, *Chem. Commun.* **1998**, 2005.
- [188] S. R. Batten, R. Robson, *Angew. Chem.* **1998**, *110*, 1558; *Angew. Chem. Int. Ed.* **1998**, *37*, 1460.



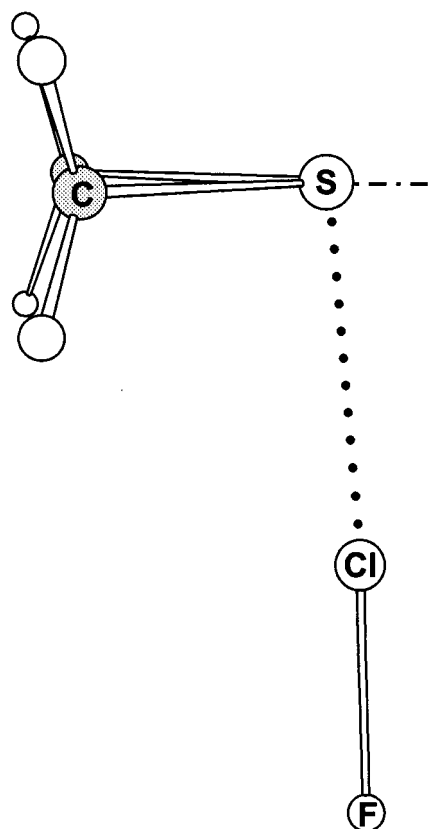
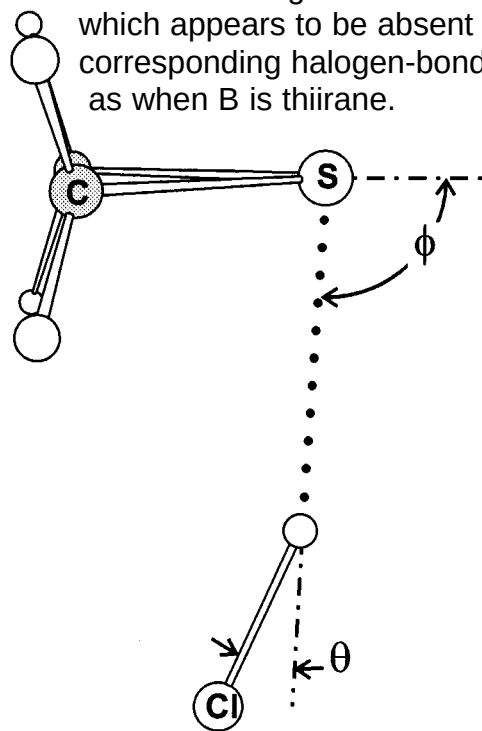
Pseudo- π model
of cyclopropane



The hydrogen bond resembles the “halogen” bond so that complexes $B \cdots \text{HCl}$ and $B \cdots \text{ClF}$ are isostructural, as when B is cyclopropane.



When symmetry allows, the hydrogen bond can show a significant nonlinearity, which appears to be absent in the corresponding halogen-bonded system, as when B is thiirane.



Prereactive Complexes of Dihalogens XY with Lewis Bases B in the Gas Phase: A Systematic Case for the Halogen Analogue $B \cdots XY$ of the Hydrogen Bond $B \cdots HX$

Anthony C. Legon*

Reactions between dihalogen molecules XY and simple Lewis bases B are of fundamental interest in organic and inorganic chemistry and, consequently, have featured prominently in the history of these subjects. When XY is F_2 or ClF, such reactions can be especially violent. Accordingly, it is a challenge for the chemist to isolate and characterize in detail the species produced in the initial, prereactive encounter of B/XY pairs in a potentially reactive mixture. Moreover, prereactive complexes of this type impact on our understanding of the mechanisms of the reactions, for they have been invoked as intermediates. Mulliken postulated that two types of complexes

exist: those of the outer type $B \cdots XY$ (weak, no significant charge transfer) and those of the inner type $[BX]^+ \cdots Y^-$ (strong, substantial charge transfer). Here we demonstrate how prereactive adducts of both the Mulliken outer and inner types can be isolated in the gas phase by using supersonic coexpansion of the components, and then characterized precisely by observation of their rotational spectra. Generalizations about the properties of $B \cdots XY$, obtained by investigating carefully tailored series in which B and XY are systematically varied, can be understood on the basis of a simple electrostatic model of the XY interaction. Among the properties of importance

are the extent of electric charge redistribution in XY, the radial and angular geometries, and the strength of the intermolecular binding. A close parallelism of the properties of $B \cdots XY$ and the corresponding $B \cdots HX$ suggests the existence of a halogen bond analogue of the hydrogen bond. The main difference between halogen and hydrogen bonds lies in the propensity for significant nonlinearity in the latter that is absent in the former.

Keywords: gas-phase chemistry • halogens • hydrogen bonds • intermediates • prereactive complexes

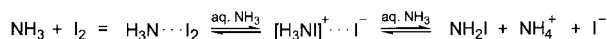
1. Introduction

This year marks an important anniversary in the history of molecular interactions. Fifty years ago, Benesi and Hildebrand^[1] published their landmark paper describing the UV/Vis spectrum of molecular iodine dissolved in liquid benzene. “Charge-transfer” complexes, subsequently renamed electron donor–acceptor complexes by Mulliken, have been a matter of serious interest in chemistry ever since. In the decade or so after the Benesi–Hildebrand paper, much experimental work followed, notable among which were some important X-ray diffraction studies of complexes of Lewis bases and dihalogen molecules in the solid state by Hassel and co-workers.^[2] In the same period, Mulliken developed a detailed theory of such

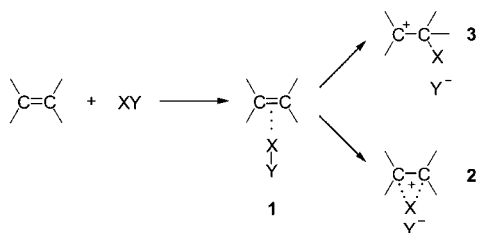
interactions.^[3] An important thread running through Mulliken’s work is the classification of complexes according to whether the intermolecular interaction $B \cdots XY$ is weak and there is little charge transfer between the components (outer complexes in Mulliken’s notation) or whether there is extensive charge redistribution to give $[BX]^+ \cdots Y^-$ (an inner complex). In this review B is used as the symbol for a generalized Lewis base and XY for a generalized dihalogen molecule, either homonuclear (F_2 , Cl_2 , Br_2) or heteronuclear (ClF, BrCl). An inner complex is written $[BX]^+ \cdots Y^-$ without any prejudice as to whether complete transfer of X^+ to B has occurred. This notation is meant only to imply significant charge transfer.

Both outer and inner complexes have been invoked in describing the mechanisms of reactions of halogens with simple Lewis bases in solution. For example, $[H_3NX]^+ \cdots Y^-$ was invoked^[4] as an intermediate in reactions of halogens with ammonia (Scheme 1), while the halogenium ion **2** in Scheme 2 was identified in the reactions of halogens and alkenes in polar solvents and in the dark.^[5] In Schemes 1 and 2, the

[*] Prof. Dr. A. C. Legon
School of Chemistry
University of Exeter
Stocker Road, Exeter EX44QD (UK)
Fax: (+44) 1392-263434
E-mail: a.c.legon@exeter.ac.uk



Scheme 1. A mechanism proposed for the reaction of molecular iodine with aqueous ammonia solution. It involves an outer complex $\text{H}_3\text{N} \cdots \text{I}_2$ and then an inner complex $[\text{H}_3\text{NI}]^+ \cdots \text{I}^-$ as intermediates.



Scheme 2. Possible mechanisms for the reaction of halogen molecules with alkenes in polar solvents in the dark; **1** and **2** are Mulliken outer and inner complexes, respectively.

initial, presumably weak, complex $\text{B} \cdots \text{XY}$ is often referred to as a preequilibrium complex. In general, we shall use the phrase prereactive complex (or intermediate) to describe the complex formed in the initial interaction prior to chemical reaction or significant charge transfer. This article is concerned with prereactive complexes which are mainly of the outer type but occasionally of the inner type.

Theoretical approaches to $\text{B} \cdots \text{XY}$ have almost invariably involved the isolated complex, while most experimental work has been conducted in condensed phases (liquids, solutions, or the solid state). If one wishes to provide experimental evidence that makes direct contact with theory, it is clearly desirable for it to be derived from the investigation of complexes in isolation, either in inert gas matrices at low temperature or, preferably, in the gas phase at low pressure, so that molecules undergo few or no collisions. In the latter case, the observed properties are unperturbed by lattice or solvent effects and hence refer to the isolated molecule.

The objectives of the investigations described in this review are to examine experimentally how the properties of complexes $\text{B} \cdots \text{XY}$ change as first B and then XY are systematically varied, with the aim of deducing the nature of the $\text{B} \cdots \text{XY}$ interaction and its dependence on the Lewis base and the halogen involved. Inevitably, this approach requires that simple Lewis bases B are chosen, but many of them are highly reactive with respect to halogens. For example, mixtures of $\text{F}_2/$

NH_3 and of $\text{ClF}/\text{C}_2\text{H}_4$ react violently in the gas phase. Therefore, to achieve the above objectives, it is necessary to mix B and XY and allow the component molecules to interact to give $\text{B} \cdots \text{XY}$ but to preclude further progress along the reaction coordinate, that is, to isolate the prereactive complex.

There are two ways of isolating prereactive complexes. The first involves the use of low-temperature inert gas matrices, as exemplified by the work of Pimentel et al.,^[6] Ault et al.,^[7] Andrews et al.,^[8] Barnes et al.,^[9] and others. These authors used mainly IR spectroscopy to probe the matrix-isolated complexes. There have been several reviews of this important general method.^[10–13]

The second method for forming and isolating prereactive complexes is more recent^[14] but in many ways similar. It involves the rapid mixing and supersonic coexpansion of the components from the gas phase at moderate pressure into a vacuum. This approach allows prereactive complexes to be investigated by means of their rotational spectra in the collisionless phase of expansion and therefore in the absence of interaction with any other molecule. It thus brings to bear on the species so isolated all the precision and detailed knowledge that are typical of rotational spectroscopy. The results obtained in this way are the subject of discussion here.

We shall first consider how to characterize complexes $\text{B} \cdots \text{XY}$ by rotational spectroscopy, assuming they can be produced and isolated before chemical reaction. This involves a brief description of FT microwave spectroscopy and a survey of the spectroscopic constants that can be extracted from analysis of the rotational spectra. A delineation of those relevant molecular properties of the complex that can be derived from the spectroscopic constants follows. These are radial and angular geometries, the strength of the intermolecular binding, and the extent of electric charge redistribution accompanying complex formation.

The main body of the review is concerned with an examination of the properties of isolated complexes $\text{B} \cdots \text{XY}$ and how they change as B and XY are varied. From this systematic investigation of the properties, generalizations about $\text{B} \cdots \text{XY}$ complexes are deduced and the nature of the $\text{B} \cdots \text{XY}$ interaction inferred. An important part of the process are comparisons of the properties of $\text{B} \cdots \text{XY}$ complexes with those of their hydrogen-bonded analogues $\text{B} \cdots \text{HX}$ (X = halogen). The work on hydrogen-bonded complexes has been reviewed elsewhere.^[15]



Tony Legon was born in Suffolk, England but was educated in London: at the Coopers' Company School in Bow and later in the Chemistry Department at University College London (UCL). He conducted his doctoral research at UCL under the supervision of Jim Millen, with whom he subsequently had a long and happy collaboration. Following a period as Turner and Newall Fellow in the University of London, he became Lecturer and then Reader in Chemistry at UCL. He spent 1980 working at the University of Illinois with the late W. H. Flygare. In 1984 he moved to the Chair of Physical Chemistry at the University of Exeter where he has remained, apart from a year (1989/90) as Thomas Graham Professor of Chemistry at UCL. His main research interests are in understanding gas-phase interactions of molecules through the rotational spectra of hydrogen-bonded and charge-transfer complexes. This work was recognized by the award of the Tilden Lectureship and Medal of the Royal Society of Chemistry (RSC) in 1989, an EPSRC Senior Fellowship in 1997, and the Spectroscopy Award of the RSC in 1998.

2. Prereactive Complexes $B \cdots XY$: Formation, Isolation, and Characterization

This section consists of two parts. First, the means of detecting and characterizing the species $B \cdots XY$ by their rotational spectra will be described, under the assumption that the complexes can somehow be formed and isolated before chemical reaction between the components B and XY . In the second part, the means by which prereactive complexes can be formed and isolated prior to chemical reaction are discussed.

2.1. How to Detect and Characterize Prereactive Complexes

Rotational spectroscopy is a powerful method of measuring the precise properties of molecules in effective isolation in the gas phase. The rotational spectra of complexes with a reasonably strong intermolecular bond have been observed in equilibrium gas mixtures of the two components at low temperature by using Stark modulation microwave spectroscopy.^[16] For more weakly bound complexes, techniques that involve supersonic jets or beams must be employed, namely, molecular beam electric resonance spectroscopy (MBERS, pioneered by Klemperer et al.)^[17] and pulsed-nozzle, Fourier-transform microwave spectroscopy (developed by Flygare et al.).^[18] In each technique, a supersonic jet or beam of gas mixture—formed by premixing the components and then strongly diluting them with, for example, argon—is expanded from a reservoir held at a relatively high pressure through a small circular nozzle into a vacuum. The gas emerging from the nozzle is rich in weakly bound complexes which achieve collisionless expansion on a short time scale (ca. 10 μ s), after which they are frozen in their lowest rotational and vibrational energy states until the gas hits a wall of the vessel, for example. While in the state of collisionless expansion, the complexes can be interrogated by microwave radiation and their rotational spectra recorded. The results presented here were obtained, for the most part, by pulsed-nozzle, FT microwave spectroscopy. Good descriptions of the MBERS technique and its achievements are given in refs. [19] and [20], respectively.

Figure 1 shows a schematic diagram of the spectrometer.^[21] In the first of a sequence of carefully timed events, a short pulse of a mixture of the appropriate components is expanded with the aid of a solenoid valve from a pressure of a few bar into the evacuated chamber of the spectrometer. This chamber contains a pair of nearly confocal, concave aluminum mirrors that constitute a microwave (mw) Fabry–Pérot (FP) cavity. When the gas pulse has reached the center of the FP cavity, a 1- μ s pulse of monochromatic radiation of frequency ν , to which the cavity is tuned, is allowed to enter the cavity, where it forms a standing wave pattern. Molecules in the gas pulse that have a rotational transition within the bandwidth of the FP cavity (ca. 0.5 MHz) are rotationally polarized by the radiation. The half-life for spontaneous coherent emission from the polarized gas at frequency ν_m is on

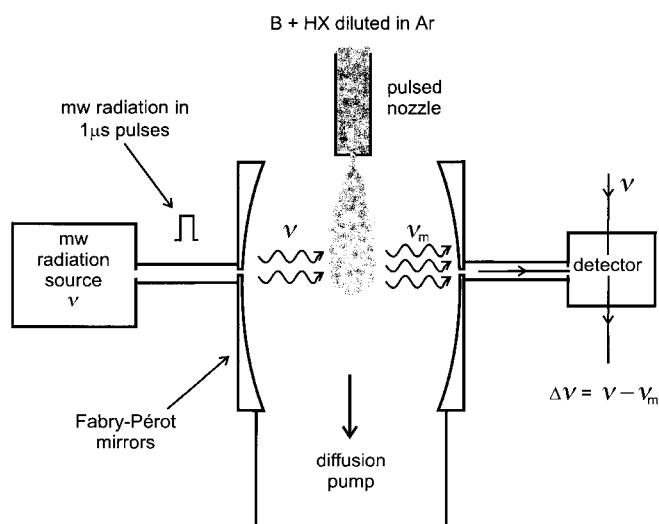


Figure 1. Schematic diagram showing the essential components of a pulsed-nozzle, FT microwave spectrometer. The nozzle is of the conventional type, suitable only for observing rotational spectra of complexes $B \cdots HX$ that can be formed from premixed components B and HX .

the order of 100 μ s, while the polarizing pulse has a half-life of only about 0.1 μ s. Consequently, by delaying detection for a few microseconds, the free-induction decay at the rotational transition frequency ν_m can be detected in the effective absence of the initial microwave pulse. The emission at ν_m is processed by mixing it down in two stages (although only one is shown in Figure 1), as a signal proportional to the strength of the oscillating electric field of frequency $|\nu - \nu_m|$, which normally lies in the range 0–500 kHz. Fourier transformation then gives the intensity versus frequency spectrum in the range ± 500 kHz centered on ν . The experiment is an exact analogue of FT NMR spectroscopy, except that the molecules undergo an electric polarization in the former, instead of the magnetic polarization of the latter.

By analysis of rotational spectra observed in this way, a variety of spectroscopic constants that contain much information about the complexes can be determined. Those of most direct interest to the present discussion are listed in Table 1. Rotational constants are inversely proportional to principal moments of inertia, which are in turn simple functions of the distribution of the mass of the complex in space. Accordingly, these quantities can be used to determine the separation of the two subunits B and XY and their relative orientation in space, that is, the radial and angular geometries of the complex.

The centrifugal distortion constant D_J (linear or symmetric-top molecules) or Δ_J (asymmetric-rotor molecules) is simply related to the intermolecular stretching force constant k_o for the approximation of rigid, unperturbed subunits B and XY with the neglect of terms higher than quadratic in the intermolecular potential energy function.^[22] Since k_o is the restoring force per unit infinitesimal extension of the weak bond, it provides one measure of strength of the interaction (the other is the dissociation energy).

The final spectroscopic constants of particular interest here are the halogen nuclear quadrupole coupling constants $\chi_{a\beta}(X)$ and $\chi_{a\beta}(Y)$, where α and β are to be permuted over the

Table 1. Spectroscopic constants from rotational spectroscopy and the molecular properties to which they lead.

Spectroscopic constant	Molecular property	Comment
Nature of the spectrum	Symmetry	Spectral pattern is different for linear, symmetric-top, and asymmetric-top molecules. Observation of a particular pattern often allows molecular symmetry to be established.
Rotational constants, A_0, B_0, C_0	Radial and angular geometry	$B_0 = h/8\pi^2 I_b$, where $I_b = \sum m_i(a_i^2 + c_i^2)$ is a principal moment of inertia. I_b depends on the relative positions (i.e., principal axis coordinates a_i, c_i) of atoms.
Centrifugal distortion constant, D_J or Δ_J	Intermolecular stretching force constant k_σ of a weakly bound complex	For weakly bound complexes $B \cdots XY$, the components B and XY can in good approximation be assumed rigid. Then, if higher than quadratic force constants can be neglected, D_J is proportional to k_σ^{-1} .
Nuclear quadrupole coupling constants $\chi_{a\beta}(X) = -(eQ_X/h)\partial^2 V_X/\partial\alpha\partial\beta$	Electric field gradient at a nucleus X having a nonzero electric quadrupole moment Q_X	Depends on the detailed electric charge distribution within the molecule. If a molecule XY is subsumed into a complex, $\partial^2 V/\partial\alpha\partial\beta$ at X and Y change. The $\chi(X)$ and $\chi(Y)$ can be used as a probe of the change.

principal inertial axis directions a, b , and c . The importance of these quantities lies in the definition of the nuclear quadrupole coupling tensor $\chi_{a\beta}(X) = -(eQ_X/h)\partial^2 V_X/\partial\alpha\partial\beta$, where Q_X is the conventional electric quadrupole moment of nucleus X and $-\partial^2 V/\partial\alpha\partial\beta$ is the electric field gradient (EFG) tensor at nucleus X. Further details of the nuclear quadrupole interaction are given in Section 3.1. For present purposes, the fact that $\chi_{a\beta}(X)$ is proportional to the electric field gradient at nucleus X means that changes in $\chi_{a\beta}(X)$ and $\chi_{a\beta}(Y)$ on formation of $B \cdots XY$ provide a quantitative measurement of the changes in the EFGs at X and Y, and hence in the electric charge distribution of XY. In addition, when the complete tensor $\chi_{a\beta}(X)$ or $\chi_{a\beta}(Y)$ is available, it provides important information about the orientation of the XY subunit with respect to the principal inertial axis system a, b, c and hence about the angular geometry of $B \cdots XY$.^[23]

2.2. How to Form and Isolate Prereactive Complexes

Section 2.1 outlines how to determine certain properties of a complex $B \cdots XY$ from spectroscopic constants obtained by analysis of its rotational spectrum, as observed in a supersonically expanded jet by pulsed-nozzle FT microwave spectroscopy. Normally, the mixture of the two components of interest, diluted in argon, would be held in a stagnation tank at a total pressure of about 3 bar prior to its expansion in short pulses (produced by a solenoid valve) into the vacuum chamber. For most of the complexes of interest here this approach could not be used because the two components B and XY would undergo chemical reaction. This is a particular problem with, for example, mixtures B/XY in which B is ammonia, ethene, or ethyne and XY is F_2 , ClF, or Cl_2 , for which the reaction can be rapid. Clearly, to observe the prereactive complexes $B \cdots XY$, a device is required which achieves a time between mixing of the components and the collisionless phase of the supersonic expansion short enough to preclude chemical reaction.

Such a device is the fast-mixing nozzle^[14] shown schematically in Figure 2. It consists essentially of a pair of concentric, nearly coterminal tubes of circular cross-section and is attached to the outlet of a solenoid valve. One of the reactive components flows (usually undiluted) continuously through the central glass capillary (0.3 mm internal diameter) into the evacuated chamber of the spectrometer. The other compo-

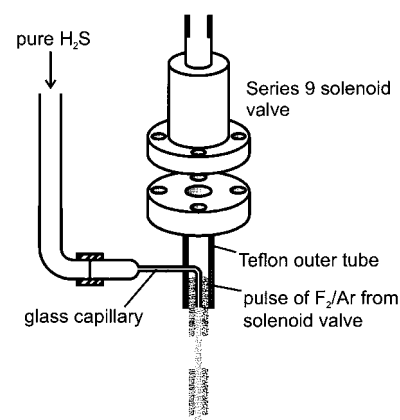


Figure 2. Schematic diagram of a fast-mixing nozzle. The component gases illustrated are those required to detect the rotational spectrum of $H_2S \cdots F_2$, a transition of which is shown in Figure 3. The glass capillary used in this experiment had an internal diameter of 0.3 mm.

nent diluted in, say, argon, is sent in short pulses from a stagnation pressure of about 3 bar down the outer tube. The gas pulses are produced by the solenoid valve. The two components meet only in the approximately cylindrical interface between the concentric gas streams as they emerge in simultaneous expansion from the tubes. Moreover, they encounter each other while moving at high speed away from surfaces, so the possibility of surface-initiated radical reactions is reduced. We shall see that complexes formed at the interface of the gas flows achieve states of low internal energy and collisionless expansion on the order of 10 μ s. Thereafter, there is no possibility of unimolecular, bimolecular, or surface-initiated reaction until the gas flow hits a wall of the vacuum chamber. The complexes are effectively frozen as prereactive intermediates for about 300 μ s, during which their rotational spectrum can be recorded by the method outlined in Section 2.1.

Figure 3 shows a rotational transition of $H_2S \cdots F_2$ recorded by using the fast-mixing nozzle in an FT microwave spectrometer. The effectiveness of the device becomes clear when it is recalled that ignition is observed in H_2S/F_2 mixtures at room temperature at pressures as low as 10^{-6} bar.^[24] The reasons for its success may be sought in the properties of the supersonic expansion which can be discussed conveniently in terms of the ratio X/d , where X is the distance traveled by the gas downstream from the circular nozzle exit of diameter d .

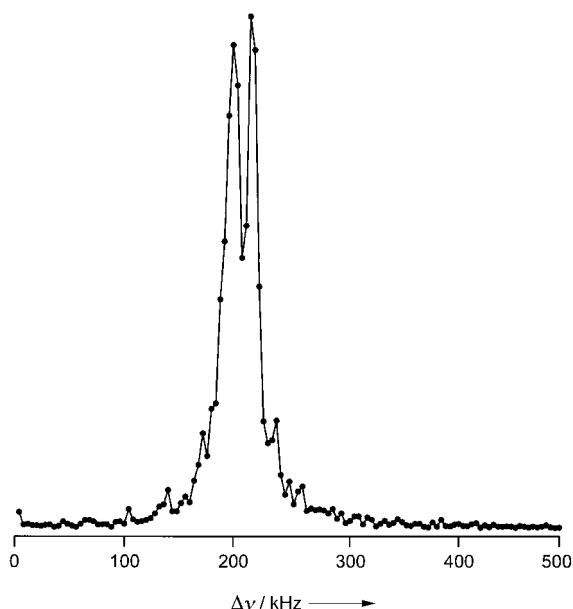


Figure 3. A frequency domain recording of the $3_{03}-2_{02}$ transition in the ground state of $\text{H}_2\text{S}\cdots\text{HF}$. Frequencies are offset from 10384.1660 MHz at a rate of 3.90625 kHz per point. Solid dots have been joined by straight lines. The transition is centered at 10383.9668 MHz. The doublet structure arises from F,F spin–spin splitting. See reference [64] for further details.

Gas dynamics calculations^[25] show that for an axisymmetric expansion of room-temperature argon from a pressure of a few bar through a circular nozzle with $d=0.3$ mm, the gas flow reaches its terminal speed of $5 \times 10^4 \text{ cm s}^{-1}$ after a few nozzle diameters of travel downstream from the exit, and the temperature drops to around 1 K by about $X/d=10$ or soon after. The number of three-body collisions Z_3 for each molecule diminishes very rapidly, so that the formation of complexes, which requires three-body collisions, is effectively over within a few nozzle diameters. Two-body collisions cease after the gas has traveled about ten nozzle diameters, that is, after about 10 μs . Clearly, if the complexes formed in the first few microseconds survive until then, there is no mechanism by which they can undergo reaction and they are effectively frozen. Hence, the rapid expansion in the absence of surfaces, coupled with the dilution of one component in argon, appears to be responsible for the efficacy of the fast-mixing nozzle.

3. Systematic Variation of B and XY: The Nature of the $\text{B}\cdots\text{XY}$ Interaction

This part of the review is concerned with examining how the properties of $\text{B}\cdots\text{XY}$ (see Section 2.1 and Table 1) change as B and XY are systematically varied and the conclusions about the nature of the $\text{B}\cdots\text{XY}$ interaction that can be thereby deduced. The first question to be addressed is whether the observed complexes belong to the weak, outer type or to the strong, inner type in the classification of Mulliken.^[3] The most important criterion is the extent of electric charge redistribution that accompanies formation of $\text{B}\cdots\text{XY}$, since it will be minor for an outer complex $\text{B}\cdots\text{XY}$ but major for an inner complex $[\text{BX}]^+\cdots\text{Y}^-$. A less direct criterion is the binding

strength, as measured by k_a . Once it has been established that certain $\text{B}\cdots\text{XY}$ species belong to the outer type, it will be profitable to consider their angular and radial geometries.

3.1. Electric Charge Redistribution in XY on Formation of $\text{B}\cdots\text{XY}$

A powerful probe of electric charge redistribution is provided by the nuclear quadrupole coupling constants, particularly those associated with the XY subunit, since they lead to the electric field gradients at the nuclei (Section 2.1). This information is most straightforwardly interpreted in terms of changes in the electronic distribution when XY is a homonuclear dihalogen, such as Cl_2 or Br_2 . Less directly obtainable, but equally valuable, information about electronic structure results when XY is a heteronuclear dihalogen such as BrCl or ClF . The absence of a nuclear electric quadrupole moment for ^{19}F means that a similar probe of the modified charge distribution of F_2 when subsumed into $\text{B}\cdots\text{F}_2$ is not available. However, indirect evidence of a negligible modification in most $\text{B}\cdots\text{F}_2$ will be adduced below.

3.1.1. Nuclear Quadrupole Coupling as a Probe of Electric Charge Redistribution in a Homonuclear Dihalogen X_2 in $\text{B}\cdots\text{X}_2$

Apart from ^{19}F , halogen nuclei have an electric quadrupole moment $\mathbf{Q}_x$ and an intrinsic (or spin) momentum $\mathbf{I}_x$. The nuclear spin vector $\mathbf{I}_x$ can couple in only a limited number of discrete orientations to the rotational angular momentum vector $\mathbf{J}$ of the framework of a molecule carrying the atom X. This corresponds to different orientations of $\mathbf{Q}_x$ with respect to the electric field gradient ∇E_x at X and therefore to a set of different potential energies of interaction. The result is a hyperfine splitting of rotational energy levels and transitions. Analysis of this hyperfine structure gives nuclear quadrupole coupling constants $\chi_{\alpha\beta}(\text{X}) = -(eQ_x/h)\partial^2 V_x/\partial\alpha\partial\beta$, where α and β are to be permuted over the principal inertial axes a , b , and c . Only zero-point values of the $\chi_{\alpha\beta}(\text{X})$ are measured.

The analysis that follows^[26–28] applies to complexes $\text{B}\cdots\text{X}_2$ of axial symmetry (C_{3v} or higher) or of C_{2v} symmetry in which the X_2 internuclear axis z coincides in the equilibrium conformation with the C_2 axis and with the a axis. The equilibrium nuclear quadrupole coupling constants along z (or a) are denoted $\chi_{zz}^e(\text{X}_i)$ and $\chi_{zz}^e(\text{X}_o)$, where the subscripts i and o refer to the inner and outer X nuclei in $\text{B}\cdots\text{X}_2$ and it is assumed implicitly that both atoms X belong to the same nuclide.

Although there is only one coupling constant $\chi_0(\text{X})$ for free X_2 , the formation of $\text{B}\cdots\text{X}_2$ leads to a divergence of the zero-point values $\chi_{zz}^e(\text{X}_i)$ and $\chi_{zz}^e(\text{X}_o)$, as the former increases and the latter decreases in magnitude. This is a result mainly of the polarization of the electric charge distribution of X_2 by the molecule B. Ab initio calculations have shown^[29] that when $\text{N}_2\cdots\text{HX}$ is formed, the effect of HX on the equilibrium ^{14}N nuclear quadrupole coupling constants leads to the relation $\chi_{zz}^e(^{14}\text{N}_i) + \chi_{zz}^e(^{14}\text{N}_o) \approx 2\chi_0(^{14}\text{N})$ for all but very small intermolecular separations. Similarly, $\chi_{zz}^e(\text{X}_i)$ of $\text{B}\cdots\text{X}_2$ increases in

magnitude while $\chi_{zz}^e(X_o)$ suffers a nearly equal decrease,^[30] leading to $\chi_{zz}^e(X_i) + \chi_{zz}^e(X_o) \approx 2\chi_0(X)$. This means that the quotient f defined in Equation (1) can be written as Equation (2) to a high degree of approximation, where $\Delta\chi_{zz}^e(X) =$

$$f = \{\chi_{zz}^e(X_i) - \chi_{zz}^e(X_o)\} / \{\chi_{zz}^e(X_i) + \chi_{zz}^e(X_o)\} \quad (1)$$

$$f = \Delta\chi_{zz}^e(X_i) / 2\chi_0(X) \quad (2)$$

$\chi_{zz}^e(X_i) - \chi_{zz}^e(X_o)$. In view of the definition of nuclear quadrupole coupling constants, it follows that f is related to the EFG at the two nuclei X_i and X_o by Equation (3), where F_0 is the

$$f = \Delta F_{zz} / 2F_0 \quad (3)$$

electric field gradient along z at X in free X_2 and ΔF_{zz} is the difference in EFG between the nuclei X_i and X_o in $B \cdots X_2$.

The Townes–Dailey model^[31] provides a conveniently simple approximate method of estimating the EFG at nuclei in terms of the contributions of p, d, ... valence electrons. It predicts that when a fraction δ of a $3p_z$ electron is transferred from Cl_i to Cl_o in Cl_2 to give $Cl_i^+ \cdots Cl_o^-$, the difference $\Delta F_{zz} = F_{zz}^i - F_{zz}^o = 2\delta F_0$. Then Equation (3) becomes Equation (4).

$$f = \delta \quad (4)$$

Hence, the quotient defined in Equation (1) is, in the approximation of the Townes–Dailey model, the fraction δ of an electronic charge transferred from X_i to X_o when $B \cdots X_2$ is formed. This analysis ignores intermolecular charge transfer, but in view of the small values of δ thus found this neglect seems reasonable.

The fact that zero-point quantities $\chi_{zz}(X_i)$ and $\chi_{zz}(X_o)$ are observed rather than their equilibrium counterparts is not a problem. For an axially symmetric complex $B \cdots X_2$, zero-point averaging can be taken into account in good approximation by Equation (5) with an analogous equation in X_o ,

$$\chi_{zz}(X_i) \approx \frac{1}{2}\chi_{zz}^e(X_i)(3\cos^2\phi - 1) \quad (5)$$

where ϕ is the instantaneous angle between the X_2 axis and its equilibrium direction z . Equation (5) is an exact equality if the EFGs at X_i and X_o are independent of the motion of B and if intermolecular stretching is ignored. It then follows that Equation (2) also holds when zero-point coupling constants are used instead of equilibrium values.

Figure 4 plots values of δ for a series of complexes $B \cdots Cl_2$ ^[27, 28, 32–38] and $B \cdots Br_2$ ^[39, 40] against k_o , which is a measure of the strength of the interaction. Two features of Figure 4 are noteworthy. First, apart from the $H_3N \cdots Br_2$ complex, the values of δ are all on the order of a few hundredths of an electronic charge. Second, the δ values all lie on the same straight line. Evidently, these complexes are Mulliken complexes of the outer type, with very small electric charge redistribution on complex formation. The values of δ are in accord with those from ab initio calculations. For example, values of $\delta = -0.015$ and 0.018 were obtained for ethene $\cdots Cl_2$ ^[41] for the changes in electronic population at Cl_i and Cl_o , respectively. A Sternheimer-like response property $g_{zz,z}$ was

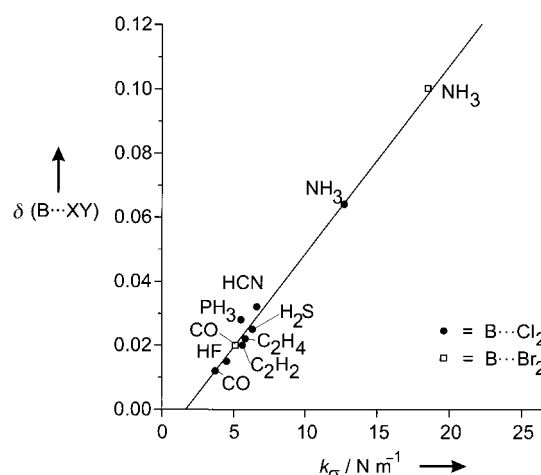


Figure 4. Systematic variation of the fraction of an electronic charge δ transferred from X_i to X_o on formation of $B \cdots X_2$ ($X = Cl$ and Br). The intermolecular stretching force constant k_o is used to order the $B \cdots X_2$ according to the strength of the interaction.

deduced for free Cl_2 from the observed variation of δ with B .^[30] A similar approach was applied to the δ value of $H_3N \cdots Br_2$.^[42]

3.1.2. Nuclear Quadrupole Coupling as a Probe of Electric Charge Redistribution in a Heteronuclear Dihalogen XY in $B \cdots XY$

The foregoing treatment needs some modification when XY is a heteronuclear dihalogen such as $BrCl$. According to the Townes–Dailey model, if the formation of $B \cdots XY$ in its equilibrium conformation leads to transfer of a fraction δ of an electronic charge from X to Y , the equilibrium coupling constants $\chi_{zz}^e(X)$ and $\chi_{zz}^e(Y)$ (z is the XY internuclear axis) are related to those of the free XY molecule $\chi_0(X)$ and $\chi_0(Y)$ by Equations (6) and (7) where $\chi_A(X)$ and $\chi_A(Y)$ are the nuclear

$$\chi_{zz}^e(X) = \chi_0(X) + \delta\chi_A(X) \quad (6)$$

$$\chi_{zz}^e(Y) = \chi_0(Y) - \delta\chi_A(Y) \quad (7)$$

quadrupole coupling constants of the halogen atoms X and Y , respectively. Values of $\chi_A(X)$ and $\chi_A(Y)$ are well established.^[43]

With the same approximation that holds in Equation (5), the zero-point values $\chi_{zz}(X)$ and $\chi_{zz}(Y)$ are related to the equilibrium quantities by Equations (8) and (9). Given $\chi_A(X)$, $\chi_A(Y)$, $\chi_0(X)$, and $\chi_0(Y)$, solutions of Equations (8) and (9) with the experimental values of $\chi_{zz}(X)$ and $\chi_{zz}(Y)$ provide δ and $\phi_{av} = \cos^{-1}(\cos^2\phi)^{1/2}$.

$$\chi_{zz}(X) = \frac{1}{2}[\chi_0(X) + \delta\chi_A(X)](3\cos^2\phi - 1) \quad (8)$$

$$\chi_{zz}(Y) = \frac{1}{2}[\chi_0(Y) - \delta\chi_A(Y)](3\cos^2\phi - 1) \quad (9)$$

Values of δ so obtained for the series of complexes $B \cdots BrCl$ ^[44–50] are plotted in Figure 5 against k_o as a measure of the intermolecular binding strength. Note that δ is again an approximately linear function of k_o and is small ($\delta \leq 0.06$) except for the fairly strong complex $H_3N \cdots BrCl$ ($\delta = 0.11$).^[50] We therefore conclude that electric charge redistribution within $BrCl$ on formation of $B \cdots BrCl$ is small. In fact, comparison of Figures 4 and 5 indicates that, for a given B , the

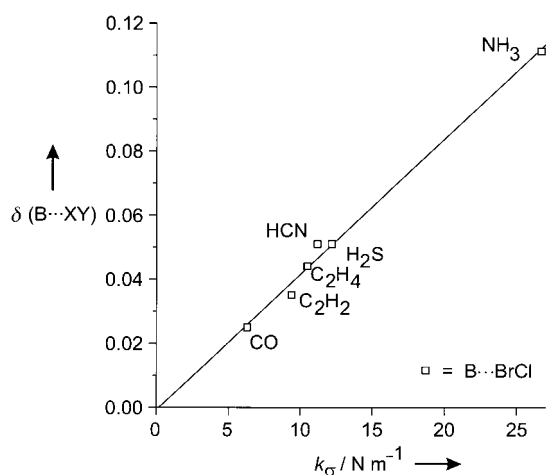


Figure 5. Systematic variation of the fraction of an electronic charge δ transferred from Br to Cl on formation of $B \cdots BrCl$. The intermolecular stretching force constant k_σ is used to order the $B \cdots XY$ according to the strength of the interaction.

value of δ for $B \cdots BrCl$ is approximately twice that of $B \cdots Cl_2$. It is of interest that $k_\sigma(B \cdots BrCl) \approx 2k_\sigma(B \cdots Cl_2)$ for a given B also (see Section 3.2).

Application of a similar approach to complexes $B \cdots ClF$ encounters the problem that F does not possess a nuclear electric quadrupole moment, and hence only Equation (8) is available for $X = Cl$. To deconvolute δ and ϕ_{av} , some assumption is then necessary. One approach is to make sensible assumptions about ϕ_{av} , which are discussed in detail elsewhere.^[51] The result is that, for the $B \cdots ClF$ in which B is N_2 ,^[52] CO ,^[53] C_2H_2 ,^[54] C_2H_4 ,^[55] HCN ,^[56] H_2S ,^[57] or H_2O ,^[58] δ lies in the range 0.00 to 0.040. $H_3N \cdots ClF$ ^[59] is excluded from the list of $B \cdots ClF$ complexes discussed because there is evidence from the value of $\chi_{zz}(Cl)$ for a contribution of a few percent of the ionic structure $[H_3NCl]^+ \cdots F^-$ to a valence bond description of the molecule (see Section 4.2).

3.1.3. Are $B \cdots XY$ Complexes Considered Here of the Mulliken Outer or Inner Type?

The discussion of Sections 3.1.1 and 3.1.2 is based on a simple interpretation of the changes in the XY nuclear quadrupole coupling constants when $B \cdots XY$ is formed. Some general conclusions about the nature of the intermolecular interaction are possible by consideration of the fractional electronic charge transferred from X to Y so determined.

First, with the exceptions of $H_3N \cdots BrCl$ ^[50] and $H_3N \cdots ClF$,^[59] which are both fairly strongly bound according to the k_σ criterion (see Section 3.2), δ is only a few hundredths of an electronic charge. Evidently, the XY molecule suffers only a minor electronic perturbation. Accordingly, we describe all the complexes $B \cdots ClF$, $B \cdots BrCl$, $B \cdots Cl_2$ so far mentioned as belonging to the weak, outer type defined by Mulliken.^[3] This is the reason why intermolecular charge transfer was ignored in the analysis of XY nuclear quadrupole coupling constants in Section 3.1.1.

Second, we note that for a given B the values of δ are in the order $B \cdots BrCl > B \cdots Br_2 > B \cdots Cl_2 > B \cdots ClF$. For example, when B is CO the values of δ are 0.025,^[45] 0.020,^[40] 0.012,^[28]

and 0.013,^[51] respectively. This order is that which might be expected in terms of the axial dipole polarizabilities of the interhalogen/halogen molecules, which follow the same pattern.^[60]

We shall show in Section 4 that it is possible to observe complexes that do show significant charge transfer between the Lewis base and Lewis acid.

3.2. Systematic Behavior among Intermolecular Stretching Force Constants k_σ of $B \cdots XY$

Intermolecular stretching force constants k_σ have been determined from centrifugal distortion constants D_J or Δ_J for a sufficient number of halogen or interhalogen complexes with Lewis bases B to establish whether there is any systematic behavior of k_σ when B or XY is systematically varied. Such behavior has already been identified^[61, 62] in the series of complexes $B \cdots HX$ ($X = F, Cl, Br$).

Table 2 displays the values of k_σ for some $B \cdots XY$ complexes with axial or C_{2v} symmetry ($H_2S \cdots XY$ complexes are an exception, but they differ inertially so little from axial

Table 2. Values of the intermolecular stretching force constant k_σ [$N m^{-1}$] for complexes $B \cdots XY$.^[a]

B	XY				
	F ₂	Cl ₂	Br ₂	BrCl	ClF
CO	– (1.3)	3.7 ^[32] (3.6)	5.1 ^[40] (6.3)	6.3 ^[45] (6.3)	7.0 ^[53] (6.9)
C ₂ H ₂	– (2.0)	5.6 ^[36] (5.4)	– (7.8)	9.4 ^[47] (9.5)	10.0 ^[54] (10.3)
C ₂ H ₄	– (2.2)	5.9 ^[27] (6.0)	– (8.7)	10.5 ^[46] (10.6)	11.0 ^[55] (11.5)
HCN	2.6 ^[63] (2.3)	6.6 ^[37] (6.2)	– (9.1)	11.1 ^[49] (11.0)	12.3 ^[56] (12.0)
H ₂ S	2.4 ^[64] (2.6)	6.3 ^[35] (6.9)	– (10.0)	12.2 ^[48] (11.0)	13.3 ^[57] (13.2)
NH ₃	4.7 ^[65] (4.7)	12.7 ^[38] (12.6)	18.5 ^[39] (18.3)	26.7 ^[50] (22.3)	34.3 ^[59] (24.3)

[a] Values in parentheses are calculated from the N_B and E_{XY} values of Table 5 by using Equation (10). See text for discussion of the discrepancy of observed and calculated k_σ for $H_3N \cdots ClF$.

symmetry that they can be considered here with negligible error). Several conclusions are immediately evident from Table 2. First, for a given XY, the order of k_σ is $OC < HCCH \approx H_2CCH_2 < HCN \lesssim H_2S < NH_3$. This order also holds for $B \cdots F_2$ with $B = HCN$,^[63] H_2S ,^[64] or NH_3 ,^[65] for these complexes the interaction is extremely weak. Second, for a given B, the order of k_σ is $F_2 < Cl_2 < BrCl < ClF$. Both sets of observations are consistent with the deductions about δ in Section 3.1 and with the conclusion that the interaction is, for the most part, of the weak electrostatic type.

It is of interest to compare the behavior of the k_σ in the $B \cdots XY$ series with those in the related hydrogen-bonded series $B \cdots HX$. Values for the latter^[66] are listed in Table 3. In general the $B \cdots HX$ interactions are of the weak electrostatic type,^[67, 68] and the k_σ values of a large number of complexes can be reproduced by the empirical Equation (10)^[61, 62] where

$$k_\sigma = c N_B E_{HX} \quad (10)$$

N_B and E_{HX} are gas-phase nucleophilicities and electrophilicities assigned to the individual molecules B and HX, respectively, and c is a constant. Values of N_B and E_{HX} for a range of B and HX are given in Table 4 and, with the value

$c = 0.25 \text{ N m}^{-1}$, reproduce the observed k_{σ} of the $\text{B} \cdots \text{HX}$ in Table 3 very well. Questions that immediately suggest themselves are: Can the k_{σ} of the $\text{B} \cdots \text{XY}$ series be reproduced by an equation such as Equation (10) and, if so, are the

Table 3. Values of the intermolecular stretching force constant k_{σ} [N m^{-1}] for a selection of hydrogen-bonded complexes $\text{B} \cdots \text{HX}$.^[a]

B	HX		
	HF	HCl	HBr
CO	8.5 (8.5)	3.9 (4.2)	3.0 (3.6)
C_2H_2	– (12.8)	6.4 (6.4)	– (5.4)
C_2H_4	– (11.8)	5.9 (5.9)	5.2 ^[118] (4.9)
H_2S	12.0 (12.0)	6.8 (6.0)	5.9 (5.0)
HCN	18.2 (18.2)	9.1 (9.1)	7.3 (7.7)
NH_3	32.8 (30.0) ^[b]	17.6 (14.9) ^[76]	13.4 (12.5) ^[77]

[a] Experimental values are from references [61] or [62], unless otherwise noted. Values in parenthesis were calculated by using the appropriate N_{B} and E_{XY} values from Table 4 and the analogue of Equation (10). [b] Calculated by using the value of D_{H} communicated to the author by P. R. R. Langridge-Smith and B. J. Howard, in the appropriate expression from reference [22].

Table 4. Values of nucleophilicities N_{B} of Lewis bases B and electrophilicities E_{HX} of HX, as determined from k_{σ} values of $\text{B} \cdots \text{HX}$.

nucleophilicities ^[a]						
B	CO	C_2H_2	C_2H_4	H_2S	HCN	NH_3
N_{B}	3.4	5.1	4.7	4.8	7.3	11.9
electrophilicities ^[b]						
HX	HF	HCl	HBr			
E_{HX}	10.0	5.0	4.2			

[a] Values of N_{B} were obtained from the k_{σ} values of a wide range of $\text{B} \cdots \text{HX}$ in references [61] and [62], except for N_{NH_3} , which was estimated by using only the k_{σ} for $\text{H}_3\text{N} \cdots \text{HCN}$ and $\text{H}_3\text{N} \cdots \text{HCCH}$. [b] Values of E_{HX} from references [61] and [62].

nucleophilicities of B with respect to the XY identical with those obtained from the k_{σ} of the $\text{B} \cdots \text{HX}$ series.

We begin by assuming that c in Equation (10) has the same value for both the $\text{B} \cdots \text{HX}$ and $\text{B} \cdots \text{XY}$ series. We choose arbitrarily that $E_{\text{BrCl}} = 9.0$ and then use k_{σ} for the $\text{B} \cdots \text{BrCl}$ series^[45–49] in Equation (10) to obtain the N_{B} values for CO, C_2H_2 , C_2H_4 , HCN, and H_2S shown in Table 5. We do not use the $\text{H}_3\text{N} \cdots \text{BrCl}$ value^[50] to obtain N_{NH_3} because the approx-

Table 5. Values of nucleophilicities N_{B} of Lewis bases B and electrophilicities E_{XY} of dihalogen molecules XY calculated from k_{σ} values of $\text{B} \cdots \text{XY}$.^[a]

nucleophilicities						
B	CO	C_2H_2	C_2H_4	H_2S	HCN	NH_3
N_{B}	2.8	4.2	4.7	5.4	4.9	9.9
electrophilicities						
XY	F_2	Cl_2	Br_2	BrCl	ClF	
E_{XY}	1.9	5.1	7.4	9.0	9.8	

[a] Values of N_{B} and E_{XY} were obtained from the k_{σ} values of a wide range of $\text{B} \cdots \text{XY}$, as described in detail in the text.

imation of weak interaction probably does not hold in this complex, which has $k_{\sigma} = 26.7(3) \text{ N m}^{-1}$. Instead, we employ $k_{\sigma} = 12.7 \text{ N m}^{-1}$ of $\text{H}_3\text{N} \cdots \text{Cl}_2$ ^[38] with $E_{\text{Cl}_2} = 5.1$ (see below) to obtain $N_{\text{NH}_3} = 9.9$ from Equation (10). The choices of $E_{\text{F}_2} = 1.9$, $E_{\text{Cl}_2} = 5.1$, $E_{\text{Br}_2} = 7.4$, $E_{\text{BrCl}} = 9.0$, and $E_{\text{ClF}} = 9.8$ together

with the N_{B} values of Table 5 then reproduce the observed k_{σ} values (see Table 3) reasonably well; exceptions are for $\text{H}_3\text{N} \cdots \text{BrCl}$ and $\text{H}_3\text{N} \cdots \text{ClF}$, which have observed k_{σ} values considerably larger than those predicted on the basis of the E_{XY} and N_{B} values of Table 5 by using Equation (10). These larger values are thought to arise from a nonnegligible charge transfer, as represented by a small contribution of the ionic structure $[\text{H}_3\text{N}^+ \cdots \text{Y}^-]$ to the valence bond description of these complexes.^[59] In the case of $\text{H}_3\text{N} \cdots \text{ClF}$, evidence in favor of this conclusion can also be adduced from the Cl nuclear quadrupole coupling constant. (See Section 4 for further discussion.)

Table 4 contains the N_{B} values determined for the $\text{B} \cdots \text{HX}$ series, while Table 5 lists those derived from $\text{B} \cdots \text{XY}$ in the manner described above. The magnitude of N_{B} for the two classes of complex is similar for a given B, except for the case of HCN, which appears to exhibit a much greater nucleophilicity with respect to hydrogen halides than it does with respect to diatomic halogen or interhalogen molecules. The E_{XY} values of Table 5 should be compared with the set of E_{HX} derived previously from k_{σ} of $\text{B} \cdots \text{HX}$ complexes (Table 4). The order $E_{\text{F}_2} < E_{\text{Cl}_2} < E_{\text{Br}_2} < E_{\text{BrCl}} < E_{\text{ClF}}$ is reasonable in view of the order of the electric quadrupole moments^[69, 70] of $2.76 \times 10^{-40} \text{ C m}^2$, $10.79(54) \times 10^{-40} \text{ C m}^2$, and $17.52 \times 10^{-40} \text{ C m}^2$ for F_2 , Cl_2 , and Br_2 , respectively, and the fact that BrCl and ClF have small electric dipole moments of similar magnitude.^[71, 72]

3.3. Systematic Behavior among Angular Geometries of $\text{B} \cdots \text{XY}$

3.3.1. Introduction

The analysis of the halogen nuclear quadrupole coupling constants of $\text{B} \cdots \text{XY}$ (Section 3.1) established that most complexes involve only a minor perturbation of the electric charge distribution of the halogen. Similarly, the intermolecular stretching force constants k_{σ} , considered in Section 3.2, are usually small and indicate that the intermolecular binding is weak. The systematic behavior of the k_{σ} as B and XY are varied is similar to that observed previously for a large number of hydrogen-bonded complexes $\text{B} \cdots \text{HX}$, the properties of which can be understood on the basis of a simple electrostatic model. It seems likely that the properties of the series $\text{B} \cdots \text{XY}$ may also be accounted for by such a model. In this section we consider angular geometries of $\text{B} \cdots \text{XY}$ determined from the rotational spectra under the assumption of unperturbed monomer geometries. This assumption is reasonable in view of the conclusions about electric charge redistribution and the strength of the interaction given above. Moreover, ab initio calculations on some $\text{B} \cdots \text{XY}$ confirm that this assumption is unlikely to lead to serious errors.^[41, 73, 74]

The angular geometries of the $\text{B} \cdots \text{HX}$ were rationalized some time ago by using a set of empirical rules^[67, 75] that are electrostatic in origin. These rules may be stated in three parts: The angular geometry of a hydrogen-bonded complex $\text{B} \cdots \text{HX}$ can be predicted by assuming that, in the equilibrium arrangement, the axis of the HX molecule lies 1) along the axis of a nonbonding electron pair (n-pair) of the electron-

donor atom of B, with $H^{\delta+}$ closer to the n-pair than $X^{\delta-}$, or 2) if B carries no n-pairs, along the local symmetry axis of a π or pseudo- π orbital, whereby $H^{\delta+}$ interacts with the π density. 3) If B carries both n- and π pairs, rule (1) defines the angular geometry.

3.3.2. n-Type Complexes of Simple Lewis Bases ($B = CO, HCN, NH_3, H_2O, H_2S, HF$)

In this section we shall examine whether these rules apply to $B \cdots XY$ complexes and, if so, how accurate is the parallelism between the $B \cdots XY$ and $B \cdots HX$ angular geometries. We shall use mostly $B \cdots HCl$ as the example of the latter because this is the series within $B \cdots HX$ that is most extensively investigated.

We consider first those complexes $B \cdots XY$ for which the symmetry of B is such that the assumption of linearity of the systems $Z \cdots X-Y$ and $Z \cdots H-Cl$ (Z is the electron-donor atom/center in B), implicit in the rules as stated in Section 3.3.1, will hold. We shall then consider examples where the hydrogen and halogen bonds can be nonlinear.

The complexes $H_3N \cdots F_2$,^[65] $H_3N \cdots Cl_2$,^[38] $H_3N \cdots Br_2$,^[39] $H_3N \cdots BrCl$,^[50] and $H_3N \cdots ClF$ ^[59] all have C_{3v} geometry of the type shown in Figure 6. Hence they are consistent with rule (1), when it is restated to take into account that the electrophilic region of the halogen ($\delta+$ in $\delta^+X^{\delta-}X^{\delta+}$ or $\delta^+X-Y^{\delta-}$) interacts with the n-pair on N so that XY lies along

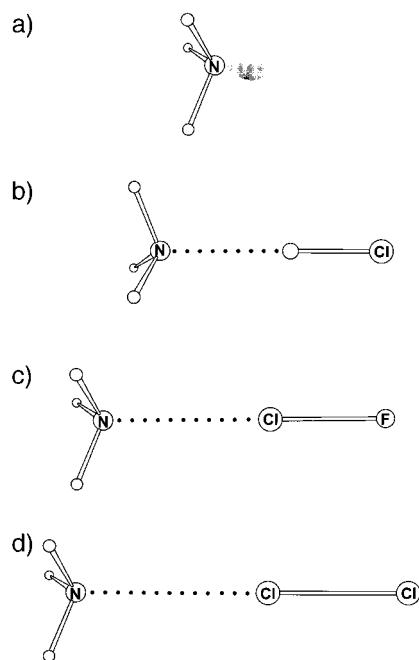


Figure 6. a) Nonbonding pair electron density model of NH_3 and the observed C_{3v} geometries of b) $H_3N \cdots HCl$, c) $H_3N \cdots ClF$, and d) $H_3N \cdots Cl_2$. All diagrams in this review are drawn to scale. Hydrogen atoms are shown as small open circles and are unlabeled. All other atoms are labeled. The orbitals of nonbonding electron pairs are drawn in the exaggerated “rabbit’s ear” form that is conventional in chemistry; they are not to be taken literally. Component geometries are assumed to be unperturbed by complex formation. Distances $r(Z \cdots X)$ for all complexes $B \cdots XY$ and $B \cdots HX$ considered here, where Z is the acceptor atom or center in B, can be found in Tables 7–10.

the C_3 axis. Similar geometries have been observed for $H_3N \cdots HX$ complexes ($X = Cl$,^[76] Br ,^[77] I ^[78]) as shown in Figure 6 for $H_3N \cdots HCl$. A similar interpretation applies to the C_{3v} complex $H_3P \cdots Cl_2$,^[34] which is isostructural with $H_3P \cdots HX$ ($X = F$,^[79] Cl ,^[80] Br ,^[81] I ^[82]).

The complexes $OC \cdots Cl_2$,^[32] $OC \cdots Br_2$,^[40] $OC \cdots BrCl$,^[45] and $OC \cdots ClF$ ^[53] all have linear arrangements in which the n-pair on C is the center of interaction with the $\delta+$ region of the halogen or interhalogen molecule. This arrangement is isomorphous with those observed for all $OC \cdots HX$ ($X = F$,^[83] Cl ,^[84] Br ,^[85] I ^[86]) and is that predicted by a suitably modified rule (3), since OC carries both n-pairs and π pairs, but the n-pair on C takes precedence. The complexes $HCN \cdots F_2$,^[63] $HCN \cdots Cl_2$,^[37] $HCN \cdots BrCl$,^[49] and $HCN \cdots ClF$ ^[56] also have a linear geometry, in which XY is preferentially attached to the axial nonbonding pair on N rather than to the π electrons of the $C \equiv N$ bond. Hence rule (3) is obeyed by this series also. The $HCN \cdots HX$ ^[87–90] have a similar geometry.

The symmetries of the Lewis bases B so far discussed lead to complexes in which the $Z \cdots X-Y$ and $Z \cdots H-X$ systems are linear in the equilibrium geometry, where Z is the electron-donor atom or the center of the π bond in B. The first, and simplest, examples in which the conventional nonbonding or π electron model of the Lewis base B leads to the possibility of a nonlinear $Z \cdots X-Y$ or $Z \cdots H-X$ system occur when B is H_2O or H_2S . The nonbonding electron pair model of H_2O is shown in Figure 7 and leads, according to

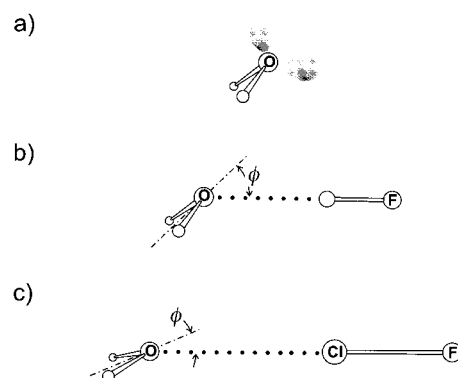


Figure 7. a) Nonbonding electron pair model of H_2O and the observed geometries (pyramidal, C_s) of b) $H_2O \cdots HF$ and c) $H_2O \cdots ClF$. The equilibrium geometry for $H_2O \cdots HF$ is shown, for which the angle $\phi = 46(5)^\circ$, as determined in reference [92]. For $H_2O \cdots ClF$, the estimated value is $\phi \approx 20^\circ$, but this is an effective value for the zero-point state (see reference [58]).

rule (1), to the prediction of a pyramidal equilibrium geometry for $H_2O \cdots ClF$ and $H_2O \cdots F_2$. In fact, the available experimental data are insufficient to determine whether the $O \cdots Cl-F$ or $O \cdots F-F$ nuclei are strictly collinear in the equilibrium arrangement and therefore collinearity was assumed. The experimental evidence was sufficient, however, to show that $H_2O \cdots ClF$ ^[58] and $H_2O \cdots F_2$ ^[91] are either effectively planar or planar in the equilibrium geometry. In this context effectively planar means that, although the equilibrium configuration at O is pyramidal, the energy

barrier at the planar conformation is low enough that the vibrational wavefunctions can be classified according to the representations of the C_{2v} point group, that is, even in the zero-point state, the molecule tunnels rapidly between the equivalent pyramidal conformers. There are some indications that $\text{H}_2\text{O} \cdots \text{ClF}$ is, like $\text{H}_2\text{O} \cdots \text{HF}$, effectively planar, so that the equilibrium geometry is pyramidal, as required by the rules and the model of Figure 7. A detailed analysis of rotational spectra in vibrationally excited states associated with the intermolecular bending modes in $\text{H}_2\text{O} \cdots \text{HF}$ showed^[92] that although the barrier to the planar form is low, it is nonzero and the equilibrium geometry is as shown in Figure 7, with the angle $\phi = 46^\circ$ between the HF axis and the C_2 axis close to half the tetrahedral angle required by rule (1). The preferred angular geometry of $\text{H}_2\text{O} \cdots \text{ClF}$ is also shown in Figure 7. It is not possible to determine whether $\text{H}_2\text{O} \cdots \text{F}_2$ is planar or effectively planar, but in view of the weakness of its binding ($k_0 = 3.63(7) \text{ N m}^{-1}$) and the fact that the barrier is below the zero-point energy level in the more strongly bound $\text{H}_2\text{O} \cdots \text{HF}$ ($k_0 = 25(2) \text{ N m}^{-1}$), it is likely to be planar for all practical purposes and is so drawn in Figure 8. Both $\text{H}_2\text{O} \cdots \text{HCl}$ ^[93] and $\text{H}_2\text{O} \cdots \text{HBr}$ ^[94] are also effectively planar. Thus, all of the $\text{H}_2\text{O} \cdots \text{HX}$ and $\text{H}_2\text{O} \cdots \text{XY}$ complexes considered here can be viewed as “floppy” with respect to intermolecular bending.



Figure 8. The observed geometry of $\text{H}_2\text{O} \cdots \text{F}_2$, which is effectively planar in the zero-point state (see reference [91]).

A nonbonding electron pair model of H_2S in which the two nonbonding pairs occupy two sp hybrid orbitals whose axes are at 180° to each other and at 90° to the plane of the H_2S nuclei (Figure 9a) is consistent with the observed geometries

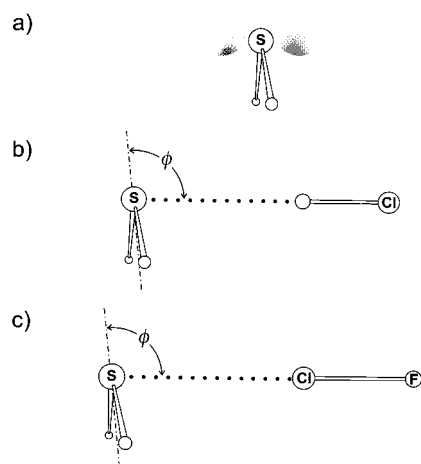


Figure 9. a) Nonbonding electron pair model of H_2S and the observed geometries of b) $\text{H}_2\text{S} \cdots \text{HCl}$ ($\phi = 93.8(5)^\circ$) and c) $\text{H}_2\text{S} \cdots \text{ClF}$ ($\phi = 95.8(5)^\circ$).

of $\text{H}_2\text{S} \cdots \text{XY}$. According to rule (1), in the equilibrium geometry of $\text{H}_2\text{S} \cdots \text{XY}$ complexes the axis of the XY molecule should lie perpendicular to the H_2S plane. In fact,

detailed interpretations of the halogen nuclear quadrupole coupling constants in $\text{H}_2\text{S} \cdots \text{Cl}_2$,^[35] $\text{H}_2\text{S} \cdots \text{BrCl}$,^[48] and $\text{H}_2\text{S} \cdots \text{ClF}$ ^[57] allow the conclusion that the $\text{S} \cdots \text{X}-\text{Y}$ nuclei in these three complexes lie within a degree or so of collinearity. The determined geometry of one such complex is shown in Figure 9c. Again it is remarkably similar to that in the series $\text{H}_2\text{S} \cdots \text{HX}$ ($\text{X} = \text{F}$,^[95] Cl ,^[96] Br ^[97]) which is exemplified by $\text{H}_2\text{S} \cdots \text{HCl}$ in Figure 9b. In none of the $\text{H}_2\text{S} \cdots \text{XY}$ or $\text{H}_2\text{S} \cdots \text{HX}$ molecules is there any evidence of other than a high potential energy barrier at the planar form, and it is concluded that, on the time scale of the microwave experiment, they are permanently pyramidal.

The situation is somewhat different for $\text{H}_2\text{S} \cdots \text{F}_2$,^[64] however. The geometry determined from zero-point rotational constants of four isotopomers is shown in Figure 10 and is

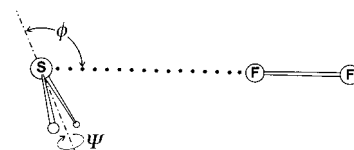


Figure 10. The observed geometry of $\text{H}_2\text{S} \cdots \text{F}_2$. The angle $\phi = 113(5)^\circ$, and the internal rotation of H_2S about its local C_2 axis (angle ψ) gives rise to a low-energy vibrational satellite in the rotational spectrum. (See text and reference [64] for discussion).

pyramidal, as for the other $\text{H}_2\text{S} \cdots \text{XY}$, with $\phi = 113(5)^\circ$. In addition, even at the low effective temperature of the supersonic expansion used for the $\text{H}_2\text{S} \cdots \text{F}_2$ complexes, a vibrational satellite is observed in the rotational spectrum. This suggests that a low potential energy barrier separates two equivalent pyramidal conformations. The barrier corresponds either to the planar C_{2v} geometry, with motion between the two equilibrium conformers like the conventional inversion of ammonia or, more likely, to the planar C_s conformation, through which the molecule passes as a result of internal rotation of the H_2S subunit about its local C_2 axis. The observation of a vibrational satellite here is consistent with the conclusion of Section 3.2 that complexes $\text{B} \cdots \text{F}_2$ are very weakly bound compared with those of the other halogens or interhalogens, at least according to the k_0 criterion. In the limit of weak binding and a long distance $r(\text{S} \cdots \text{F}_1)$, a less rigid geometry is to be expected.^[75] Nevertheless, it is significant that $\text{H}_2\text{S} \cdots \text{F}_2$ is still isostructural with the other $\text{H}_2\text{S} \cdots \text{HX}$ (see Figures 9 and 10).

In the $\text{H}_2\text{O} \cdots \text{XY}$ and $\text{H}_2\text{S} \cdots \text{XY}$ series, the electron-donor atom O or S of the Lewis base B carries two equivalent nonbonding electron pairs. There is one example of a set $\text{B} \cdots \text{XY}/\text{B} \cdots \text{HX}$ so far investigated in which B carries three equivalent nonbonding pairs in the conventional model, namely, when B is HF (Figure 11). The three complexes $\text{HF} \cdots \text{ClF}$,^[98] $\text{HF} \cdots \text{Cl}_2$,^[33] and $\text{HF} \cdots \text{HCl}$ ^[99] are again isostructural, as illustrated by the determined geometries of $\text{HF} \cdots \text{ClF}$ and $\text{HF} \cdots \text{HCl}$ drawn to scale in Figure 11. The angles ϕ are consistent with rule (1). Interestingly, the isomer $\text{HCl} \cdots \text{HF}$ has also been observed^[100] and has a right-angled geometry, as expected from rule (1) if the n-pairs on the second-row atom Cl are at 90° to each other, as is commonly assumed.

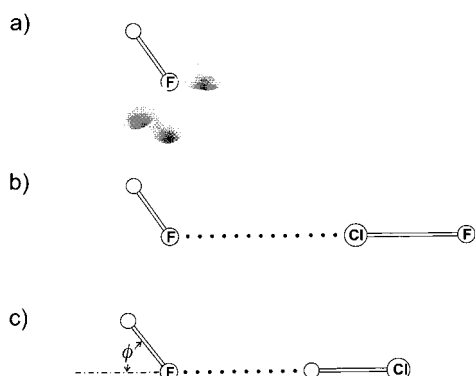


Figure 11. a) Nonbonding electron pair model of HF and the observed geometries (planar, C_s) of b) $\text{HF} \cdots \text{CIF}$ ($\phi = 55^\circ$) and c) $\text{HF} \cdots \text{HCl}$ ($\phi = 50^\circ$).

3.3.3. *n*-Type Complexes of More Complicated Lewis Bases: Deviations of $\text{Z} \cdots \text{X}-\text{Y}$ Nuclei from Collinearity

If a complex involving XY or HX with B has C_s symmetry or lower, the halogen or hydrogen bonds can be nonlinear, that is, the nuclei $\text{Z} \cdots \text{X}-\text{Y}$ or $\text{Z} \cdots \text{H}-\text{X}$ can deviate from collinearity, where Z is the electron-donor atom or center of B. This section outlines the method for measuring the angular deviation of the nuclei from collinearity and then compares the results for the two series of complexes $\text{B} \cdots \text{CIF}$ and $\text{B} \cdots \text{HCl}$, where B is an *n*-pair donor. The reasons why the method has so far been restricted largely to CIF complexes in the $\text{B} \cdots \text{XY}$ series will become apparent.

We shall focus our attention on complexes in which the Lewis base B is 2,5-dihydrofuran, formaldehyde, oxirane, or thiirane. All complexes $\text{B} \cdots \text{CIF}$ ^[101–104] and $\text{B} \cdots \text{HCl}$ ^[105–109] of these Lewis bases have C_s symmetry, and therefore the molecular symmetry plane must coincide with one of the principal inertial planes (in fact, *ab* or *ac*). Then one of the off-diagonal elements of the Cl nuclear quadrupole coupling tensor χ_{ab} or χ_{ac} will be nonzero. For such complexes it can be shown^[23, 105] that, to a good degree of approximation, the equilibrium angle α_{az} between the *a* inertial axis and the CIF or HCl axis *z* is given by Equation (11) or by the corresponding expression in which the right hand side involves χ_{ac} , χ_{aa} , and χ_{cc} .

$$\tan(2\alpha_{az}) = -2\chi_{ab}/(\chi_{aa} - \chi_{bb}) \quad (11)$$

The angle α_{az} is an important geometrical quantity because it defines the position of the CIF or HCl subunit in the equilibrium conformation of the complex and can be combined with the principal moments of inertia of appropriate isotopomers to determine precisely the relative positions and orientations of the subunits B and CIF or HCl in space. It then follows that the positions of the electron-donor atom Z and the Cl and F nuclei in, for example, $\text{B} \cdots \text{CIF}$ are precisely known and hence so is the deviation of the $\text{Z} \cdots \text{Cl}-\text{F}$ system from linearity.

Figure 12 compares the angular geometries of the two C_s planar molecules $\text{H}_2\text{CO} \cdots \text{CIF}$ ^[102] and $\text{H}_2\text{CO} \cdots \text{HCl}$ ^[106, 107] as determined by fitting their principal moments of inertia under the constraint that the geometry obtained must also repro-

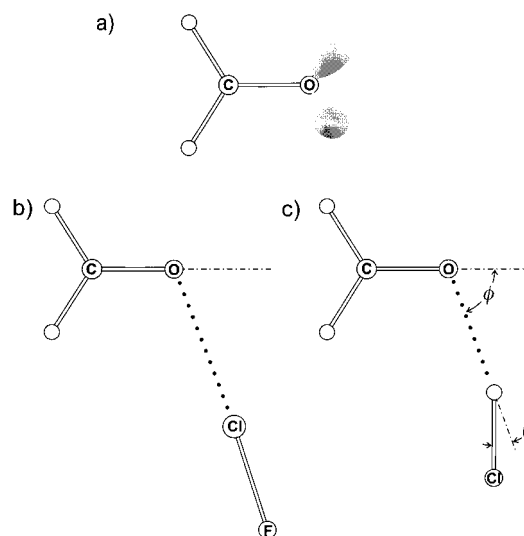


Figure 12. a) Nonbonding electron pair model of H_2CO and the observed angular geometries (C_s , planar) of b) $\text{H}_2\text{CO} \cdots \text{CIF}$ ($\phi = 69.1(7)^\circ$; $\theta = 3.2(7)^\circ$) and c) $\text{H}_2\text{CO} \cdots \text{HCl}$ ($\phi = 70.0(10)^\circ$; $\theta = 20.5(8)^\circ$). The angle θ is a measure of the angular deviation of the $\text{O} \cdots \text{Cl}-\text{F}$ or $\text{O} \cdots \text{H}-\text{Cl}$ nuclei from collinearity.

duce the angle α_{az} from Equation (11). Details of the fitting method and of the method for estimating errors are given elsewhere.^[23] The diagrams in Figure 12 are drawn to scale. The angle ϕ is nearly identical in the two complexes and is close to that expected from the rules enunciated above and the familiar *n*-pair model of formaldehyde, in which O carries nonbonding electron pairs in two sp^2 hybrid orbitals (Figure 12a). However, the angle θ , which defines the angular deviations of the nuclei in $\text{O} \cdots \text{Cl}-\text{F}$ and $\text{O} \cdots \text{H}-\text{Cl}$ from collinearity, is close to zero in $\text{H}_2\text{CO} \cdots \text{CIF}$ but is $20.5(8)^\circ$ in $\text{H}_2\text{CO} \cdots \text{HCl}$. This pattern of a highly nonlinear hydrogen bond in $\text{B} \cdots \text{HCl}$ but a nearly linear halogen bond in the corresponding $\text{B} \cdots \text{CIF}$ is common, as demonstrated below.

A Lewis base that has an oxygen atom with two nonbonding electron pairs with the tetrahedral angle between them is 2,5-dihydrofuran. The C-O-C angle in this cyclic ether is 108° ,^[110] and presumably therefore the conventional approach would require the two *n*-pairs on O to complete a nearly tetrahedral environment for the atom. The complexes of 2,5-dihydrofuran with CIF ^[101] and HCl ^[105] are of C_s symmetry and have the geometries displayed in Figure 13. The angle ϕ is again similar in both complexes and is as required if the CIF/HCl molecules lie along the axis of one of the *n*-pairs on O. As for the complexes involving H_2CO , the angular deviation $\theta = 9.5^\circ$ of the $\text{O} \cdots \text{H}-\text{Cl}$ nuclei from collinearity is significant, while that for $\text{O} \cdots \text{Cl}-\text{F}$ is negligible.

If we proceed from the cyclic ether 2,5-dihydrofuran to oxirane, the accepted view is that in closing the C-O-C angle from 108° to about 60° the angle between the *n*-pairs on O should increase. The determined geometries of the complexes of oxirane with HCl ^[108] and CIF ^[103] are drawn to scale in Figure 14. The angle ϕ is essentially identical in the two complexes and its value is indeed consistent with the rules for predicting angular geometries, as the angle between the *n*-pairs on O is increased from its value of about 110° in 2,5-

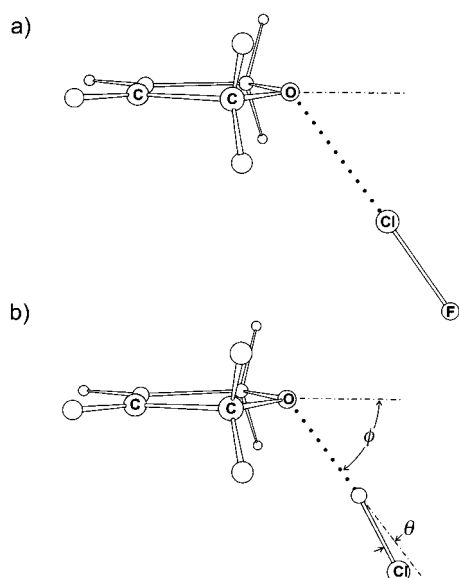


Figure 13. Observed geometries (C_s) of a) 2,5-dihydrofuran...ClF ($\phi = 53.0(3)^\circ$; $\theta = 2.0(2)^\circ$) and b) 2,5-dihydrofuran...HCl ($\phi = 54.3(3)^\circ$; $\theta = 9.5(1)^\circ$).

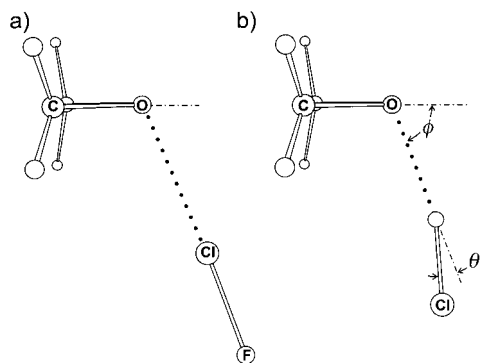


Figure 14. Observed geometries (C_s) of a) oxirane...ClF ($\phi = 67.3(1)^\circ$; $\theta = 2.9(1)^\circ$) and b) oxirane...HCl ($\phi = 69.1(1)^\circ$; $\theta = 16.5(1)^\circ$).

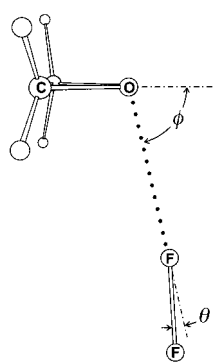


Figure 15. Observed geometry of oxirane... F_2 ($\phi = 76(4)^\circ$). Angle θ was assumed to take the value 10° . This leads to a value of $r(O \cdots F_i)$ similar to that of O-F in oxirane...HF. See Table 7 and text for discussion.

dihydrofuran. However, the hydrogen bond in $(CH_2)_2O \cdots HCl$ is significantly nonlinear ($\theta = 16.5^\circ$), while the $O \cdots Cl-F$ system in $(CH_2)_2O \cdots ClF$ deviates by only a few degrees from linearity.

The observation of complexes of oxirane with ClF and HCl is a testimony to the efficacy of the fast-mixing nozzle, given the reactivity of ClF and the facile opening of the oxirane ring by HCl. Perhaps even more remarkable is the detection and characterization of the complex of oxirane with F_2 .^[111] The resulting angular geometry of $(CH_2)_2O \cdots F_2$ is shown in Figure 15. Unfortunately, the absence of any nuclear quadrupole coupling associated with the F_2 subunit means that the angle α_{az} between the F_2 axis (z)

and the a axis cannot be determined in this case, and hence the extent of the nonlinearity of the $O \cdots F-F$ system could not be quantified. The geometry shown in Figure 15 is based on the assumption of $\theta = 10^\circ$ (minor nonlinearity), which leads to $\phi = 76(4)^\circ$, where the error arises from the assumption $\theta = 10 \pm 5^\circ$. Interestingly, even though the $O \cdots F$ interaction is weak ($k_o = 3.1 \text{ Nm}^{-1}$), there is no evidence of vibrational satellites or inversion doubling, as there was in $H_2S \cdots F_2$, for example.

The cyclic thioether thiirane forms isostructural complexes with ClF^[104] and HCl^[109] (Figure 16). The perpendicular structures with the angles $\phi \approx 90^\circ$ are readily understood on

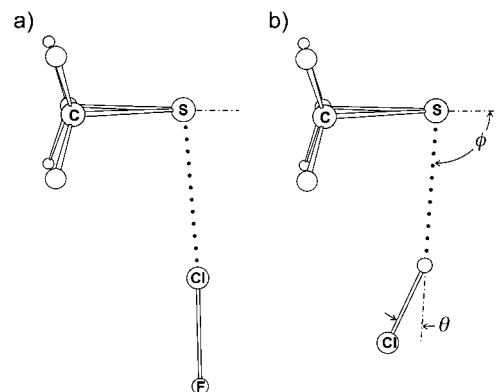


Figure 16. Observed geometries (C_s) of a) thiirane...ClF ($\phi = 85.0(2)^\circ$; $\theta = 3.5(2)^\circ$) and b) thiirane...HCl ($\phi = 94.5(20)^\circ$; $\theta = 21.0(5)^\circ$). There is some evidence for a significant contribution of the ionic structure $[(CH_2)_2S]^+ \cdots F^-$ to the valence-bond description of thiirane...ClF, which may account for the discrepancy between ϕ for these two complexes (see reference [104] for discussion).

the basis of an n-pair model of thiirane like that of H_2S (see Figure 9) and the rules for predicting angular geometries. They are also reminiscent of those of their acyclic analogues $H_2S \cdots ClF$ ^[57] and $H_2S \cdots HCl$ ^[96] (see Figure 9). Although it was shown that the $S \cdots Cl-F$ nuclei are nearly collinear in $H_2S \cdots ClF$, such a conclusion was not available for $H_2S \cdots HCl$. However, application of Equation (11) to the $(CH_2)_2S$ complexes shows that while the $S \cdots Cl-F$ nuclei in $(CH_2)_2S \cdots ClF$ deviate from collinearity by only $\theta = 3.5^\circ$, the hydrogen bond in $(CH_2)_2S \cdots HCl$ is highly nonlinear ($\theta = 21.0^\circ$).

For all complexes considered in this section so far, the electron-donor atom Z of B carries two equivalent non-bonding electron pairs. A prototype Lewis base that offers the possibility of a pair of inequivalent nonbonding electron pairs on the electron-donor atom is sulfur dioxide, the conventional n-pair model of which is shown in Figure 17. The complexes $SO_2 \cdots ClF$,^[112] $SO_2 \cdots HCl$,^[23, 113] and $SO_2 \cdots HF$ ^[114] have very similar angular geometries, the first two of which are included in Figure 17. In each case the ClF or HX molecule lies approximately along the axis of the n-pair that is *cis* to the S=O bond. The microwave spectrum of $SO_2 \cdots HCl$ provides evidence of considerable nonrigidity, so in the geometry displayed in Figure 17 the deviation of ϕ from the expected value may not be significant. The nuclei $O \cdots H-Cl$ in $SO_2 \cdots HCl$ ^[23] and $O \cdots Cl-F$ in $SO_2 \cdots ClF$ ^[112] are within a degree or so of collinearity, as indicated by precise determination of θ

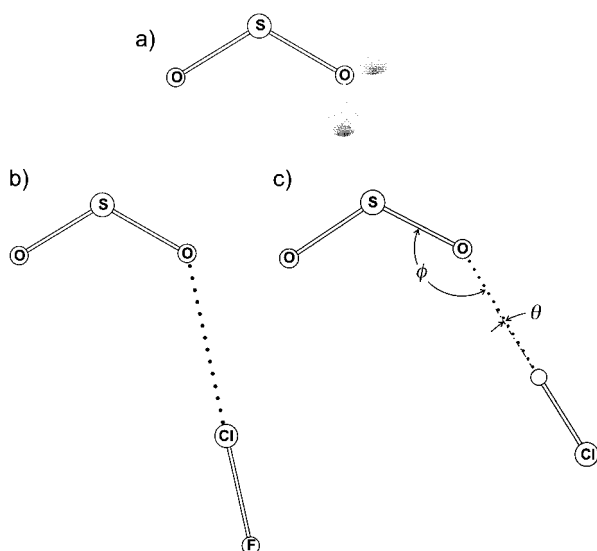


Figure 17. a) Nonbonding electron pair model of SO_2 and observed geometries of b) $\text{SO}_2 \cdots \text{ClF}$ ($\phi = 131.9(6)^\circ$; $\theta = -0.7(2)^\circ$) and c) $\text{SO}_2 \cdots \text{HCl}$ ($\phi = 143.0(1)^\circ$; $\theta = -2.5(7)^\circ$). The “floppiness” of the complex $\text{SO}_2 \cdots \text{HCl}$ may account for its larger angle ϕ .

from the off-diagonal element χ_{ab} of the Cl nuclear quadrupole coupling tensor. This fact is of importance in the simple model for describing deviations of hydrogen bonds and halogen bonds from linearity that is discussed in Section 3.5.2.

The discussions in this section reveal a parallel between the angular geometries of $\text{B} \cdots \text{ClF}$ and $\text{B} \cdots \text{HCl}$ complexes of C_s symmetry when B is an n-pair donor, but with the main difference that the hydrogen bond deviates significantly from linearity while the $\text{Z} \cdots \text{Cl}-\text{F}$ nuclei remain nearly collinear as B varies. A simple interpretation of this behavior is possible but will be postponed until after the angular geometries of complexes $\text{B} \cdots \text{XY}$ and $\text{B} \cdots \text{HX}$ in which B is a nonaromatic π donor or an aromatic π donor are considered in the following two sections.

3.3.4. π -Type Complexes in Which B is a Nonaromatic π -Electron Donor

Figures 18 and 19 show the experimentally determined angular geometries of the complexes of the two simplest π -electron donors ethene^[27] and ethyne,^[26] respectively, with Cl_2 , as well as those of ethene $\cdots\text{HCl}$ ^[115] and ethyne $\cdots\text{HCl}$,^[116] which are clearly isostructural with those of the corresponding chlorine complexes. Other complexes ethene $\cdots\text{XY}$ ($\text{XY} = \text{BrCl}$,^[46] ClF ,^[55] HF ,^[117] HBr ^[118]) also have the angular geometry shown in Figure 18 and, correspondingly, other complexes ethyne $\cdots\text{XY}$ ($\text{XY} = \text{BrCl}$,^[47] ClF ,^[54] and HF ^[119]) have been shown to have the planar T shape illustrated in Figure 19. In all cases, $\text{X}^{\delta+}$ of XY interacts with the π -electron density. All of these angular geometries are readily understood on the basis of rule (2) in Section 3.3.1, that is, the electrophile Cl_2 or HCl lies along the symmetry axis of a π orbital of the Lewis base. The familiar π bonding electron density distributions of ethene and ethyne are shown in Figures 18 and 19, respectively.

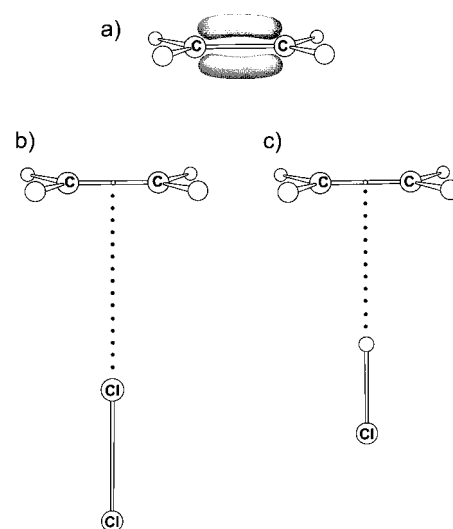


Figure 18. a) π -Bonding electron density model of ethene and observed geometries (perpendicular, C_{2v}) of b) ethene $\cdots\text{ClF}$ and c) ethene $\cdots\text{HCl}$. In this, and subsequent figures, the symbol $\circ$ marks the center of the C–C multiple bond.

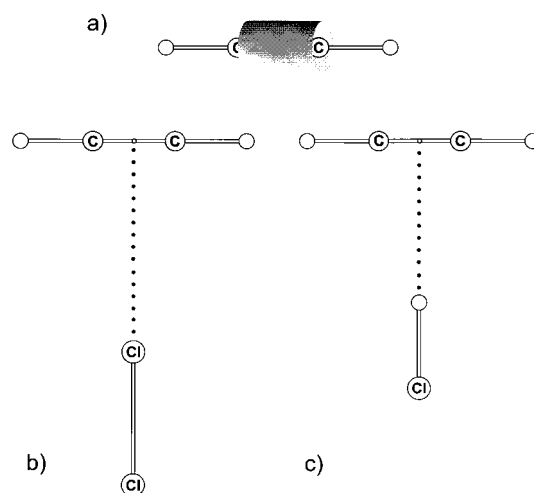


Figure 19. a) π -Bonding electron density model of ethyne (schematic; cylindrical symmetry) and observed geometries (planar, C_{2v}) of b) ethyne $\cdots\text{ClF}$ and c) ethyne $\cdots\text{HCl}$.

The similarity of cyclopropane in its chemical behavior to an olefin led to a description of the molecule (from Coulson and Moffitt)^[120] in which its unsaturated character was accounted for by a pseudo- π carbon–carbon bond formed by overlap of a pair of sp^3 hybrid orbitals on adjacent carbon atoms. A schematic electron-density distribution for one of the bonds of cyclopropane resulting from the Coulson–Moffitt model is displayed in Figure 20. Such bonds have often been referred to as “banana” bonds. The symmetry axis of the pseudo- π orbital coincides with a median of the cyclopropane equilateral triangle. Hence, according to rule (2), the angular geometry of complexes such as cyclopropane $\cdots\text{ClF}$ ^[121] and cyclopropane $\cdots\text{HCl}$ ^[122] should have C_{2v} symmetry with the ClF or HCl internuclear axis coincident with the median and with the electrophilic end $\text{Cl}^{\delta+}$ of ClF or $\text{H}^{\delta+}$ of HCl closer to the C–C bond than $\text{F}^{\delta-}$ or $\text{Cl}^{\delta-}$, respectively. The observed geometries of the two complexes (Figure 20b, c) reveal that this is indeed the case.

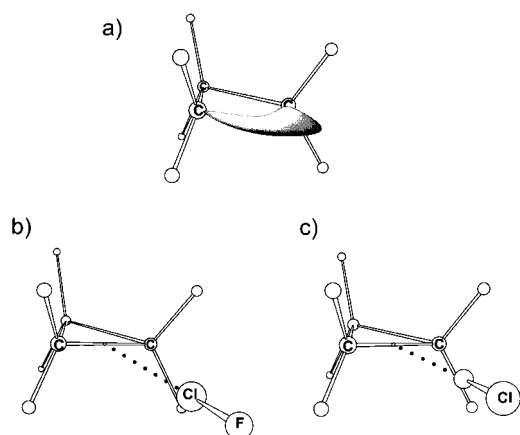


Figure 20. a) Pseudo- π electron density model (Coulson and Moffit^[120]) of cyclopropane and observed geometries of b) cyclopropane $\cdots$ CIF and c) cyclopropane $\cdots$ HCl.

The prototype Lewis base that carries a pair of conjugated, nonaromatic π bonds is 1,3-butadiene. According to rule (2), the axis of a CIF or HCl molecule, for example, will lie along the local symmetry axis of one of the π orbitals. Two possibilities then exist, however. Either the CIF/HCl interaction is localized and involves only one of the π bonds (if the potential energy barrier to tunneling between the four equivalent positions is sufficiently high), or tunneling occurs between the four positions for a low barrier. The geometry of the complex of CIF with 1,3-butadiene^[123] is drawn to scale in Figure 21. The ground-state rotational spectrum of this

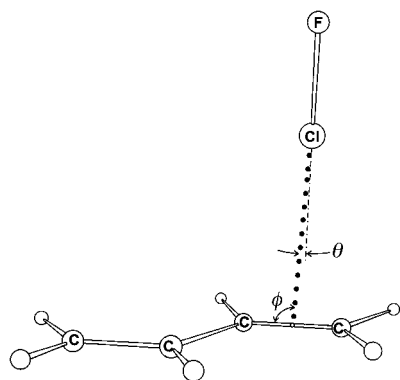


Figure 21. Observed geometry of 1,3-butadiene $\cdots$ CIF. The CIF molecular axis is perpendicular to the plane of the nuclei of 1,3-butadiene, with $\phi = 95.0(2)^\circ$ and $\theta = 2.6(10)^\circ$. θ defines the angular deviation of the $\cdots$ Cl-F system from linearity.

complex showed no evidence of quantum mechanical tunneling between the equivalent structures, and therefore, on the time scale of the microwave experiment, we conclude that the $\pi \cdots$ CIF interaction is localized at a single site. The geometry displayed in Figure 21 is consistent with rule (2) in that the CIF axis is perpendicular to the plane of the nuclei in 1,3-butadiene and the angle ϕ is 95° , where $\circ$ indicates the center of the $C_1=C_2$ bond. A comparison with the corresponding HCl complex is not yet possible, because the rotational spectrum of 1,3-butadiene $\cdots$ HCl exhibits the characteristics of nonrigid

rotor behavior, probably as a result of a low potential energy barrier between the four equivalent conformers.^[124]

Four equivalent centers of interaction between a π orbital and a Lewis acid such as CIF or HCl are also possible when the π donor is the prototype system carrying two cumulative π bonds, namely, allene. The π -electron density model of allene is displayed in Figure 22, together with the experimentally

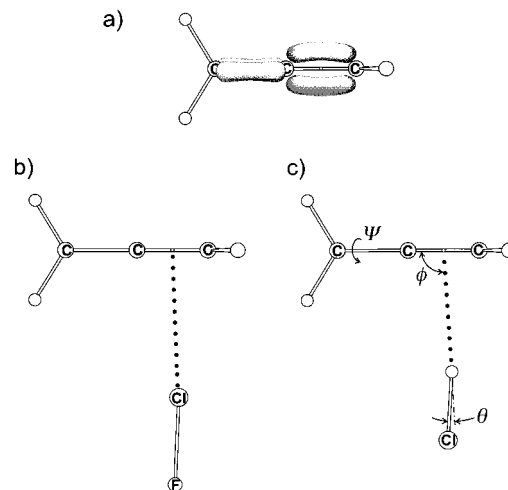


Figure 22. a) π -Bonding electron density model of allene and observed geometries (C_s) of b) allene $\cdots$ CIF ($\phi = 92.5(7)^\circ$; $\theta = 4.9(15)^\circ$) and c) allene $\cdots$ HCl ($\phi = 93(4)^\circ$; $\theta \approx 7^\circ$). ψ is the angle of rotation of the allene subunit with respect to its C_2 axis (the geometry with $\psi = 0$ is shown here).

determined angular geometries of allene $\cdots$ HCl^[125] and allene $\cdots$ CIF.^[126] Although all angles of rotation ψ about the $C=C=C$ axis are consistent with the spectroscopic constants observed in both investigations because allene is a symmetric-top molecule, the chemically reasonable choice $\psi = 0$ is shown in Figure 22. In that case, the electrophilic end $H^{\delta+}$ or $Cl^{\delta+}$ of HCl or CIF interacts with the maximum of π -electron density. The angle $\psi = 90^\circ$ would correspond to the interaction of these atoms with the nodal plane of a π orbital.

The C_s symmetry of allene $\cdots$ HCl and allene $\cdots$ CIF leads to nonzero elements χ_{ab} of the Cl nuclear quadrupole coupling tensor and hence, by the method described in Section 3.3.3, to the angles θ defining the nonlinearities of the $Z \cdots H-Cl$ and $Z \cdots Cl-F$ systems as well as the angles ϕ (see Figure 22 for definitions). We note again that the angle ϕ for each complex is close to the value of 90° required by rule (2). The value of $\theta \approx 7^\circ$ for allene $\cdots$ HCl^[125] and $\theta = 4.9(15)^\circ$ ^[126] for allene $\cdots$ CIF are both in a direction that suggests a secondary interaction of $Cl^{\delta-}$ and $F^{\delta-}$, respectively, with the nearest H atom on the C atom remote from the center of the π interaction. Recall that secondary interactions of this kind were observed for the $B \cdots HCl/B \cdots CIF$ complexes of C_s symmetry in which the primary interaction is with an n-pair donor.

The final example of a Lewis base that is a nonaromatic π donor is methylenecyclopropane. In the sense that methylenecyclopropane has two pseudo- π C-C bonds of a cyclopropane ring contiguous with the $C_1=C_2$ π bond, it may be taken as the prototype that carries cumulative π and pseudo- π bonds. The observed geometries of complexes of this Lewis base with CIF^[127] and HCl^[128] are shown in Figure 23. Clearly,

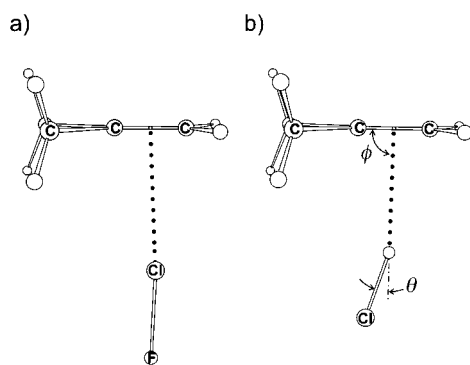


Figure 23. Observed geometries of a) methylenecyclopropane $\cdots$ CIF ($\phi = 92.5(5)^\circ$; $\theta = 4.9(1)^\circ$) and b) methylenecyclopropane $\cdots$ HCl ($\phi = 90.8^\circ$; $\theta = 17.5^\circ$). The similarity between the geometries of methylenecyclopropane $\cdots$ CIF and allene $\cdots$ CIF (Figure 22) is noteworthy.

the intermolecular interaction involves $\text{Cl}^{\delta+}$ or $\text{H}^{\delta+}$ and the π bond rather than the pseudo- π bond, and the fact that the angles ϕ are close to 90° in both complexes is consistent with rule (2). The $\text{Z} \cdots \text{H}-\text{Cl}$ system again shows considerable deviation from linearity, while that of $\text{Z} \cdots \text{Cl}-\text{F}$ system is small. If the values of $\theta \neq 0^\circ$ were an artefact of an unsymmetrical π bond, one would expect similar values for both the HCl and CIF complexes of methylenecyclopropane.

3.3.5. π -Type Complexes in Which B is an Aromatic π -Electron Donor

It is clear from the preceding section that rule (2) applies to all complexes $\text{B} \cdots \text{CIF}/\text{B} \cdots \text{HCl}$ so far investigated in which B is a nonaromatic π -electron donor. Thus, for those cases in which both $\text{B} \cdots \text{CIF}$ and $\text{B} \cdots \text{HCl}$ have been investigated, the pairs have isomorphous angular geometries that differ only in the extent of the nonlinearities of the $\text{Z} \cdots \text{Cl}-\text{F}$ and $\text{Z} \cdots \text{H}-\text{Cl}$ systems. In this section, we discuss the angular geometries of complexes in which B is potentially an aromatic π -electron donor. The molecules B considered are the prototype aromatic π -electron donor benzene and the two simple heteroaromatic molecules furan and thiophene. Although complexes $\text{B} \cdots \text{HX}$ have been investigated for $\text{X} = \text{F}, \text{Cl}$, and Br , the $\text{B} \cdots \text{XY}$ systems examined have so far been restricted to those with $\text{XY} = \text{CIF}$, since they are spectroscopically more tractable than other $\text{B} \cdots \text{XY}$.

When B is the prototype aromatic molecule benzene, rule (2) predicts that the electrophilic end $\text{Cl}^{\delta+}$ of CIF or $\text{H}^{\delta+}$ of HX will interact with the π -electron system, but the equivalence of the six maxima in the π -electron density that occur at the midpoints of the C–C bonds leads to an ambiguity. Two possibilities exist: $\text{Cl}^{\delta+}/\text{H}^{\delta+}$ is localized at the center of a C–C bond, as is the case for all of the nonaromatic π -electron donors (except for the interaction of allene with HCl), or internal motion of the CIF/HX subunit allows $\text{Cl}^{\delta+}/\text{H}^{\delta+}$ to sample the six equivalent positions.

The rotational spectra of benzene $\cdots \text{HX}$ ($\text{X} = \text{F},^{[129]} \text{Cl},^{[130]} \text{Br},^{[131]} \text{CN}^{[132]}$) and benzene $\cdots \text{CIF}^{[133]}$ are of the symmetric-top type in the vibrational ground state under supersonic-expansion conditions. However, benzene $\cdots \text{CIF}$ exhibits an additional rotational spectrum in such experiments and,

because of the low effective temperature of the gas, the satellite spectrum must be associated with a low-energy vibrationally excited state. The behavior of this vibrational satellite spectrum can be interpreted in terms of a Coriolis interaction between the ground state and the vibrationally excited state, which in turn leads to the conclusion that the observed geometry of benzene $\cdots \text{CIF}$ is as shown in Figure 24.

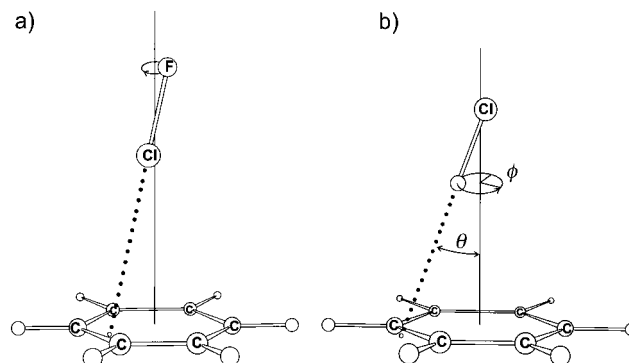


Figure 24. Observed geometries of a) benzene $\cdots$ CIF and b) benzene $\cdots$ HCl. The C_{6v} geometry ($\theta = 0^\circ$) represents a potential energy maximum in benzene $\cdots$ CIF, and the $\text{Cl}^{\delta+}$ end of CIF samples the π -electron density in the zero-point state as a result of the angular motion ϕ as defined in (b). This motion is therefore governed by a “Mexican-hat” type of potential function. The point $\circ$ represents the intersection of the extrapolated CIF internuclear axis with the benzene nuclear plane and lies 0.24 Å from the center of the C–C bond, inside the ring. See text and reference [133] for discussion.

The C_{6v} structure corresponding to $\theta = 0$ occurs at a potential energy maximum, while in the zero-point state the CIF subunit executes the angular motion defined by ϕ in Figure 24. Thus, the electrophilic atom $\text{Cl}^{\delta+}$ samples the entire π -electron density, and the motion in the ϕ coordinate follows a nearly circular path along the potential energy minimum that encircles the maximum at $\theta = 0$ and encompasses the six carbon atoms. It is likely that the benzene $\cdots \text{HX}$ ($\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{CN}$) complexes behave similarly, but no vibrational satellite spectra were observed. Unfortunately, it is not possible to distinguish on the basis of ground-state rotational spectra alone between a strictly C_{6v} equilibrium geometry and a geometry of the type observed for benzene $\cdots \text{CIF}$. However, in either case, the vibrational wavefunctions will have C_{6v} symmetry.

The heteroatoms of furan and thiophene formally carry a nonbonding electron pair in an orbital whose symmetry axis coincides with the C_2 axis of the molecule. It is of interest to examine whether rule (3) applies to complexes of furan and thiophene with CIF and HX, for the Lewis base carries an n-pair and aromatic π pairs in each case. The usual model of the n-pair and π -electron density in furan is shown in Figure 25a. The experimentally determined geometry of furan $\cdots \text{HCl}^{[134]}$ is depicted in Figure 25b. It has C_{2v} symmetry, and the HCl molecule lies along the C_2 axis of furan and forms a hydrogen bond to O. Evidently, rule (3) holds for furan $\cdots \text{HCl}$ because the n-pair on O, rather than the π electrons, defines the angular geometry. The result for furan $\cdots \text{HF}^{[135]}$ is similar.

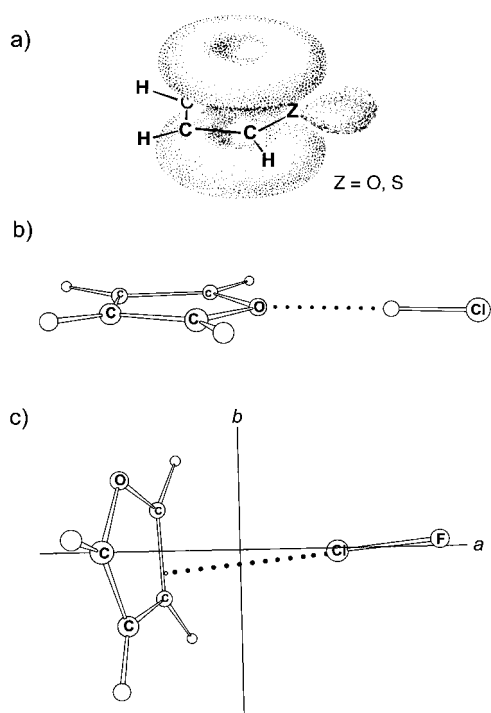


Figure 25. a) π -Bonding and nonbonding electron density model of furan ($Z = \text{O}$) or thiophene ($Z = \text{S}$) and the observed geometries of b) furan...HCl (planar, C_{2v}) and c) furan...ClF (C_1). Note that the point $\circ$ of the intersection of the extrapolated ClF internuclear axis and the furan nuclear plane lies close to the center of the $\text{C}_2\text{--C}_3$ bond.

All of the results established so far for pairs of complexes B...ClF and B...HCl show that they are isostructural for a given B (see Sections 3.3.2–3.3.5). The case in which B is furan is the first for which this conclusion does not hold, and furan...ClF is the first in either series to contravene rule (3). The observed geometry^[136] (see Figure 25c) demonstrates unambiguously that the ClF subunit interacts with the electron density associated with the π system in the manner expected if rule (2) applies. An intriguing question then concerns the closely related molecule thiophene: Does it behave like furan with regard to its complexes with HCl and ClF, or is the pair thiophene...HCl/thiophene...ClF isostructural? If the latter, is the π system or the n-pair on S the center of the intermolecular interaction?

Some light may be shed on the electric charge distributions of furan and thiophene by considering their electric moments. Table 6 compares the electric dipole moments μ ^[137–140] and the three components Q_{aa} , Q_{bb} , Q_{cc} of the electric quadrupole

moments^[140, 141] of pyridine, furan, and thiophene. There is good agreement between the experimental values and those from ab initio calculations. All the electric dipole moments are negative, with the heteroatom at the negative end in each case. The component Q_{aa} of the electric quadrupole moment changes from a large negative value in pyridine, through zero for furan, and becomes positive in thiophene. The magnitudes of the electric dipole moments also decrease along this series. This behavior of the electric moments suggests a progressive withdrawal of negative charge along the C_2 axis from the n-pair on the heteroatom into the ring. However, Q_{cc} and hence the extension of the π cloud above and below the nuclear plane, is greatest for thiophene. The electric moments suggest that the aromatic π system of thiophene might be more nucleophilic than the n-pair on sulfur and, moreover, suggest that furan might represent a crossover point of the relative nucleophilicities of the two types of site.

The angular geometry of thiophene...HCl determined from analyses of the rotational spectra of several isotopomers is shown in Figure 26 in projection on the ab principal inertial

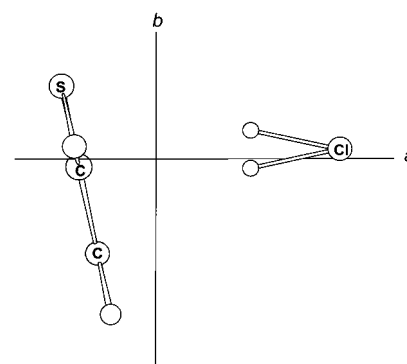


Figure 26. Observed geometry (C_s) of thiophene...HCl shown in projection in the ab principal inertial plane, which coincides with the molecular symmetry plane. Both orientations of the HCl subunit shown are consistent with the observed rotational constants and Cl nuclear quadrupole coupling constants of several isotopomers. See text for discussion.

plane.^[142] This plane is either a plane of symmetry (i.e., the complex has C_s symmetry) or there is a fairly low potential energy barrier at the C_s geometry, and the H atom oscillates backwards and forwards through the plane and samples electron density on each side of one face of the ring. It is not possible to distinguish between these possibilities on the basis of the rotational spectrum alone. Moreover, the angle α_{az} between the HCl axis (z) and the a axis is known in magnitude

Table 6. Molecular electric moments of pyridine, furan, and thiophene.

Molecular electric moment ^[a]	Pyridine		Furan		Thiophene	
	exptl.	theory	exptl.	theory	exptl.	theory
μ_a [10^{-30} Cm]	−7.17(15) ^[137]	−8.324	−2.285(3) ^[138]	−2.899	−1.83(3) ^[139]	−2.374
Q_{aa} [10^{-40} Cm ²]	−11.7(30)	−10.79	0.7(13)	0.06	5.7(53)	4.55
Q_{bb} [10^{-40} Cm ²]	32.4(30)	33.96	20.0(10)	22.72	22.0(50)	23.20
Q_{cc} [10^{-40} Cm ²]	−20.7(50)	−23.16	−20.0(10)	−22.78	−27.7(73)	−27.75

[a] The principal inertial axis a coincides with the C_2 symmetry axis of each molecule, while c is perpendicular to the plane of the nuclei in each case. The positive direction of a is towards the heteroatom. All theoretical values of the molecular electric moments are taken from reference [140]. [c] All experimental values of the electric quadrupole moments are due to Flygare et al.^[141]

(see Section 3.3.3) but not in sign, and hence both orientations of HCl with respect to the a axis shown in Figure 26 are possible. Whatever the detail, it is clear that thiophene $\cdots$ HCl resembles benzene $\cdots$ HCl (Figure 24) in its angular geometry and that the HCl molecule samples the π -electron density on one face of the ring. It is clearly not isostructural with furan $\cdots$ HCl (see Figure 25). Thiophene $\cdots$ HF^[143] is similar in geometry to thiophene $\cdots$ HCl, with a similar ambiguity in the sign of α_{az} .

Analogous difficulties exist with the exact placement of the ClF unit in thiophene $\cdots$ ClF^[144] and both structures implied in Figure 27 are consistent with all the observables from the

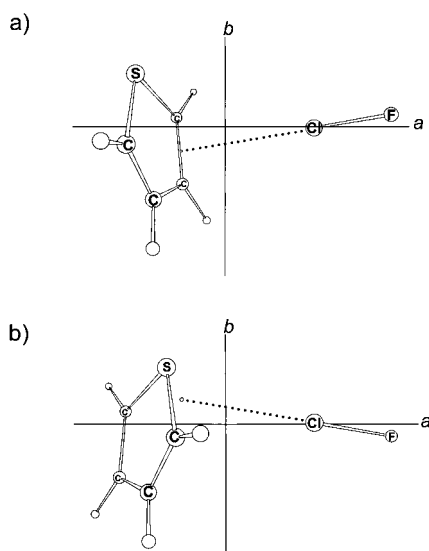


Figure 27. a), b) The two preferred geometries of thiophene $\cdots$ ClF (C_1) that are consistent with the observed rotational constants and the complete Cl nuclear quadrupole coupling tensor of the ^{35}Cl and ^{37}Cl isotopomers. Note that geometry (a) is similar to that observed for furan $\cdots$ ClF.

rotational spectrum, including the three angles α_{az} , α_{bz} , and α_{cz} . All three angles are available because the molecule has no symmetry and therefore all three off-diagonal elements χ_{ab} , χ_{ac} , and χ_{bc} of the Cl nuclear quadrupole coupling tensor are nonzero and experimentally determinable. It is clear from Figure 27 that the electrophilic end $\text{Cl}^{\delta+}$ of ClF interacts with the π -electron density on one face of the thiophene ring. We

note that one of the structures implied in Figure 27 is very similar to that established for furan $\cdots$ ClF (see Figure 25) in that the extension of the ClF axis intersects the nuclear plane of thiophene near to the center of one of the $\text{C}_2=\text{C}_3$ bonds.

With reference to Table 6, a question of interest is now whether pyridine $\cdots$ ClF and pyridine $\cdots$ HCl are isostructural and if so whether the subunit ClF/HCl interacts with the n-pair as the nucleophilic center rather than the π -electron density. Certainly, the electric moments of Table 6 tend to suggest this. The observed geometry of pyridine $\cdots$ HCl^[145] has C_{2v} symmetry, with a hydrogen bond between HCl and N (Figure 28). The complex pyridine $\cdots$ ClF has yet to be investigated.

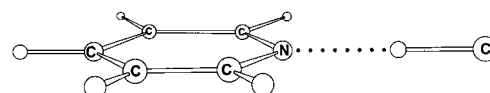


Figure 28. Observed geometry (C_{2v} , planar) of pyridine $\cdots$ HCl.

3.4. Systematic Behavior among Radial Geometries of $\text{B} \cdots \text{XY}$

So far, in discussing complexes $\text{B} \cdots \text{XY}$ and comparing them with the corresponding hydrogen-bonded complexes $\text{B} \cdots \text{HX}$, we have focused on systematic relationships among angular geometries, the strength of binding (as measured by k_o), and the redistribution of electric charge within the XY subunit. It is also possible to identify systematic behavior in the radial geometries, that is, the distances $r(\text{Z} \cdots \text{X})$, where Z is the electron-donor atom in B for σ -type complexes or the electron-donor center in B for π -type complexes and X is the inner halogen atom of $\text{B} \cdots \text{XY}$.

We begin with the most weakly bound group of complexes, namely, those $\text{B} \cdots \text{X}_2$ in which the halogen is molecular fluorine. Table 7 compares the distances $r(\text{Z} \cdots \text{F}_i)$ in the two series $\text{B} \cdots \text{F}_2$ and $\text{B} \cdots \text{HF}$, where B is H_2S ,^[64, 95] HCN ,^[63, 87] CH_3CN ,^[146, 147] H_2O ,^[91, 92] $(\text{CH}_2)_2\text{O}$,^[111, 148] and NH_3 .^[65, 149] It is evident that $r(\text{Z} \cdots \text{F})$ is insignificantly different between the pair $\text{B} \cdots \text{F}_2$ and $\text{B} \cdots \text{HF}$ for a given B. Moreover, $r(\text{Z} \cdots \text{F})$ is identical to the sum of the van der Waals radii $\sigma(\text{Z}) + \sigma(\text{F})$ ^[150] of Z and F, given that the latter are not known better than to about 0.05 Å and hence that $\sigma(\text{Z}) + \sigma(\text{F})$ has an uncertainty of

Table 7. Comparison of angular geometries and distances $r(\text{Z} \cdots \text{F})$ in complexes $\text{B} \cdots \text{F}_2$ and $\text{B} \cdots \text{HF}$.

$\text{B} \cdots \text{XF}$	Angular geometry		$r(\text{Z} \cdots \text{F}_i/\text{F})$ [Å]		$\sigma(\text{Z}) + \sigma(\text{F})$ [Å] ^[a]
	symmetry	details	$\text{B} \cdots \text{F}_2$	$\text{B} \cdots \text{HF}$	
$\text{H}_2\text{S} \cdots \text{XF}$	C_s (Figure 10; X = F) C_s (Figure 9; X = H)	$\phi = 113(5)^\circ$ ^[64] $\phi = 91^\circ$ ^[95]	3.20(1) ^[64]	3.246 ^[95]	3.20
$\text{HCN} \cdots \text{XF}$	$C_{\infty v}$ (X = F ^[63] and X = H ^[87])		2.803(3) ^[63]	2.805(1) ^[87]	2.85
$\text{CH}_3\text{CN} \cdots \text{XF}$	C_{3v} (X = F ^[146] and X = H ^[147])		2.748(3) ^[146]	2.751(1) ^[147]	2.85
$\text{H}_2\text{O} \cdots \text{XF}$	C_{2v} (Figure 8; X = F ^[91]) C_s (Figure 7; X = H ^[92])		2.719(4) ^[91]	2.684(16) ^[b]	2.75
 $\cdots \text{XF}$	C_s (Figure 15; X = F) C_s (Figure 14; X = H)	$\phi = 76(4)^\circ$ ^[111] $\phi = 72.0(2)^\circ$ ^[148]	2.63(6) ^[111]	2.629(5) ^[148]	2.75
$\text{H}_3\text{N} \cdots \text{XF}$	C_{3v} (X = F ^[65] and X = H ^[149])		2.708(7) ^[65]	2.71 ^[149]	2.85

[a] Sum of van der Waals radii from reference [150]. [b] Fitted to rotational constants given by J. W. Bevan, Z. Kisiel, A. C. Legon, D. J. Millen, S. C. Rogers, *Proc. R. Soc. London A* **1980**, 372, 441–51 but with $\phi = 46^\circ$ as given in reference [92].

about 0.1 Å. This result is not unreasonable when the k_o for complexes $B \cdots F_2$ are considered.

In Section 3.2, it was noted that $B \cdots F_2$ interactions are extremely weak. The values of k_o recorded in Table 2 of Section 3.2 are in fact similar in magnitude to those of complexes of inert gas atoms with various partners. This similarity can be understood when it is recognized that not only does F_2 possess no electric dipole moment but also its electric quadrupole moment is close to zero.^[70] Consequently, F_2 appears to another molecule B as though it has a spherical electric charge distribution, that is, it behaves like an inert gas atom. It is then not unreasonable that the interaction distance $r(Z \cdots F)$ in the various $B \cdots F_2$ should be the sum of the van der Waals radii. Presumably, the dispersion interaction is relatively more important in $B \cdots F_2$ than other $B \cdots XY$. Nevertheless, the comparison of the angular geometries of $B \cdots F_2$ and $B \cdots HF$ for $B = H_2S, HCN, CH_3CN, H_2O, (CH_2)_2O$, and NH_3 in Table 7 indicates that electrostatic interaction involving δ^+F of $\delta^+F_{\delta^-}F^{\delta+}$ with B controls the shape of $B \cdots F_2$ in the same way that the B/δ^+H interaction does for $B \cdots HF$.

The fact that $r(Z \cdots F)$ is essentially identical in the two series $B \cdots HF$ and $B \cdots F_2$ suggests that, in modeling distances $r(Z \cdots F)$ in hydrogen-bonded complexes, the H atom of HF should be ignored. This procedure was used in the electrostatic model proposed by Buckingham and Fowler.^[68]

Molecular chlorine has no electric dipole moment, but its electric quadrupole moment is substantially larger than that of F_2 .^[70] This is reflected in the larger binding strengths of $B \cdots Cl_2$ complexes compared with those of $B \cdots F_2$ (see Section 3.2 and Table 2 for a discussion of k_o values). The distances $r(Z \cdots Cl)$ in various $B \cdots Cl_2$ ^[27, 32–38] are given in Table 8, where they are compared with those in the corresponding series $B \cdots HCl$ ^[76, 80, 84, 88, 96, 99, 115, 116] and with the sum $\sigma(Z) + \sigma(Cl)$ of

Table 8. Comparisons of distances $r(Z \cdots Cl)$ ^[a] in complexes $B \cdots Cl_2$ and $B \cdots HCl$.

B	$r(Z \cdots Cl_2/Cl) [\text{\AA}]$		$\Delta r [\text{\AA}]^{[b]}$		$\sigma(Z) + \sigma(Cl) [\text{\AA}]^{[c]}$	
	$B \cdots Cl_2$	ref.	$B \cdots HCl$	ref.		
H_3P	3.240	[34]	3.883	[80]	0.643	3.7
H_2S	3.249	[35]	3.809	[96]	0.560	3.65
OC	3.134	[32]	3.710	[84]	0.576	3.50
C_2H_4	3.128	[27]	3.724	[115]	0.596	3.50
C_2H_2	3.163	[36]	3.699	[116]	0.536	3.50
HF	2.96	[33]	3.367	[99]	0.41	3.15
HCN	2.915	[37]	3.405	[88]	0.490	3.30
NH_3	2.724	[38]	3.136	[76]	0.412	3.30

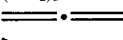
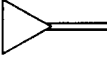
[a] Z is the electron-donor atom or electron-donor center in B. Values of $r(Z \cdots Cl)$ were taken from the indicated reference or calculated from data in the reference by the method of A. C. Legon, D. J. Millen, *Chem. Phys. Lett.* **1988**, *147*, 484–489. [b] $\Delta r = r(B \cdots HCl) - r(B \cdots Cl_2)$. [c] Sum of van der Waals radii taken from reference [150]. A radius of $\sigma(C) = 1.70$ Å was assumed for C in CO and for C–C multiple bonds.

the van der Waals radii^[150] of the atoms Z and Cl. Three conclusions are evident from Table 8. First, $r(Z \cdots Cl)$ contracts systematically by about 0.5 Å from $B \cdots HCl$ to $B \cdots Cl_2$. Secondly, the contraction Δr tends to decrease as the length $r(Z \cdots Cl)$ decreases. Thirdly, $r(Z \cdots Cl)$ for $B \cdots HCl$ is within about 0.1 Å of the sum of the van der Waals radii $\sigma(Z) + \sigma(Cl)$

of the acceptor center in B and Cl for all B, and $r(Z \cdots Cl)$ tends to become shorter than $\sigma(Z) + \sigma(Cl)$ for the more strongly bound species.

A similar pattern of contractions is observed (see Table 9) for the series $B \cdots ClF/B \cdots HCl$ for 17 different B (already referred to throughout this article), except that the contrac-

Table 9. Comparisons of distances $r(Z \cdots Cl)$ ^[a] in complexes in $B \cdots ClF$ and $B \cdots HCl$.

B	$r(Z \cdots Cl) [\text{\AA}]$		$\Delta r [\text{\AA}]^{[b]}$		$\sigma(Z) + \sigma(Cl) [\text{\AA}]^{[c]}$	
	$B \cdots ClF$	ref.	$B \cdots HCl$	ref.		
n-pair donors						
H_2S	2.857	[57]	3.809	[96]	0.952	3.65
OC	2.770	[53]	3.710	[84]	0.940	3.50
HF	2.77	[98]	3.367	[99]	0.60	3.15
SO_2	2.732	[112]	3.472	[23, 113]	0.740	3.20
HCN	2.639	[56]	3.405	[88]	0.766	3.30
H_2O	2.580	[58]	3.215	[93]	0.635	3.20
	2.472 ^[d]	[104]	3.62	[109]	1.15	3.65
	2.438	[103]	3.094	[23, 108]	0.656	3.20
	2.422	[101]	3.071	[105]	0.649	3.20
H_3N	2.376	[59]	3.136	[76]	0.760	3.30
π -pair donors						
C_2H_2	2.873	[54]	3.699	[116]	0.826	3.50
C_2H_4	2.766	[55]	3.724	[115]	0.958	3.50
$(CH_2)_3$	2.957	[121]	3.567	[122]	0.610	3.50
	2.774	[126]	3.55	[125]	0.78	3.50
	2.675	[127]	3.571	[128]	0.896	3.50
	3.313	[133]	3.903	[130]	0.590	3.50
	2.825	[144]	3.693	[142]	0.868	3.50

[a] See Table 8. [b] $\Delta r = r(B \cdots HCl) - r(B \cdots ClF)$. [c] Sum of van der Waals radii taken from reference [150]. A radius of $\sigma(C) = 1.70$ Å was assumed for C in CO and for C–C multiple bonds. [d] This $B \cdots ClF$ has a significant contribution from $[BCl]^+ \cdots F^-$ to the valence-bond description of the complex. See reference [104] and Section 4.2.

tions are systematically larger (mean value $\Delta r = 0.79$ Å compared with 0.53 Å). This is understandable, given that complexes $B \cdots ClF$ are systematically more strongly bound than those of $B \cdots Cl_2$, no doubt because ClF possesses an electric dipole moment while Cl_2 does not. The mean contraction of $r(Z \cdots Br)$ in complexes $B \cdots BrCl$ relative to the corresponding $B \cdots HBr$ —where B is CO ,^[45, 85] C_2H_4 ,^[46, 118] H_2S ,^[48, 97] HCN ,^[49, 89] and NH_3 ^[50, 77] (see Table 10)—of 0.83 Å is similar to that for the $B \cdots ClF/B \cdots HCl$ pairs. An insufficient number of $B \cdots Br_2$ have been investigated so far to allow any firm conclusions, except that there is again a substantial contraction of $r(Z \cdots Br)$ from $B \cdots HBr$ to $B \cdots Br_2$.^[39, 40, 77, 85]

Table 10. Comparisons of distances $r(\text{Z} \cdots \text{Br})^{[a]}$ in complexes $\text{B} \cdots \text{BrCl}$ or $\text{B} \cdots \text{Br}_2$ and $\text{B} \cdots \text{HBr}$.

B	$r(\text{Z} \cdots \text{Br}_1/\text{Br})$ [Å]				Δr [Å] ^[b]	$\sigma(\text{Z}) + \sigma(\text{Br})$ [Å] ^[c]
	$\text{B} \cdots \text{BrCl}/\text{Br}_2$	ref.	$\text{B} \cdots \text{HBr}$	ref.		
B ⋯ BrCl						
H ₂ S	3.096	[48]	3.991	[97]	0.895	3.80
C ₂ H ₂	3.059	[47]	–	–	–	3.65
OC	3.004	[45]	3.917	[85]	0.913	3.65
C ₂ H ₄	2.979	[46]	3.917	[118]	0.938	3.65
HCN	2.834	[49]	3.610	[89]	0.776	3.45
NH ₃	2.628	[50]	3.255	[77]	0.627	3.45
B ⋯ Br₂						
OC	3.050	[40]	3.917	[85]	0.867	3.65
NH ₃	2.72	[39]	3.255	[77]	0.535	3.45

[a] Z is the electron-donor atom or electron-donor center in B. Values of $r(\text{Z} \cdots \text{Br})$ were taken from the indicated reference or calculated from data in the reference by the method of A. C. Legon, D. J. Millen, *Chem. Phys. Lett.* **1988**, 147, 484–489.

[b] $\Delta r = r(\text{B} \cdots \text{HBr}) - r(\text{B} \cdots \text{BrCl})$ or $r(\text{B} \cdots \text{HBr}) - r(\text{B} \cdots \text{Br}_2)$. [c] See Table 8.

The systematic behavior in $r(\text{Z} \cdots \text{X})$ between $\text{B} \cdots \text{HX}$ and $\text{B} \cdots \text{XY}$ noted above can be explained in terms of the shape of halogen atoms in dihalogen molecules and anisotropic repulsion. The example of the $\text{B} \cdots \text{HCl}/\text{B} \cdots \text{Cl}_2$ pairs has been dealt with in detail and is discussed below. Similar considerations are likely to apply to $\text{B} \cdots \text{HBr}/\text{B} \cdots \text{BrCl}$.

Ab initio SCF calculations were carried out by using a helium atom to probe the repulsive potentials around the Cl_2 and HCl molecules.^[151] Two sets of energy calculations were carried out. Repulsive energy curves were calculated first for an end-on approach of He to Cl_2 and then for approach to each end of the HCl molecule, by obtaining the total energy and subtracting from it the induction contribution at a series of points. A repulsive wall was encountered about 0.6 Å earlier in the approach to the H end of HCl than to the Cl of Cl_2 or indeed to Cl in ClF. Moreover, a map of the repulsion-energy surface for approaches of He to Cl_2 shows that the Cl atom of Cl_2 is flattened by about 0.32 Å for head-on as opposed to perpendicular approach. The Cl_2 molecule therefore has the “snub-nosed” shape anticipated by Buckingham, as quoted in reference [26]. A similar conclusion was obtained for ClF. This snub-nosed character is evident when van der Waals spheres are placed on the atoms in $\text{H}_2\text{O} \cdots \text{ClF}$ and $\text{H}_2\text{O} \cdots \text{HCl}$, as shown by the spherical nets of appropriate radius drawn in Figure 29. It is clear that the van der Waals spheres of O and Cl just touch in $\text{H}_2\text{O} \cdots \text{HCl}$ but substantially interpenetrate in $\text{H}_2\text{O} \cdots \text{ClF}$, a situation that is highly unlikely in view of the repulsive energy involved. Presumably, the “sphere” on Cl in ClF should be drawn as “snub-nosed”, as suggested by the calculations of reference [151].

The situation in the related pair $\text{H}_2\text{O} \cdots \text{F}_2$ and $\text{H}_2\text{O} \cdots \text{HF}$, shown in a similar format in Figure 30, is quite different, however. The van der Waals spheres of oxygen and F just touch in both cases. This suggests that F_2 is not snub-nosed like Cl_2 and ClF. Ab initio calculations of the type carried out on Cl_2/HCl or ClF/HCl would be of interest for the F_2/HF pair. The conclusions of this section lead to the prediction that the F atom in F_2 is not anisotropic in the sense that Cl is in Cl_2 or ClF, or only slightly anisotropic.

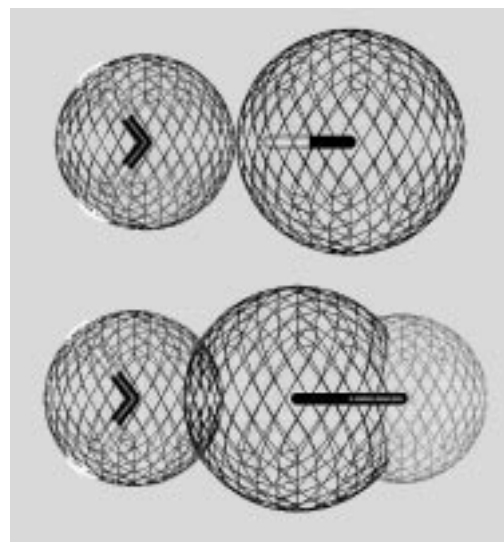


Figure 29. Stick models of $\text{H}_2\text{O} \cdots \text{HCl}$ (top) and $\text{H}_2\text{O} \cdots \text{ClF}$ (bottom) with spherical nets of the appropriate van der Waals radii centered on O, Cl, and F. Each model is drawn to scale at the experimental separation, with the configuration at O as planar for convenience. No van der Waals sphere is drawn on the H of HCl while (white) spheres of token radius are drawn on the H atoms of H_2O . Note that the O and Cl spheres just touch in $\text{H}_2\text{O} \cdots \text{HCl}$ but interpenetrate in $\text{H}_2\text{O} \cdots \text{ClF}$, leading to the hypothesis of a snub-nosed character for the Cl atom in ClF. See text for discussion.

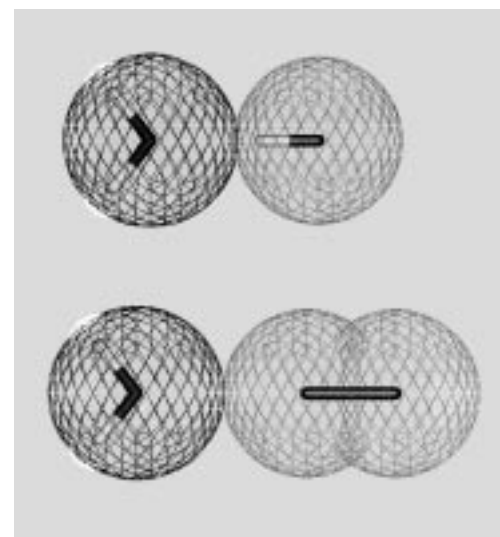


Figure 30. Stick models of $\text{H}_2\text{O} \cdots \text{HF}$ (top) and $\text{H}_2\text{O} \cdots \text{F}_2$ (bottom) with spherical nets of the appropriate van der Waals radii centered on O and F. Each model is drawn to scale at the experimental separation, with the configuration at O as planar for convenience. Note that the van der Waals spheres of O and F just touch in both complexes; hence that F_2 is not “snub-nosed” like Cl_2 and ClF. (Reproduced with permission from A. C. Legon, *Chem. Commun.* **1998**, 2737–2738.)

3.5. Conclusions about the Nature of $\text{B} \cdots \text{XY}$ from Systematic Behavior of Properties

3.5.1. Parallelisms among Properties of $\text{B} \cdots \text{XY}$ and $\text{B} \cdots \text{HX}$: A Model for the Halogen Bond

In Sections 3.1–3.4, the ways in which the properties of complexes $\text{B} \cdots \text{XY}$, where B is a Lewis base and XY is a homo- or heteronuclear dihalogen, change as B and XY are

systematically varied were considered. These properties include the electric charge redistribution in XY, the intermolecular stretching force constant k_{σ} , and the angular and radial geometries of the complex.

For most of the complexes considered so far, it was shown in Section 3.1 that the extent of the electric charge redistribution within the XY subunit is small. The intermolecular force constants k_{σ} , which were discussed in Section 3.2, indicate that these complexes are, for the most part, weakly bound. The combination of small electric charge redistribution and weak binding suggested that the simple electrostatic term (i.e., that involving interaction of the permanent, unperturbed electric charge distributions of the two molecules) is an important contribution to the interaction energy.

When in Section 3.3 the angular geometries of various series $B \cdots XY$ were discussed and compared with those in corresponding series of hydrogen-bonded complexes $B \cdots HX$, a strong parallelism was identified, and it became clear that the rules first enunciated^[67, 75] to rationalize angular geometries of $B \cdots HX$ also apply, after suitable modification, to $B \cdots XY$. The rules for the $B \cdots HX$ are implicitly electrostatic in origin, involving the identification of directions of greatest nucleophilicity (n-pair and π -pair directions) in the "electron donor" B. Subsequently, these rules were given a quantitative basis in the Buckingham–Fowler electrostatic model.^[68]

A further parallel between the $B \cdots XY$ and $B \cdots HX$ series was identified for the distances $r(Z \cdots X)$, where Z is the electron-donor atom/center in B. It was shown in Section 3.4 that this distance is systematically shorter in $B \cdots XY$ than in the corresponding $B \cdots HX$ for each of the series $B \cdots Cl_2/B \cdots HCl$, $B \cdots ClF/B \cdots HCl$, $B \cdots Br_2/B \cdots HBr$, and $B \cdots BrCl/B \cdots HBr$. This shortening can be attributed, in part at least, to an anisotropy of the X atom radius in molecules XY, and this effect was demonstrated by ab initio calculations^[151] in the case of Cl_2 and ClF . On the other hand, no such shortening is evident in the pair of series $B \cdots F_2/B \cdots HF$, a result which, when taken with the very weak intermolecular binding (as indicated by k_{σ}) in the $B \cdots F_2$ series, suggests that $B \cdots F_2$ complexes represent a limiting case. Evidently, F_2 is not snub nosed in the sense outlined for the other dihalogen molecules.

Given the remarkable parallelism of the $B \cdots XY$ and $B \cdots HX$ series summarized above and that (for the B and HX considered so far) the hydrogen bond in $B \cdots HX$ is accepted as being mainly electrostatic in origin, it seems reasonable to draw the conclusion that the interaction that predominates in defining the properties of the $B \cdots XY$ complexes is the electrostatic term (with the possible qualification in the case of $B \cdots F_2$ outlined in Section 3.4). Then, for example, the fact that the rules for angular geometries apply to both $B \cdots HX$ and $B \cdots XY$ is readily understood.

In view of the foregoing, it seems worthwhile to define a halogen bond^[152] that is an analogue of the hydrogen bond. Thus, the halogen bond is predominantly electrostatic in origin and involves the interaction of unperturbed electric charge distributions of B and XY. By analogy with the usual shorthand $B \cdots \delta^+H-X^{\delta-}$ for hydrogen-bonded complexes, we may likewise write $B \cdots \delta^+X-Y^{\delta-}$ for a halogen bond when XY is a heteronuclear dihalogen molecule. This shorthand

involves only the leading term (electric dipole moment) in the description of the electric charge distribution of XY. On the other hand, when XY is a homonuclear dihalogen, the halogen bond becomes $B \cdots \delta^+X^{\delta-}_2$, since the electric quadrupole moment of X_2 is the leading term in the description of its charge distribution.

With such an operational definition of the halogen bond, the fact that $B \cdots ClF$ and $B \cdots BrCl$ complexes are isomorphous with $B \cdots HX$ ($X = F, Cl, Br$) can be understood if the electrophilic end δ^+ of each XY or HX molecule seeks the axis of a nonbonding or π -bonding electron pair on B. It has been argued elsewhere^[153] that, in the absence of secondary interactions between the nucleophilic region $X^{\delta-}$ of HX and electrophilic regions of B, hydrogen bonds prefer a linear arrangement $Z \cdots H-X$, where Z is the electron-donor atom/region of B. Bending of the hydrogen bond tends to bring the two nucleophilic regions Z and X into contact, and this is energetically unfavorable. Presumably, similar considerations apply to halogen-bonded complexes $B \cdots XY$.

This last point raises an interesting question: Under what conditions do halogen bonds exhibit nonlinearity (i.e., non-collinear arrangements of the nuclei $Z \cdots X-Y$) and how do nonlinearities of hydrogen-bonded complexes $B \cdots HX$ compare with those of isomorphous halogen-bonded complexes $B \cdots XY$? These questions are addressed in the next section.

3.5.2. Nonlinearity in Hydrogen Bonds and "Halogen" Bonds

The angular geometries of a wide range of complexes $B \cdots XY$ and $B \cdots HX$ were considered in Section 3.3. For complexes $B \cdots ClF$ and $B \cdots HCl$ of C_s symmetry, it was also possible to determine the precise deviation of the $Z \cdots Cl-F$ or $Z \cdots H-Cl$ system from linearity by means of the off-diagonal element χ_{ab} or χ_{ac} (depending on whether the principal inertial plane ab or ac coincides with the molecular symmetry plane) of the Cl nuclear quadrupole coupling tensor. The method of establishing the angular deviation θ , as defined in the general case for the nuclei $Z \cdots X-Y$ in Figure 31, from the collinear ($\theta = 0^\circ$) arrangement was discussed in Section 3.3.3.

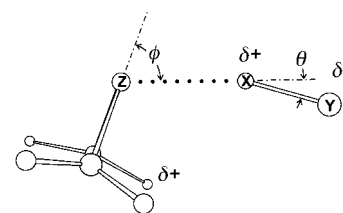
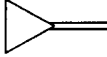


Figure 31. Definitions of the angles ϕ and θ in the general case of a complex $B \cdots XY$ of C_s symmetry, where B is, for example, H_2CO , oxirane, thiirane, 2,5-dihydrofuran, allene, or methylenecyclopropane. Z is the acceptor atom of B in n-pair complexes or the center of the π bond in π complexes.

The complexes $B \cdots ClF$ and $B \cdots HCl$ that were found to have C_s symmetry were those for which $B = H_2CO$,^[102, 107] 2,5-dihydrofuran,^[101, 105] oxirane,^[103, 108] thiirane,^[104, 109] allene,^[125, 126] and methylenecyclopropane.^[127, 128] Their angular geometries—which are displayed in Figures 12–14, 16, 22, and 23, respectively—were established to be isostructural in the pair

$B \cdots \text{ClF}/B \cdots \text{HCl}$ for a given B . As remarked in Sections 3.3.3 and 3.3.4, although the angles ϕ (see Figure 31) are virtually identical in $B \cdots \text{ClF}$ and $B \cdots \text{HCl}$ for a given B , the non-linearity θ is somewhat larger for the hydrogen-bonded complex. Table 11 summarizes the angles ϕ and θ for the two series of C_s complexes in question. It is evident that θ is very small in the $B \cdots \text{ClF}$. These observations about ϕ and θ will now be explained in terms of the simple electrostatic model

Table 11. Angles ϕ and θ determined for complexes $B \cdots \text{ClF}$ and $B \cdots \text{HCl}$ of C_s symmetry.^[a]

B	B $\cdots$ ClF			B $\cdots$ HCl		
	ϕ [°]	θ [°]	ref.	ϕ [°]	θ [°]	ref.
H ₂ CO	69.1(7)	3.2(7)	[102]	70.0(10)	20.5(8)	[107]
	53.0(3)	2.0(2)	[101]	54.3(3)	9.5(1)	[105]
	67.3(1)	2.9(1)	[103]	69.1(1)	16.5(1)	[23, 108]
	85.0(2)	3.5(2)	[104]	94.5(20)	21.0(5)	[109]
	92.5(7)	4.9(15)	[126]	94 (3)	≈ 7	[125]
	92.5(5)	4.9(1)	[127]	90.8(5)	17.5	[128]
SO ₂	131.9(6)	−0.7(2)	[112]	143.0(1)	−2.5(7)	[23, 113]

[a] The angles ϕ and θ are defined in Figures 12–14, 16, 17, 22, and 23 for the complexes $B \cdots \text{ClF}/B \cdots \text{HCl}$.

for the $B \cdots \text{ClF}$ and $B \cdots \text{HCl}$ interactions, the general outline of which was given in Section 3.5.1.

First, the subunit ClF or HCl is considered to form a halogen or hydrogen bond to the electron-donor atom or center in B according to the rules, that is, ClF or HCl lies along the axis of a nonbonding electron pair on Z or a π -bonding electron pair. When B is such that the rules predict a complex of C_s symmetry, as in the cases considered here, there is the possibility of a secondary interaction between the nucleophilic end $F^{\delta-}$ or $Cl^{\delta-}$ of ClF or HCl , respectively, and the more electrophilic region of B , as shown schematically in Figure 31. This secondary interaction can then be envisaged to cause $F^{\delta-}$ or $Cl^{\delta-}$ to move towards its electrophilic partner, whereby the pivot is the primary interaction site. At equilibrium, the force resisting the bending of the halogen or hydrogen bond, the secondary attractive force, and any repulsive force are balanced.

This model readily explains why the angles ϕ are identical for a given pair $B \cdots \text{ClF}/B \cdots \text{HCl}$, since whatever the strength of the secondary interaction, the pivot of the motion is $Cl^{\delta+}$ or $H^{\delta+}$ and ϕ does not change. On the other hand, it is clear why θ for $B \cdots \text{HCl}$ is larger than θ for $B \cdots \text{ClF}$. In general, the distance $r(Z \cdots \text{Cl})$ in $B \cdots \text{HCl}$ is smaller than the distance $r(Z \cdots \text{F})$ in $B \cdots \text{ClF}$, the $Z \cdots \text{ClF}$ primary interaction is stronger than that of $Z \cdots \text{HCl}$, and $F^{\delta-}$ is a poorer nucleophile than $Cl^{\delta-}$. All these factors operate in the same direction, that is, to make bending of the “chlorine” bond in $B \cdots \text{ClF}$ more difficult than bending of the hydrogen bond in $B \cdots \text{HCl}$ through the same angle θ . Data for $\text{SO}_2 \cdots \text{ClF}$ ^[112] and $\text{SO}_2 \cdots \text{HCl}$,^[113] both of which have planar C_s symmetry, are also included in Table 11. We note that in $\text{SO}_2 \cdots \text{HCl}$ ^[23, 113] and

$\text{SO}_2 \cdots \text{ClF}$ ^[112] the nucleophiles $Cl^{\delta-}$ and $F^{\delta-}$ are far removed from the electrophilic region of the molecule B , so that both the $O \cdots \text{H}-\text{Cl}$ and $O \cdots \text{Cl}-\text{F}$ systems are nearly linear (see Figure 17).

In view of the established very small deviation of θ from zero in the $B \cdots \text{ClF}$ complexes, a reasonable corollary to the rules for the prediction of angular geometries (Section 3.3.1) might be that the ClF molecule is a good probe of the directions of nonbonding electron pairs. Because of the significant nonlinearity of hydrogen bonds, HX is a less satisfactory indicator of nonbonding pair directions. This may be of relevance to VSEPR theory.

It will be of interest to examine the nonlinearities θ in complexes $B \cdots \text{Cl}_2$, $B \cdots \text{BrCl}$ and $B \cdots \text{Br}_2$ of appropriate symmetry. This will be a difficult task because of the considerable complications in the rotational spectra of such species that arise from multiple quadrupole coupling nuclei and a variety of naturally occurring isotopomers. Some values of θ were measured in a few $B \cdots \text{HBr}$ ^[23, 154–157] and $B \cdots \text{HF}$ ^[148, 158, 159] complexes, where B is oxirane, thiirane, methylenecyclopropane, 2,5-dihydrofuran, or formaldehyde. Unfortunately, the absence of quadrupolar nuclei in F_2 means that values of θ cannot be obtained for $B \cdots \text{F}_2$ by the method considered here.

4. The Existence of Mulliken Inner Complexes $[\text{BX}]^+ \cdots \text{Y}^-$ and $[\text{BH}]^+ \cdots \text{X}^-$ in the Gas Phase

This review is concerned with the properties of complexes of the type $B \cdots \text{XY}$, as determined for the ground state of the molecule from its rotational spectrum. It has also compared these properties with those of hydrogen-bonded complexes $B \cdots \text{HX}$ similarly determined. All the discussion so far has centered on complexes $B \cdots \text{XY}$ and $B \cdots \text{HX}$ that are of the Mulliken outer type, that is, those that are weakly bound and exhibit only minor electric charge redistribution. The $B \cdots \text{XY}$ were shown explicitly to be of the outer type by consideration of the changes in the halogen nuclear quadrupole coupling constants of XY on complex formation and the generally small values of k_a . The $B \cdots \text{HX}$ were also implicitly assumed to be of the same type. In fact, this conclusion can be established by a detailed consideration of molecular properties, as set out elsewhere.^[75]

The final question to be addressed here is: Are there circumstances in which Mulliken inner complexes $[\text{BX}]^+ \cdots \text{Y}^-$ or $[\text{BH}]^+ \cdots \text{X}^-$ can be detected in the ground state in the gas phase? This question was first formulated and answered in connection with the ammonium and methylammonium halides.

4.1. The Hydrogen Bond $B \cdots \text{HX}$ and How to Encourage Proton Transfer

Systematic investigations of members of the series $(\text{CH}_3)_{3-n}\text{H}_n\text{N} \cdots \text{HX}$ ($n=3, 2, 0$; Table 12) were made by means of their rotational spectra,^[76–78, 160–164] which were observed in a supersonically expanded jet produced in one of the two following ways. Either the vapor above the heated

Table 12. Series of complexes $(\text{CH}_3)_{3-n}\text{H}_n\text{N}\cdots\text{HX}$ investigated by rotational spectroscopy and the estimated percentage contributions of $[(\text{CH}_3)_{3-n}\text{H}_n\text{NH}]^+\cdots\text{X}^-$ to valence-bond descriptions of the molecules.

$\text{H}_3\text{N}\cdots\text{HCl}$ 0 %	$\text{CH}_3\text{NH}_2\cdots\text{HCl}$ 23 %	$(\text{CH}_3)_3\text{N}\cdots\text{HF}$ 5 %
$\text{H}_3\text{N}\cdots\text{HBr}$ 0 %		$(\text{CH}_3)_3\text{N}\cdots\text{HCl}$ 62 %
$\text{H}_3\text{N}\cdots\text{HI}$ 0 %		$(\text{CH}_3)_3\text{NH}^+\cdots\text{Br}^-$ 80 %
		$(\text{CH}_3)_3\text{NH}^+\cdots\text{I}^-$ 93 %

ionic solid $[(\text{CH}_3)_{3-n}\text{H}_n\text{NH}]^+\cdots\text{X}^-$ was entrained in argon and the resulting mixture expanded or $(\text{CH}_3)_{3-n}\text{H}_n\text{N}$ and HX were mixed in the fast-mixing nozzle and the resulting complexes observed as described above.

Analysis of the rotational spectra led to various properties of the complexes $(\text{CH}_3)_{3-n}\text{H}_n\text{N}\cdots\text{HX}$. Of particular importance in assessing the extent of proton transfer from HX to $(\text{CH}_3)_{3-n}\text{H}_n\text{N}$ were the halogen nuclear quadrupole coupling constants $\chi_{zz}(\text{X})$, where z is the HCl internuclear axis, and the intermolecular stretching force constant k_σ , as determined from the centrifugal distortion constant D_J or Δ_J . A detailed review of the arguments for the whole series $(\text{CH}_3)_{3-n}\text{H}_n\text{N}\cdots\text{HX}$ has been presented elsewhere.^[165] Only a summary is given here.

In a weakly bound complex such as $\text{HCN}\cdots\text{HX}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$), for which k_σ values are close to 10 Nm^{-1} or less, the value of $\chi_{zz}(\text{X})$ can be modeled by allowing first for the modified electric field gradient at X resulting from the electric charge distribution of HCN and then for the zero-point motion of the complex. Details of how to do this are not important here and are discussed elsewhere.^[165, 166] No significant extension of the $\text{H}-\text{X}$ bond, and therefore no appreciable extent of proton transfer, needed to be invoked. $\text{HCN}\cdots\text{HX}$ are thus used as models for the weak limit. The values of $\chi_{zz}(\text{Cl})$ and k_σ for $\text{HC}^{14}\text{N}\cdots\text{H}^{35}\text{Cl}$ ^[88] are given in Table 13.

Table 13. Comparison of ^{35}Cl nuclear quadrupole coupling constants $\xi_{zz}(\text{Cl})$ and intermolecular stretching force constants k_σ of complexes $(\text{CH}_3)_{3-n}\text{H}_n\text{N}\cdots\text{HCl}$ with those of model systems.

Complex	$\xi_{zz}(\text{Cl})$ [MHz] ^[a]	$k_\sigma\text{ Nm}^{-1}$
$\text{HCN}\cdots\text{HCl}$ ^[88]	− 53.720	9.1
$\text{H}_3\text{N}\cdots\text{HCl}$ ^[76]	− 47.607(9)	17.6(3)
$\text{CH}_3\text{NH}_2\cdots\text{HCl}$ ^[160]	− 37.89(1)	—
$(\text{CH}_3)_3\text{N}\cdots\text{HCl}$ ^[162]	− 21.625(5)	84(3)
$\text{Na}^+\cdots\text{Cl}^-$	− 5.643(4) ^[167]	108.6 ^[168]

[a] z is the HCl internuclear axis.

The model molecules taken to represent the properties of the ion pair limit $[(\text{CH}_3)_{3-n}\text{H}_n\text{NH}]^+\cdots\text{X}^-$ were the sodium halides $\text{Na}^+\cdots\text{X}^-$, which are known to be ionic in the gas phase. These have force constants $k_\sigma \approx 100\text{ Nm}^{-1}$ and coupling constants $\chi_{zz}(\text{X}) \approx 0\text{ MHz}$, the latter being that expected for a spherically symmetric ion X^- , perturbed slightly by the nearby cation Na^+ . The values of $\chi_{zz}(\text{Cl})$ ^[167] and k_σ ^[168] for $\text{Na}^+\cdots\text{Cl}^-$ are included in Table 13.

The approach to the nature of $(\text{CH}_3)_{3-n}\text{H}_n\text{N}\cdots\text{HX}$ for a particular value of n can then be summarized by considering the measured $\chi_{zz}(\text{Cl})$ and k_σ values for $n = 3, 2$, and 0 , which are also given for the $(\text{CH}_3)_{3-n}\text{H}_n\text{N}\cdots\text{HCl}$ in Table 13.^[76, 160, 162] It is clear that $\text{H}_3\text{N}\cdots\text{HCl}$ lies close to the simple hydrogen bond limit, as exemplified by $\text{HCN}\cdots\text{HCl}$,

both in terms of $\chi_{zz}(\text{Cl})$ and k_σ . As NH_3 is progressively methylated, however, $\chi_{zz}(\text{Cl})$ decreases in magnitude while k_σ increases. Qualitatively, it is clear that the extent of proton transfer increases as n decreases from 3 to 2 to 0 . A quantitative interpretation of $\chi_{zz}(\text{Cl})$, with details as described in reference [165], shows that the percentage of proton transfer changes from approximately 0% when $n = 3$, to 23% when $n = 2$, to 62% when $n = 0$ (see Table 12). These results are in accord with chemical intuition, since the $+I$ effect of CH_3 groups increases the proton affinity of NH_3 as it is progressively methylated.^[165]

Chemical intuition also suggests that, as the HX molecule becomes easier to dissociate into ions H^+ and X^- along the series $\text{X} = \text{F}, \text{Cl}, \text{Br}$, or I , the extent of proton transfer should increase in this order for the $(\text{CH}_3)_3\text{N}\cdots\text{HX}$ series. Values of the percentage of proton transfer for $(\text{CH}_3)_3\text{N}\cdots\text{HX}$, $\text{X} = \text{Cl}$,^[162] Br ,^[163] or I ,^[164] as calculated from halogen nuclear hyperfine coupling constants (see reference [165]), are included in Table 12. We note again a monotonic increase in this quantity along the series $(\text{CH}_3)_3\text{N}\cdots\text{HX}$ ($\text{X} = \text{Cl}, \text{Br}$, or I). Indeed, even in the vapor phase, trimethylammonium iodide exists as the ion pair $[(\text{CH}_3)_3\text{NH}]^+\cdots\text{I}^-$, and the bromide is nearly so. Detailed energetic arguments, set out in reference [165], are in accord with these experimental results.

The conclusion from the preceding paragraphs is clear. The progressive methylation of ammonia and the progressive decrease of the dissociation energy for $\text{HX} \rightarrow \text{H}^+ + \text{X}^-$ along the series $\text{X} = \text{F}, \text{Cl}, \text{Br}$, and I lead eventually to a situation in which the Mulliken inner complex $[(\text{CH}_3)_{3-n}\text{H}_n\text{NH}]^+\cdots\text{X}^-$ becomes more stable than the Mulliken outer complex $(\text{CH}_3)_{3-n}\text{H}_n\text{N}\cdots\text{HX}$ (for $\text{X} = \text{Br}$ and I , $n = 0$). Interestingly, the percentage proton transfer in the right-hand vertical series and the horizontal series in Table 12 shows clearly that the proton is gradually being transferred, either as HX becomes progressively easier to dissociate or as n decreases from 3 to 0 . The extent of proton transfer for the $(\text{CH}_3)_3\text{N}\cdots\text{HX}$ complexes in low-temperature argon matrices is similar to that in the gas phase, while that for $\text{H}_3\text{N}\cdots\text{HX}$ complexes appears to be significantly greater in the matrix.^[9c] A detailed discussion^[165] of the complexes $\text{H}_3\text{P}\cdots\text{HX}$ and $(\text{CH}_3)_3\text{P}\cdots\text{HX}$ on the basis of similar criteria shows that even for $(\text{CH}_3)_3\text{P}\cdots\text{HBr}$ there is no evidence of proton transfer from HBr to $(\text{CH}_3)_3\text{P}$ in the gas phase. Energetic considerations reveal that this difference of behavior between the N and P series originates in the larger ionic radius of $(\text{CH}_3)_3\text{PH}^+$ relative to $(\text{CH}_3)_3\text{NH}^+$ and therefore a loss of Coulombic stabilization of the ion pair $(\text{CH}_3)_3\text{PH}^+\cdots\text{X}^-$ relative to the N analogue. It remains to discover whether any evidence exists for Mulliken inner complexes $[\text{BX}]^+\cdots\text{Y}^-$ involving dihalogen molecules XY .

4.2. The Halogen Bond $\text{B}\cdots\text{XY}$ and How to Encourage Charge Transfer

The first evidence that, in the valence bond description of a gas-phase complex $\text{B}\cdots\text{XY}$, it might be necessary to include a significant contribution from the ionic form $[\text{BX}]^+\cdots\text{Y}^-$ came from an analysis of the rotational spectrum of $\text{H}_3\text{N}\cdots\text{ClF}$ and, in particular, the magnitudes of the Cl nuclear quadru-

pole coupling constant and the intermolecular stretching force constant k_o .^[59] The latter is large (34.3 N m^{-1}) while the former is smaller than predicted from those of more weakly bound $\text{B} \cdots \text{ClF}$ and the considerations outlined in Section 3.1.2. In fact, the detailed arguments suggest a contribution of $\text{H}_3\text{NCl}^+ \cdots \text{F}^-$ of a few percent.

Given the enhancement of ion-pair character that accompanies complete methylation of $\text{H}_3\text{N} \cdots \text{HX}$ to give $(\text{CH}_3)_3\text{N} \cdots \text{HX}$, it seemed important to examine the corresponding system $(\text{CH}_3)_3\text{N} \cdots \text{ClF}$ by means of its rotational spectrum.^[169] The properties established in this way provided strong evidence of a nontrivial contribution of the form $[(\text{CH}_3)_3\text{NCl}]^+ \cdots \text{F}^-$ to the valence bond description.

First, the centrifugal distortion constant D_J is consistent with a large value of k_o . Second, the distance $r(\text{N} \cdots \text{Cl}) = 2.090 \text{ \AA}$, determined by isotopic substitution at both N and Cl, is short compared with the value of $2.639(3) \text{ \AA}$ in the weakly bound ($k_o = 12.3 \text{ N m}^{-1}$) $\text{HCN} \cdots \text{ClF}$.^[56] In fact, $r(\text{N} \cdots \text{Cl})$ in $(\text{CH}_3)_3\text{N} \cdots \text{ClF}$ is closer to the covalent distances $r(\text{N} - \text{Cl}) = 1.84 \text{ \AA}$ and $1.754(2) \text{ \AA}$ in O_2NCl ^[170] and NCl_3 ,^[171] respectively. Third, $\chi_{zz}(\text{Cl})$ in $(\text{CH}_3)_3\text{N} \cdots \text{ClF}$ can be interpreted in terms of about a 60 % contribution of the form $[(\text{CH}_3)_3\text{NCl}]^+ \cdots \text{F}^-$ by using arguments based on comparisons with values of $\chi_{zz}(\text{Cl})$ along the Cl bond direction z in molecules such as CH_3OCl , as discussed in detail in reference [169]. Fourth, the ^{14}N nuclear quadrupole coupling constant $\chi(^{14}\text{N})$ of $(\text{CH}_3)_3\text{N} \cdots \text{ClF}$ indicates a substantial ion pair contribution. Figure 32 shows the

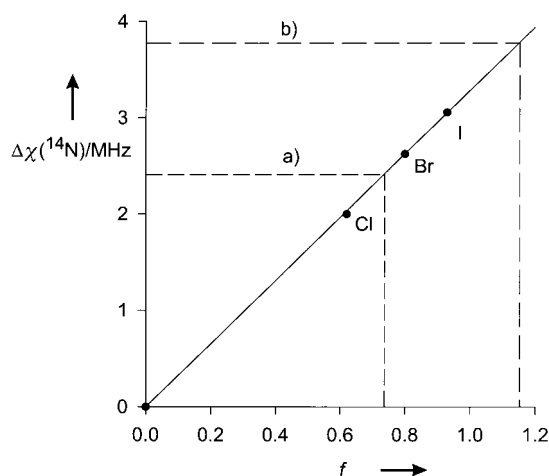


Figure 32. A plot of the change $\Delta\chi(^{14}\text{N})$ in the ^{14}N nuclear quadrupole coupling constant of $(\text{CH}_3)_3\text{N}$ on formation of $(\text{CH}_3)_3\text{N} \cdots \text{HX}$ against the fractional contribution f of the ionic structure $[(\text{CH}_3)_3\text{NH}]^+ \cdots \text{X}^-$ to the valence-bond description of the complex. Values of f were estimated from the nuclear quadrupole coupling constants of X (see text and reference [165] for discussion). The horizontal lines a) and b) mark the values of $\Delta\chi(^{14}\text{N})$ for $(\text{CH}_3)_3\text{N} \cdots \text{ClF}$ and $(\text{CH}_3)_3\text{N} \cdots \text{F}_2$, respectively, and indicate a significant contribution of $[(\text{CH}_3)_3\text{NX}]^+ \cdots \text{Y}^-$ to the valence-bond description of the complex in each case.

change $\Delta\chi(^{14}\text{N})$ of $\chi(^{14}\text{N})$ relative to free trimethylamine on formation of the trimethylammonium halides $(\text{CH}_3)_3\text{N} \cdots \text{HX}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$)^[162–164] plotted against the fractional ionic character f , which was determined from the halogen nuclear quadrupole coupling constant. The result is a straight line through the origin (which is a proper point). Onto this line is

drawn $\Delta\chi(^{14}\text{N})$ for the formation of $(\text{CH}_3)_3\text{N} \cdots \text{ClF}$. The value implies that $f \approx 0.7$, although this result should not be taken literally since we are effectively assuming that the $\chi(^{14}\text{N})$ for the two ions $[(\text{CH}_3)_3\text{NCl}]^+$ and $[(\text{CH}_3)_3\text{NH}]^+$ are identical, and this is unlikely. Finally, there is evidence from the behavior of rotational transitions of $(\text{CH}_3)_3\text{N} \cdots \text{ClF}$ with increasing microwave power that the complex has a very large electric dipole moment.^[169]

The above evidence strongly supports a detectable contribution of the ion-pair structure $[(\text{CH}_3)_3\text{NCl}]^+ \cdots \text{F}^-$ to the valence-bond description of the complex $(\text{CH}_3)_3\text{N} \cdots \text{ClF}$. A contribution on the order of 50 % seems likely. Hence, a Mulliken complex of the inner type, with substantial charge transfer from the halogen molecule to the amine, appears to have been identified in the gas phase. Interestingly, IR matrix-isolation studies^[7c] on ClF complexes with both NH_3 and $(\text{CH}_3)_3\text{N}$ also suggest considerable ionic character in $\text{R}_3\text{N} \cdots \text{ClF}$ species. Are there other examples of this type? There is some evidence of ion-pair character in $(\text{CH}_3)_2\text{S} \cdots \text{ClF}$.^[104]

In view of the extreme weakness of $\text{B} \cdots \text{F}_2$ complexes referred to in Section 3.2, it was a surprise to find that $(\text{CH}_3)_3\text{N} \cdots \text{F}_2$ has a large electric dipole moment ($\approx 10 \text{ D}$) compared with that (ca. 1 D) expected from the weak binding model, a large intermolecular stretching force constant k_o , a short distance $r(\text{N} \cdots \text{F})$, and a small value of the ^{14}N - nuclear quadrupole coupling constant.^[172] If the value of $\Delta\chi(^{14}\text{N}) = \chi_{\text{complex}}(^{14}\text{N}) - \chi_0(^{14}\text{N})$, where $\chi_0(^{14}\text{N})$ refers to free trimethylamine, is placed on the straight line in Figure 32, it implies a substantial contribution from $[(\text{CH}_3)_3\text{NF}]^+ \cdots \text{F}^-$ to a valence-bond description of the complex (but with the same caveat raised in connection with $(\text{CH}_3)_3\text{N} \cdots \text{ClF}$), as do all the other properties mentioned. Evidently the $(\text{CH}_3)_3\text{N} \cdots \text{F}_2$ complex, unlike other $\text{B} \cdots \text{F}_2$, involves substantial charge transfer from F_2 to the base and may be described as a Mulliken inner complex. Recent ab initio calculations^[173, 174] indicate that the arguments concerning $\Delta\chi(^{14}\text{N})$ overestimate f and that the assumption of an unperturbed $(\text{CH}_3)_3\text{N}$ geometry, necessarily used to obtain $r(\text{N} \cdots \text{F}_i)$ in reference [172], leads to values of $r(\text{N} \cdots \text{F}_i)$ and $r(\text{F} \cdots \text{F})$ that are too small and too large, respectively.

In summary, there is evidence that the valence-bond description of complexes of trimethylamine with HCl , HBr , HI , ClF , and F_2 requires a significant contribution of the ionic structure $[(\text{CH}_3)_3\text{NH}]^+ \cdots \text{X}^-$ or $[(\text{CH}_3)_3\text{NX}]^+ \cdots \text{Y}^-$ to be invoked. In particular, proton transfer is effectively complete in $[(\text{CH}_3)_3\text{NH}]^+ \cdots \text{X}^-$ for $\text{X} = \text{Br}$ and I . This result means that although we begin with separate samples of trimethylamine and HX in the fast-mixing nozzle, about $10 \mu\text{s}$ after their first encounter, when collisionless expansion begins, the proton has been transferred. On the same time scale, there also appears to be a significant extension of the XY bond in $(\text{CH}_3)_3\text{N} \cdots \text{XY}$.

5. Summary and Outlook

Through the use of a fast-mixing nozzle in conjunction with a pulsed-jet, FT microwave spectrometer, the rotational

spectra of complexes $B \cdots XY$, formed from a wide range of simple Lewis bases B and homo- or heteronuclear dihalogen molecules XY , can be detected and analyzed to give several properties. The efficacy of the mixing nozzle is such that complexes can be observed in gas mixtures as reactive as H_2S/F_2 , NH_3/F_2 , and C_2H_2/ClF . It has been established in this article that the properties of the $B \cdots XY$ so observed exhibit a systematic behavior when B and XY are varied. In addition, a close relationship exists with properties in the corresponding series $B \cdots HX$. The properties in question are angular geometries (shapes), intermolecular separations $r(Z \cdots X)$, where Z is the electron-donor atom or center in B , the intermolecular binding strength (as indicated by the intermolecular stretching force constant k_0), and the fraction δ of an electronic charge redistributed from X to Y when $B \cdots XY$ is formed.

Except for the most strongly bound complexes, such as $(CH_3)_3N \cdots HX$ ($X = Cl, Br, \text{ or } I$) and $(CH_3)_3N \cdots XY$ ($XY = F_2$ or ClF), the complexes discussed are mostly of the Mulliken outer type. This conclusion is demonstrated by values of δ on the order of a few hundredths of an electronic charge and by values of k_0 on the order of 10 N m^{-1} . In fact, there is an approximately linear relation between δ and k_0 for those series $B \cdots Cl_2$, $B \cdots Br_2$ and $B \cdots BrCl$ for which δ can be determined from the nuclear quadrupole coupling constants $\chi(X)$ and $\chi(Y)$ associated with both ends of XY . A similar relation may exist for the $B \cdots ClF$ series, but the absence of a quadrupolar probe of the electric charge distribution at F precludes an equivalent analysis.

A systematic relationship was also detected for k_0 values in the series $B \cdots XY$, where $XY = F_2, Cl_2, Br_2, BrCl$ and ClF . The k_0 for most of these complexes can be reproduced by the simple equation $k_0 = cE_{XY}N_B$, where c is constant and E_{XY} and N_B are the electrophilicity and nucleophilicity of the component molecules XY and B . Analogous behavior was noted previously in a wide range of hydrogen-bonded complexes $B \cdots HX$, for which the same equation applies. Moreover, when the same value of c was assumed for both the $B \cdots HX$ and the $B \cdots XY$ series, the nucleophilicities N_B of a given B generated from consideration of the two series are in good agreement. All members of the $B \cdots F_2$ series, except $(CH_3)_3N \cdots F_2$, are very weakly bound, a result understandable in terms of the electric charge distribution of F_2 , which is nearly spherical. Thus, F_2 behaves like a spherical inert gas atom as a first approximation when it interacts with B . The electrophilicities E_{XY} lie in the order $F_2 < Cl_2 < Br_2 < BrCl < ClF$, which is that of the dihalogen electric quadrupole and dipole moments. This suggests that electrostatic interactions are important in the description of the $B \cdots XY$ interaction, except perhaps when XY is F_2 .

The angular geometries of the $B \cdots XY$ show a remarkable pattern. For a given B , the complexes $B \cdots F_2$, $B \cdots Cl_2$, $B \cdots ClF$, and $B \cdots BrCl$ have isomorphous angular geometries. In addition, for the same B , the $B \cdots HX$ ($X = F, Cl, Br$) are also isostructural with $B \cdots XY$. It then follows that some simple rules, initially enunciated to rationalize the angular geometries of $B \cdots HX$, also apply, after appropriate reformulation, to the $B \cdots XY$. These rules are electrostatic in origin, since they require the electrophilic end $H^{\delta+}$ or $X^{\delta+}$ of HX or

XY , respectively, to seek the direction of greatest nucleophilicity in B , that is, the axis of a nonbonding or π -bonding electron pair. Evidently, the electrostatic component of the interaction energy is important in defining the angular geometry of $B \cdots XY$, as well as that of $B \cdots HX$. The main difference between $B \cdots XY$ and $B \cdots HX$ in this context is that, when symmetry allows, the deviation θ of the $Z \cdots H-X$ system from linearity is greater than that of the corresponding $Z \cdots X-Y$ arrangement.

Radial geometries of $B \cdots XY$ and $B \cdots HX$ are also systematically related. The difference $\Delta r = r_{HX}(Z \cdots X) - r_{XY}(Z \cdots X)$ is positive and nearly constant in each series $B \cdots HX/B \cdots XY$ ($XY = Cl_2, Br_2, BrCl, ClF$), and this leads to the conclusion that the van der Waals radius of the atom X in the dihalogen XY is shorter along the XY axis than perpendicular to it. Thus, the XY molecule can be described as snub-nosed. For the two series $B \cdots HF/B \cdots F_2$, however, Δr is very small; this indicates that the F atom in F_2 is nearly isotropic in its van der Waals radius.

The parallelism among the properties of $B \cdots XY$ and $B \cdots HX$ alluded to earlier in this section suggests that one might invoke the existence of a halogen bond that is an analogue of the hydrogen bond, that is, an interaction of electrostatic character involving largely unperturbed electric charge distributions of either B and XY or B and HX , respectively. The propensity of $B \cdots HCl$ to exhibit greater deviations of their $Z \cdots H-Cl$ nuclei from collinearity than those of $Z \cdots X-Y$ in $B \cdots XY$ may then be understood on the basis of a secondary interaction of $Cl^{\delta-}$ or $Y^{\delta-}$ with the nearest electrophilic region E of B in $B \cdots HCl$ or $B \cdots XY$, respectively. The distance $E \cdots \delta-F$ in $B \cdots ClF$ is larger than the corresponding distance $E \cdots \delta-Cl$ in $B \cdots HCl$ for a given B , and hence the force required to produce a given angular distortion of the stronger $Z \cdots Cl-F$ system is greater.

Finally, the existence of Mulliken inner complexes in the gas phase has been established. The proton affinity and X^+ affinity of NH_3 are both increased by progressive methylation. Examination of the properties of the series $(CH_3)_{3-n}H_nN \cdots HX$ as n is varied from 3 to 2 to 0 and X is varied from F through to I reveals that $(CH_3)_3N \cdots HBr$ and $(CH_3)_3N \cdots HI$ are more appropriately described in terms of the ion pairs $[(CH_3)_3NH]^+ \cdots X^-$, even in the gas phase. Yet again, there is evidence of parallel behavior in the corresponding series $(CH_3)_{3-n}H_nN \cdots XY$. For the two members of this series so far investigated ($n = 0$; $XY = F_2$ or ClF), it is necessary to invoke a contribution from $[(CH_3)_3NX]^+ \cdots Y^-$ in a valence-bond description of the complex.

In future, it will be desirable to investigate other dihalogen species XY and other Lewis bases, with the aim of establishing the limits of the generalizations established here. More quantitative models than those presented in this article will also be of interest, as will the systematic application of ab initio SCF calculations to selected series $B \cdots XY$.

Addendum

Since this review was submitted the rotational spectra of the series of complexes $B \cdots ICl$ ($B = Ar,^{[175]} CO,^{[176]} C_2H_2,^{[177]}$

C_2H_4 ,^[178] H_2O ,^[179] H_2S ,^[180] NH_3 ,^[181]) have been detected and analyzed. Table 14 displays the properties $r(\text{Z} \cdots \text{I})$, k_{σ} , δ_1 , and δ_2 , as determined from the spectroscopic constants (see Section 2.1). The definitions of Z and k_{σ} are given in Sections 3.3 and 3.2, respectively. The quantities δ_1 and δ_2 are the fractions of an electronic charge transferred from Z to I and from I to Cl, respectively, on complex formation—that is, inter- and intramolecular electron transfer—and were determined from modified versions of Equations (8) and (9), as described below.

The k_{σ} values of the $\text{B} \cdots \text{ICl}$ complexes given in Table 14 indicate, on comparison with those of other $\text{B} \cdots \text{X}_2$ and $\text{B} \cdots \text{XY}$ complexes (Table 2), that $\text{B} \cdots \text{ICl}$ is the most strongly bound of the series for a given base B. If $E_{\text{ICl}} = 9.9$ is chosen for the electrophilicity of ICl, the k_{σ} values for $\text{B} \cdots \text{ICl}$ ($\text{B} = \text{CO}$, C_2H_2 , C_2H_4 , H_2S , NH_3) are well reproduced by $k_{\sigma} = cN_{\text{B}}E_{\text{XY}}$ (see Section 3.2), as shown by the calculated values given in Table 14.

Table 14. Comparison of some properties of the complexes $\text{B} \cdots \text{ICl}$.

B	$r(\text{Z} \cdots \text{I})$ [Å] ^[a]	$\sigma(\text{Z}) + \sigma(\text{I})$ [Å]	k_{σ} [N m ⁻¹] ^[b]	δ_1 ^[c]	δ_2 ^[d]	Ref.
Ar	3.576(1)	4.05	3.20	0.0 ^[e]	0.0054	[175]
CO	3.011(1)	3.85	8.0 (8.3)	0.025	0.048	[176]
C_2H_2	3.115(1)	3.85	12.1 (12.4)	0.026	0.056	[177]
C_2H_4	3.033(2)	3.85	14.0 (14.0)	0.054	0.080	[178]
H_2O	2.807(1)	3.55	15.9	0.010	0.065	[179]
H_2S	3.155(1)	4.00	16.6 (16.0)	0.055	0.084	[180]
NH_3	2.711(2)	3.65	30.4 (29.5)	0.078	0.150	[181]

[a] Z is the electron-donor atom or electron-donor center in B. [b] Values of k_{σ} in italics and in parenthesis were calculated from the expression $k_{\sigma} = cN_{\text{B}}E_{\text{ICl}}$, with $E_{\text{ICl}} = 11.9$ and N_{B} values from Table 5. Values of N_{B} for Ar and H_2O are unavailable. [c] δ_1 is the fraction of an electronic charge transferred from Z to I on complex formation. See the text for the method of calculation from $\chi_{\text{zz}}(\text{I})$ and $\chi_{\text{zz}}(\text{Cl})$ values. [d] δ_2 is the fraction of an electronic charge transferred from I to Cl on complex formation. See the text for the method of calculation from $\chi_{\text{zz}}(\text{I})$ and $\chi_{\text{zz}}(\text{Cl})$ values. The net gain of electronic charge by I is $(\delta_1 - \delta_2)e$. [e] δ_1 is assumed to be negligible for $\text{Ar} \cdots \text{ICl}$.

The values of δ_1 and δ_2 in Table 14 were obtained by using the appropriate forms of Equation (8) and (9) (Section 3.1.2), that is, with δ in Equation (8) replaced by $(\delta_1 - \delta_2)$ and δ in Equation (9) replaced by δ_2 (see reference [176] for the detailed arguments). It was found that if the reasonable assumption $\delta_1 = 0.0$ is made for the weakly bound complex $\text{Ar} \cdots \text{ICl}$, the result is $\delta_2 = 5.4(1) \times 10^{-3}$ and $\phi_{\text{av}} = 5.45(1)^{\circ}$.^[175] The assumption $\delta_1 = 0.0$ proved unsatisfactory for the other $\text{B} \cdots \text{ICl}$ species because it led to ϕ_{av} values that become progressively larger along the series $\text{B} = \text{Ar}$, CO , C_2H_2 , C_2H_4 , H_2S , and NH_3 . This result is unreasonable in view of the increase in binding strength k_{σ} along the series (see Table 14). On the contrary, we expect ϕ_{av} to decrease as k_{σ} increases. Fortunately, ϕ_{av} is already small for $\text{Ar} \cdots \text{ICl}$, and if we assume $\phi_{\text{av}} = 4.5(5)^{\circ}$ for $\text{B} = \text{CO}$, C_2H_2 , and C_2H_4 and $4(1)^{\circ}$ for the more strongly bound cases $\text{B} = \text{H}_2\text{S}$, H_2O , and NH_3 we can be confident that the actual value of ϕ_{av} in each case is included in the range. The δ_1 and δ_2 values given in Table 14 were calculated from the modified versions of Equations (8) and (9) by using these values of ϕ_{av} . This procedure is tantamount to using $\text{Ar} \cdots \text{ICl}$ as the reference point $\delta_1 = 0$ for intermolecular electron transfer. It cannot be applied to the

other series ($\text{B} \cdots \text{Br}_2$ and $\text{B} \cdots \text{BrCl}$) in which δ_1 might be significant because the rotational spectra of $\text{Ar} \cdots \text{Br}_2$ and $\text{Ar} \cdots \text{BrCl}$, and hence the upper limits to the angles ϕ_{av} , are not known. It is interesting to note that the δ_1 values show a systematic decrease as the first ionization energy of the Lewis base B increases, with the exception of CO .^[182] This phenomenon will be discussed elsewhere.

Finally, the distances $r(\text{Z} \cdots \text{I})$ are systematically shorter than the sum $\sigma(\text{Z}) + \sigma(\text{I})$ of the van der Waals radii $\sigma(\text{Z})$ and $\sigma(\text{I})$ of Z and I (Table 14). This is consistent with the behavior noted for $\text{B} \cdots \text{Cl}_2$, $\text{B} \cdots \text{ClF}$, $\text{B} \cdots \text{Br}_2$, and $\text{B} \cdots \text{BrCl}$ (see Tables 8–10) and indicates that the ICl molecule is, like Cl_2 and ClF , snub-nosed (see Section 3.4).

I am grateful to my co-workers, whose experimental skills and tenacity made possible the work described in this article. Their names are evident in the literature cited here. In particular, the investigations of dihalogen complexes conducted by Joanna Thorn, David Lister, Hugh Warner, Hannelore Bloemink, Kelvin Hinds, Gina Cotti, Christopher Evans, Stephen Cooke, and Gary Corlett are mentioned. The earlier work on the hydrogen bond benefited especially from the efforts of Charles Willoughby, Zbigniew Kisiel, Annette Travis, Elizabeth Goodwin, Nigel Howard, Christopher Rego, Andrew Suckley, and Andrew Wallwork. I thank Professor John Holloway for providing ClF and F_2 and instructing us on their safe handling. I am grateful to the EPSRC for research grants and a Senior Fellowship. Finally, I am pleased to acknowledge the patience of Janet Jones and Robin Batten in preparing the typescript and the graphics, respectively.

Received: October 28, 1998 [A 309 IE]
German version: *Angew. Chem.* **1999**, *111*, 2850–2880

- [1] H. A. Benesi, J. H. Hildebrand, *J. Am. Chem. Soc.* **1949**, *71*, 2703–2727.
- [2] O. Hassel, C. Rømming, *Q. Rev. Chem. Soc.* **1962**, *16*, 1–18.
- [3] R. S. Mulliken, W. B. Person, *Molecular Complexes: A Lecture and Reprint Volume*, Wiley-Interscience, New York, **1969**, and references therein.
- [4] A. J. Downs, C. J. Adams in *Comprehensive Inorganic Chemistry* (Ed.: A. Trotman-Dickenson), Pergamon Press, Oxford, **1973**, chap. 26, pp. 1214–1220.
- [5] See, for example: a) C. K. Ingold, *Structure and Mechanism in Organic Chemistry* (Ed.: G. Bell), 2nd. ed., London, **1969**, pp. 964–988; b) J. E. Dubois, F. Garnier, *Spectrochim. Acta A* **1967**, *23*, 2279–2288; c) R. S. Brown, H. Slebocka-Tilk, A. J. Bennet, G. Bellucci, R. Bianchini, R. Ambrosetti, *J. Am. Chem. Soc.* **1990**, *112*, 6310–6316.
- [6] See, for example: a) H. Frei, G. C. Pimentel, *J. Chem. Phys.* **1983**, *78*, 3698–3712; b) A. K. Knudsen, G. C. Pimentel, *J. Chem. Phys.* **1983**, *78*, 6780–6792; c) S. N. Cesaro, H. Frei, G. C. Pimentel, *J. Phys. Chem.* **1983**, *87*, 2142–2147; d) K. A. Singmaster, G. C. Pimentel, *J. Phys. Chem.* **1990**, *94*, 5226–5229; e) S. A. Abrash, G. C. Pimentel, *J. Phys. Chem.* **1989**, *93*, 5828–5834.
- [7] See, for example: a) H. Bai, B. S. Ault, *J. Phys. Chem.* **1990**, *94*, 199–203; b) N. P. Machara, B. S. Ault, *Inorg. Chem.* **1988**, *27*, 2383–2385; c) N. P. Machara, B. S. Ault, *J. Phys. Chem.* **1988**, *92*, 2439–2442; d) N. P. Machara, B. S. Ault, *J. Phys. Chem.* **1988**, *92*, 73–77; e) B. S. Ault, *J. Phys. Chem.* **1987**, *91*, 4723–4727; f) C. E. Sass, B. S. Ault, *J. Phys. Chem.* **1987**, *91*, 3207–3211; g) N. P. Machara, B. S. Ault, *J. Phys. Chem.* **1987**, *91*, 2046–2050; h) B. S. Ault, *J. Phys. Chem.* **1986**, *90*, 2825–2829; i) N. P. Machara, B. S. Ault, *Inorg. Chem.* **1985**, *24*, 4251–4254.

- [8] See, for example: a) L. Andrews, T. C. McInnis, Y. Hannachi, *J. Phys. Chem.* **1992**, 96, 4248–4254; b) T. C. McInnis, L. Andrews, *J. Phys. Chem.* **1992**, 96, 2051–2059; c) P. Hassanzadeh, L. Andrews, *J. Phys. Chem.* **1992**, 96, 79–84; d) L. Andrews, T. C. McInnis, *Inorg. Chem.* **1991**, 30, 2990–2993; e) R. B. Bohn, R. D. Hunt, L. Andrews, *J. Phys. Chem.* **1989**, 93, 3979–3983; f) L. Andrews, R. Withnall, *Inorg. Chem.* **1989**, 28, 494–499; g) L. Andrews, R. D. Hunt, *J. Chem. Phys.* **1988**, 89, 3502–3504; h) R. D. Hunt, L. Andrews, *J. Phys. Chem.* **1988**, 92, 3769–3774; i) R. Lascola, R. Withnall, L. Andrews, *Inorg. Chem.* **1988**, 27, 642–648; j) L. Andrews, R. Lascola, *J. Am. Chem. Soc.* **1987**, 109, 6243–6247.
- [9] See, for example: a) A. J. Barnes, M. P. Wright, *THEOCHEM* **1986**, 28, 21–30; b) U. P. Agarwal, A. J. Barnes, W. J. Orville-Thomas, *Can. J. Chem.* **1985**, 63, 1705–1707; c) A. J. Barnes, T. R. Beech, Z. Mielke, *J. Chem. Soc. Faraday Trans. 2* **1984**, 80, 455–463; d) A. J. Barnes, J. N. S. Kuzniarski, Z. Mielke, *J. Chem. Soc. Faraday Trans. 2* **1984**, 80, 465–476; e) A. J. Barnes, A. C. Legon, *J. Mol. Struct.* **1998**, 448, 101–106.
- [10] B. S. Ault, *Rev. Chem. Intermed.* **1988**, 9, 233–269.
- [11] a) A. J. Barnes, *J. Mol. Struct.* **1983**, 100, 259–280; b) A. J. Barnes, *J. Mol. Struct.* **1988**, 177, 209–220.
- [12] L. Andrews, *J. Phys. Chem.* **1984**, 88, 2940–2949.
- [13] H. Frei, G. C. Pimentel, *Annu. Rev. Phys. Chem.* **1985**, 36, 491–524.
- [14] A. C. Legon, C. A. Rego, *J. Chem. Soc. Faraday Trans.* **1990**, 86, 1915–1921, and references therein.
- [15] A. C. Legon, *Chem. Soc. Rev.* **1990**, 19, 197–237.
- [16] A. C. Legon, D. J. Millen, *Chem. Rev.* **1986**, 86, 635–657.
- [17] T. R. Dyke, B. J. Howard, W. Klemperer, *J. Chem. Phys.* **1972**, 56, 2442–2454.
- [18] a) T. J. Balle, E. J. Campbell, M. R. Kennan, W. H. Flygare, *J. Chem. Phys.* **1980**, 72, 922–932; b) E. J. Campbell, L. W. Buxton, T. J. Balle, M. R. Keenan, W. H. Flygare, *J. Chem. Phys.* **1981**, 74, 829–840; c) E. J. Campbell, L. W. Buxton, T. J. Balle, W. H. Flygare, *J. Chem. Phys.* **1981**, 74, 813–829.
- [19] T. R. Dyke, *Top. Curr. Chem.* **1984**, 120, 85–113.
- [20] K. R. Leopold, G. T. Fraser, S. E. Novick, W. Klemperer, *Chem. Rev.* **1994**, 94, 1807–1827.
- [21] For a detailed description, see A. C. Legon in *Atomic and Molecular Beam Methods*, Vol. 2 (Ed.: G. Scoles), Oxford University Press, New York, **1992**, chap. 9, pp. 289–308.
- [22] D. J. Millen, *Can. J. Chem.* **1985**, 63, 1477–1479.
- [23] A. C. Legon, *Faraday Discuss. Chem. Soc.* **1994**, 97, 19–33.
- [24] *Gmelins Handbuch der Anorganischen Chemie, Fluorine Supplement*, Vol. 2, Springer, Berlin, **1980**, p. 169.
- [25] D. R. Miller in *Atomic and Molecular Beam Methods*, Vol. 1 (Ed.: G. Scoles), Oxford University Press, New York, **1988**, chap. 2, pp. 14–53.
- [26] H. I. Bloemink, K. Hinds, A. C. Legon, J. C. Thorn, *Chem. Phys. Lett.* **1994**, 223, 162–166.
- [27] H. I. Bloemink, K. Hinds, A. C. Legon, J. C. Thorn, *Chem. Eur. J.* **1995**, 1, 17–25.
- [28] A. C. Legon, *Chem. Phys. Lett.* **1995**, 237, 291–298.
- [29] A. C. Legon, P. W. Fowler, *Z. Naturforsch. A* **1992**, 47, 367–370.
- [30] P. W. Fowler, A. C. Legon, S. A. Peebles, *Mol. Phys.* **1996**, 88, 987–996.
- [31] For an account of the Townes–Dailey model see: C. H. Townes, A. L. Schawlow, *Microwave Spectroscopy*, McGraw-Hill, New York, **1955**, chap. 9.
- [32] W. Jäger, Y. Xu, M. C. L. Gerry, *J. Phys. Chem.* **1993**, 97, 3685–3689.
- [33] F. A. Biaoocchi, T. A. Dixon, W. Klemperer, *J. Chem. Phys.* **1982**, 77, 1632–1638.
- [34] A. C. Legon, H. E. Warner, *J. Chem. Phys.* **1993**, 98, 3827–3832.
- [35] H. I. Bloemink, S. J. Dolling, K. Hinds, A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1995**, 91, 2059–2066.
- [36] H. I. Bloemink, S. A. Cooke, K. Hinds, A. C. Legon, J. C. Thorn, *J. Chem. Soc. Faraday Trans.* **1995**, 91, 1891–1900.
- [37] A. C. Legon, J. C. Thorn, *J. Chem. Soc. Faraday Trans.* **1993**, 89, 4157–4162.
- [38] A. C. Legon, D. G. Lister, J. C. Thorn, *J. Chem. Soc. Faraday Trans.* **1994**, 90, 3205–3212.
- [39] H. I. Bloemink, A. C. Legon, *J. Chem. Phys.* **1995**, 103, 876–882.
- [40] P. W. Fowler, A. C. Legon, J. M. A. Thumwood, E. R. Waclawik, *Mol. Phys.* **1999**, 97, 159–166.
- [41] M. Jaszunski, E. Kochanski, *J. Am. Chem. Soc.* **1977**, 99, 4624–4628.
- [42] P. W. Fowler, S. A. Peebles, A. C. Legon in *Advances in Quantum Chemistry*, Vol. 28 (Ed.: P. Löwdin), Academic Press, San Diego, **1997**, pp. 248–255.
- [43] “Microwave Molecular Spectra”: W. Gordy, R. L. Cook in *Techniques of Chemistry*, Vol. XVIII (Ed.: A. Weissberger), 3rd ed., Wiley, New York, **1984**, chap. XIV, pp. 725–802. Note that $\chi_A(X)$ and $\chi_A(Y)$ used in this review are identical with the $eQq_{n,1,0}$ described on p. 738 of this text.
- [44] A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1995**, 91, 1881–1883.
- [45] S. Blanco, A. C. Legon, J. C. Thorn, *J. Chem. Soc. Faraday Trans.* **1994**, 90, 1365–1371.
- [46] H. I. Bloemink, K. Hinds, A. C. Legon, J. C. Thorn, *Angew. Chem.* **1994**, 106, 1577–1579; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1512–1513.
- [47] H. I. Bloemink, K. Hinds, A. C. Legon, J. C. Thorn, *J. Chem. Soc. Chem. Commun.* **1994**, 1229–1230.
- [48] H. I. Bloemink, A. C. Legon, *Chem. Eur. J.* **1996**, 2, 265–270.
- [49] K. Hinds, A. C. Legon, *Chem. Phys. Lett.* **1995**, 240, 467–473.
- [50] H. I. Bloemink, A. C. Legon, J. C. Thorn, *J. Chem. Soc. Faraday Trans.* **1995**, 91, 781–787.
- [51] A. C. Legon, *Chem. Phys. Lett.* **1997**, 279, 55–64.
- [52] S. A. Cooke, G. Cotti, K. Hinds, J. H. Holloway, A. C. Legon, D. G. Lister, *J. Chem. Soc. Faraday Trans.* **1996**, 92, 2671–2676.
- [53] K. Hinds, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1995**, 242, 407–414.
- [54] K. Hinds, J. H. Holloway, A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1996**, 92, 1291–1296.
- [55] H. I. Bloemink, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1996**, 250, 567–575.
- [56] K. Hinds, A. C. Legon, J. H. Holloway, *Mol. Phys.* **1996**, 88, 673–682.
- [57] H. I. Bloemink, K. Hinds, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1995**, 242, 113–120.
- [58] S. A. Cooke, G. Cotti, C. M. Evans, J. H. Holloway, A. C. Legon, *Chem. Commun.* **1996**, 2327–2328.
- [59] H. I. Bloemink, C. M. Evans, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1996**, 248, 260–268.
- [60] A. Maryott, F. Buckley, *NSRDS-NBS Circular 537*, US GPO, Washington, **1953**, quoted in: D. R. Lide, *CRC Handbook of Chemistry*, 75th ed., CRC Press, Raton, FL, **1994**.
- [61] A. C. Legon, D. J. Millen, *J. Am. Chem. Soc.* **1987**, 109, 356–358.
- [62] A. C. Legon, D. J. Millen, *J. Chem. Soc. Chem. Commun.* **1987**, 986–987.
- [63] S. A. Cooke, G. Cotti, C. M. Evans, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1996**, 262, 308–314.
- [64] G. Cotti, C. M. Evans, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1997**, 264, 513–521.
- [65] H. I. Bloemink, K. Hinds, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1995**, 245, 598–604.
- [66] Convenient collections of k_a values for $B \cdots HF$, $B \cdots HCl$, $B \cdots HBr$ and $B \cdots HCN$ for a range of Lewis bases B are given in references [61] and [62]. The values in Table 3 are taken from these sources.
- [67] A. C. Legon, D. J. Millen, *Faraday Discuss. Chem. Soc.* **1982**, 73, 71–87.
- [68] A. D. Buckingham, P. W. Fowler, *Can. J. Chem.* **1985**, 63, 2018–2025.
- [69] A. D. Buckingham, C. Graham, J. H. Williams, *Mol. Phys.* **1983**, 49, 703–710.
- [70] S. A. Peebles, P. W. Fowler, A. C. Legon, unpublished results.
- [71] K. P. R. Nair, J. Hoeft, E. Tiemann, *Chem. Phys. Lett.* **1978**, 58, 153–156.
- [72] B. Fabricant, J. S. Muentner, *J. Chem. Phys.* **1977**, 66, 5274–5277.
- [73] R. Herges, *Angew. Chem.* **1995**, 107, 57–59; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 51–53, and references therein.
- [74] H. Matsuzawa, S. Iwata, *Chem. Phys.* **1992**, 163, 297–305.
- [75] A. C. Legon, D. J. Millen, *Chem. Soc. Rev.* **1987**, 16, 467–498.
- [76] N. W. Howard, A. C. Legon, *J. Chem. Phys.* **1988**, 88, 4694–4701.
- [77] N. W. Howard, A. C. Legon, *J. Chem. Phys.* **1987**, 86, 6722–6730.
- [78] A. C. Legon, D. Stephenson, *J. Chem. Soc. Faraday Trans.* **1992**, 88, 761–762.
- [79] A. C. Legon, L. C. Willoughby, *Chem. Phys.* **1983**, 74, 127–136.
- [80] A. C. Legon, L. C. Willoughby, *J. Chem. Soc. Chem. Commun.* **1982**, 997–998.
- [81] L. C. Willoughby, A. C. Legon, *J. Phys. Chem.* **1983**, 87, 2085–2090.

- [82] N. W. Howard, A. C. Legon, G. J. Luscombe, *J. Chem. Soc. Faraday Trans.* **1991**, 87, 507–512.
- [83] A. C. Legon, P. D. Soper, W. H. Flygare, *J. Chem. Phys.* **1981**, 74, 4944–4950.
- [84] P. D. Soper, A. C. Legon, W. H. Flygare, *J. Chem. Phys.* **1981**, 74, 2138–2142.
- [85] M. R. Keenan, T. K. Minton, A. C. Legon, T. J. Balle, W. H. Flygare, *Proc. Natl. Acad. Sci. USA* **1980**, 77, 5583–5587.
- [86] Z. Wang, R. R. Lucchese, J. W. Bevan, A. P. Suckley, C. A. Rego, A. C. Legon, *J. Chem. Phys.* **1993**, 98, 1761–1767.
- [87] A. C. Legon, D. J. Millen, L. C. Willoughby, *Proc. R. Soc. London A* **1985**, 401, 327–347.
- [88] A. C. Legon, E. J. Campbell, W. H. Flygare, *J. Chem. Phys.* **1982**, 76, 2267–2274.
- [89] E. J. Campbell, A. C. Legon, W. H. Flygare, *J. Chem. Phys.* **1982**, 76, 3494–3500.
- [90] P. W. Fowler, A. C. Legon, S. A. Peebles, *Chem. Phys. Lett.* **1994**, 226, 501–508.
- [91] S. A. Cooke, G. Cotti, J. H. Holloway, A. C. Legon, *Angew. Chem.* **1997**, 109, 81–83; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 129–130.
- [92] Z. Kisiel, A. C. Legon, D. J. Millen, *Proc. R. Soc. London A* **1982**, 381, 419–442.
- [93] A. C. Legon, L. C. Willoughby, *Chem. Phys. Lett.* **1983**, 95, 449–452.
- [94] A. C. Legon, A. P. Suckley, *Chem. Phys. Lett.* **1988**, 150, 153–158.
- [95] a) R. Viswanathan, T. R. Dyke, *J. Chem. Phys.* **1982**, 77, 1166–1174; b) L. C. Willoughby, A. J. Fillery-Travis, A. C. Legon, *J. Chem. Phys.* **1984**, 81, 20–26.
- [96] E. J. Goodwin, A. C. Legon, *J. Chem. Soc. Faraday Trans. 2* **1984**, 80, 51–65.
- [97] A. I. Jaman, A. C. Legon, *J. Mol. Struct.* **1986**, 145, 261–276.
- [98] S. E. Novick, K. C. Janda, W. Klemperer, *J. Chem. Phys.* **1976**, 65, 5115–5121.
- [99] K. C. Janda, J. M. Steed, S. E. Novick, W. Klemperer, *J. Chem. Phys.* **1977**, 67, 5162–5172.
- [100] G. T. Fraser, A. S. Pine, *J. Chem. Phys.* **1989**, 91, 637–645.
- [101] S. A. Cooke, G. K. Corlett, C. M. Evans, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1997**, 275, 269–277.
- [102] S. A. Cooke, G. K. Corlett, C. M. Evans, A. C. Legon, J. H. Holloway, *J. Chem. Phys.* **1998**, 108, 39–45.
- [103] H. I. Bloemink, C. M. Evans, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1996**, 251, 275–286.
- [104] C. M. Evans, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1996**, 255, 119–128.
- [105] A. C. Legon, J. C. Thorn, *Chem. Phys. Lett.* **1994**, 227, 472–479.
- [106] G. T. Fraser, C. W. Gillies, J. Zozom, F. J. Lovas, R. D. Suenram, *J. Mol. Spectrosc.* **1987**, 126, 200–209.
- [107] A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1996**, 92, 2677–2679.
- [108] A. C. Legon, C. A. Rego, A. L. Wallwork, *J. Chem. Phys.* **1992**, 97, 3050–3059.
- [109] C. M. Evans, A. C. Legon, *Chem. Phys.* **1995**, 198, 119–131.
- [110] G. G. Engerholm, Dissertation, University of California, Berkeley, **1965**; *Diss. Abstr. Inf.* **1966**, 26, 3580.
- [111] C. M. Evans, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1997**, 267, 281–287.
- [112] G. Cotti, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1996**, 255, 401–409.
- [113] A. J. Fillery-Travis, A. C. Legon, *Chem. Phys. Lett.* **1986**, 123, 4–8.
- [114] A. J. Fillery-Travis, A. C. Legon, *J. Chem. Phys.* **1986**, 85, 3180–3187.
- [115] P. D. Aldrich, A. C. Legon, W. H. Flygare, *J. Chem. Phys.* **1981**, 75, 2126–2134.
- [116] A. C. Legon, P. D. Aldrich, W. H. Flygare, *J. Chem. Phys.* **1981**, 75, 625–630.
- [117] J. A. Shea, W. H. Flygare, *J. Chem. Phys.* **1982**, 76, 4857–4864.
- [118] P. W. Fowler, A. C. Legon, J. M. A. Thumwood, E. R. Wacławik, *Coord. Chem. Rev.*, in press.
- [119] W. G. Read, W. H. Flygare, *J. Chem. Phys.* **1982**, 76, 292–300.
- [120] C. A. Coulson, W. E. Moffitt, *Philos. Mag.* **1949**, 40, 1–35.
- [121] K. Hinds, J. H. Holloway, A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1997**, 93, 373–378.
- [122] A. C. Legon, P. D. Aldrich, W. H. Flygare, *J. Am. Chem. Soc.* **1982**, 104, 1486–1490.
- [123] S. A. Cooke, J. H. Holloway, A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1997**, 93, 2361–2365.
- [124] Z. Kisiel, P. W. Fowler, A. C. Legon, unpublished results.
- [125] A. J. Fillery-Travis, A. C. Legon, unpublished results.
- [126] S. A. Cooke, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1997**, 266, 61–69.
- [127] S. A. Cooke, J. H. Holloway, A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1997**, 93, 4253–4258.
- [128] Z. Kisiel, P. W. Fowler, A. C. Legon, *J. Chem. Phys.* **1994**, 101, 4635–4643.
- [129] F. A. Baiocchi, J. H. Williams, W. Klemperer, *J. Phys. Chem.* **1983**, 87, 2079–2084.
- [130] W. G. Read, E. J. Campbell, G. Henderson, *J. Chem. Phys.* **1983**, 78, 3501–3508.
- [131] S. A. Cooke, G. K. Corlett, C. M. Evans, A. C. Legon, *Chem. Phys. Lett.* **1997**, 272, 61–68.
- [132] H. S. Gutowsky, E. Arunan, T. Emilsson, S. L. Tschopp, C. E. Dykstra, *J. Chem. Phys.* **1995**, 103, 3917–3927.
- [133] S. A. Cooke, C. M. Evans, J. H. Holloway, A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1998**, 94, 2295–2302.
- [134] J. A. Shea, S. G. Kukolich, *J. Chem. Phys.* **1983**, 78, 3545–3551.
- [135] A. Lesarri, J. C. Lopez, J. L. Alonso, *J. Chem. Soc. Faraday Trans.* **1998**, 94, 729–733.
- [136] S. A. Cooke, G. K. Corlett, J. H. Holloway, A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1998**, 94, 2675–2680.
- [137] B. B. De More, W. S. Wilcox, J. H. Goldstein, *J. Chem. Phys.* **1954**, 22, 876–877.
- [138] J. J. Oh, K. W. Hillig, R. L. Kuczkowski, R. K. Bohn, *J. Phys. Chem.* **1990**, 94, 4453–4455.
- [139] T. Ogata, K. Kozima, *J. Mol. Spectrosc.* **1972**, 42, 38–46.
- [140] A. Hinchliffe, *Ab Initio Determination of Molecular Properties*, Adam Hilger, Bristol, **1987**, chap. 5, pp. 68–99.
- [141] a) W. H. Flygare, R. C. Benson, *Mol. Phys.* **1971**, 20, 225–250; b) D. H. Sutter, W. H. Flygare, *Top. Curr. Chem.* **1976**, 63, 89–196, and references therein.
- [142] S. A. Cooke, G. K. Corlett, A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1998**, 94, 1565–1570.
- [143] S. A. Cooke, G. K. Corlett, A. C. Legon, *Chem. Phys. Lett.* **1998**, 291, 269–276.
- [144] S. A. Cooke, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1998**, 298, 151–160.
- [145] S. A. Cooke, G. K. Corlett, D. G. Lister, A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1998**, 94, 837–841.
- [146] S. A. Cooke, G. Cotti, C. M. Evans, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1996**, 260, 388–394.
- [147] P. Cope, D. J. Millen, L. C. Willoughby, A. C. Legon, *J. Chem. Soc. Faraday Trans. 2* **1986**, 82, 1197–1206.
- [148] A. C. Legon, A. L. Wallwork, D. J. Millen, *Chem. Phys. Lett.* **1991**, 178, 279–284.
- [149] Values in Table 7 for $\text{H}_3\text{N} \cdots \text{HF}$ were calculated from unpublished spectroscopic constants communicated to the author by P. R. R. Langridge-Smith and B. J. Howard.
- [150] L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, NY, **1960**, chap. 7, pp. 258–264.
- [151] S. A. Peebles, P. W. Fowler, A. C. Legon, *Chem. Phys. Lett.* **1995**, 240, 130–134.
- [152] A. C. Legon, *Chem. Eur. J.* **1998**, 4, 1890–1897.
- [153] A. C. Legon, D. J. Millen, S. C. Rogers, *J. Mol. Struct.* **1980**, 67, 29–34.
- [154] A. C. Legon, A. L. Wallwork, *J. Chem. Soc. Faraday Trans.* **1990**, 86, 3975–3982.
- [155] A. C. Legon, A. L. Wallwork, H. E. Warner, *J. Chem. Soc. Faraday Trans.* **1991**, 87, 3327–3334.
- [156] S. A. Cooke, G. K. Corlett, C. M. Evans, A. C. Legon, *J. Chem. Soc. Faraday Trans.* **1997**, 93, 2973–2976.
- [157] A. C. Legon, D. G. Lister, *J. Chem. Soc. Faraday Trans.* **1999**, in press.
- [158] M. J. Atkins, A. C. Legon, H. E. Warner, *Chem. Phys. Lett.* **1994**, 229, 267–272.
- [159] F. A. Baiocchi, W. Klemperer, *J. Chem. Phys.* **1983**, 78, 3509–3520.

- [160] A. C. Legon, C. A. Rego, *J. Chem. Soc. Faraday Trans.* **1993**, 89, 1173–1178.
- [161] a) A. C. Legon, C. A. Rego, *Chem. Phys. Lett.* **1989**, 154, 468–472;
b) A. C. Legon, C. A. Rego, *Chem. Phys. Lett.* **1989**, 157, 243–250.
- [162] A. C. Legon, C. A. Rego, *J. Chem. Phys.* **1989**, 90, 6867–6876.
- [163] A. C. Legon, A. L. Wallwork, C. A. Rego, *J. Chem. Phys.* **1990**, 92, 6397–6407.
- [164] A. C. Legon, C. A. Rego, *J. Chem. Phys.* **1993**, 99, 1463–1468.
- [165] A. C. Legon, *Chem. Soc. Rev.* **1993**, 22, 153–163.
- [166] A. C. Legon, D. J. Millen, *Proc. R. Soc. London A* **1988**, 417, 21–30.
- [167] F. H. de Leeuw, R. Van Wachem, A. Dymanus, *Abstr. Pap. Symposium on Molecular Structure and Spectroscopy* (Ohio, OH) **1969**, R5.
- [168] Calculated by using $\omega_e = (2\pi c)^{-1}(k_s/\mu)^{1/2}$ from ω_e given by: P. L. Clouser, W. Gordy, *Phys. Rev. A* **1964**, 134, 863.
- [169] H. I. Bloemink, J. H. Holloway, A. C. Legon, *Chem. Phys. Lett.* **1996**, 254, 59–68.
- [170] D. J. Millen, K. M. Sinnott, *J. Chem. Soc.* **1958**, 350–355.
- [171] G. Cazzoli, P. G. Favero, A. Del Borgo, *J. Mol. Spectrosc.* **1974**, 50, 82–92.
- [172] H. I. Bloemink, S. A. Cooke, J. H. Holloway, A. C. Legon, *Angew. Chem.* **1997**, 109, 1399–1401; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1340–1342.
- [173] A. Karpfen, *Chem. Phys. Lett.* **1999**, 299, 493–502.
- [174] C. Domene, P. W. Fowler, A. C. Legon, *Chem. Phys. Lett.*, in press.
- [175] J. B. Davey, A. C. Legon, E. R. Waclawik, *Chem. Phys. Lett.* **1999**, 306, 133–144.
- [176] J. B. Davey, A. C. Legon, E. R. Waclawik, *Phys. Chem. Chem. Phys.* **1999**, 1, 3097–3102.
- [177] J. B. Davey, A. C. Legon, *Phys. Chem. Chem. Phys.* **1999**, 1, 3721–3726.
- [178] J. M. A. Thumwood, A. C. Legon, *Chem. Phys. Lett.* **1999**, 310, 88–96.
- [179] J. B. Davey, A. C. Legon, E. R. Waclawik, unpublished results.
- [180] A. C. Legon, E. R. Waclawik, unpublished results.
- [181] E. R. Waclawik, A. C. Legon, *Phys. Chem. Chem. Phys.* submitted.
- [182] A. C. Legon, unpublished results.

Improving the Yield of α -Tocopherol from Natural Sources—Chemistry versus Molecular Biology

Wolf-D. Woggon*

The tocopherols **1–4** and the corresponding tocotrienols which can be isolated from photosynthetic organisms are structurally related derivatives of chroman-6-ol displaying vitamin E activity (Table 1).^[1] Although the significance of

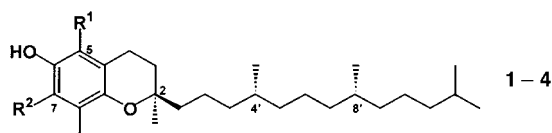


Table 1. Comparison of the relative biological activities A_{rel} of tocopherols **1–4**.

Compound	R ¹	R ²	A_{rel} [%]
α -tocopherol (1)	CH ₃	CH ₃	100
β -tocopherol (2)	CH ₃	H	50
γ -tocopherol (3)	H	CH ₃	10
δ -tocopherol (4)	H	H	3

these compounds for mammalian nutrition has been known for almost 80 years, our understanding of the basic principle of action of these compounds has only recently evolved. According to Burton and Ingold^[2] α -tocopherol (**1**), the biologically most active member of the vitamin E group, is an important lipophilic radical chain breaking antioxidant in living tissues. Substructures such as the lipophilic side chain at C2 allow **1** to be easily incorporated into bilayer membranes and, hence, protect cell walls against oxidative damage.

Since the chirality and the three ring methyl groups of **1** are essential to maximal biological activity,^[3] **1** became a target of many synthetic approaches; the *R* configuration at C2 was the most difficult to establish. Though some of these procedures^[4] are quite elegant and even efficient, they never became economically competitive with the synthesis of racemic α -tocopherol,^[5] which covers about 90 % of the worldwide need of over 22 500 t per year,^[6] or with isolation of the chiral tocopherols from natural sources such as oil extracts from sun flowers, soya, palm, and wheat. From these plants, however, the tocopherols **1–4** are obtained in mixtures of different

compositions,^[1] posing the principal problem of converting these mixtures in favor of the desired **1**. Two interesting solutions to this problem have been published recently.

The “metabolic engineering” approach of DellaPenna et al.^[7] takes the following points into consideration:

- The methylation of γ -tocopherol (**3**) is the last step in the biosynthesis of α -tocopherol (**1**).^[8]
- The γ -tocopherol methyltransferase (γ -TMT) has been already purified from *Capsicum annuum*, and its primary structure elucidated by Camara et al.^[9]
- Organisms in which γ -TMT could be overexpressed would convert the internal pool of **3**—often the most abundant vitamin E component—into the desired **1**.

Since related biosynthetic genes in bacteria are often organized into operons, DellaPenna et al. speculated that the γ -TMT gene might be located on the operon containing the gene that encodes for *p*-hydroxy-phenylpyruvate dioxygenase (HPPDase).^[10] This enzyme catalyzes an important step in the catabolism of aromatic amino acids, that is, the formation of homogentisinic acid, inter alia the precursor of the monomethylated aromatic ring of the vitamin E family.

Two complementary organisms were chosen for the experiments: the cyanobacterium *Synechocystis* PCC6803 and the plant *Arabidopsis thaliana* because the tocopherol pool of the photosynthetic tissues of both species contain greater than 95 % of **1**; however, only about 1 % of **1** is found in the seeds of *Arabidopsis thaliana*. This suggests that γ -TMT activity is not limited in the former parts but is virtually absent in the seeds, which are the major vitamin E source for human nutrition.

Based on sequence data from Camara et al.^[9] and the known gene encoding the *Arabidopsis* HPPDase,^[10] DellaPenna et al. characterized the γ -TMT genes both in *Synechocystis* PCC6803 and *Arabidopsis thaliana* by construction of a “null mutant” in *Synechocystis* and functional expression of both genes in *E. coli*. The recombinant wild-type γ -TMT proteins catalyzed the transformation of **3** to **1**, whereas the null mutant was devoid of methyltransferase activity. When *Arabidopsis* was transformed with a vector containing its own γ -TMT gene under the control of a seed-specific promoter from carrot, its seeds produced 95 % of α -tocopherol (**1**), 1 % of β -tocopherol (**2**), and 4 % of γ -tocopherol (**3**). This indicated that most of the internal γ - and δ -tocopherols had been methylated; that is, the enzyme γ -TMT catalyzes regiospecifically the methylation at C5 of the chromanol

[*] Prof. Dr. W.-D. Woggon

Institut für Organische Chemie der Universität
St. Johannis-Ring 19, CH-4056 Basel (Switzerland)
Fax: (+41) 61-267-11-02
E-mail: woggon@wolff.chemie.unibas.ch

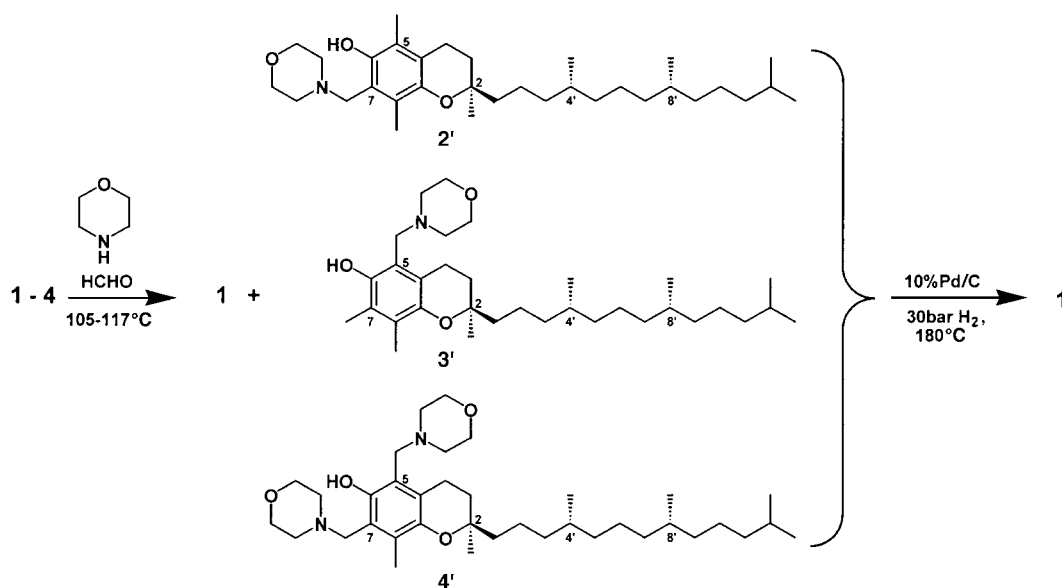
substructure. Given the relative biological activities of the different tocopherols (Table 1) the seeds from *Arabidopsis* lines overexpressing γ -TMT are ninefold more potent than the wild type; the overall vitamin E content, however, remained unchanged.

The aim of the “chemical approach” was to convert any naturally occurring mixture of **1–4** into the biologically most significant α -tocopherol (**1**). To accomplish this target Müller and Schneider^[11] systematically investigated the Mannich reaction and subsequent catalytic reduction of the intermediate benzylamines. Optimal results were obtained when a mixture of the tocopherols **1–4** was heated neat with the Mannich reagent, prepared from morpholin and paraformaldehyde (1:1), and the resulting aminomethylated tocopherols **2'**, **3'**, and **4'** were directly reduced on 10% Pd/C with H₂. The tocopherol yield was nearly quantitative, and the GC analysis revealed the following composition: 98% of **1**, 0.8% of **2**, and

To elevate the content of tocopherols in any organism clearly the focus must be shifted to enzymes that occur earlier in the pathway of the tocopherol biosynthesis. Generating a plant that produces a scarce lipophilic metabolite in economically useful concentrations probably needs a joint, long-term effort of plant biologists, chemists, and molecular biologists to investigate every step carefully and define the consequences of overexpression of the individual genes on the plant's life cycle. After all a combination of chemistry and molecular biology approaches might be successful.

German version: *Angew. Chem.* **1999**, *111*, 2881–2883

Keywords: cyanobacteria • gene technology • methyltransferases • tocopherols • vitamins



1.2% of **3**. Because any given mixture of natural occurring tocopherols can be converted into **1** in high yield and on a kilogram scale, at present the chemical approach exceeds the method of DellaPenna et al. Both concepts, however, are handicapped with regard to the low level of vitamin E in photosynthetic organisms.

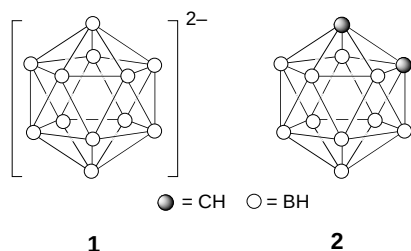
The approach of DellaPenna et al. seemingly opens the door to transgenic plants overproducing **1**. It may be naive, however, to believe this can be accomplished soon since the deregulation of quite a number of enzymatic steps would be required. After all DellaPenna et al. have only modified the last, most simple step of the tocopherol biosynthesis, which is unrelated to the regulation of preceding enzymatic reactions. Moreover it is quite obscure why his approach was successful because it seems quite unlikely that functionally and structurally unrelated enzymes such as HPPDase and γ -TMT should be located on the same operon: His interesting result is a surprise!

- [1] A. Kamal-Eldin, L.-A. Appelqvist, *Lipids* **1996**, *31*, 671–701; *Vitamin, Physiologie, Pathophysiologie, Therapie* (Eds.: H. K. Biesalski, J. Schrezenmeir, P. Weber, H. E. Weiss), Thieme, Stuttgart, **1997**.
- [2] G. W. Burton, K. U. Ingold, *Acc. Chem. Res.* **1986**, *19*, 194–201.
- [3] J. Kreimayer, M. Schmidt, *Pharm. Ztg.* **1998**, *143*, 823–828.
- [4] L. F. Tietze, J. Görlitzer, *Synthesis* **1997**, 877–885; E. Mizuguchi, K. Achiwa, *Tetrahedron: Asymmetry* **1993**, *4*, 2303–2306; T. Sugai, N. Watanabe, H. Ohta, *Tetrahedron: Asymmetry* **1991**, *2*, 371–376; S. Takano, Y. Shimazaki, K. Ogazawara, *Heterocycles* **1990**, *31*, 917–921.
- [5] T. Netscher, *Chimia* **1996**, *50*, 563–567.
- [6] M. Eggersdorfer, *Wirkstoffe* **1996**, 24–32 (brochure of the BASF AG).
- [7] D. Shintani, D. DellaPenna, *Science* **1998**, *282*, 2098–2100.
- [8] A. Stocker, H. Fretz, H. Frick, A. Rüttimann, W.-D. Woggon, *Bioorg. Med. Chem.* **1996**, *4*, 1129–1134; A. Stocker, T. Netscher, A. Rüttimann, R. K. Müller, H. Schneider, L. J. Todaro, G. Derungs, W.-D. Woggon, *Helv. Chim. Acta* **1994**, *77*, 1721–1737; A. Stocker, A. Rüttimann, W.-D. Woggon, *Helv. Chim. Acta* **1993**, *76*, 1729–1738.
- [9] A. d'Harlingue, B. Camara, *J. Biol. Chem.* **1985**, *260*, 15200–15203.
- [10] S. R. Norris, T. R. Barette, D. DellaPenna, *Plant Cell* **1995**, *7*, 2139–2143.
- [11] R. K. Müller, H. Schneider (Hoffmann-LaRoche AG), EP-B 0 735 033 A1, **1996**.

Icosahedral Building Blocks: Towards Dendrimers with Twelve Primary Branches?

Catherine E. Housecroft*

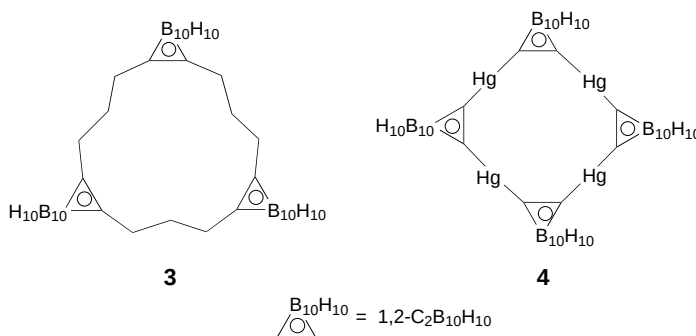
One of the early advances in the development of boron cluster chemistry was the structural characterization of $[B_{12}H_{12}]^{2-}$ by Lipscomb et al.,^[1] and with it the confirmation of the icosahedral symmetry of the cage. In the last 40 years^[2, 3] an astonishing wealth of boron-containing cluster derivatives including those based on carbaborane cores has been prepared, and these species have presented theorists with seemingly never-ending questions regarding bonding and electron bookkeeping. The icosahedral $[B_{12}H_{12}]^{2-}$ (**1**), 1,2- $C_2B_{10}H_{12}$ (**2**), and the 1,7- and 1,12-isomers of **2** remain some of the most studied clusters; their high stability has allowed an extensive chemistry to be developed.



Nonetheless, the bulk of the documented compounds contain *single* cages. Multifunctionalization of borane and carbaborane clusters has been reported relatively rarely. Early contributions were chlorination and bromination reactions of $[B_{10}H_{10}]^{2-}$ and $[B_{12}H_{12}]^{2-}$.^[4] The last few years have witnessed further progress with results, for example, from the groups of Hawthorne (permethylation of $C_2B_{10}H_{12}$ and $Me_2C_2B_{10}H_{10}$ and related species, and formation of 1,2- $C_2H_2B_{10}(CHCl_2)_{10}$),^[5–7] Paetzold (perbrominated, periodinated, and permethylated derivatives of the azaboranes 4- $ClC_6H_4NB_9H_9$ and $MeNB_{11}H_{11}$),^[8] Wilbur (periodination of 1,2- and 1,7- $C_2B_{10}H_{12}$ and monocarbon carboranes),^[9] and Michl (preparation of $[CB_{11}Me_{12}]^-$ and the stable radical $CB_{11}Me_{12}^{\cdot}$, the first neutral metal-free, boron cluster radical to be isolated).^[10, 11] Multifunctionalization of the cage is a significant step forward and should allow a breakthrough in the development of a new field of borane and carbaborane cluster chemistry, one which should take boron clusters firmly into the realm of the supramolecular explorer.

To date, functionalization at the C atoms of carbaborane cages has led to numerous derivatives, and of particular interest to the present perspective is the connection of clusters into cyclic arrays: for example arene-coupled systems,^[12] a related cyclic trimer formed by treatment of 2,6- $Br_2H_3C_5N$ with 1,7- Cu_2 -1,7- $C_2B_{10}H_{10}$ from Wade and co-workers,^[13] and

macrocycles such as **3** and **4** from the Hawthorne group.^[14–16] Macrocycle **4** is of special interest because it acts as a host for



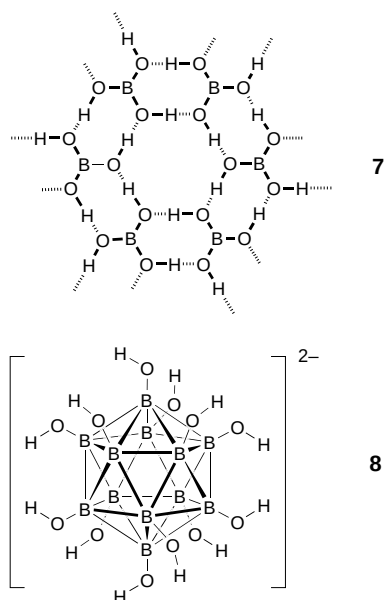
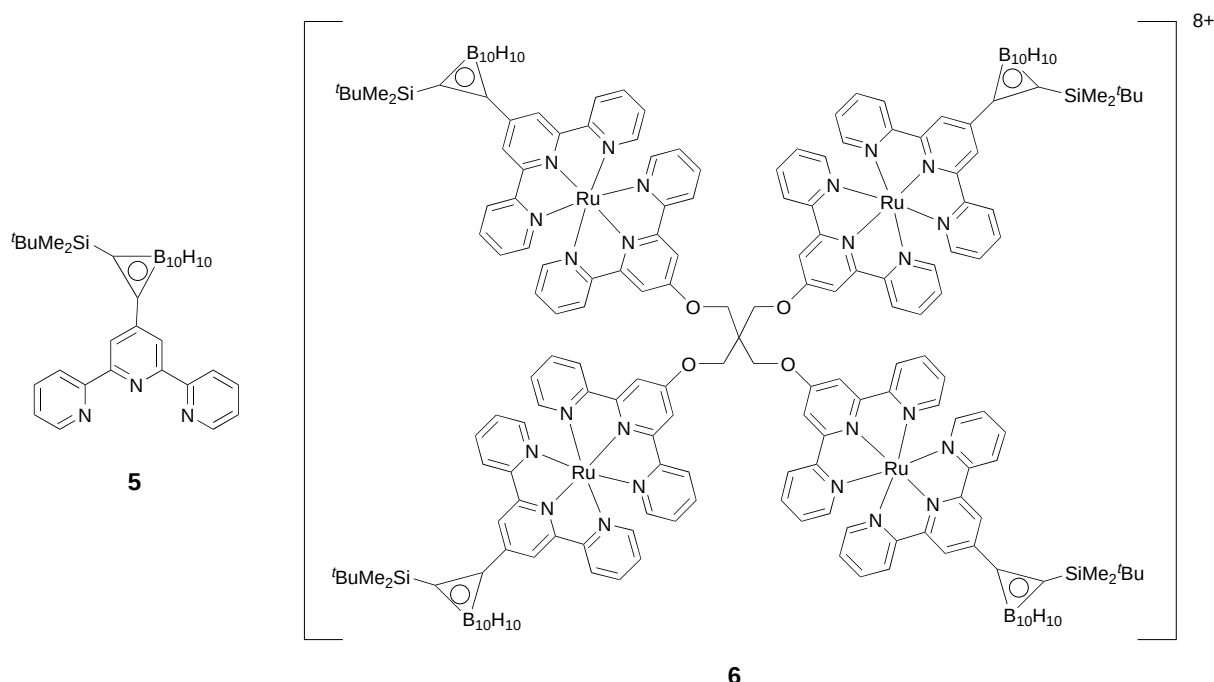
a halide ion, and, thus, we approach the convergence of borane and supramolecular chemistries. Protection of the carbon sites of the C_2B_{10} cage has allowed access to an $Hg_3(cage)_3$ macrocycle with a framework which is supported by Hg–B links.^[17] This step highlights an important synthetic strategy developed by Hawthorne et al.:^[18] the production of mono- or bis-C-protected carbaborane clusters which will allow 1) controlled syntheses of monosubstituted clusters, or 2) complete protection of the carbon sites and synthesis of B-functionalized compounds. C-Protection by an alternative route has been developed by Teixidor, Viñas, and co-workers.^[19]

Within our own group, the coupling of cluster and supramolecular chemistries has been a recent goal; it has been the strategy of C-protection that has led to the successful preparation of, for example, 2,2':6',2''-terpyridine derivative **5** and the incorporation of $C_2B_{10}H_{10}$ cluster units on the surface of a number of dendrimers as in the first-generation dendrimer **6**. Here, the interactions that make the system “supramolecular” are the coordinate bonds: the octahedral coordination sphere of each Ru^{II} center directs the assembly which is initially centered on a tetrahedral carbon atom.^[20]

Assembly through hydrogen bonding is exemplified by vast numbers of systems, of which two of the most cited are ice and DNA. Hydrogen bonding is essential to the stabilization of the crystalline frameworks of boric acid (**7**) and borate minerals. This point is made in the introduction to the watershed paper by Hawthorne et al.^[21] in which the per-B-hydroxylated boron clusters $[B_{12}(OH)_{12}]^{2-}$ (**8**), $[1-H-1-CB_{11}(OH)_{11}]^-$, and 1,12- H_2 -1,12- $C_2B_{10}(OH)_{10}$ are reported; structural data for **8** and 1,12- H_2 -1,12- $C_2B_{10}(OH)_{10}$ show the retention of icosahedral cages.

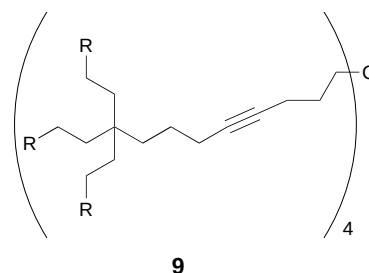
The perhydroxylated derivatives^[21] are made by treating alkali metal salts of $[B_{12}H_{12}]^{2-}$ and $[CB_{11}H_{12}]^-$, as well as 1,12- $(CH_2OH)_2$ -1,12- $C_2B_{10}H_{10}$ with 30% hydrogen peroxide at reflux temperature. The use of 1,12- $(CH_2OH)_2$ -1,12- $C_2B_{10}H_{10}$ in place of 1,12- $C_2B_{10}H_{12}$ was required for the sake of

[*] Prof. Dr. C. E. Housecroft
Institut für Anorganische Chemie der Universität
Spitalstrasse 51, CH-4056 Basel (Switzerland)
Fax: (+41) 61-267-1014
E-mail: housecroft@ubaclu.unibas.ch



solubility in aqueous medium; the CH_2OH substituents are converted into H substituents during the course of the reaction. That a hydrogen-bonded, supramolecular network is formed is reflected, for example, in the insolubility of 1,12- H_2 -1,12- $\text{C}_2\text{B}_{10}(\text{OH})_{10}$ in water; it crystallizes as the dihydrate, and the hydrogen-bonded lattice involves the cage OH groups, the waters of crystallization, and the cage CH groups. Alkali metal salts of **8** show an interesting trend in solubilities: the Cs^+ salt can be crystallized from water, but the Li^+ , Na^+ , and K^+ salts precipitate when MCl ($\text{M} = \text{Li}, \text{Na}, \text{K}$) is added to aqueous solutions of the Cs^+ salt. This trend is attributed to the ability of **8** to function as a polyhapto ligand, entering and displacing the hydration spheres of the smaller M^+ ions and forming a hydrogen-bonded network that results in an insoluble salt.

The hydrogen-bonded arrays observed in the new clusters by Hawthorne and co-workers are, in themselves, fascinating. They point to the potential that $[\text{B}_{12}(\text{OH})_{12}]^{2-}$ **8** has in the development of species which are a marriage of polyhedral borane and borate chemistries.^[21] However, the isolation of icosahedral cages, the surfaces of which are covered in OH substituents, surely begs the question of using these cages as the central cores for the divergent growth of dendrimers.^[22] The core is rigid and the directions of the “arms” within the first generation should be sterically favorable. In our own work, dendrimers such as **6** arise from polyhydroxylated cores, for example pentaerythritol.^[20, 23] Our aim is to generate surface-functionalized dendrimers. A rather different approach has been taken by Newkome et al. in the reactions of dendritic skeletons, represented by **9**, with $\text{B}_{10}\text{H}_{14}$ to generate carbaborane-containing dendrimers.^[24] In contrast to our strategy and that of Newkome et al., the perhydroxylated



clusters described by Hawthorne et al.^[21] offer a new direction to the field. Will a twelve-arm star molecule followed by dendritic derivatives be achievable targets?

German version: *Angew. Chem.* **1999**, *111*, 2883–2885

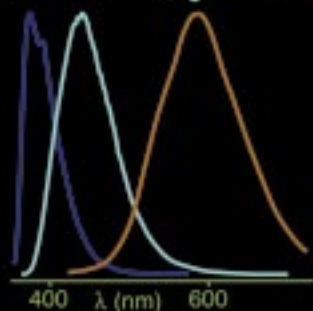
Keywords: boron • carboranes • dendrimers • polyhydroxyl compounds

- [1] J. A. Wunderlich, W. N. Lipscomb, *J. Am. Chem. Soc.* **1960**, *82*, 4427–4428.
- [2] T. Onak in *Comprehensive Organometallic Chemistry*, Vol. 1 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1995**, pp. 411–457; R. N. Grimes in *Comprehensive Organometallic Chemistry*, Vol. 1 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1995**, pp. 459–542; L. J. Todd in *Comprehensive Organometallic Chemistry*, Vol. 1 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1995**, pp. 543–553.
- [3] T. Onak in *Comprehensive Organometallic Chemistry II*, Vol. 1 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1995**, pp. 217–255; L. J. Todd in *Comprehensive Organometallic Chemistry II*, Vol. 1 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1995**, pp. 257–273; L. Barton, D. K. Srivastava in *Comprehensive Organometallic Chemistry II*, Vol. 1 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1995**, pp. 275–372; R. N. Grimes in *Comprehensive Organometallic Chemistry II*, Vol. 1 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1995**, pp. 373–430.
- [4] W. H. Knoth, H. C. Miller, J. C. Sauer, J. H. Balthis, Y. T. Chia, E. L. Muettterties, *Inorg. Chem.* **1964**, *3*, 159–167.
- [5] W. Jiang, C. B. Knobler, M. D. Mortimer, M. F. Hawthorne, *Angew. Chem.* **1995**, *107*, 1470–1473; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1332–1334.
- [6] A. Herzog, A. Maderna, G. N. Harakas, C. B. Knobler, M. F. Hawthorne, *Chem. Eur. J.* **1999**, *5*, 1212–1217.
- [7] a) W. Jiang, C. B. Knobler, M. F. Hawthorne, *Angew. Chem.* **1996**, *108*, 2653–2655; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2536–2537. b) T. Peymann, C. B. Knobler, M. F. Hawthorne, *J. Am. Chem. Soc.* **1999**, *121*, 5601–5602.
- [8] P. Lomme, M. Roth, U. Englert, P. Paetzold, *Chem. Ber.* **1996**, *129*, 1227–1231.
- [9] R. R. Srivastava, D. K. Hamlin, D. S. Wilbur, *J. Org. Chem.* **1996**, *61*, 9041–9044.
- [10] B. T. King, Z. Janousek, B. Grüner, M. Trammell, B. C. Noll, J. Michl, *J. Am. Chem. Soc.* **1996**, *118*, 3313–3314.
- [11] B. T. King, B. C. Noll, A. J. McKinley, J. Michl, *J. Am. Chem. Soc.* **1996**, *118*, 10902–10903.
- [12] R. Coult, M. A. Fox, W. R. Gill, P. L. Herbertson, J. A. H. MacBride, K. Wade, *J. Organomet. Chem.* **1993**, *462*, 19–29.
- [13] W. R. Gill, P. L. Herbertson, J. A. H. MacBride, K. Wade, *J. Organomet. Chem.* **1996**, *507*, 249–255.
- [14] W. Jiang, I. T. Chizhevsky, M. D. Mortimer, W. L. Chen, C. B. Knobler, S. E. Johnson, F. A. Gomez, M. F. Hawthorne, *Inorg. Chem.* **1996**, *35*, 5417–5426.
- [15] See for example: M. F. Hawthorne, X. G. Yang, Z. P. Zheng, *Pure Appl. Chem.* **1994**, *66*, 245–254; X. G. Yang, C. B. Knobler, Z. P. Zheng, M. F. Hawthorne, *J. Am. Chem. Soc.* **1994**, *116*, 7142–7159; Z. P. Zheng, C. B. Knobler, M. D. Mortimer, G. G. Kong, M. F. Hawthorne, *Inorg. Chem.* **1996**, *35*, 1235–1243.
- [16] Highlight: R. N. Grimes, *Angew. Chem.* **1993**, *105*, 1350–1352; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1289–1290.
- [17] Z. P. Zheng, M. Diaz, C. B. Knobler, M. F. Hawthorne, *J. Am. Chem. Soc.* **1995**, *117*, 12338–12339.
- [18] F. A. Gomez, M. F. Hawthorne, *J. Org. Chem.* **1992**, *57*, 1384–1390.
- [19] C. Viñas, R. Benakki, F. Teixidor, J. Casabo, *Inorg. Chem.* **1995**, *34*, 3844–3845.
- [20] D. Armspach, M. Cattalini, E. C. Constable, C. E. Housecroft, D. Phillips, *Chem. Commun.* **1996**, 1823–1824.
- [21] T. Peymann, A. Herzog, C. B. Knobler, M. F. Hawthorne, *Angew. Chem.* **1999**, *111*, 1130–1132; *Angew. Chem. Int. Ed.* **1999**, *38*, 1062–1064.
- [22] G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendritic Molecules. Concepts, Syntheses, Perspectives*, VCH, Weinheim, **1996**.
- [23] E. C. Constable, C. E. Housecroft, M. Cattalini, D. Phillips, *New J. Chem.* **1998**, 193–200.
- [24] G. R. Newkome, C. N. Moorefield, J. M. Keith, G. R. Baker, G. H. Escamilla, *Angew. Chem.* **1994**, *106*, 701–703; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 666–668.

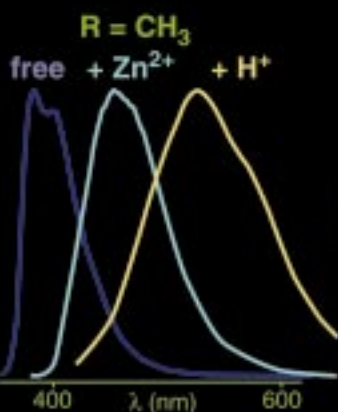


Tunable Fluorophores

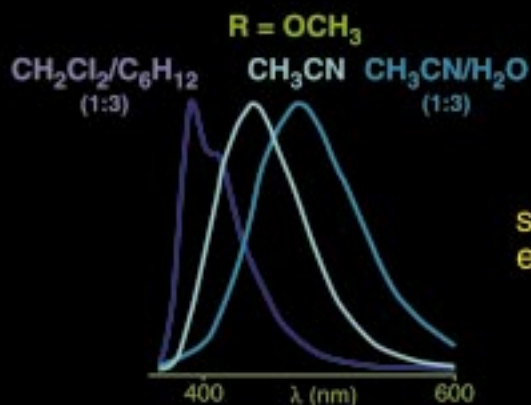
$R = H$ $R = OCH_3$ $R = N(CH_3)_2$



substituent
effect



exogenous
ion effect



solvent
effect



For more information see the following pages.

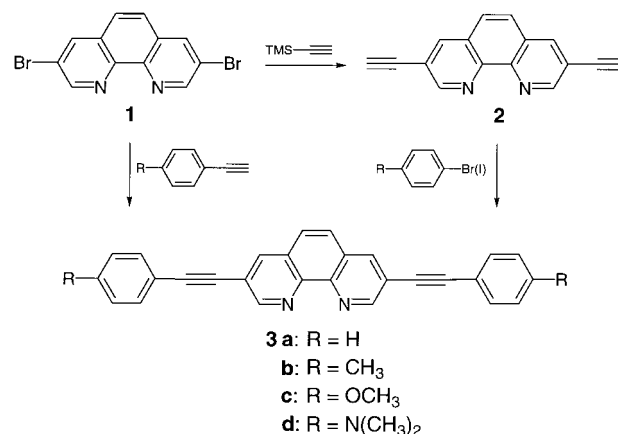
Conjugated 1,10-Phenanthrolines as Tunable Fluorophores**

Hima S. Joshi, Ramin Jamshidi, and Yitzhak Tor*

One of the most exciting developments in molecular electronics is the utilization of organic materials for optoelectronic applications, particularly light-emitting devices.^[1] A critical element in designing and fabricating such materials is the control of their emission wavelength.^[1c] Conjugated oligomers and polymers, such as poly(*p*-phenylene vinylene) and polythiophenes, permit color tuning through changes in their length, substitution, regioregularity, and degree of conjugation.^[1c–3] An alternative approach for controlling the emitted color of organic materials is to append fluorescent chromophores to a polymeric backbone or to blend such dyes into inert polymeric matrices.^[4] Ideally, one would like to utilize one family of modular chromophores and tune their photophysical characteristics at will. Herein, we present a novel family of highly fluorescent 1,10-phenanthrolines. The emission wavelength of any derivative is dictated by the nature of its substituents and can be further modulated by exogenous additives such as protons or metal ions. Thus, the same derivative can be utilized for the generation of multiple emission colors.

The rigid framework of 1,10-phenanthroline and its high affinity toward various cations are attractive features for the construction of tunable chromophores.^[5] Unfortunately, the parent 1,10-phenanthroline possesses a low fluorescence quantum yield ($\phi_F \leq 0.01$) and a rather short emission wavelength ($\lambda_{em} \approx 360$ nm).^[6] Since the most intense electronic transition of the 1,10-phenanthroline skeleton is polarized along the 3–8 positions,^[7] we hypothesized that increasing the conjugation along this axis may provide highly fluorescent derivatives with emission in the visible range. Acetylenic linkages are attractive candidates for this purpose as they have previously been shown to effect substantial electron delocalization in the excited state of conjugated arenes and provide intensely fluorescent chromophores.^[8] For example, substituting anthracene ($\lambda_{em} = 388$ nm, $\phi_F = 0.25$ in benzene) with two phenylethynyl groups at the 9 and 10 positions results in a 100 nm red-shift in the emission wavelength and extremely enhanced fluorescence intensity ($\lambda_{em} = 486$ nm, $\phi_F = 0.96$).^[8] In contrast, direct substitution with phenyl rings to give 9,10-diphenylanthracene, while improving fluorescence quantum yield, produces only a moderate shift in emission wavelength ($\lambda_{em} = 407$ nm, $\phi_F = 0.84$ in benzene).^[8] We have therefore targeted 3,8-bis(arylethynyl)-1,10-phenanthrolines **3** as our novel fluorescent chromophores.

Two complementary routes have been utilized for the synthesis of **3**: a) cross-coupling reactions of 3,8-dibromo-1,10-phenanthroline (**1**) with substituted phenylacetylenes, or b) cross-coupling reactions of 3,8-diethynyl-1,10-phenanthroline (**2**) with substituted halo arenes (Scheme 1).^[9–11] Both approaches are applicable to most derivatives; however, when an unstable or highly volatile alkyne is required for route (a), the route (b) is preferred.



Scheme 1. Synthesis of conjugated 1,10-phenanthrolines **3** by Pd-mediated cross-coupling reactions. TMS = trimethylsilyl.

Figure 1 shows normalized absorption and emission spectra of **3a–d** in acetonitrile at room temperature, and Table 1 summarizes the photophysical data. Comparing the absorption spectra of the new ligands **3** to that of the parent 1,10-phenanthroline shows a substantial red-shift of the major

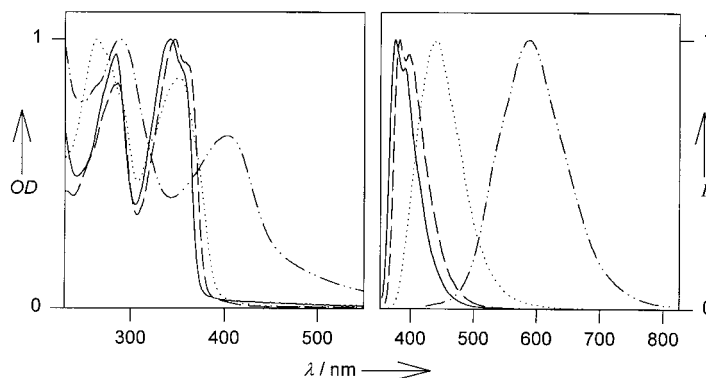


Figure 1. Normalized absorption and emission spectra of **3a** (—), **3b** (---), **3c** (....), and **3d** (— · —) in acetonitrile. Emission spectra were obtained upon excitation at the absorption maximum.

electronic transitions.^[11] Upon excitation at 342 nm, the unsubstituted derivative **3a** exhibits an intense purple emission that tails into the visible and displays maxima at 375 and 392 nm. Although only modestly red-shifted when compared to the emission of the parent 1,10-phenanthroline, a substantial increase in fluorescence quantum yield is observed ($\phi_F = 0.41$). An additional bathochromic shift is obtained by substituting electron-donating groups into the conjugated

[*] Prof. Dr. Y. Tor, H. S. Joshi, R. Jamshidi
Department of Chemistry and Biochemistry
University of California, San Diego
La Jolla, CA 92093-0358 (USA)
Fax: (+1) 858-534-5383
E-mail: ytor@ucsd.edu

[**] This work was supported by the National Institutes of Health (GM58447). We are grateful to Professor Doug Magde (UCSD) for his help and insightful comments.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

Table 1. Photophysical data for conjugated phenanthrolines **3**.

Compd.	λ_{max} [nm] ^[a]	λ_{em} [nm] ^[b]	$\lambda_{\text{max}}(\text{Zn}^{2+})$ [nm] ^[c]	$\lambda_{\text{em}}(\text{Zn}^{2+})$ [nm] ^[d]	$\lambda_{\text{max}}(\text{H}^+)$ [nm] ^[e]	$\lambda_{\text{em}}(\text{H}^+)$ [nm] ^[f]	ϕ_{F} ^[g]	τ [ns] ^[h]
3a	342 (346)	375, 392 (376, 395)	372 (384)	434 (415)	394 (394)	490 (472)	0.41 (0.49)	2.93
3b	346 (350)	383, 396 (384, 404)	374 (394)	453 (436)	398 (414)	525 (514)	1.0 (0.73)	1.50
3c	350 (358)	441 (416)	382 (392)	530 ^[i] (490)	378 (418)	532 ^[i] (489)	0.64 (0.87)	1.71
3d	402 (410)	587 (523)	454 (474)	— ^[j] (646) ^[i]	352 (368)	408 (398, 417)	— ^[k]	— ^[k]

[a] Absorption maxima in acetonitrile and dichloromethane (in parenthesis), ± 2 nm. [b] Emission maxima in acetonitrile and dichloromethane (in parenthesis), ± 2 nm. Emission wavelengths are not corrected for instrument response. Correction gives a slight red-shift (6–10 nm) for the emission maxima of **3c** and **3d**. [c] Absorption maxima in acetonitrile and dichloromethane (in parenthesis) in the presence of excess ZnCl_2 , ± 2 nm. [d] Emission maxima in acetonitrile and dichloromethane (in parenthesis) in the presence of excess ZnCl_2 , ± 2 nm. [e] Absorption maxima in acetonitrile and dichloromethane (in parenthesis) in the presence of excess $\text{CH}_3\text{SO}_3\text{H}$, ± 2 nm. [f] Emission maxima in acetonitrile and dichloromethane (in parenthesis) in the presence of excess $\text{CH}_3\text{SO}_3\text{H}$, ± 2 nm. [g] Fluorescence quantum yield in acetonitrile and dichloromethane (in parenthesis) determined relative to 9,10-diphenylanthracene (see Experimental Section). [h] Excited-state lifetime, ± 0.02 ns. [i] Weak emission. [j] Quenched emission. [k] Not determined; see ref. [12].

phenyl rings. Thus, the tolyl derivative **3b** emits at 383 and 396 nm with an excellent fluorescent quantum efficiency ($\phi_{\text{F}}=1.0$). Exciting a dilute solution of the 4-methoxyphenyl derivative **3c** in acetonitrile results in a bright blue emission, well within the visible range ($\lambda_{\text{em}}=441$ nm, $\phi_{\text{F}}=0.64$). A remarkable red-shift of the emission is observed with the *N,N*-dimethylamino derivative **3d**. In acetonitrile, a broad emission centered around $\lambda_{\text{em}}=587$ nm gives rise to an orange emission.^[12] Extending the 1,10-phenanthroline skeleton with arylethynyl groups thus shifts the emission into the visible region and results in considerable increase in fluorescence quantum efficiency with certain ligands approaching unity.^[13]

Solvent polarity has little influence on the absorption maxima of the conjugated ligands and a profound effect on their emission behavior. As illustrated in Figure 2, the parent derivative **3a** is rather insensitive to solvent composition,

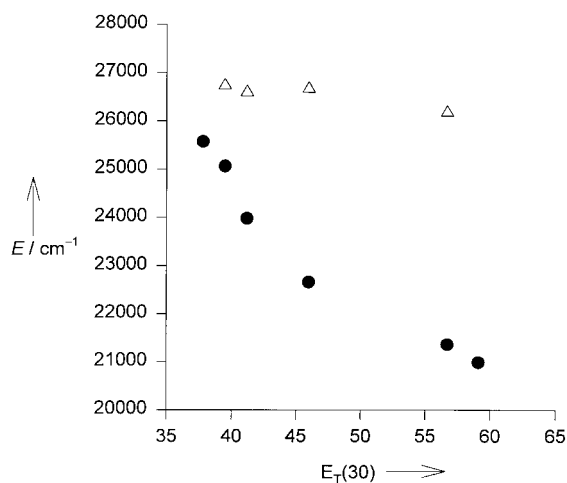


Figure 2. Solvent-dependent emission energies for **3a** (Δ) and **3c** ($\bullet$) (see Experimental Section).

while the emission maximum of the anisyl derivative **3c** is much more susceptible to solvent polarity. The red-shift observed for **3c** upon increasing solvent polarity is indicative of greater stabilization of the excited state. This trend occurs in polar molecules that are likely to have enlarged dipoles and charge-transfer character in their excited state.^[14] Importantly, the weak emission of 1,10-phenanthroline is blue-shifted upon increasing solvent polarity.^[6] This behavior was attributed to a close proximity of the $\pi-\pi^*$ and $n-\pi^*$ singlet excited states,

with the latter becoming more contributing in nonpolar solvents.^[6] This may explain the low fluorescence quantum efficiency of 1,10-phenanthroline, since $n-\pi^*$ excited states often decay by nonradiative pathways. In contrast, the conjugated phenanthroline ligands **3** exhibit high fluorescence quantum efficiencies in various solvents and short excited-state lifetimes (1.5–3 ns, Table 1), suggesting that the emitting excited state is a singlet $\pi-\pi^*$ state.^[15]

Further modulation of emission wavelengths is attained by the addition of exogenous ions. Upon titrating Zn^{2+} ions into a solution of the phenylethynyl derivative **3a** in acetonitrile, the emission color dramatically changes from purple to bright blue (Table 1). Similarly, a shift of approximately 70 nm is observed upon addition of Zn^{2+} ions to the tolyl derivative **3b** yielding an intense blue emission. A bright yellow fluorescence, centered at 530 nm, is observed when Zn^{2+} ions are added to a solution of the 4-methoxyphenylethynyl derivative **3c** in acetonitrile. More profound shifts are observed when strong acids are added to protonate the conjugated ligands. While the parent derivative **3a** exhibits a bright purple emission centered slightly below 400 nm, addition of methanesulfonic acid to its solution in acetonitrile causes a bathochromic shift of approximately 100 nm, and an intense yellow-green emission centered at 490 nm is observed.^[16] A slightly smaller shift to longer wavelengths is observed in dichloromethane, as expected for a less polar solvent (Table 1). Importantly, a relatively small drop in fluorescence quantum efficiency is observed upon protonation ($\phi_{\text{F}}=0.33$ for **3a**· H^+ in CH_2Cl_2). Figure 3 illustrates the dramatic spectral changes ligand **3b** undergoes upon the addition of exogenous ions.^[17]

Fluorescent compounds have been attracting considerable interest in recent years as components for fluorescent sensors and switches.^[18–22] Yet, highly emissive tunable chromophores are rare.^[23, 24] The combination of a highly coordinating diimine functionality and an extended conjugation through ethynyl linkages provides a unique family of tunable intrinsic fluorophores, where changes in the electronic polarization, solvation, and coordination are translated into dramatic spectral changes. The simple synthesis, together with the availability of numerous precursors and cross-coupling methodologies, make the preparation of other 1,10-phenanthroline-based chromophores with diverse absorption and emission characteristics almost trivial. The visible emission of the conjugated ligands and their complexes, as well as their

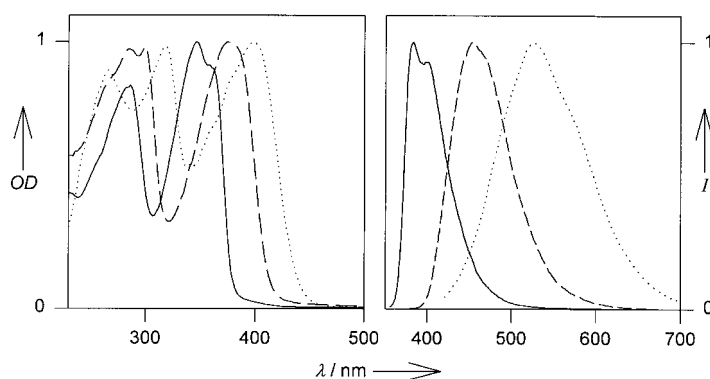


Figure 3. Normalized absorption and emission spectra of **3b** (—), **3b** + excess Zn^{2+} (---), and **3b** + excess methanesulfonic acid (....) in acetonitrile. Emission spectra were obtained upon excitation at the absorption maximum.

relatively long excitation wavelengths (> 340 nm), may facilitate the incorporation of these chromophores into biologically useful chemosensors as well as novel light-emitting materials.

Experimental Section

The synthesis of 3,8-dibromo-1,10-phenanthroline^[9, 10] and 3,8-bis(aryl-ethynyl)-1,10-phenanthrolines^[11] has been previously reported. Representative data for **3b**: m.p. 243 °C; MS: m/z 408 [M^+]; IR (KBr): $\tilde{\nu}$ 2210 cm^{-1} ($\text{C}\equiv\text{C}$); UV (CH_3CN): λ_{max} ($\epsilon \times 10^{-4}$) = 286 (5.1), 346 (6.1), 362 nm (5.4); ^1H NMR (400 MHz, CDCl_3): δ = 9.28 (d, J = 2.2 Hz, 2H, phen H2/9), 8.37 (d, J = 2.2 Hz, 2H, phen H4/7), 7.80 (s, 2H, phen H5/6), 7.52 (d, J = 8 Hz, 4H, ph), 7.22 (d, J = 8 Hz, 4H, ph), 2.41 (s, 6H, CH_3).

Fluorescence quantum yields (ϕ_F) were measured by using a Perkin Elmer LS50B Luminescence Spectrometer with optically thin solutions ($\text{OD} = 0.04$) at room temperature. Argon-degassed, isoabsorptive solutions of the standard and conjugated phenanthroline derivatives **3a–d** were excited at the wavelength of maximum absorption of the ligands. Values are reported relative to 9,10-diphenylanthracene and calculated according to Equation (1),^[25] where ϕ_{unk} is the fluorescence quantum yield of the sample, ϕ_{std} is the quantum yield of the standard ($\phi_F = 0.91$ in ethanol),^[26] I_{unk} and I_{std} are the integrated emission intensities of the sample and the standard, respectively, A_{unk} and A_{std} are the absorbances of the sample and the standard at the excitation wavelength, respectively, and n_{unk} and n_{std} are the refractive indexes of the corresponding solutions (pure solvents were assumed).

$$\phi_{\text{unk}} = \phi_{\text{std}} \left(\frac{I_{\text{unk}}}{A_{\text{unk}}} \right) \left(\frac{A_{\text{std}}}{I_{\text{std}}} \right) \left(\frac{n_{\text{unk}}}{n_{\text{std}}} \right)^2 \quad (1)$$

Multiple measurements indicated a precision of about 5% for the ϕ_F values determined. The fluorescence quantum yields were qualitatively confirmed by calculating $\phi_F = \tau_s/\tau_0$ (where τ_0 is the “native” lifetime and τ_s is the experimentally determined one). The native lifetime is obtained by integrating the absorption band and determining the oscillator strength.^[27, 28]

The dependence of emission energies on solvent polarity was determined in dichloromethane/cyclohexane mixtures (low polarity), and acetonitrile/water mixtures (high polarity). Emission spectra were converted from wavelength (nm) to frequency (cm^{-1}) units. $E_T(30)$ values were experimentally determined for each solvent mixture using Reichardt’s salt.^[29]

Received: March 18, 1999 [Z13185IE]

German version: *Angew. Chem.* **1999**, *111*, 2888–2891

Keywords: chromophores • conjugation • fluorescence spectroscopy • N ligands • phenanthrolines

- [1] For recent reviews, see: a) S. A. Jenekhe, *Adv. Mater.* **1995**, *7*, 309–311; b) F. Hide, M. A. Diaz-Garcia, B. J. Schartz, A. J. Heeger, *Acc. Chem. Res.* **1997**, *30*, 430–436; c) A. Kraft, A. C. Grimsdale, A. B. Holmes, *Angew. Chem.* **1998**, *110*, 416–443; *Angew. Chem. Int. Ed.* **1998**, *37*, 402–428.
- [2] R. D. McCullough, *Adv. Mater.* **1998**, *10*, 93–116.
- [3] T. Noda, H. Ogawa, N. Noma, Y. Shirota, *Adv. Mater.* **1997**, *9*, 720–722.
- [4] M. Berggren, O. Inganäs, G. Gustafsson, J. Rasmussen, M. R. Andersson, T. Hjertberg, O. Wennerström, O. *Nature* **1994**, *372*, 444–446. M. Aguiar, F. E. Karasz, L. Akcelrud, *Macromolecules* **1995**, *28*, 4598–4602. S.-J. Chung, J.-I. Jin, K.-K. Kim, *Adv. Mater.* **1997**, *9*, 551–554. T. Christ, A. Greiner, R. Sander, V. Stümpfen, J. H. Wendorff, *Adv. Mater.* **1997**, *9*, 219–222. S. E. Döttinger, M. Hohloch, J. L. Segura, E. Steinhuber, M. Hanack, A. Tompert, D. Oelkrug, *Adv. Mater.* **1997**, *9*, 233–236. E. M. Girotto, M.-A. De Paoli, *Adv. Mater.* **1998**, *10*, 790–793. L. Dähne, E. Biller, H. Baumgärtel, *Angew. Chem.* **1998**, *110*, 669–672; *Angew. Chem. Int. Ed.* **1998**, *37*, 646–649.
- [5] For recent articles discussing the modulation of the electronic properties of 2,2':6,2''-terpyridine-containing chromophores and complexes, see: a) F. Barigelletti, L. Flamigni, G. Calogero, L. Hammarström, J.-P. Sauvage, J.-P. Collin, *Chem. Commun.* **1998**, 2333–2334; b) M. Hissler, A. El-Ghayoury, A. Harriman, R. Ziessel, *Angew. Chem.* **1998**, *110*, 1804–1807; *Angew. Chem. Int. Ed.* **1998**, *37*, 1717–1720; c) G. Albano, V. Balzani, E. C. Constable, M. Maestri, D. R. Smith, *Inorg. Chim. Acta* **1998**, *277*, 225–231.
- [6] B. N. Bandyopadhyay, A. Harriman, *J. Chem. Soc. Faraday Trans. 1* **1977**, *73*, 663–674.
- [7] B. Bosnich, *Acc. Chem. Res.* **1969**, *2*, 266–273.
- [8] D. R. Maulding, B. G. Roberts, *J. Org. Chem.* **1969**, *34*, 1734–1736.
- [9] D. Tzalis, Y. Tor, S. Failla, J. S. Siegel, *Tetrahedron Lett.* **1995**, *36*, 3489–3490.
- [10] P. J. Connors, Jr., D. Tzalis, A. L. Dunnick, Y. Tor, *Inorg. Chem.* **1998**, *37*, 1121–1123.
- [11] D. Tzalis, Y. Tor, *Tetrahedron Lett.* **1995**, *36*, 6017–6020.
- [12] Derivative **3d** is somewhat susceptible to oxidation. Its fluorescence quantum yield was not determined since its emission wavelength is significantly red-shifted compared to the standard’s emission.
- [13] Derivatives with other alkyl substituents (e. g., $R = t\text{Bu}$) behave very similarly to **3b**. A derivative with strong electron-withdrawing groups ($R = \text{CF}_3$) also shows tunability of emission wavelengths. This ligand is, however, a poorer binder due to the reduced electron density on the chelating nitrogens. Monosubstituted derivatives (e. g., 3-(tolylethynyl)-1,10-phenanthroline) typically show shorter absorption and emission wavelengths as well as lower fluorescence quantum efficiency, when compared to their disubstituted derivatives. This may enable fine-tuning of the absorption and emission characteristics. See Supporting Information for spectral data.
- [14] C. S. Creaser, J. R. Sodeau, in *Perspectives in Modern Chemical Spectroscopy*, (Ed.: D. L. Andrews), Springer, Berlin, **1990**, pp. 103–136.
- [15] The emission spectra of the various ligands are insensitive to dioxygen. This further supports the assignment of a singlet $\pi-\pi^*$ as the emissive state.
- [16] Binding stoichiometry determined by using absorbance mixing curves (job plots) indicate a 1:1 binding of H^+ and Zn^{2+} .
- [17] Other metal ions also induce spectral changes. Emission maxima for solutions of **3a** in acetonitrile with excess metal ions: Cd^{2+} (423 nm), Pd^{2+} (444 nm), and Ag^+ (415 nm).
- [18] A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.* **1997**, *97*, 1515–1566, and references therein.
- [19] B. M. Krasovitskii, B. M. Bolotin, *Organic Luminescent Materials*, VCH, Weinheim, **1988** and references therein.
- [20] A. W. Czarnik, *Chem. Biol.* **1995**, *2*, 423–428.
- [21] A. W. Czarnik, *Fluorescent Chemosensors for Ion and Molecule Recognition*, American Chemical Society, Washington DC, **1992**.
- [22] J.-M. Lehn, in *Supramolecular Chemistry—Concepts and Perspectives*, VCH, Weinheim **1995**, Ch. 8, pp. 89–138.
- [23] For 2,9-bisaryl-1,10-phenanthrolines and their luminescence properties, see: N. Armaroli, L. De Cola, V. Balzani, J.-P. Sauvage, C. O.

- Dietrich-Buchecker, J.-M. Kern, *J. Chem. Soc. Faraday Trans.* **1992**, 88, 553–556.
- [24] For an intriguing tunable 2-catenand, see: N. Armaroli, L. De Cola, V. Balzani, J.-P. Sauvage, C. O. Dietrich-Buchecker, J.-M. Kern, A. Bailal, *J. Chem. Soc. Dalton Trans.* **1993**, 3241–3247. For metal-binding conjugated polymers, see: S. S. Zhu, P. J. Carroll, T. M. Swager, *J. Am. Chem. Soc.* **1996**, 118, 8713–8714; B. Wang, M. R. Wasielewski, *J. Am. Chem. Soc.* **1997**, 119, 12–21; K. B. Crawford, M. B. Goldfinger, T. M. Swager, *J. Am. Chem. Soc.* **1998**, 120, 5187–5192; M. Kimura, T. Horai, K. Hanabusa, H. Shirai, *Adv. Mater.* **1998**, 10, 459–462.
- [25] J. N. Demas, G. A. Crosby, *J. Phys. Chem.* **1971**, 75, 991–1024.
- [26] M. Mardelli, J. Olmsted, III, *J. Photochem.* **1977**, 7, 277–285.
- [27] N. J. Turro, *Modern Molecular Photochemistry*, University Science Books, Sausalito, California, **1991**.
- [28] A value of $\phi_F = 0.94$ is predicted for **3b**. See Supporting Information for detailed calculations.
- [29] C. Reichardt, *Chem. Rev.* **1994**, 94, 2319–2358.

Synthesis of Giant Zeolite Crystals by a Bulk-Material Dissolution Technique**

Shinichi Shimizu* and Hideaki Hamada

Zeolites are crystalline microporous materials that are attracting much attention owing to their applications as high-performance catalysts, in separation processes, and in optical, magnetic, and electronic devices.^[1] Major efforts have been undertaken to synthesize large single crystals with a well-defined habit, because some applications require large zeolite crystals to allow effective use of their micropores. In 1971 Charnell synthesized zeolite Na-A (LTA) crystals (ca. 65 μm) and zeolite Na-X (FAU) crystals (ca. 140 μm) under hydrothermal conditions from gels of sodium metasilicate, sodium aluminate, and triethanolamine, which were purified to remove particles by a precision filtration technique.^[2] In 1993 a novel method to synthesize zeolites in nonaqueous media was developed to obtain giant zeolite crystals by controlling the release and solubility of reactive solution

species in organothermal systems.^[3] Giant crystals of dodecasil-3C, a clathrasil having the MTN framework, were prepared by using a combination of silica rods and fumed silica by Klemperer and Marquart.^[4] Other attempts to obtain large zeolite crystals have also been made.^[5]

Recently, we developed a novel technique for synthesizing giant zeolite crystals in aqueous media by controlling the solubility in hydrothermal systems. Both silicalite-1 (all-silica MFI) and analcime (ANA) crystals with sizes of about 3 mm, which were unknown until now, were successfully synthesized by using bulk materials as the silica and alumina sources (bulk-material dissolution (BMD) technique). The compositions of the reaction mixtures and the experimental results are summarized in Table 1. A typical procedure is as follows: A

Table 1. Synthesis of zeolite crystals by the BMD technique.

Zeolite framework (Figure)	Bulk source [mmol]	Liquid phase [mmol]	<i>T</i> [°C]	<i>t</i> [d]	Maximum crystal size [μm]
MFI (2, 3)	SiO ₂ tube SiO ₂ (25.2)	TPAOH (8.9) HF (9.7) H ₂ O (870)	200	25	2000 × 1000 × 1000
MFI (4)	SiO ₂ tube SiO ₂ (18.4)	TPAOH (8.9) HF (14.6) H ₂ O (885)	200	46	3200 × 2800 × 2600
ANA (5)	ceramic boat SiO ₂ (12.1) Al ₂ O ₃ (3.0)	NaOH (20.3) H ₂ O (847)	200	31	3000 × 2800 × 2500
JBW & CAN (6)	ceramic tube SiO ₂ (12.6) Al ₂ O ₃ (9.6)	NaOH (51.2) H ₂ O (683)	200	7	640 × 320 × 100 (JBW) 300 × 5 × 5 (CAN)
CAN	ceramic boat SiO ₂ (11.4) Al ₂ O ₃ (2.8)	NaOH (99.0) H ₂ O (832)	200	13	100 × 20 × 20
SOD	ceramic boat SiO ₂ (11.0) Al ₂ O ₃ (2.7)	NaOH (51.0) H ₂ O (833)	100	19	60 × 60 × 60
SOD	ceramic tube SiO ₂ (21.7) Al ₂ O ₃ (11.7)	NaOH (98.7) H ₂ O (697)	200	12	120 × 120 × 120

piece of quartz glass tube (ca. 24 mm long, 10 mm external and 8 mm internal diameter; 25.2 mmol SiO₂) was placed in a PTFE sleeve (capacity 23 mL) equipped for an autoclave. The sleeve was filled with an aqueous solution containing tetra-*n*-propylammonium hydroxide (TPAOH) and hydrogen fluoride (HF). The experimental setup is illustrated in Figure 1.

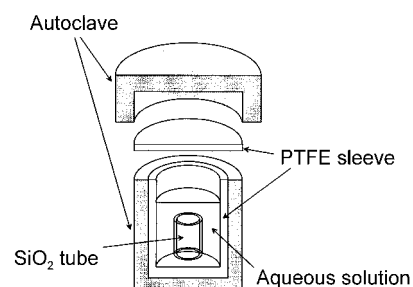


Figure 1. Schematic illustration of the experimental setup for BMD crystallization.

[*] Dr. S. Shimizu^[+]
Joint Research Center for Harmonized Molecular Materials
Japan Chemical Innovation Institute
1-1, Higashi, Tsukuba, Ibaraki 305-8565 (Japan)
Fax: (+81) 298-50-4103
E-mail: shinichi@nimc.go.jp

Dr. H. Hamada
National Institute of Materials and Chemical Research
1-1, Higashi, Tsukuba, Ibaraki 305-8565 (Japan)

[+] Present address:
Advanced Technology Laboratory
Kubota Corporation
5-6, Koyodai, Ryugasaki, Ibaraki 301-0852 (Japan)
Fax: (+81) 297-64-7266
E-mail: si-simiz@kubota.co.jp

[**] This work is supported by NEDO for an AIST project on Technology for Novel High Functional Materials: Harmonized Molecular Materials. We thank S. Sato of Rigaku Co. for his technical support and assistance with single-crystal XRD analysis.

After 25 d of crystallization at 200 °C, some crystals were found on the surface of the residual quartz-glass tube, and others at the bottom of the PTFE sleeve (Figure 2). Most of

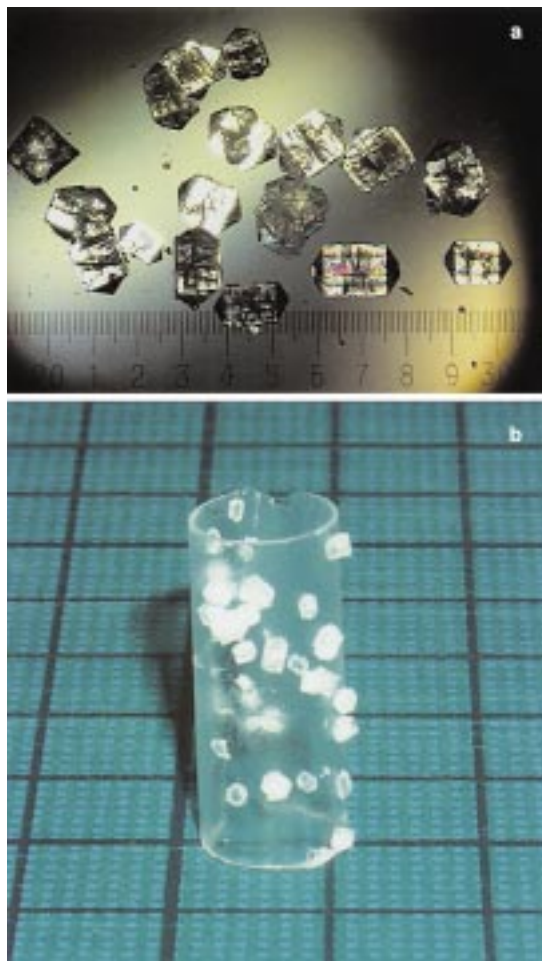


Figure 2. Giant crystals of all-silica MFI zeolite were synthesized at 200 °C for 25 d from SiO₂, TPAOH, HF, and water (25.2, 8.9, 9.7, and 870 mmol, respectively). a) Giant MFI crystals formed at the bottom of the PTFE sleeve. The finest notch on the ruler indicates 0.1 mm. b) The MFI crystals formed on the tubular source. One block on the grid indicates 1 cm².

the product crystals are larger than about 1 × 1 × 1 mm³. They were identified as all-silica MFI zeolite by powder X-ray diffraction (XRD) (Figure 3a). The XRD reflections were also collected from one of the giant MFI crystals with its

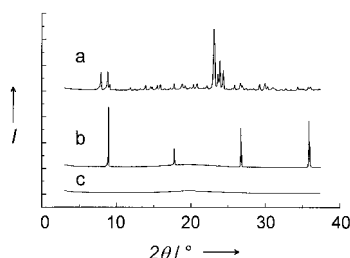


Figure 3. XRD patterns of the giant crystals of all-silica MFI zeolite. a) XRD pattern of the powder obtained by grinding some of the crystals in an agate mortar. b) XRD pattern of reflections from one crystallographic plane parallel to the surface of the giant MFI crystal fixed on the specimen holder by aluminum adhesive tape. c) Blank pattern of the specimen holder equipped with aluminum adhesive tape. *I* = intensity.

surface parallel to the horizontal plane of the specimen holder (Figure 3b). The reflections were assigned as those from the (*h*00) or the (0*k*0) planes (*h* = 2, 4, 6, 8; *k* = 2, 4, 6, 8). No reflections from other crystallographic planes emerged in the XRD pattern. These XRD measurements indicate that the MFI crystals are single crystals. The largest of the MFI crystals shown in Figure 4 has dimensions of about 3.2 × 2.8 × 2.6 mm³. It was synthesized at 200 °C for 46 d (Table 1). When the solution was stirred in the PTFE sleeve, no MFI crystals larger than 0.5 mm were obtained from a similar reaction mixture.

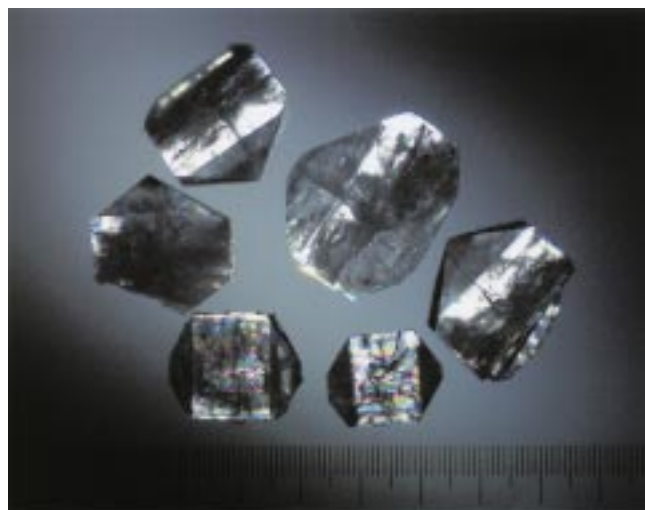


Figure 4. Giant crystals of MFI zeolite synthesized at 200 °C for 46 d from SiO₂, TPAOH, HF, and water (18.4, 8.9, 14.6, and 885 mmol, respectively). The finest notch on the ruler indicates 0.1 mm.

We also investigated a small ceramic boat, which is usually used as a container for combustion of a specimen, as an aluminosilicate source for zeolites. The ceramic boat weighed 1.036 g and was found to contain 12.1 mmol of SiO₂ and 3.0 mmol of Al₂O₃ (SiO₂/Al₂O₃ = 4.0) by X-ray fluorescence analysis. The boat was placed in a PTFE sleeve (capacity 23 mL) equipped for an autoclave, and the sleeve was filled with an aqueous solution of sodium hydroxide. The crystals obtained after heating the reaction mixture at 200 °C for 31 d in a convection oven were identified as ANA zeolite by XRD measurements. The largest ANA crystal had approximate dimensions of 3.0 × 2.8 × 2.5 mm³ (Figure 5).

When a ceramic tube with composition (SiO₂/Al₂O₃ = 1.3) different from that of the ceramic boat was used as an aluminosilicate source, different crystals were obtained. In this case, crystallization was carried out by heating a reaction mixture consisting of a piece of the ceramic tube, NaOH, and water at 200 °C for 7 d. The product consisted of large parallelepipedal crystals and fine needlelike crystals, and was identified as a mixture of JBW and CAN zeolites by powder XRD measurements. The larger crystals were identified as JBW by single-crystal XRD analysis. The largest JBW (ca. 640 × 320 × 100 μm³) and CAN crystals (ca. 300 × 5 × 5 μm³) are shown in Figure 6.

We believe that the BMD technique with glassy or sintered bulk material is one of the most attractive techniques for synthesizing large crystals of all-silica and aluminosilicate

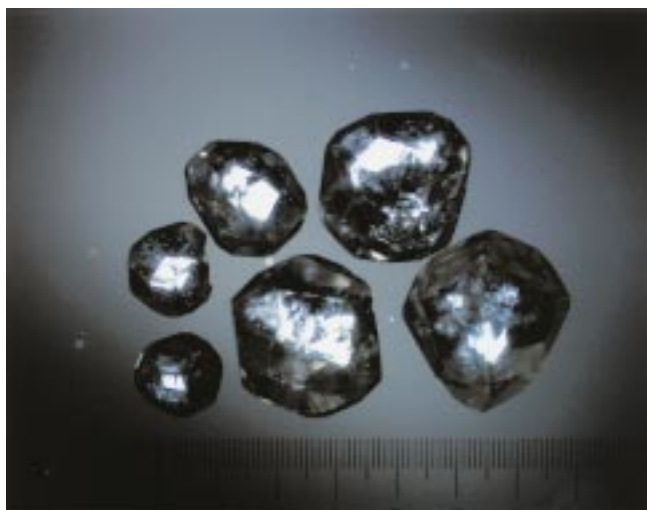


Figure 5. Giant crystals of ANA zeolite synthesized at 200 °C for 31 d from SiO_2 , Al_2O_3 , NaOH, and water (12.1, 3.0, 20.3, and 847 mmol, respectively). The finest notch on the ruler indicates 0.1 mm.

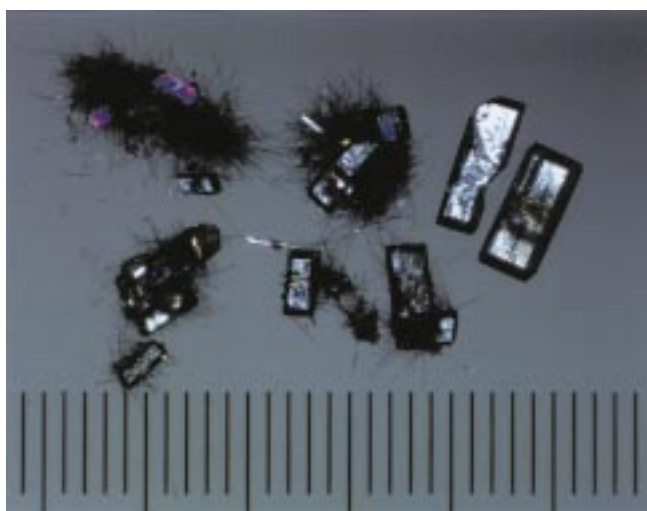


Figure 6. Giant crystals of JBW zeolite synthesized at 200 °C for 7 d from SiO_2 , Al_2O_3 , NaOH, and water (12.6, 9.6, 51.2, and 683 mmol, respectively). The numerous fine crystals around the JBW crystals were identified as CAN zeolite by XRD measurement. The finest notch on the ruler indicates 0.1 mm.

zeolites. In comparison with conventional hydrothermal synthesis, in which colloidal materials or powders are used as raw materials, the most distinctive feature of this technique is that the total surface area of the bulk raw materials is extremely small. Accordingly, the rate of dissolution of the raw materials in the aqueous phase is much smaller than in the conventional hydrothermal process. When the concentration of the chemical species increases very slowly and reaches a slight supersaturation level, the concentration is considered to remain approximately at the saturation level because of a balance between the consumption by the growing nuclei and the supply from the bulk raw materials. As a result, only a few nuclei are produced in the first stage of the hydrothermal reaction and grow to giant zeolite crystals. It is interesting that no giant zeolite crystals are obtained in the stirred reaction. This suggests that the presence of concentration gradients

plays an important role in transferring the chemical species from the bulk raw material to the zeolite nuclei. Consequently, both the small total surface area of the bulk raw materials and the concentration gradient produced in the static crystallization process are assumed to be essential factors in the BMD technique.

Natural zeolites can occur as large single crystals, but it has so far proven difficult to synthesize them in the laboratory. It is believed that the natural crystals were formed from bulk minerals in a static natural process, whereas artificial zeolite crystals are usually synthesized from powdered or colloidal raw materials. The BMD process therefore can be considered to resemble the natural process.

Experimental Section

Powder XRD measurements: The specimen powder was obtained by grinding the crystals in an agate mortar. Powder XRD patterns were measured on a Rigaku Rint 2500 diffractometer with $\text{CuK}\alpha$ radiation with $\theta/2\theta$ scans and 1 deg min^{-1} 2θ scan rate.

XRD measurement on an MFI single crystal: An MFI crystal was fixed at the center of a through-type specimen holder for the Rigaku Rint 2500 diffractometer by aluminum adhesive tape. After the position of the crystal surface was adjusted to the horizontal plane of the holder, the XRD pattern was measured. The reflections were assigned as those from the ($h00$) or the ($0k0$) plane ($h = 2, 4, 6, 8; k = 2, 4, 6, 8$). It is very difficult to distinguish between these reflections in such a simple measurement because the crystallographic cell of the MFI framework is primitive orthorhombic with dimensions: $a = 20.022$, $b = 19.899$, and $c = 13.383$ Å, and these reflections are observed in very similar positions.^[6]

Single-crystal XRD measurement on a JBW single crystal: XRD data were collected on a Rigaku AFC5R diffractometer with $\text{MoK}\alpha$ graphite monochromated radiation. The structure of the specimen crystal is orthorhombic, space group $Pna2_1$ (no. 33) with $a = 16.457(3)$, $b = 15.009(2)$, $c = 5.234(5)$ Å, $Z = 4$, and $\rho_{\text{calcd}} = 2.400 \text{ g cm}^{-3}$. It is in good agreement with the published structure of JBW.^[7]

Received: March 12, 1999 [Z13150IE]
German version: *Angew. Chem.* **1999**, *111*, 2891–2894

Keywords: crystal growth • synthetic methods • zeolites

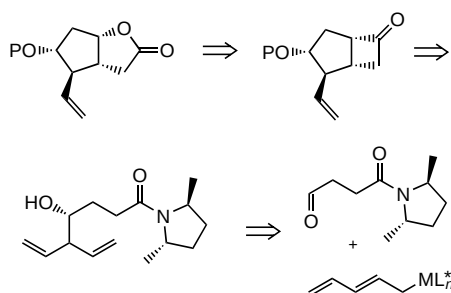
- [1] a) G. A. Ozin, A. Kuperman, A. Stein, *Angew. Chem.* **1989**, *101*, 373–390; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 359–376; b) G. D. Stucky, J. E. MacDougall, *Science* **1990**, *247*, 669–678; c) J. Caro, G. Finger, J. Kornatowski, J. Richter-Mendau, L. Werner, B. Zibrowius, *Adv. Mater.* **1992**, *4*, 273–276; d) G. A. Ozin, *Adv. Mater.* **1992**, *4*, 612–649.
- [2] a) J. F. Charnell, *J. Cryst. Growth* **1971**, *8*, 291–294; b) W. M. Meier, D. H. Olson, C. Baerlocher, *Zeolites* **1996**, *17*, 1–230 (Atlas of Zeolite Structure Types, 4th ed.).
- [3] A. Kuperman, S. Nadimi, S. Oliver, G. A. Ozin, J. M. Garcés, *Nature* **1993**, *365*, 239–242.
- [4] W. G. Klemperer, T. A. Marquart, *Mater. Res. Soc. Symp. Proc.* **1994**, *346*, 819–824.
- [5] a) J. Kornatowski, *Zeolites* **1988**, *8*, 77–78; b) Z. Daping, Q. Shilun, P. Wenqin, *J. Chem. Soc. Chem. Commun.* **1990**, 1313–1314; c) I. Girnus, K. Hoffmann, F. Marlow, J. Caro, G. Döring, *Microporous Mater.* **1994**, *2*, 537–541; d) Y. Yokomori, Y. Kawachi, *Zeolites* **1995**, *15*, 637–639; e) Y. Sun, T. Song, S. Qiu, W. Pang, J. Shen, D. Jiang, Y. Yue, *Zeolites* **1995**, *15*, 745–753; f) T. Okubo, *Zeolites* **1996**, *13*, 49–55.
- [6] M. M. J. Treacy, J. B. Higgins, R. von Ballmoos, *Zeolites* **1996**, *16*, 522–523 (Collection of Simulated XRD Powder Patterns for Zeolites, 3rd ed.).
- [7] S. Hansen, L. Fäth, *Zeolites* **1982**, *2*, 162–166.

A Convergent Strategy for the Asymmetric Synthesis of Enantiomerically Pure Bicyclic Compounds by Using a Silicon-Directed Cycloaddition Reaction: The Synthesis of Enantiomerically Pure Bicyclo[3.2.0]-hept-2-en-6-one**

Jean-Michel Adam, Léon Ghosez,* and Kendall N. Houk

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday

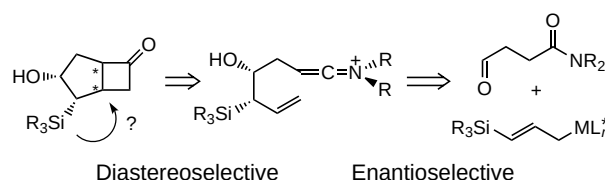
Bicyclic cyclobutanones are extremely versatile building blocks that have been used for the total synthesis of several important biologically active products.^[1] Our group recently developed a convergent strategy for the synthesis of enantiopure bicyclo[3.2.0]heptanones that were further converted into various prostanoids intermediates (Scheme 1).^[2] This



Scheme 1. Former approach using two chiral auxiliaries.

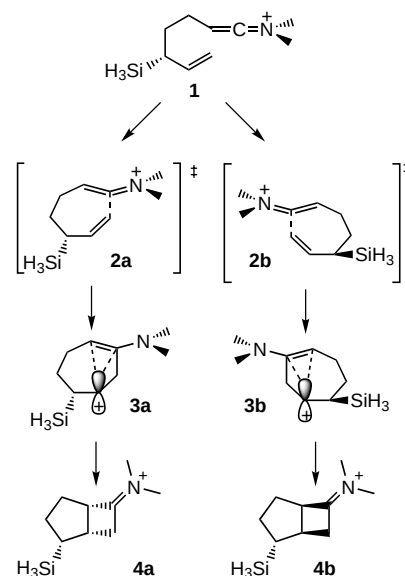
convergent strategy required two sources of chirality: the ligands L^* of the metal direct the stereochemistry of the allylmetalation step, while the dimethylpyrrolidine controls the facial selectivity of the cycloaddition step. Asymmetric induction by the protected hydroxy group (1,3-induction) was indeed very poor as shown by a control experiment without a chiral pyrrolidine.^[2b]

We recently considered the possibility of controlling the facial selectivity by a properly selected allylic substituent.^[3] A silyl group was chosen as the stereodirecting functionality. It should be efficiently installed with the required relative and absolute configuration by the stereoselective addition of a chiral allylmatal reagent to an aldehyde (Scheme 2).



Scheme 2. Present strategy: use of a silicon-directed [2+2] cycloaddition.

We anticipated that the silyl substituent would not only activate the double bond towards electrophilic attack but would also control the facial selectivity.^[4] However, since the rate and selectivity determining step of the cycloaddition involved the formation of a seven membered ring intermediate^[5] (such as **3a** and **3b**, Scheme 3) we assessed our hypothesis by computational studies.



Scheme 3. Cycloaddition mechanism and face selection by the allylic silyl group.

Investigations of this reaction with *ab initio* and density functional theory methods^[6] have led to a mechanistic scenario involving initial electrophilic attack of the keteniminium group on the alkene to form a bridged enamine cation (a distorted cyclopropylcarbanyl cation) which cyclizes with a very low activation barrier to form the cyclobutaneiminium ion (Scheme 3). In the case of the silyl-substituted substrate **1** RHF/6-31G* calculations^[7] located four low-energy transition structures for the initial step of the reaction. Single point Becke3LYP/6-31G* calculations are consistent with the restricted Hartree–Fock (RHF) results. The lowest energy transition structures that lead to **4a** and **4b** (Scheme 3) are shown in Figure 1.

The favored transition structure (**2a**, which leads to **4a**) has a nearly perfect staggered tether between the alkene and the keteniminium group, and with the C–Si bond aligned with the alkene π orbitals. This alignment provides stabilization of the transition state by a β effect. By contrast, the lowest energy transition state for attack on the opposite face of the alkene has the silyl group disposed in the plane of the alkene where it

[*] Prof. Dr. L. Ghosez, J.-M. Adam
Laboratoire de Chimie Organique de Synthèse
Université catholique de Louvain
place L. Pasteur 1, B-1348 Louvain-la-Neuve (Belgium)
Fax: (+32) 10-474-168
E-mail: ghosez@chor.ucl.ac.be
Prof. Dr. K. N. Houk
Department of Chemistry and Biochemistry
University of California
405 Hilgard Avenue, Los Angeles, CA 90095-1569 (USA)

[**] This work was supported by FRIA (fellowship to J.-M.A.), FNRS (fellowship to J.-M.A.), the Ministère de l'Éducation et de la Recherche Scientifique de la Communauté française de Belgique (Actions concertées 91/96-145 and 96/01–197), and the University of California, Los Angeles (grant to J.-M.A.).

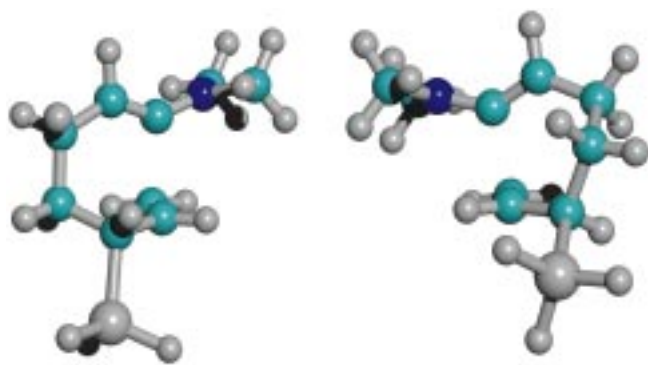
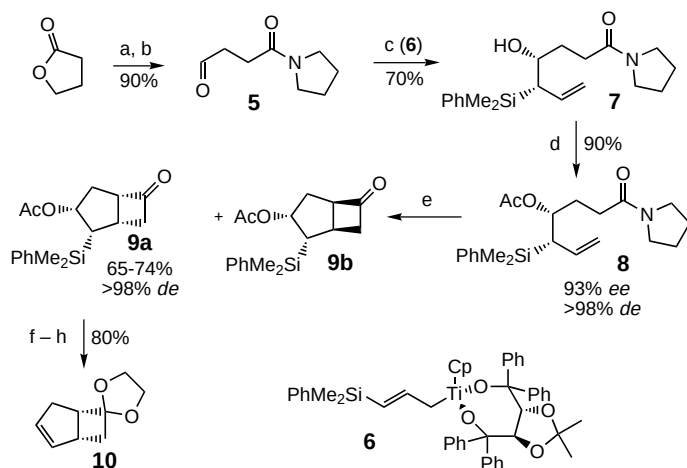


Figure 1. Relevant transition states for the cycloaddition of **1**: left: **2a**, 0 kcal mol⁻¹ (RHF/6-31G**/RHF/6-31G*), 0 kcal mol⁻¹ (Becke3LYP/6-31G**/RHF/6-31G*); right: **2b**, 2.98 kcal mol⁻¹ (RHF/6-31G**/RHF/6-31G*), 3.21 kcal mol⁻¹ (Becke3LYP/6-31G**/RHF/6-31G*).

provides negligible stabilization. Having these predictions in hand, we compared them with the experimental results.

The precursor for the cycloaddition was readily obtained by the addition of aldehyde **5**^[8] to a solution of the (*E*)- γ -silyl-substituted allyltitanium reagent **6**^[9] which was generated in situ at -78 °C (Scheme 4). Work-up and flash chromatography gave a single homoallylic alcohol (70% yield) with



Scheme 4. Asymmetric synthesis of **10**: a) Et₃N, pyrrolidine, reflux, 15 h; b) (COCl)₂, DMSO, Et₃N, CH₂Cl₂; c) *n*BuLi (1.13 equiv), Me₂Ph-SiCH₂CHCH₂ (1.13 equiv), THF, 25 min, RT, (*R,R*)-Cl-TiCpTADDOL (1.25 equiv; TADDOL = $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol), 1 h, -78 °C, **5**, 4 h, -78 °C, NH₄F_{sat}, 15 h, RT, flash chromatography (100% AcOEt); d) AcCl (4 equiv), pyridine (5 equiv), 4 h, RT, CH₂Cl₂; e) di-*tert*-butylmethylpyridine (1.5 equiv), Tf₂O (1.1 equiv, addition over 3 h), CH₂Cl₂, 3 h, RT, 1 M HCl, 40 h, flash chromatography (Et₂O/hexane 50/50); f) 1,2-ethanediol, *p*-toluenesulfonic acid, toluene, Dean-Stark distillation; g) KOH/MeOH, reflux; h) NaH/THF, reflux, flash chromatography.

93% *ee*. Acetylation of the alcohol gave the amide **7**, which was treated with triflic anhydride (Tf₂O) in the presence of a hindered base to generate the keteniminium triflate. Intramolecular [2+2] cycloaddition^[10] followed by hydrolysis gave a 32:1 mixture of bicyclo[3.2.0]heptanones **9a** and **9b**. This high facial selectivity is in complete agreement with the theoretical prediction. Flash chromatography gave pure **9a**

(yield 65–74%, 93% *ee*, >98% *de*). The absolute configuration of **9a** was established by an X-ray diffraction analysis on an enantiopure sample (>99% *ee*) obtained by recrystallization from hexane.^[11]

Compound **9a** was readily converted (three steps, no purification of intermediates) into the enantiopure protected bicyclo[3.2.0]hept-2-en-6-one **10** (80% yield).^[12] This compound and the corresponding cyclobutanone were until now only accessible by routes involving a resolution step.^[1g, 13] They are key intermediates in the reported syntheses of brefeldin A,^[11b] vasiprost,^[14] numerous prostanoids,^[1c,f,g, 15] and magellaninone.^[16] They have also been used in the design of new ligands for rhodium-catalyzed asymmetric hydrogenation.^[17]

The results reported here illustrate a highly convergent synthetic strategy that should be applicable to a wide variety of cyclobutanones fused to a carbo-^[10] or heterocycle^[18] by selecting the appropriate aldehyde–amide precursor. Also, the replacement of the keteniminium moiety by another functional group capable of undergoing (cyclo)addition to the allylsilane group should extend the scope of this synthetic strategy considerably.

Experimental Section

7: [α]_D²⁰ = -45 (*c* = 1 in CH₂Cl₂); IR (KBr): $\tilde{\nu}$ = 3386 (O–H), 1628 (C=O), 1451 cm⁻¹ (C=C); ¹H NMR (300 MHz, [D₆]DMSO, 20 °C): δ = 7.2–7.6 (m, 5H, Ph), 5.87 (ddd, ³*J*(H,H) = 17.1, 10.4, 10.4 Hz, 1H, HC=CH₂), 4.89 (dd, ³*J*(H,H) = 10.3, ²*J*(H,H) = 2 Hz, 1H, H–CH=CH (*cis*)), 4.74 (dd, ³*J*(H,H) = 17.25, ²*J*(H,H) = 2 Hz, 1H, H–CH=CH (*trans*)), 4.66 (dd, ³*J*(H,H) = 5.8 Hz, 1H, HO), 3.6 (m, 1H, HCOH), 3.31 (t, ³*J*(H,H) = 6.32 Hz, 2H, CH₂N), 3.20 (t, ³*J*(H,H) = 6.59 Hz, 2H, CH₂N), 2.15 (t, ³*J*(H,H) = 7.42 Hz, 2H, CH₂C=O), 1.65–1.9 (m, 5H, CH₂CH₂NCO, CHSi), 1.4–1.65 (m, 2H, CH₂CH₂C=O) (assignments were confirmed by COSY); ¹³C NMR (50 MHz, [D₆]DMSO): δ = 170.6, 138.4, 135.95, 133.97, 128.63, 127.42, 113.86, 69.67, 45.97, 45.19, 41.39, 32.51, 30.90, 25.62, 23.95, -3.36, -3.56; MS (CI, CH₄/N₂O, +Q1MS): *m/z* (%): 360 (4) [*M*+29], 332 (6) [*M*+1], 314 (64), 254 (12), 180 (100), 135 (18); HPLC (Chiralpack AS, hexane/*i*PrOH 95/5, 1 mL min⁻¹, 30 °C, 224 nm): *t*_R = 33 min (other enantiomer at 23 min, other diastereoisomer at 20 and 26 mins); elemental analysis calcd for C₁₉H₂₉NO₂Si: C 68.84, H 8.82, N 4.22; found: C 68.58, H 9.09, N 4.24.

9a: [α]_D²⁰ = +24 (*c* = 1.25 in CH₂Cl₂); IR (KBr): $\tilde{\nu}$ = 3040 (C–H), 1782 (C=O), 1739 cm⁻¹ (C=O); ¹H NMR (200 MHz, CDCl₃, 20 °C, TMS): δ = 7.3–7.5 (m, 5H, Ph), 5.44 (dd, ³*J*(H,H) = 4, 4 Hz, 1H, HCOAc), 3.66 (m, 1H, CHC=O), 3–3.2 (m, 3H, CHCH₂C=O), 2.29 (d, ³*J*(H,H) = 14.8 Hz, 1H, CHCOAc (*endo*)), 1.87 (s, 3H, CH₃C=O), 1.76–1.94 (dd below signal at 1.87, 1H, CHCOAc (*exo*)), 1.53 (dd, ³*J*(H,H) = 7, 3.9 Hz, 1H, CHSi), 0.40 (s, 3H, MeSi), 0.39 (s, 3H, MeSi) (assignments were confirmed by COSY); ¹³C NMR (50 MHz, CDCl₃): δ = 212.7, 169.9, 138.1, 133.6, 129.3, 128, 80.6, 64.5, 51.4, 39.5, 37.6, 32.5, 21.3, -2.1; MS (EI, 70 eV): *m/z* (%): 302 (4) [*M*⁺], 260 (20), 182 (22), 135 (100); HPLC (Chiralpack AD, hexane (0.1% diethylamine)/EtOH 97.5/2.5, 1 mL min⁻¹, 20 °C, 254 nm): *t*_R = 10.6 min (other enantiomer at 8.6 min); GC (MN-OPTIMA5 column, He 70 kPa, 200 °C → 290 °C at 3 °C min⁻¹): *t*_R = 13.95 min (minor isomer at 13.63 min); elemental analysis calcd for C₁₇H₂₂O₃Si: C 67.51, H 7.33; found: C 67.47, H 7.35.

Received: April 9, 1999 [Z13267IE]
German version: *Angew. Chem.* **1999**, *111*, 2897–2899

Keywords: asymmetric synthesis • cycloadditions • cyclobutanones • metalations • silicon

- [1] a) L. A. Paquette, T. M. Heidelbaugh, *Synthesis* **1998**, 495–508; b) E. J. Corey, P. Carpino, *Tetrahedron Lett.* **1990**, 31, 7555–7558; c) P. W. Collins, S. Djuric, *Chem. Rev.* **1993**, 93, 1533–1564; d) D. J. Kertesz, A. F. Kluge, *J. Org. Chem.* **1988**, 53, 4962–4968; e) A. F. Kluge, D. J. Kertesz, C. O. Yang, H. Y. Wu, *J. Org. Chem.* **1987**, 52, 2860–2868; f) E. W. Collington, H. F. Finch, C. J. Wallis, *Tetrahedron Lett.* **1983**, 24, 3121–3124; g) E. W. Collington, C. J. Wallis, I. Waterhouse, *Tetrahedron Lett.* **1983**, 24, 3125–3128; h) G. Audran, K. Mori, *Eur. J. Org. Chem.* **1998**, 57–62; i) I. A. Cotterill, S. M. Roberts, *J. Chem. Soc. Perkin Trans. I* **1992**, 2585–2586; j) A. E. Greene, M. J. Luche, J. P. Depr s, *J. Am. Chem. Soc.* **1983**, 105, 2435–2439.
- [2] a) D. Depr , PhD thesis, Universit  catholique de Louvain (Belgium), **1998**; b) L. Y. Chen, L. Ghosez, *Tetrahedron: Asymmetry* **1991**, 2, 1181–1184.
- [3] T. J. Cholerton, E. W. Collington, H. Finch, D. Williams, *Tetrahedron Lett.* **1988**, 29, 3369–3372. Diastereocontrol of an intramolecular [2+2] cycloaddition of a keteniminium salt by an allylic alkoxy group has been reported albeit in low yield. In our case, however, this approach failed, and gave a 1:1 mixture of diastereoisomers in low yields.
- [4] For nice examples of diastereoselective reactions on chiral allylsilanes, see a) C. E. Masse, L. A. Dakin, B. S. Knight, J. S. Panek, *J. Org. Chem.* **1997**, 62, 9335–9338; b) C. E. Masse, J. S. Panek, *Chem. Rev.* **1995**, 95, 1293–1316; c) K. Mikami, T. Maeda, N. Kishi, T. Nakai, *Tetrahedron Lett.* **1984**, 25, 5151–5154.
- [5] H. Saimoto, C. Houge, A. M. Hesbain-Frisque, A. Mockel, L. Ghosez, *Tetrahedron Lett.* **1983**, 24, 2251–2254.
- [6] J. M. Adam, K. N. Houk, unpublished results.
- [7] Gaussian 94 (Revision A.1), M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Peterson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian Inc., Pittsburgh, PA, **1995**.
- [8] L. Ghosez, I. Mark , A. M. Hesbain-Frisque, *Tetrahedron Lett.* **1986**, 27, 5211.
- [9] A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit, F. Schwarzenbach, *J. Am. Chem. Soc.* **1992**, 114, 2321–2336.
- [10] I. Mark , B. Ronsmans, A. M. Hesbain-Frisque, S. Dumas, L. Ghosez, B. Ernst, H. Greuter, *J. Am. Chem. Soc.* **1985**, 107, 2192.
- [11] J. M. Adam, L. Ghosez, B. Tinant, Z. Kristallogr. NCS **1999**, in press (CCDC no. 1267/187).
- [12] a) R. F. Newton, D. P. Reynolds, N. M. Crossland, D. R. Kelly, S. M. Roberts, *J. Chem. Soc. Chem. Commun.* **1979**, 683–684; b) for ¹³C NMR references, see R. Benn, H. Butensch n, R. Mynott, W. Wisniewski, *Magn. Reson. Chem.* **1987**, 25, 653–655.
- [13] a) For leading references on enzymatic resolutions, see G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini, *Tetrahedron: Asymmetry* **1996**, 7, 277–282; b) K. Tanaka, O. Kakinoki, F. Toda, *Tetrahedron: Asymmetry* **1992**, 3, 517–520; c) H. Greuter, J. Dingwall, P. Martin, D. Bellus, *Helv. Chim. Acta* **1981**, 64, 2812–2820.
- [14] a) K. Mills (Glaxo Group Ltd), EP-B 297853, **1989**; b) Glaxo Group Ltd, BE-B 897763, **1984**; P. Hallett, E. W. Collington, N. F. Hayes, C. J. Wallis, A. Wadsworth, GB-B 2097397A, **1982**; and references therein.
- [15] a) A. M. M. Mjalli, S. M. Roberts, *J. Chem. Soc. Perkin Trans. I* **1989**, 2105; b) R. F. Newton, S. M. Roberts, *Tetrahedron* **1980**, 36, 2163–2196; c) T. W. Hart, M. T. Comt , *Tetrahedron Lett.* **1985**, 26, 2713–2716; d) B. F. Reifling, *Tetrahedron Lett.* **1985**, 26, 2063–2064; e) C. O. Meese, *Liebigs Ann. Chem.* **1992**, 1217–1223.
- [16] G. C. Hirst, T. O. Johnson, Jr., L. E. Overman, *J. Am. Chem. Soc.* **1993**, 115, 2992–2993.
- [17] B. Adger, U. Berens, M. J. Griffiths, M. J. Kelly, R. McCague, J. A. Miller, C. F. Palmer, S. M. Roberts, R. Selke, U. Vitinius, G. Ward, *Chem Commun.* **1997**, 1713–1714.
- [18] B. Gobeaux, L. Ghosez, *Heterocycles* **1989**, 28, 29.

SMTP-1: The First Functionalized Metalloporphyrin Molecular Sieves with Large Channels**

Kuan-Jiuh Lin*

In memory of Ta-shue Chou

Zeolites have emerged as an exciting area of supramolecular chemistry. In particular, crystalline zeolites or zeotypes with uniform pore sizes of 10–20   have diverse applications as catalysts, molecular sieves, and biosensors.^[1–3] Recently, attention has turned toward organic and coordination zeolites to perform specific functions that are not available with inorganic zeolites. However, only a few examples of network structures with large cavities or channels have been demonstrated.^[4] Moreover, the problems of fragility, acidity, and thermal stability of the host lattice have not been overcome.^[5] Hence, the design and preparation of robust, air-stable, porous coordination zeolites provides a considerable challenge in materials chemistry.

We are exploring ways to construct new classes of coordination zeolites by hydrothermal synthesis,^[6] a powerful technique often applied to the synthesis of zeolites. Encouraged by our recent success in exploiting the symmetry and functionality of the dianionic squarate ligand C₄O₄^{2–} as a robust and rigid tether for the construction under hydrothermal conditions of coordination solids having open frameworks, we turned to the dianion tpyp (H₂tpyp = 5,10,15,20-tetrakis(4-pyridyl)porphyrin) as the molecular building block, as it has four equally spaced pyridyl groups linked to a porphyrin ring that gives it a rigid conformation. We surmised that the reaction of tpyp with a divalent first-row transition metal should yield a metalloporphyrinate material with nanometer-scale voids.^[4c, 7] Porphyrin-based architectures have diverse potential applications as biomimetic models and as functional materials for the transport of energy, charge, molecules, and ions.^[8]

We synthesized one cobalt(II) and two manganese(II) porphyrinates, which we collectively named SMTP-1 (supramolecular materials in Taiwan porphyrin, number 1), by employing hydro(solvent)thermal conditions. Crystals of all products were grown in a static autoclave at 200  C under autogenous pressure for 48 h. Most reactions yielded bunched aggregates of individual crystals, but single crystals large enough for X-ray diffraction studies were also obtained.^[9] Crystalline SMTP-1 is stable in air and is insoluble in water.

[*] Prof. K.-J. Lin^[+]
Institute of Chemistry, Academia Sinica
Nankang, 11529, Taipei (Taiwan)
Fax: (+886) 2-27831237
E-mail: kjlin@chem.sinica.edu.tw

[+] Current address:
Department of Chemistry, National Chung-Hsing University
Taichung (Taiwan)

[**] I am greatly indebted to Gene-Hsiang Lee and Prof. Yu Wang at the National Taiwan University for X-ray data collection and refinement, and to Dr. Chin-Ti Chen and Prof. Sunney I. Chan for constructive discussions. This work was supported by the Academia Sinica and the National Science Council of the Republic of China.

The products were identified as neutral porous networks with the general formula $[\{M(\text{tpyp})\}_6] \cdot G$ (**1**: $M = \text{Co}^{\text{II}}$, $G = 12\text{CH}_3\text{COOH} \cdot 12\text{H}_2\text{O}$; **2**: $M = \text{Mn}^{\text{II}}$, $G = 60\text{H}_2\text{O}$; **3**: $M = \text{Mn}^{\text{II}}$, $G = 12\text{C}_2\text{H}_5\text{OH} \cdot 24\text{H}_2\text{O}$) by single-crystal X-ray structure analysis, elemental analysis, thermogravimetric analysis, and FT-IR spectroscopy.

The structure of SMTP-1 consists of a layered framework with large cavities (Figure 1). In each layer, the secondary building blocks consist of the cyclic metalloporphyrin hexamer and spiropentamer.^[10] Each metal center has local

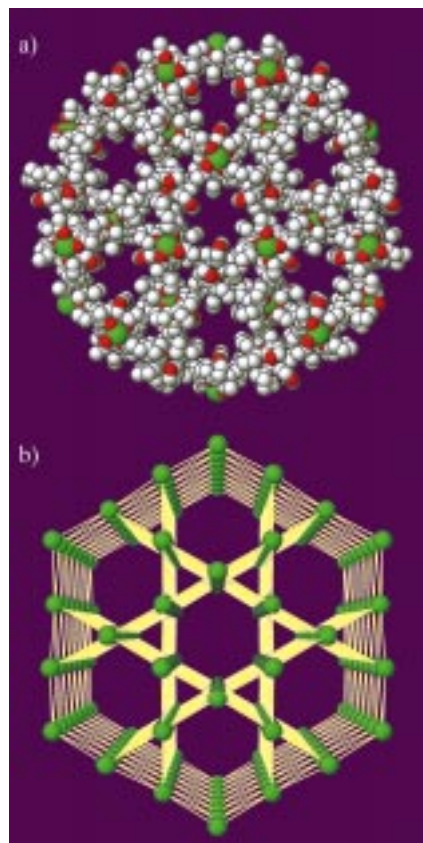


Figure 1. Perspective view of the open-framework structure of SMTP-1 along the crystallographic c axis. a) Space-filling representation. b) Skeletal representation ($M \cdots M$ connections). The hexagonal channels have the dimensions of $a/2 \times a/\sqrt{3}$ ($17 \times 20 \text{ \AA}$). Hydrogen atoms and solvent molecules are omitted for clarity.

symmetry of $\bar{1}$ and is coordinated octahedrally by four nitrogen atoms of the porphyrin (average bond lengths: $\text{Co}-\text{N}$ 1.994(5) $\text{\AA}$ for **1**; $\text{Mn}-\text{N}$ 1.992(4) and 2.097(3) $\text{\AA}$ for **2** and **3**, respectively) and two nitrogen atoms of the *trans* pyridyl groups of tpyp ($\text{Co}-\text{N}$ 2.292(5) $\text{\AA}$ for **1**; $\text{Mn}-\text{N}$ 2.294(5) and 2.411(3) $\text{\AA}$ for **2** and **3**, respectively). The tpyp building block is engaged in a *trans*- $\mu_{1,3}$ coordination mode. As is common in 5,10,15,20-tetraarylporphyrins, large dihedral angles between the planes of the pyridine rings and the porphyrin are observed (110° for pyridine rings attached to metal centers, and 68° for the others). The compound SMTP-1 crystallizes in the rhombohedral space group $R\bar{3}$ and therefore lies around a crystallographic $\bar{3}$ position. This represents the maximum D_{3d} point group symmetry that can be attained by a $[\{M(\text{tpyp})\}_6]$ species. Notable features of the SMTP-1 struc-

ture are the hexameric cage, which has an extra-large cavity with an interior diameter of 20 $\text{\AA}$, and the functional pyridine windows (Figure 2). Furthermore, owing to the natural tendency of π overlap in porphyrin molecules, adjacent layers are "glued" by noncovalent π - π interactions, so that the cavities eclipse one another. This results in an infinite hexagonal channel along the crystallographic c axis (Figure 1). As anticipated, the hexagonal channels have the dimensions of $a/2 \times a/\sqrt{3}$ ($17 \times 20 \text{ \AA}$). The effective pore size of $13 \times 16 \text{ \AA}$ ^[11] is comparable to that of the mineral phosphate cacoxenite.^[12] Although the pendant pyridyl groups protrude into the window, this metalloporphyrinate has an extremely

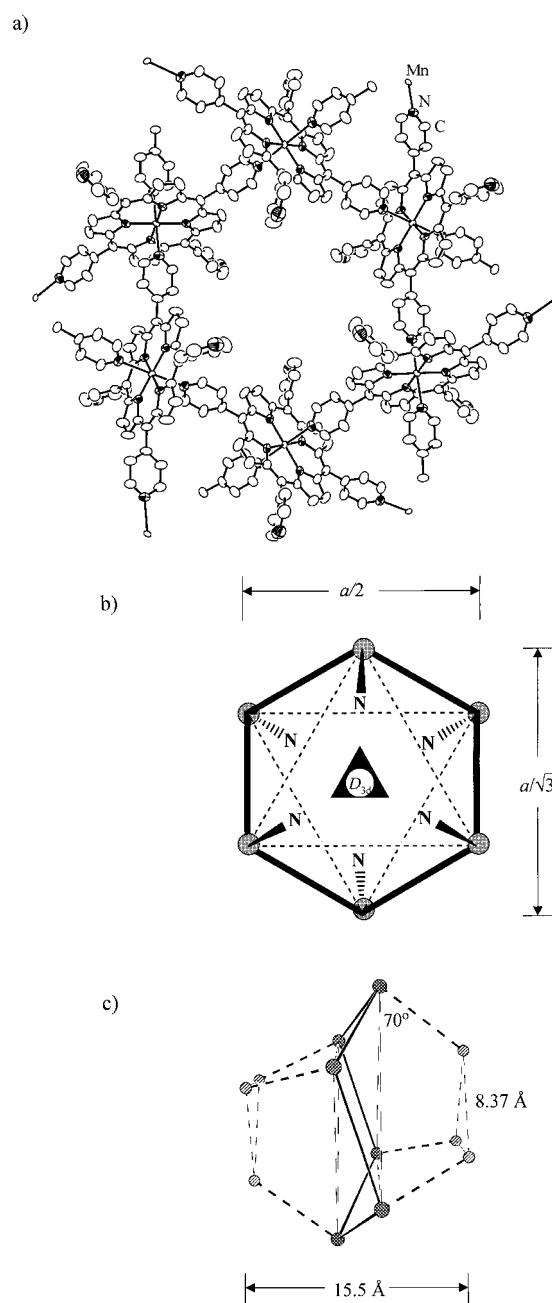


Figure 2. The hexameric cage has a polar cavity $17 \times 20 \text{ \AA}$ across and $15 \text{ \AA}$ deep. a) ORTEP plot along the threefold c axis (50% probability ellipsoids). b) Skeletal representation in D_{3d} point group symmetry. c) View perpendicular to the C_3 axis. Cross-hatched: $M = \text{Co}^{\text{II}}$ or Mn^{II} ; Shaded: N.

open structure due to the long N...N distance (8.37 Å) between the pyridyl groups and the high projection angle (70°) (Figure 2c).

The most intriguing feature of the SMTP-1 structure is the presence of the highly disordered solvent molecules trapped in the pores or channels. The pore solvent molecules could not be completely located in the structure analysis and are not discussed here. Further studies by other methods are required to characterize them. Thermogravimetric analysis reveals that the guest molecules are liberated below 200 °C; however, the crystal lattice is thermally stable up to 400 °C.^[13] Moreover, powder X-ray diffraction patterns showed that the porous framework was retained after the loss of solvent molecules on heating the material at 200 °C for 2 h, and even after immersion of the crystals in boiling crude oil for several hours.

Given the structural and thermal stability of the SMTP-1 framework, three features of our new functional molecular sieve could potentially be exploited. The unusual windows with both hydrophobic and hydrophilic properties provide new possibilities for shape-selective molecular sieves. They can restrict the size and shape of molecules that are sorbed or desorbed, and large molecules may be flattened to pass through the window. Moreover, the extra-cage could provide space for the formation of bulky intermediates in a catalytic reaction, and the nitrogen atoms of the pendant pyridine rings might serve as coordination sites for intercalation.^[14]

This study suggests that a large family of metalloporphyrinate structures might exist that have yet to be synthesized. Some phases possessing unusual pore openings should be accessible by hydrothermal synthesis. Investigations of the organic-functionalized SMTP-1 as a shape-selective catalyst are in progress.^[15]

Experimental Section

1: A mixture of CoCl₂·2H₂O (0.2384 g), H₂tpyp (0.1243 g), aqueous CsOH (0.3 mL, 50 wt %), CH₃COOH (4 mL), and H₂O (4 mL) was sealed in a 23-mL Teflon-lined stainless autoclave, heated to 200 °C for 48 h, and cooled to 70 °C at 9 K h⁻¹. Needle-shaped purple crystals were filtered off and washed with methanol. Monophase crystalline material was confirmed by X-ray powder diffraction. The yield of crystalline material was 85 % (0.1416 g) based on tpyp, and the synthesis was highly reproducible. Elemental analysis (%): calcd: C 63.54, N 13.48, H 3.88; found: C 63.98, N 14.93, H 4.08.

2: A mixture of MnCl₂·2H₂O (0.1719 g), H₂tpyp (0.1171 g), aqueous CsOH (0.3 mL, 50 wt %), and H₂O (10 mL) was sealed in a 23-mL Teflon-lined stainless autoclave, heated to 200 °C for 48 h, and cooled to 70 °C at 9 °C h⁻¹. Needle-shaped purple crystals (yield 5 %) were accompanied by unidentified brown materials. Elemental analysis: calcd: C 56.41, N 13.16, H 7.10; found: C 56.97, N 13.20, H 3.26.

3: A mixture of MnCl₂·2H₂O (0.0839 g), H₂tpyp (0.1219 g), aqueous CsOH (0.3 mL, 50 wt %), C₂H₅OH (4 mL), and H₂O (4 mL) was sealed in a 23-mL Teflon-lined stainless autoclave, heated to 200 °C for 48 h, and cooled to 70 °C at 9 K h⁻¹. Needle-shaped purple crystals were filtered off and washed with methanol. Monophase crystalline material was confirmed by X-ray powder diffraction. The yield of crystalline material was 86 % (0.1385 g) based on tpyp, and the synthesis was highly reproducible. Elemental analysis (%): calcd: C 63.54, N 13.48, H 3.88; found: C 63.98, N 14.93, H 4.08.

Received: March 31, 1999 [Z 13233 IE]

German version: *Angew. Chem.* **1999**, *111*, 2894–2897

Keywords: microporosity • porphyrinoids • solid-state structures • supramolecular chemistry • zeolite analogues

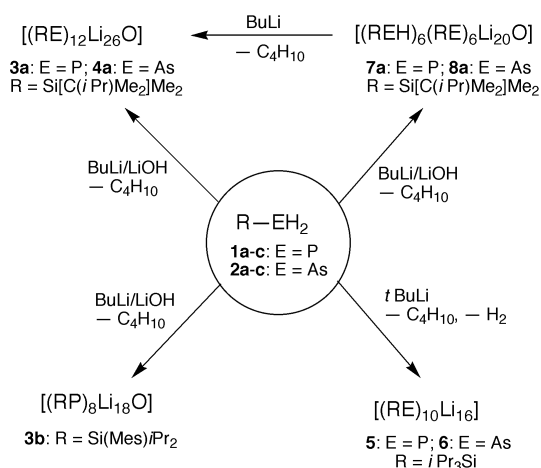
- [1] C. C. Freyhardt, M. Tsapatsis, R. F. Lobo, K. J. Balkus, Jr., M. E. Davis, *Nature* **1996**, *381*, 295–298.
- [2] X. Bu, P. Feng, G. D. Stucky, *Science* **1997**, *278*, 2080–2085.
- [3] M. Estermann, L. B. McCusker, C. Baerlocher, A. Merrouche, K. Kessler, *Nature* **1991**, *352*, 320–323.
- [4] a) O. M. Yaghi, G. Li, H. Li, *Nature* **1995**, *378*, 703–706; b) G. B. Gardner, D. Venkataraman, J. S. Moore, S. Lee, *Nature* **1995**, *374*, 792–795; c) B. F. Abrahams, B. F. Hoskins, D. M. Michail, R. Robson, *Nature* **1994**, *369*, 727–729.
- [5] a) C. Janiak, *Angew. Chem.* **1997**, *109*, 1499–1502; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1431–1433; b) M. Kondo, T. Yoshitomi, K. Seki, H. Matsuzaka, S. Kitagawa, *Angew. Chem.* **1997**, *109*, 1844–1846; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1725–1727; c) Y. Aoyama, *Top. Curr. Chem.* **1998**, *198*, 131–161.
- [6] K.-J. Lin, K.-H. Lii, *Angew. Chem.* **1997**, *109*, 2166–2167; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2076–2077.
- [7] a) M. P. Byr, C. J. Curtis, Y. Hsiou, S. I. Khan, P. A. Sawin, S. K. Tendick, A. Terzis, C. E. Strouse, *J. Am. Chem. Soc.* **1993**, *115*, 9480–9497; b) R. K. Kumar, I. Goldberg, *Angew. Chem.* **1998**, *110*, 3176–3180; *Angew. Chem. Int. Ed.* **1998**, *37*, 3027–3030; c) C. M. Drain, F. Nifatis, A. Vasenko, J. D. Batteas, *Angew. Chem.* **1998**, *110*, 2478–2481; *Angew. Chem. Int. Ed.* **1998**, *37*, 2344–2347.
- [8] V. S.-Y. Lin, S. G. DiMagno, M. J. Therien, *Science* **1994**, *264*, 1105–1111.
- [9] Siemens SMART system with CCD detector; $\lambda(\text{MoK}\alpha) = 0.7107 \text{ Å}$; the structures were solved with SHELXTL PLUS and refined with SHELXL-93 on F^2 by full-matrix least-squares methods. The highly disordered solvent molecules could not be completely located in the structure analysis. Crystal data for **1**: crystal dimensions $0.55 \times 0.05 \times 0.03 \text{ mm}$, trigonal, space group $R\bar{3}$, $a = b = 32.7432(3) \text{ Å}$, $c = 9.3124(2) \text{ Å}$, $V = 8645.9(2) \text{ Å}^3$, $Z = 9$, $2\theta_{\text{max}} = 50^\circ$, $R_1 = 0.094$, $wR_2(F^2) = 0.26$, GOF = 1.155, residual electron density $-0.48/1.539 \text{ e Å}^{-3}$; **2**: crystal dimensions $0.50 \times 0.12 \times 0.08 \text{ mm}$, trigonal, space group $R\bar{3}$, $a = b = 32.7624(2) \text{ Å}$, $c = 9.3410(2) \text{ Å}$, $V = 8683.1(1) \text{ Å}^3$, $Z = 9$, $2\theta_{\text{max}} = 50^\circ$, $R_1 = 0.074$, $wR_2(F^2) = 0.20$, GOF = 1.073, residual electron density between $-0.56/1.15 \text{ e Å}^{-3}$; **3**: crystal dimensions $0.45 \times 0.07 \times 0.06 \text{ mm}$, trigonal, space group $R\bar{3}$, $a = b = 33.3099(2) \text{ Å}$, $c = 9.3306(2) \text{ Å}$, $V = 8965.8(2) \text{ Å}^3$, $Z = 9$, $2\theta_{\text{max}} = 50^\circ$, $R_1 = 0.063$, $wR_2(F^2) = 0.175$, GOF = 1.094, residual electron density $-0.51/0.41 \text{ e Å}^{-3}$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. CCDC-116979 (**1**), CCDC-116980 (**2**), and CCDC-116981 (**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).
- [10] W. M. Meier, D. H. Olson, *Atlas of Zeolite Structure Types*, Butterworth-Heinemann, Boston, **1992**.
- [11] This is a very simplified view. The channel and cavity dimensions were derived from the distances between the nuclei of the available crystal structures. The effective cross-sectional area is about $13 \times 16 \text{ Å}^2$ if the van der Waals radius of a metalloporphyrin (ca. 2.0 Å) is taken into account. Indeed, the pore size of **1** is around 5.8 Å according to an N₂ adsorption/desorption isotherm study. Further details of adsorption activity of SMTP-1 will be reported elsewhere.
- [12] P. B. Moore, J. Shen, *Nature* **1983**, *306*, 356–358.
- [13] On heating by IR radiation (Mark 2 HP moisture analyzer), the guest molecules are completely removed below 200 °C: weight losses of 17.82 and 20.37 % for **1** (calcd. 18.77 %) and **3** (calcd. 19.65 %), respectively. After loss of the solvate molecules, the open-framework structures of **1** and **3** are thermally stable up to 420 and 450 °C, respectively.
- [14] H. P. Wu, C. Janiak, L. Uehlin, P. Klüfers, P. Mayer, *Chem. Commun.* **1998**, 2627–2628.
- [15] K.-J. Lin, C.-T. Chen, unpublished results.

Lithiated Clusters from Primary Silylphosphanes and Silylarsanes: Spherical Bodies with and without Li₂O Filling**

Matthias Driess,* Ulrich Hoffmanns, Stefan Martin, Klaus Merz, and Hans Pritzkow

Dedicated to Professor Dirk Walther on the occasion of his 60th birthday

Dilithiated primary phosphanes and arsanes are among the most important nucleophilic transfer reagents in the organo-element chemistry of phosphorus and arsenic; however, their structural chemistry (structure–reactivity relationship) has not been studied in detail.^[1] We recently showed that *soluble* molecular derivatives such as **3b** and **4a**, in which Li₂O or another coligand are encapsulated or associated, are surprisingly readily accessible by lithiation of triorgano-silyl-substituted primary phosphanes **1** and arsanes **2** (Scheme 1).^[2, 3] The



Scheme 1. Synthesis of the clusters **3–6** from **1** and **2**. Mes = 2,4,6-trimethylphenyl.

inclusion of Li₂O in ionic aggregates has also been observed for other systems,^[4] which raised the question of whether Li₂O displayed a structure-directing effect. Furthermore, clusters of this kind are potential model compounds for the dissolution and nucleation of ionic crystals.^[5]

In order to clarify how the encapsulated aggregates **3** and **4** are formed and whether the Li₂O molecule acts as a template (“aggregation nucleus”), further studies were necessary. We report here on the lithiation of the primary silylphos-

phane RPH₂ **1c** as well of the homologous arsane RAsH₂ **2c** (R = *i*Pr₃Si) with two molar equivalents of *t*BuLi in toluene, which were carried out under strict exclusion of Li₂O; these reactions led to the novel decameric clusters **5** and **6**, which are remarkable in two respects: they are not only the first Li₂O-free, closed aggregates of this type, but also unprecedented mixed-valent lithium pnictides. In addition we describe the partially lithiated dodecameric clusters **7a** and **8a**, which are formed by the partial lithiation of **1a** and **2a** with BuLi in the presence of LiOH. They display a dumbbell-shaped Li₂O core and are isolable intermediates in the formation of the fully lithiated multishell clusters **3a** and **4a**, which have a [Li₆O]⁴⁺ core.

The reaction of **1a** and **2a** with freshly sublimed *t*BuLi in the molar ratio 1:2 in toluene as solvent at –80 °C led to the decameric lithium pnictides **5** and **6**, respectively, as yellow octahedrally shaped crystals in 75 and 68 % yield, respectively. Compounds **5** and **6** are also formed when LiOH-free (freshly prepared) BuLi in Et₂O is used instead of *t*BuLi as the lithiating agent. Their single-crystal X-ray structure analyses^[6] revealed the surprising result that although decameric Li₂O-free clusters are present in both cases, these do not display a Li/E ratio of 2:1 expected for a dilithium silylphosphanediide or -arsanediide, respectively. Instead a mixed-valent, lithium-poor phosphanediyl-dilithium phosphanediide and the corresponding Li–As cluster with a Li/E ratio 1.6:1 are obtained (Figure 1). This implies, however, that the clusters are formed by a redox reaction, which is supported by evolution of H₂ during the lithiation reaction in amounts ranging between 85 and 89 % of those expected. The induced H₂ elimination appears plausible for thermodynamic reasons, since the formation of the E–H bonds in phosphanes and arsanes is endothermic,^[7] and moreover a closed cluster framework is more favorable. Remarkably the clusters are formed with H₂ evolution also if *t*BuLi is present in toluene at –80 °C and less than one molar equivalent of **1c** and **2c**, respectively, are added. That no “residual” E–H bonds are present in **5** and **6**, is also confirmed by ¹H NMR and IR spectra.

The compounds crystallize isotypically in the tetragonal space group *P4/nnc*. The topology of the oval E₁₀Li₁₆ cluster framework (E = P, As) can be described in a simplified way as a doubly capped archimedean antiprism comprising 10 E centers, and a Li center is located on each of the 16 deltahedral faces of this body (Figure 2). Thereby, two E atoms are five-coordinate, whereas the rest are six-coordinate. However, the corresponding Li–E, Si–E, and Li–Li distances show no special features in comparison to those of related lithium pnictides such as **3b** and **4a**,^[2] and the Li–E distances of the differently coordinated E centers are almost the same. The electrostatically favorable arrangement of the cation (Li) and anion building blocks (*i*Pr₃SiE) implies, however, not only two chemically different E and Si centers in the ratio of 4:1 in each case, but also two different Li centers in the ratio 1:1. This is confirmed by cross-polarization magic-angle-spinning (CP/MAS) solid-state NMR spectra of **5**; the ²⁹Si{³¹P} NMR spectrum shows two singlets at δ = 29.0 and 27.9 in the ratio 1:4 and the ⁷Li{³¹P} NMR spectrum two singlets at δ = 1.65 and 1.42 (1:1).^[8] The composition of the lithium-poor aggregates is also substantiated by correct elemental analyses (C,

[*] Prof. Dr. M. Driess, U. Hoffmanns, S. Martin, Dr. K. Merz
Lehrstuhl für Anorganische Chemie I
Fakultät für Chemie der Universität
Universitätsstrasse 150, D-44801 Bochum (Germany)
Fax: (+49) 234 709 4378
E-mail: driess@ibm.anch.ruhr-uni-bochum.de
Dr. H. Pritzkow
Institut für Anorganische Chemie der Universität
Im Neuenheimer Feld 276, D-69120 Heidelberg (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm “Polyedermoleküle”), by the Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen, and by the Fonds der Chemischen Industrie.

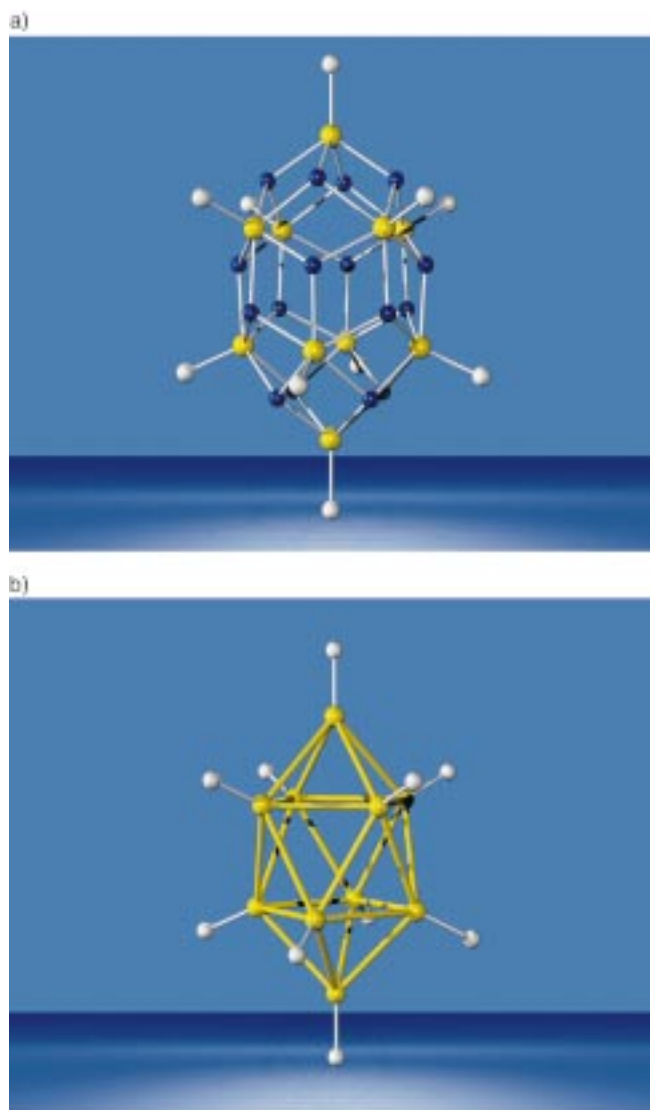


Figure 1. a) Structures of the frameworks of the isotypic compounds **5** and **6** in the crystal (without *i*Pr groups). Si = gray, Li = blue, E(P,As) = yellow. Selected distances [Å] in **5**: P–Si 2.208(3), P–Li 2.56(1), Li–Li 2.77(2)–3.05(2). b) Topology of the anionic E₁₀ framework in **5** and **6**.

H, Li, P, As), and cryoscopic investigations in benzene gave a degree of aggregation of $n \approx 8$, that is, the molecules show almost no tendency for dissociation, which appears understandable in view of the electron deficiency of the cluster. Correspondingly, the multinuclear NMR spectra of **5** and **6** in solution and in the solid state are almost identical. Thus, the ³¹P NMR spectrum of **5** in solution displays two broad singlets at $\delta = -366$ and -371 in the ratio 1:4, and in the ²⁹Si{³¹P} NMR spectrum, as in the CP/MAS solid-state NMR spectrum, two singlets occur at almost identical δ values. How can the electronic structure of these evidently mixed-valent pnictides be described simply? Formally the clusters consist of two units of the low-valent “anediyls” [RE:] and eight units of the “anediide” RELi₂ (E = P, As). Since the large E–E distances (> 4 Å) rule out localized E–E bonds, a delocalization of the framework valence electrons in the cluster is evidently achieved through multicenter bonds, which are mediated through the Li centers, and in fact without the

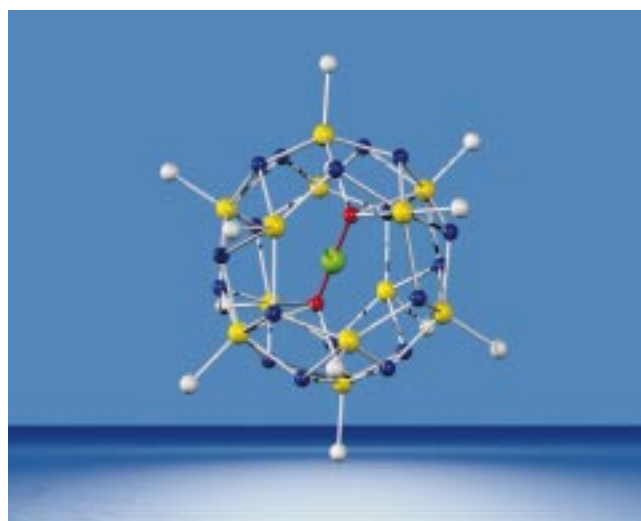


Figure 2. Structure of the cluster in the isotypic compounds **7a** and **8a** in the crystal. Selected average distances [Å] in **8a**: As–Si 2.32(2), Li–As 2.47–2.78(4), Li–O 2.14(10).

occurrence of Li–Li bonds; this is in agreement with the inconspicuous ⁷Li NMR shifts of **5** and **6**, which correspond to those of low-coordinate Li ions such as in **3b** and **4a**.^[2] As expected the addition of a small amount of LiOH or Li₂O to solutions of **5** and **6** did not lead to a cluster rearrangement to an aggregate such as **3b** or **4a**. Fascinatingly, the lithiation of **1c** and **2c** with BuLi in the presence of LiOH proceeds differently. In this reaction dodecameric Li₂ER aggregates with a [Li₆O]⁴⁺ core analogous to **4a** are formed, whose framework topology has been characterized by X-ray crystallography.^[9] The results confirm the structure-determining influence of LiOH and Li₂O on the formation of the cluster. Partial lithiation of **1a** and **2a** with BuLi in the ratio 2:3 in the presence of LiOH in toluene has led to the isolation of the intermediates **7a** and **8a** in the construction of the closed clusters **3a** and **4a**, respectively. These intermediates form colorless crystals, which are sparingly soluble in toluene, but dissolve well in THF. Their constitution was determined on the basis of a crystal structure analysis.^[6] The “open” clusters have a three-dimensional, wheel-like E₁₂Li₁₈ ladder structure (E = P, As), in which the 12 E centers form an icosahedral framework, as in the completely lithiated aggregate **3a** (see below) and in **4a**;^[2] the Li₂O guest sits inside and acts as the “stabilizing axis of the wheel” (Figure 2). The E–H hydrogen atoms, which were detected in the ¹H NMR and IR spectra, are very probably localized on the E atoms of the hexagonal E₃Li₃ “openings”. The “inner” Li atoms of Li₂O are each coordinated to four E centers, in contrast the “outer” Li atoms are only three-coordinate. This results in differently coordinated E atoms with the coordination numbers 5, 6, and 7.

Compound **7a** presumably dissociates only slightly in donor solvents such as [D₈]THF, since the ³¹P NMR spectrum shows two broad signals at $\delta = -365$ and -362 for the ³¹P cores of the different PLi₂ groups, whereas the P atoms of the PHLi groups display a doublet at $\delta = -301$ (¹J(P,H) = 152 Hz). Three broad signals at $\delta = 1.10$, 1.40 , and 5.56 in the ratio of about 1:2:4 were observed in the ⁷Li NMR spectrum; the low-field signal at $\delta = 5.56$ is unprecedented for lithium phosphan-

ides. The addition of six molar equivalents of BuLi to such solutions leads exclusively to the cluster **3a** which is analogous to **4a**. Compound **3a** exists almost in tact in solution and its ^7Li NMR spectrum shows three signals at $\delta = -1.70$, -0.80 , and 2.10 (ratio 1:2:10); the latter is almost identical with that of **4a**.^[2] The analogous transformation was also observed in the lithiation of **8a**, which leads smoothly to **4a**. As expected, compound **3a**^[6] is isotopic to **4a** and its geometric parameters do not show any special features in comparison to those of **3b**^[2] (Figure 3).

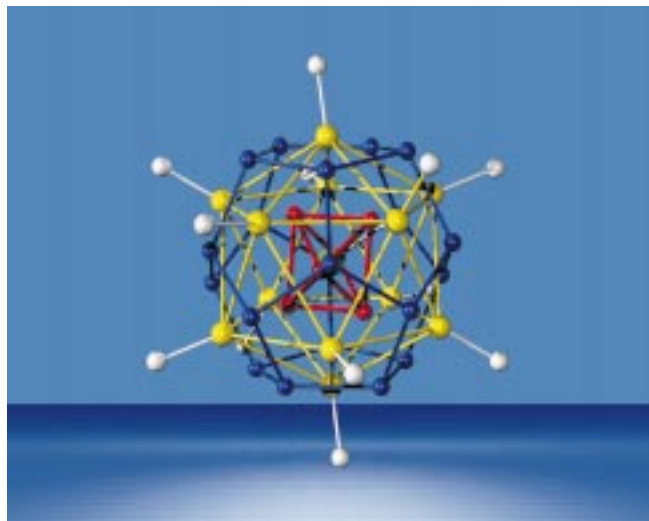


Figure 3. Shell-like structure of **3a** in the crystal. The organic groups are omitted for clarity. Si = gray, P_{12} shell = yellow, OLi_6 shell = red, green. Selected average distances [Å]: P–Si 2.205(1), Li–P 2.466(8)–2.644(7), Li–Li 2.50(1)–3.48(2), Li–O 1.863(8).

It should be possible to observe the stepwise generation of molecular dilithium pnictide clusters also in the formation of other mixed clusters of this type. Investigations are in progress on the inclusion of Li_2S and other guests instead of Li_2O .

Experimental Section

5: Compound **1c** (1.22 g, 6.42 mmol) in toluene (20 mL) was treated at -80°C with $t\text{BuLi}$ (6.6 mL of a 1.6 M solution in pentane, Aldrich), and a yellow suspension was formed with H_2 evolution. After the suspension was allowed to warm to room temperature (5 h), it was heated to about 50°C . This led to the formation of a clear yellow solution, from which yellow octahedrally shaped crystals were obtained on slow cooling. Yield: 1.00 g (0.48 mmol, 75 %); ^1H NMR (200 MHz, $[\text{D}_8]\text{toluene}$): $\delta = 1.0$ – 1.2 (m, 210 H, $i\text{Pr}$); ^{31}P NMR (81 MHz, $[\text{D}_8]\text{toluene}$): $\delta = -366$ (br., 2P), -371 (br., 8P); ^{29}Si NMR (39 MHz, $[\text{D}_8]\text{toluene}$): $\delta = 27.6$ (m, 2Si), 28.8 (m, 8Si); ^7Li NMR (97 MHz, $[\text{D}_8]\text{toluene}$): $\delta = 1.45$ (br., 8Li), 1.66 (br., 8Li); correct C,H,Li,P analysis.

6: In a reaction analogous to that for the synthesis of **5**, **6** was obtained in the form of yellow crystals from **2c** (1.22 g, 5.2 mmol) by metalation with $t\text{BuLi}$ in toluene. Yield: 0.9 g (0.36 mmol, 68 %); ^1H NMR (200 MHz, $[\text{D}_8]\text{toluene}$): $\delta = 1.0$ (s, 36H), 1.1–1.3 (m, 174H); ^{29}Si NMR (39 MHz, $[\text{D}_8]\text{toluene}$): $\delta = 16.7$ (s, 2Si), 17.5 (s, 8Si); ^7Li NMR (97 MHz, $[\text{D}_8]\text{toluene}$): $\delta = 1.40$ (s, 8Li), 1.68 (s, 8Li); correct C,H,Li,As analysis.

7a: BuLi (3.6 mL, 1.6 M solution in hexane, Aldrich) was added dropwise to a solution of **1a** (0.5 g, 2.83 mmol) and LiOH (ca. 1 mg) in toluene (60 mL) at -80°C . The reaction mixture was allowed to warm to room temperature within 5 h and then the solvent was removed in vacuo. The yellow, solid

residue was dissolved at 40°C in a little toluene, separated from a small amount of insoluble material by filtration and subsequently fractionally crystallized in the temperature range from 40 – 20°C . Yield: 0.32 g (0.14 mmol, 60 %) colorless crystals; ^1H NMR (250 MHz, $[\text{D}_8]\text{THF}$): $\delta = -1.78$ (d, 6H, PH, $^1J(\text{H,P}) = 152$ Hz), 0.26–0.33 (m, 72H, MeSi), 0.56–0.61 (m, 72H, MeC), 1.08–1.16 (m, 72H, Me_2CH), 2.22–2.51 (m, 12H, Me_2CH); ^{31}P NMR (101 MHz, $[\text{D}_8]\text{THF}$): $\delta = -301$ (br. d, 6P, $^1J(\text{P,H}) = 152$ Hz), -362 (br., 3P), -365 (br., 3P); ^7Li NMR (97 MHz, $[\text{D}_8]\text{THF}$): $\delta = 1.10$ (br.), 1.40 (br.), 5.56 (br.); IR (KBr): $\tilde{\nu} = 1930\text{ cm}^{-1}$ (P–H); correct C,H,Li analysis.

8a: In a reaction analogous to that for the synthesis of **7a**, **8a** was obtained in the form of colorless crystals from **2a** (0.45 g, 2 mmol) by lithiation with BuLi/LiOH in toluene. Yield: 0.29 g (0.1 mmol, 47 %); ^1H NMR (250 MHz, $[\text{D}_8]\text{THF}$): $\delta = -1.63$ (s, 6H, AsH), 0.24–0.33 (m, 72H, MeSi), 0.56–0.60 (m, 72H, MeC), 1.07–1.14 (m, 72H, Me_2CH), 2.20–2.50 (m, 12H, Me_2CH); ^7Li NMR (97 MHz, $[\text{D}_8]\text{THF}$): $\delta = 1.05$ (s), 1.61 (s), 5.21 (s); IR (KBr): $\tilde{\nu} = 1897\text{ cm}^{-1}$ (As–H); correct C,H,Li analysis.

3a, 4a: Compound **7a** (0.16 g, 0.07 mmol) or **8a** (0.145 g, 0.05 mmol), respectively, were dissolved in THF (ca. 40 mL) and treated at -40°C with six equivalents of BuLi in hexane. The mixture was allowed to warm to room temperature, and all volatile components were removed in vacuo (10^{-2} Torr). The pale yellow residue was dissolved in toluene (ca. 3 mL) at 40°C , and crystallized on cooling to 20°C . Yield: 0.14 g (0.061 mmol, 86 %) and 0.12 g (0.043 mmol, 82 %), respectively. **3a:** ^1H NMR (250 MHz, C_6D_6): $\delta = 1.18$ – 1.37 (br. m, 112H, $i\text{Pr}$), 2.06 (s, 12H, $p\text{-Me}$), 2.15 (s, 12H, $p\text{-Me}$), 2.79 (br., 48H, $o\text{-Me}$), 6.74 (s, 16H, arom. H); correct C,H,Li analysis. **4a:** see ref. [2].

Received: May 3, 1999 [Z13366IE]

German version: *Angew. Chem.* **1999**, *111*, 2906–2909

Keywords: arsenic • cluster compounds • lithium • phosphorus • silicon

- [1] K. Issleib, A. Tzschach, *Chem. Ber.* **1959**, *92*, 1118; G. W. Parshall, R. V. Lindsey, Jr., *J. Am. Chem. Soc.* **1959**, *81*, 6273; G. Fritz, H. Schäfer, W. Hölderich, *Z. Anorg. Allg. Chem.* **1974**, *407*, 266; R. Appel, K. Geisler, *J. Organomet. Chem.* **1976**, *112*, 61; G. Becker, O. Mundt, M. Rössler, E. Schneider, *Z. Anorg. Allg. Chem.* **1978**, *433*, 42.
- [2] M. Driess, H. Pritzkow, S. Martin, S. Rell, D. Fenske, G. Baum, *Angew. Chem.* **1996**, *108*, 1064; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 986.
- [3] M. Driess, S. Rell, H. Pritzkow, R. Janoschek, *Chem. Commun.* **1996**, 305.
- [4] H.-J. Gais, J. Vollhardt, H. Günther, D. Moskau, H. J. Lindner, S. Braun, *J. Am. Chem. Soc.* **1988**, *110*, 978; T. Chivers, A. Downard, G. P. A. Yap, *J. Chem. Soc. Dalton Trans.* **1998**, 2603; A. R. Kennedy, R. E. Mulvey, R. B. Rowlings, *Angew. Chem.* **1998**, *110*, 3321, *Angew. Chem. Int. Ed.* **1998**, *37*, 3180.
- [5] H. Ohtaki, *Adv. Inorg. Chem.* **1992**, *39*, 401.
- [6] Crystal structure analyses: **5:** tetragonal, space group $P4/nnc$, $a = 16.397(7)$, $c = 25.24(1)$ Å, $Z = 2$, $V = 6785(6)$ Å³, 2981 independent reflections ($I > 2\sigma(I)$), one $i\text{Pr}$ group is disordered, all non-hydrogen atoms were refined anisotropically and the hydrogen atoms included in calculated positions. $R1 = 0.0812$ (observed reflections), $wR2 = 0.2382$ (all data). Compound **6** is isotopic with **5**, $a = 16.496(9)$, $c = 25.629(13)$ Å, $Z = 2$, $V = 6971(6)$ Å³, 1645 independent reflections ($I > 2\sigma(I)$). $R1 = 0.0956$ (observed reflections), $wR2 = 0.2671$ (all data). Compound **3a** is isotopic with **4a**:^[5] monoclinic, space group $P2_1/n$, $a = 19.337(3)$, $b = 19.116(3)$, $c = 19.357(3)$ Å, $\beta = 92.00(1)^\circ$, $Z = 4$, $V = 7151(2)$ Å³, 12784 independent reflections ($I > 2\sigma(I)$), all non-hydrogen atoms were refined anisotropically and the hydrogen atoms were included in calculated positions. $R1 = 0.0545$ (observed reflections), $wR2 = 0.1370$ (all data). **8a:** triclinic, space group $P\bar{1}$, $a = 17.148(3)$, $b = 17.317(4)$, $c = 17.565(4)$ Å, $\alpha = 65.24(3)^\circ$, $\beta = 67.00(3)^\circ$, $\gamma = 65.13(3)^\circ$, $Z = 1$, $V = 4149(1)$ Å³, 7878 independent reflections ($I > 2\sigma(I)$). $R1 = 0.1252$ (observed reflections), $wR2 = 0.3544$ (all data). The silyl groups are disordered, As and Si atoms were refined anisotropically. The hydrogen atoms were included in calculated positions. The cell contains several other atoms (5–6 in the asymmetric unit), which probably belong to

disordered solvent molecules (Et_2O), but which cannot be unambiguously assigned. Compound **7a** is isotypic with **8a**, but the quality of the crystals was very low. The intensities were measured with a Bruker-axSMART diffractometer (**5**, **3a**, **7a**) and with a Siemens-P4 diffractometer (**6**, **8a**) ($\text{MoK}\alpha$ radiation, $\lambda = 0.71707 \text{ \AA}$, ω scan, $T = 203 \text{ K}$). The structures were solved by direct methods (SHELXS97), and refined against F^2 with all measured reflections (SHELXL97). 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-119661 (**3a**), CCDC-119662 (**5**), and CCDC-119663 (**8a**). 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] Hollemann, Wiberg, *Lehrbuch der Anorganischen Chemie*, 100th ed, de Gruyter, Berlin, **1985**, p. 277, Table 35.

[8] M. Driess, T. Schaller, A. Sebal, *Solid State Nucl. Magn. Reson.* **1997**, *9*, 219.

[9] S. Martin, Diploma thesis, Universität Heidelberg, **1995**.

$[\text{In}_3(\text{In}_2)_3(\text{PhP})_4(\text{Ph}_2\text{P}_2)_3\text{Cl}_7(\text{PEt}_3)_3]$ – A New Molecular III/V Compound Featuring an Unusual 19-Atom Cage

Carsten von Hänisch, Dieter Fenske,*
Marco Kattannek, and Reinhart Ahlrichs

In the last few years, enormous interest has been generated in the synthesis of molecular III/V cages owing to the diverse optical and electronic properties of binary III/V materials. For the In/P system, several compounds containing In_2P_2 four-membered rings,^[1] In_3P_3 six-membered rings,^[2] or In_4P_4 heterocubanes^[3] as central structural units have been synthesized and characterized by X-ray structure analysis. Furthermore, the generation of nanometer-sized particles of the binary InP phase was investigated intensively, for example, by reaction of InCl_3 or $\text{InCl}(\text{C}_2\text{O}_4)$ and $\text{P}(\text{SiMe}_3)_3$ at high temperatures^[4] or by thermolysis of molecular InP compounds.^[5] The resulting products were characterized by X-ray powder diffraction and by transmission electron microscopy (TEM) experiments. It was possible to synthesize InP nanoparticles in a size range of 2 to 10 nm.^[6]

We report here the synthesis and structure determination^[7] of the InP cluster compound **1** (Figure 1), which consists of a 19-atom cage with a diameter of about 0.7 nm.^[8] Compound **1**

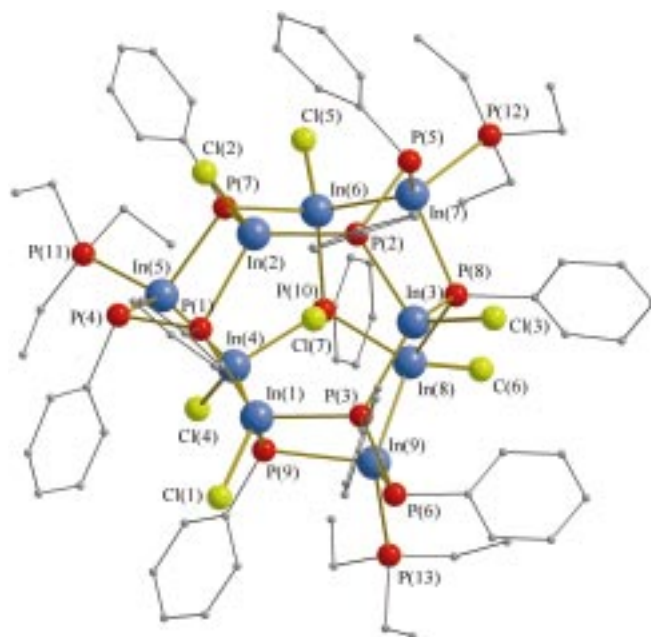
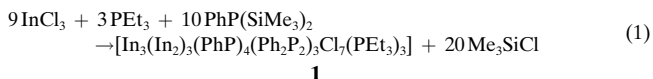


Figure 1. Molecular structure of **1** in the crystal. Selected bond lengths [pm] and angles [°]: In–Cl 241.2–245.0, In–P 253.3–261.6, In–In 273.5–275.1, P–P 220.1–223.1; P–P–In 99.2–116.3 (P(1), P(2), and P(3)), P–P–In 96.0–96.3 (P(4), P(5), and P(6)), P–In–P 101.1–126.1, In–P–In 97.3–113.1, In–In–P 102.1–126.3.

was obtained from the reaction of InCl_3 with PEt_3 and $\text{PhP}(\text{SiMe}_3)_2$ [Eq. (1)]. Besides the loss of Me_3SiCl and the formation of In–P bonds, redox processes occur during the reaction which lead to the formation of additional P–P and In–In bonds.



Compound **1** crystallizes in the space group $P\bar{1}$ as a racemate with both enantiomers appearing in the unit cell. The 19-atom polyhedron is built up by nine In and ten P atoms. If the ligands are considered as four PPh^{2-} groups (P(7) to P(10)), three $\text{P}_2\text{Ph}_2^{2-}$ groups (P(1)–P(4), P(2)–P(5), P(3)–P(6)), and seven Cl^- ligands, a total charge of 21+ can be calculated for the nine In atoms of the cluster. In(1), In(2), and In(3) show no In–In bonds and can be assigned the formal oxidation state 3+, whereas atoms In(4) to In(9) have the formal charge 2+ and correspondingly form In_2 pairs (In(4)–In(5), In(6)–In(7), In(8)–In(9)). Assuming that lone pairs are present at P atoms P(4), P(5), and P(6), the polyhedron possesses 54 valence electrons for 27 bonds and features exclusively two-electron, two-center bonds. All interatomic distances lie in the usual range for single bonds. The In–P distances range between 253.3 and 261.6 pm, the In–In bonds are 274.1 pm on average. These values correspond well to analogous bonds occurring in other In/P compounds; for example, in $[(t\text{Bu}_2\text{P})_2\text{InCl}]_2$ or $[\text{MesInPMes}]_4$ (Mes = 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2$) the In–P bonds range between 258.2 and 266.0 pm^[1–3] and in $[\text{Trip}_2\text{In}_2]$ (Trip = 2,4,6- $i\text{Pr}_3\text{C}_6\text{H}_2$)^[9] or $[\text{In}_2\text{I}_4(n\text{Pr}_3\text{P})_2]$ ^[10] the In–In single bonds are 277.5 and 274.5 pm, respectively. In contrast, longer In–In distances of

[*] Prof. Dr. D. Fenske,^[+] Dr. C. von Hänisch
Institut für Nanotechnologie
Forschungszentrum Karlsruhe GmbH
D-76021 Karlsruhe (Germany)

[+] Institut für Anorganische Chemie der Universität
Engesserstrasse Geb. 30.45, D-76128 Karlsruhe (Germany)
Fax: (+49) 721-661-921
Dipl. Chem. M. Kattannek, Prof. Dr. R. Ahlrichs
Institut für Physikalische Chemie der Universität
Kaiserstrasse 12, D-76128 Karlsruhe (Germany)

[**] This work was supported by the German-Israeli Foundation, the Deutsche Forschungsgemeinschaft (SFB 195), and the Fonds der Chemischen Industrie. We thank Prof. Dr. B. Engels (Bonn) for valuable help with the calculations.

280 to 320 pm are observed in electron-deficient In clusters, such as $R_8^*In_{12}$ ($R^* = Si^tBu_3$)^[11] synthesized recently by Wiberg and co-workers, and in the indium tetrahedron R_4In_4 ($R = C(SiMe_3)_3$).^[12] Average P–P bond lengths of 222.0 pm in **1** are similar to those in other compounds containing (RP)_n ligands.^[13]

The cluster core has near C_3 symmetry, the idealized threefold axis runs through the center of the In_3P_3 six-membered ring, formed by In(1) to In(3) and P(1) to P(3) as well as through atoms Cl(7) and P(10). Altogether the cluster core is built up by four In_3P_3 six-membered rings, three In_3P_2 five-membered rings, and three In_2P_3 five-membered rings. Considering the view of **1** given in Figure 1, the above-mentioned In_3P_3 ring (In(1) to In(3), P(1) to P(3)) acts as the top surface and the remaining three In_3P_3 rings and three In_2P_3 rings are alternately positioned as lateral limits. Finally, the three In_3P_2 rings, each connected by two In–P(10) bonds, form the bowl-shaped bottom.

Three of the In atoms (In(5), In(7), In(9)) are coordinated by PEt_3 groups, the six remaining In atoms are each bound to one terminal Cl ligand. Cl(7) is located at the center of the cluster cage and has to be viewed as Cl^- for reasons of cluster neutrality and in agreement with quantum chemical calculations. The closest neighboring atoms to Cl(7) are the atoms In(1), In(2), and In(3) at distances of 306.5, 303.2, and 300.8 pm. Intercalation compounds of halides similar to **1** have already been reported for polyoxovanadates^[14] and polyoxovanadiumorganophosphates.^[15]

The PPh groups (P(7) to P(10)) act as μ_3 -bridging ligands, thus phosphorus atoms of these ligands are four-coordinate and exhibit near tetrahedral coordination geometries. The two P atoms of the P_2Ph_2 groups show different coordination geometries. The phosphorus atoms P(1), P(2), and P(3) are four-coordinate and bond in nearly tetrahedral fashion to two In atoms, one carbon atom of a phenyl group, and one phosphorus atom. The phosphorus atoms P(4), P(5), and P(6), however, are three-coordinate and bond to one C atom of a phenyl group, one P atom, and one In atom. These P atoms show nearly trigonal-pyramidal coordination geometries. All In atoms in **1** reside in slightly distorted tetrahedral environments, in which the four binding partners are either three P atoms and one In atom or two P atoms, one In atom, and one Cl ligand, or three P atoms and one Cl ligand.

In order to better understand the bonding and stability of **1**, quantum chemical ab initio calculations were carried out using the program package TURBOMOLE within the resolution of the identity (RI) approximation to the density functional theory (RI-DFT) method.^[16] To reduce the computational effort, ethyl and phenyl ligands were replaced by methyl groups. Additionally, C_3 symmetry was assumed for the structure optimization.^[17] The deviation between calculated and experimental structural parameters was as expected. As usual, the bond lengths are somewhat overestimated by DFT, as shown by the following (experimental data in parentheses): In–Cl 244.4 (242.9), P–P 224.3 (222.0), In–P (without R_3P –In) 260.6 pm (257.8 pm). Larger deviations occur for the weak, dative R_3P –In contacts; the calculated values were 9.5 pm too long. Computed In–In distances are 6.0 pm longer than experimental ones, probably because the

DFT method does not take (attractive) dispersion effects, which play a considerable role, into consideration.

Removal of the central Cl^- ion leads, using the same computational method, to only slightly different structural parameters: bond lengths (In–In, P–P, In–P, In–Cl) less than 4 pm, angles less than 6.0° . Thus, the following two points are to be considered. First, the cationic cage $[In_3(In_2)_3(MeP)_4-(Me_2P_2)_3Cl_6(PMe_3)_3]^+$ is stable and encapsulates the Cl^- ion without strain in its center. Second, the interaction of the Cl^- ion with its neighboring In atoms is purely ionic. In both the calculated and the crystal structure of **1**, the nearest neighbors of the interstitial Cl^- ion are In atoms (In(1) to In(3)) in the formal oxidation state III.

By performing additional calculations it was possible to investigate the cluster behavior with F^- , Br^- , or I^- as the central halide ion. The distances of the halide ion to the indium atoms In(1) to In(3) increases with increasing ionic radius but remains the shortest of the indium–halide distances (In–Cl 309.4, In–Br 316.6, In–I 325.3 pm). The bond lengths between the atoms of the cage remain almost constant in the clusters with Cl^- , Br^- , and I^- as the central halide, whereas the angles widen, yielding a more spherical shape for the cationic cage. A second-order Jahn–Teller effect occurs for the F^- case distorting the cluster to C_1 symmetry and giving an energy gain of 4.7 kJ mol^{−1} (In(1)–F 230, In(2)–F 234, In(3)–F 337 pm). Complexation energies of the anions inside the cationic cage ($\Delta E = E_{cluster} - (E_{x^-} + E_{cation})$) amount to 638.8 (F^-), 494.3 (Cl^-), 438.2 (Br^-), and 334.1 kJ mol^{−1} (I^-). For a more complete characterization, vertical electronic excitations were calculated by using time-dependent density functional theory (TD-DFT). The computed singlet spectrum consists of a series of bands ending with the longest wavelength signal at 461 nm.^[18] The measured electronic excitation spectrum of the yellow compound **1** showed a structureless signal that starts at the long wavelength side at 500 nm, in agreement with the calculation, and rises in intensity to the limit of the spectrometer at 200 nm.^[19]

Experimental Section

All manipulations were performed with the rigorous exclusion of oxygen and moisture on a Schlenk line under nitrogen. Solvents were dried according to literature procedures and freshly distilled before use.

A solution of $InCl_3$ (0.22 g, 1.0 mmol) and PEt_3 (0.12 g, 1.0 mmol) was stirred in THF (10 mL) for 30 min. Then $PhP(SiMe_3)_2$ (0.25 g, 1.0 mmol) was added. After 3 h all volatile compounds were removed in vacuo, and the yellow residue was suspended in diethyl ether (5 mL). The suspension was stirred for 16 h and subsequently filtered. A yellow powder was obtained that was redissolved in THF (5 mL). The solution was again filtered in order to remove small amounts of insoluble powder, and was subsequently layered with toluene (20 mL). After a few days, very small crystals of **1** appeared. The formation of **1** was very dependent on the reaction conditions (temperature, concentration, etc.). Yield: 5–15%. ³¹P NMR (250 MHz, C_6D_6/THF): Very broad signals were observed due to many different P–P couplings and the nuclear spin of In. IR (KBr): $\tilde{\nu} = 3048$ (m), 2961 (m), 1577 (m), 1478 (s), 1432 (s), 1259 (m), 1136 (m), 1096 (vs), 1042 (m), 841 (m), 737 (vs), 692 (vs), 558 (m), 475 (m), 377 cm^{−1} (w); C, H analysis (%) calcd for $C_{78}H_{95}Cl_7In_9P_{13} \cdot 2.5 C_7H_8$ (2946.9): C 38.94, H 3.91; found: C 38.20; H 3.89; UV/Vis: $\lambda = 370$ (sh), 280 nm (m).

$PhP(SiMe_3)_2$ ^[20] and PEt_3 ^[21] were synthesized according to literature procedures, $InCl_3$ was purchased from Aldrich.

Received: April 29, 1999 [Z13335IE]
German version: *Angew. Chem.* **1999**, *111*, 2900–2902

Keywords: cluster compounds • indium • nanoparticles • phosphorus

- [1] a) K. Merzweiler, J. Spohn, *Z. Anorg. Allg. Chem.* **1993**, 619, 318–320; b) T. Douglas, K. H. Theopold, *Inorg. Chem.* **1991**, 30, 594–596.
- [2] a) B. Werner, B. Neumüller, *Organometallics* **1996**, 15, 4258–4263; b) M. A. Banks, O. T. B. Junior, L. A. Buttrey, M. R. Churchill, J. C. Fetting, *Organometallics* **1991**, 10, 1901–1906.
- [3] a) U. App, K. Merzweiler, *Z. Anorg. Allg. Chem.* **1995**, 621, 1731–1734; b) D. A. Atwood, A. H. Cowley, R. A. Joens, M. A. Mardones, *J. Organomet. Chem.* **1993**, 449, C1–C2.
- [4] a) A. A. Guzelian, J. E. B. Katari, A. V. Kadavanich, U. Banin, K. Hamad, E. Juban, A. P. Alivisatos, R. H. Wolters, C. C. Arnold, J. R. Heath, *J. Phys. Chem.* **1996**, 100, 7212–7219; b) O. I. Micic, C. J. Curtis, K. M. Jones, J. R. Sprague, A. J. Nozik, *J. Phys. Chem.* **1994**, 98, 4966–4969; c) O. I. Micic, J. R. Sprague, C. J. Curtis, K. M. Jones, J. L. Machol, A. J. Nozik, H. Giessen, B. Fluegel, G. Mohs, N. Peyghambarian, *J. Phys. Chem.* **1995**, 99, 7754–7759.
- [5] T. J. Trentler, S. C. Goel, K. M. Hickman, A. M. Viano, M. Y. Chiang, A. M. Beatty, P. C. Gibbons, W. E. Buhor, *J. Am. Chem. Soc.* **1997**, 119, 2172–2181.
- [6] a) A. P. Alivisatos, *MRS Bull.* **1998**, 23(2), 18–23; b) A. J. Nozik, O. I. Micic, *MRS Bull.* **1998**, 23(2), 24–30.
- [7] 1·2.5 toluene: crystal dimensions $0.04 \times 0.03 \times 0.01 \text{ mm}^3$, $a = 1509.7(5)$, $b = 1518.5(4)$, $c = 2623.0(5) \text{ pm}$, $\alpha = 92.98(3)$, $\beta = 94.21(3)$, $\gamma = 91.37(3)^\circ$, $V = 5986(3) \times 10^6 \text{ pm}^3$; triclinic $P\bar{1}$, $Z = 2$, $\rho_{\text{calc}} = 1.596 \text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 2.067 \text{ mm}^{-1}$, STOE IPDS, Siemens rotating anode, graphite monochromator, $\text{MoK}\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$, $T = 190 \text{ K}$, $2\theta_{\text{max}} = 45^\circ$; a total of 19264 reflections measured, 13093 independent reflections ($R_{\text{int}} = 0.0605$), 9568 independent reflections with $F_o > 4\sigma(F_o)$. The structure was solved by direct methods and refined by full-matrix least-squares techniques against F^2 , 749 parameters (In, P, Cl, refined anisotropically, C atoms of the phenyl groups refined anisotropically, C atoms of ethyl groups and solvent molecules were refined isotropically with split positions; H atoms were calculated for the phenyl groups only), $R1 = 0.0832$; $wR2 = 0.2153$, residual electron density $3.004 \text{ e \AA}^{-3}$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-118782. 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).
- [8] Corresponding to the average distance of P(10)–center of the P(1)–P(2)–P(3) three-membered ring, In(1)–In(7), and P(5)–P(9).
- [9] P. J. Brothers, K. Hübner, B. C. Noll, M. M. Olmstead, P. P. Power, *Angew. Chem.* **1996**, 108, 2528–2530; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2355–2357.
- [10] S. M. Godfrey, K. J. Kelly, P. Kramkowski, C. A. McAuliffe, R. G. Pritchard, *Chem. Comm.* **1997**, 1001–1002.
- [11] N. Wiberg, T. Blank, H. Nöth, W. Ponikwar, *Angew. Chem.* **1999**, 111, 887–890; *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 839–841.
- [12] W. Uhl, R. Graupner, M. Layh, U. Schütz, *J. Organomet. Chem.* **1995**, 493, C1–C5.
- [13] a) R. Ahlrichs, D. Fenske, H. Oesen, U. Schneider, *Angew. Chem.* **1992**, 104, 312–314; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 323–325; b) J. Queisser, D. Fenske, *Z. Anorg. Allg. Chem.* **1994**, 620, 58–66; c) J. Queisser, H. Oesen, D. Fenske, B. Lehari, *Z. Anorg. Allg. Chem.* **1994**, 620, 1821–1831.
- [14] A. Müller, M. Penk, R. Rohlfing, E. Krickemeyer, J. Döring, *Angew. Chem.* **1990**, 102, 927–929; *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 926–928.
- [15] J. Salta, Q. Chen, Y.-D. Chang, J. Zubieta, *Angew. Chem.* **1994**, 106, 781–783; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 757–759.
- [16] Calculations were performed with the program system TURBO-MOLE on UNIX workstations and parallel computers. a) R. Ahlrichs, M. Bär, M. Häser, H. Horn, C. Kölmel, *Chem. Phys. Lett.* **1989**, 162, 165–169; b) O. Treutler, R. Ahlrichs, *J. Chem. Phys.* **1995**, 102, 346–354. DFT methods employing the RI approximation and the BP-86 functional were used. c) K. Eichkorn, O. Treutler, H. Öhm, M. Häser, R. Ahlrichs, *Chem. Phys. Lett.* **1995**, 240, 283–290, d) A. D. Becke,

Phys. Rev. B. **1988**, 38, 3098–3100; e) S. H. Vosko, L. Wilk, M. Nusair, *Can. J. Phys.* **1980**, 58, 1200–1211; f) J. P. Perdew, *Phys. Rev. B.* **1986**, 33, 8822–8824. For all atoms except the central halogen atoms, split valence plus polarization (SV(P)) basis sets were used. The central halogen atoms were treated using a triple zeta valence plus polarization (TZVP) basis set; g) A. Schäfer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, 97, 2571–2577; h) A. Schäfer, C. Huber, R. Ahlrichs, *J. Chem. Phys.* **1994**, 100, 5829–5835.

- [17] The geometry was confirmed by subsequent calculations in C_1 symmetry after displacing the central Cl^- anion towards different In neighbors; the cluster structures always returned to C_3 symmetry.
- [18] Further intense bands were found at 414, 379, 351, and 337 nm. The triplet transition with the longest wavelength was at 475 nm (indium compounds should show considerable singlet–triplet mixing by spin-orbit interaction) and amplifies the long-wavelength shoulder of the singlet spectrum.
- [19] Calculations of circular dichroism (a) R. Bauernschmitt, R. Ahlrichs, *Chem. Phys. Lett.* **1996**, 256, 454–464; b) F. Furche, Diplomarbeit, Karlsruhe (Germany), **1998** produced high values of rotatory strength which merit further attention. For the 379 nm bands a rotatory strength of about $343 \times 10^{-40} \text{ erg m}^3$ (CGS) was calculated. (R)-3-Methylcyclopentene, for example, has a maximum rotatory strength of about $26 \times 10^{-40} \text{ erg m}^3$ (CGS) at 185 nm (M. Levi, D. Cohen, V. Schurig, H. Basch, A. Gedanken, *J. Am. Chem. Soc.* **1980**, 102, 6872–6875). Helicenes on the other hand are well-known for their strong circular dichroism: calculations on dodecahelicene yielded a rotatory strength of $337 \times 10^{-40} \text{ erg m}^3$ (CGS) at 386 nm (R. Ahlrichs, F. Furche, *Chem. Phys. Lett.* **1999**, submitted.)
- [20] J. Hahn, T. Nataniel, *Z. Anorg. Allg. Chem.* **1986**, 543, 7–21.
- [21] H. D. Kaesz, F. G. A. Stone, *J. Org. Chem.* **1959**, 24, 635–639.

Asymmetric Synthesis of Overcrowded Alkenes by Transfer of Axial Single Bond Chirality to Axial Double Bond Chirality**

Edzard M. Geertsema, Auke Meetsma, and Ben L. Feringa*

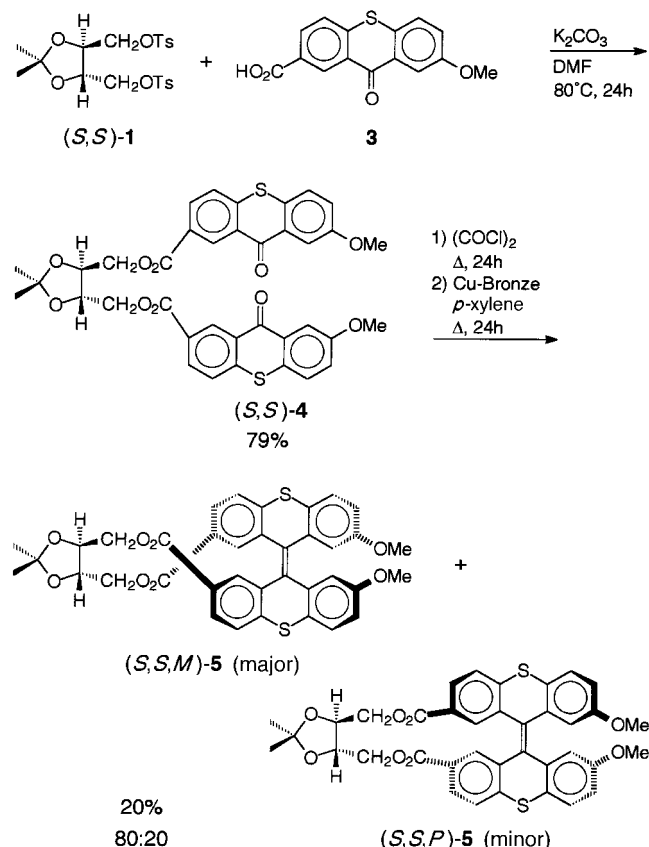
Sterically overcrowded alkenes have attracted considerable interest in view of their unique photochromic and thermochromic properties. In addition the beautiful architecture of these structures is as fascinating as their potential applications.^[1] Although they lack a stereogenic center they can exist as stable, optically active stereoisomers as a consequence of the presence of substituents that cause sufficient hindrance between the upper and lower half of the alkene and enforce a helical distortion to the entire molecule. Unsymmetrical *cis* and *trans* isomers of overcrowded alkenes were shown to act as chiroptical molecular switches suitable for reversible data storage,^[2] while other applications include photomodulation of liquid-crystalline materials^[3] and thin polymer films.^[4] A practical synthetic route towards enantiomerically pure over-

[*] Prof. Dr. B. L. Feringa, Dr. E. M. Geertsema, Dr. A. Meetsma
Department of Organic and Molecular Inorganic Chemistry
University of Groningen
Nijenborgh 4, NL-9747 AG Groningen (The Netherlands)
Fax: (+31) 50-363-4296
E-mail: feringa@chem.rug.nl

[**] This work was supported by the Dutch Foundation for Scientific Research (NWO).

crowded alkenes is still a challenging goal.^[5] Methodology has been developed for the synthesis of optically active biaryls in which control of the chirality of an axial single bond is achieved by the coupling of two aryl moieties to a chiral bridge.^[6] Based on a related principle we present the synthesis of stable enantiomers of an overcrowded alkene, which features axial double bond chirality, by using (–)-2,3-*O*-isopropylidene-L-threitol-1,4-ditosylate ((*S,S*)-**1**), (+)-(*R*)-1,1'-binaphthol ((*R*)-**2**), and (–)-(*S*)-1,1'-binaphthol ((*S*)-**2**) as chiral auxiliaries. In our most successful approach two halves of the envisioned alkene were first coupled to the binaphthol chiral bridge. A diastereoselective intramolecular coupling reaction then afforded the corresponding overcrowded alkenes. As no racemization was observed after removal of the chiral bridge this sequence implies the realization of the intriguing concept of conveying axial single bond chirality to stable axial double bond chirality. Moreover, we report for the first time the determination of the absolute configuration of enantiomerically pure bis-thioxanthylidenes as accomplished by X-ray analysis.

Initially we focussed on chiral template **1**, which is derived from tartaric acid (Scheme 1). An earlier attempt by Yip et al. to prepare optically active bifluorenylidenes^[7] along these lines resulted in the complete loss of optical activity as a result of the product having a low barrier to racemization.



Scheme 1. Synthetic route towards optically active overcrowded alkenes **5** with (*S,S*)-**1** used as a chiral template. *S,S* denotes the configuration of the threitol moiety whereas *M* (left-handed helix) and *P* (right-handed helix) define the helicity at the diester side of the overcrowded alkene part of the molecule.

The preorganized system (*S,S*)-**4** was prepared from 7-methoxy-9-oxo-9*H*-thioxanthene-2-carboxylic acid (**3**)^[8] and (*S,S*)-**1**. An intramolecular copper-promoted *gem*-dichloride coupling reaction^[9] afforded the sterically overcrowded alkenes (*S,S,M*)-**5** (major product) and (*S,S,P*)-**5** (minor product) in 20% yield.^[10] This rather low yield is a result of the extensive formation of oligomers during the coupling reaction, which unfortunately could not be suppressed by working at high dilution. The newly formed alkene moiety is chiral as a consequence of its folded structure, which explains the formation of two diastereoisomers. A diastereomeric excess of 60% was determined by ^1H NMR spectroscopy. Recrystallization from acetone gave crystals of pure (*S,S,P*)-**5** that were suitable for X-ray analysis (Figure 1). The unique

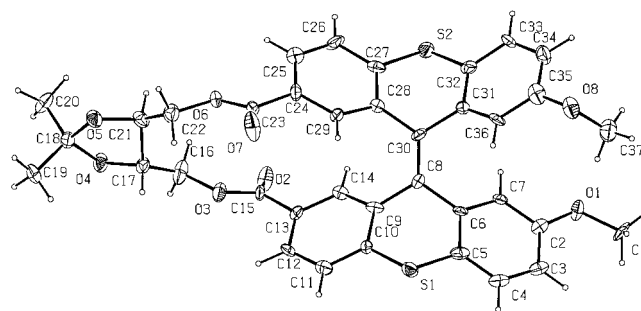
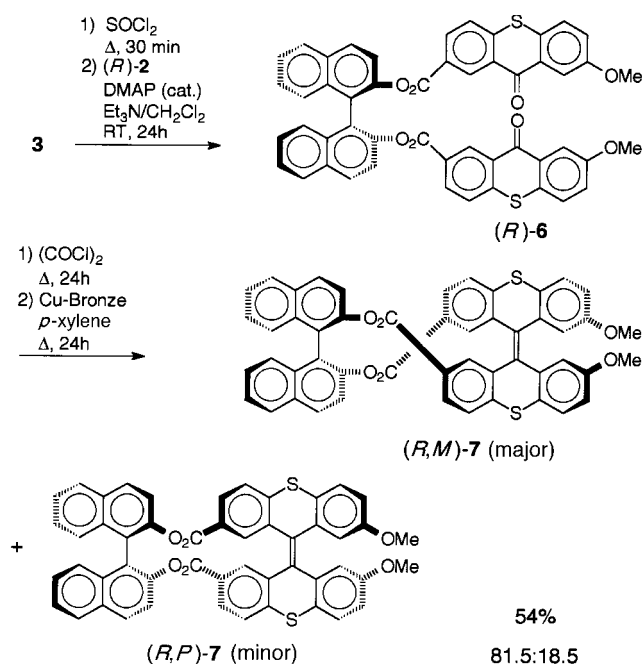


Figure 1. ORTEP plot of (*S,S,P*)-**5** (minor product).

folded structure of the overcrowded alkene part of (*S,S,P*)-**5** is clearly visible and based on the 2*S*,3*S* configuration of the L-threitol moiety a (*P*)-configuration for the diester moiety is established. The helical structure of (*S,S,P*)-**5** is quantified by torsion angles of 50.6° (C8–C30–C28–C29) and –3.9° (C9–C8–C30–C28). The major isomer (*S,S,M*)-**5** could not be obtained diastereomerically pure, despite several attempts.

In order to develop a synthetically useful asymmetric route we employed (*R*)-**2** and (*S*)-**2** as chiral templates (Scheme 2 for (*R*)-**2**, the same procedure was applied for (*S*)-**2**). The diester (*R*)-**6** was prepared from thioxanthone **3** and (*R*)-**2** in two steps in nearly quantitative yield. More importantly the yield of the subsequent intramolecular *gem*-dichloride coupling reaction with Cu-bronze increased considerably and diastereoisomers (*R,M*)-**7** (major product) and (*R,P*)-**7** (minor product) were obtained in 54% yield in a 81.5:18.5 ratio (^1H NMR). Apparently the more rigid binaphthol-based chiral diester bridge of the tetrachloride derived from (*R*)-**6** enforces a more favorable geometry to the two thioxanthene moieties and suppresses oligomer formation through intermolecular coupling. The diastereoisomers (*R,M*)-**7** and (*R,P*)-**7** were readily separated by column chromatography.

It should be emphasized that both a folded and twisted helical shaped structural moiety is present in the same molecule. The two diastereoisomers differ significantly in structure as is visualized in Scheme 2. Although the binaphthyl part is twisted and the thioxanthylidene is folded in both isomers, the formation of the “cross-coupled” product (*R,M*)-**7** is strongly favored over the “linearly coupled” product (*R,P*)-**7**. Figure 2 shows an optimized space filling model^[11] of (*R,M*)-**7** revealing a double-helix-type structure that is



Scheme 2. Synthetic route towards optically active overcrowded alkenes **7** with (*R*)-**2** used as a chiral template. *R* and *S* denote the configuration of the binaphthol moiety whereas *M* (left-handed helix) and *P* (right-handed helix) define the helicity at the diester side of the overcrowded alkene part of the molecule.

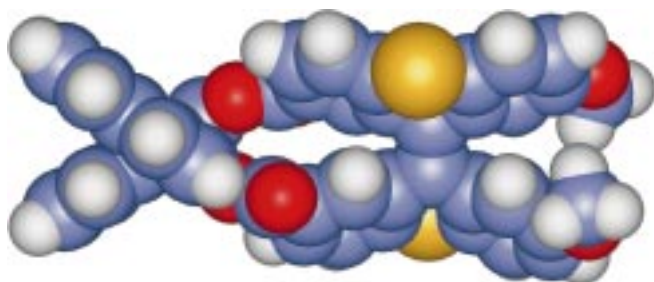
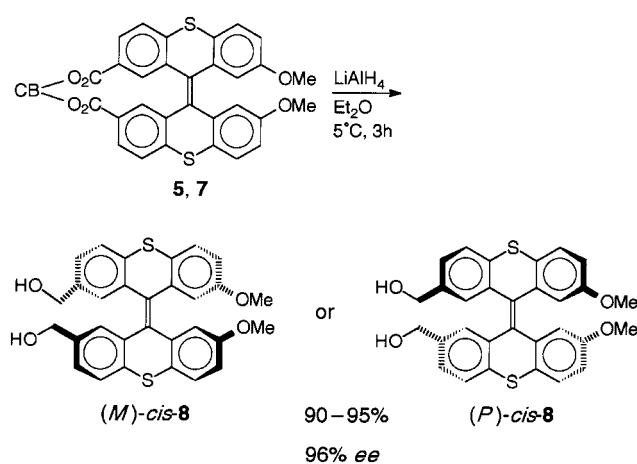


Figure 2. A model of (*R,M*)-**7** (major product) optimized with a CHARMM 23 force field as implemented in Quanta97/CHARMM. The structure is viewed along the binaphthol single bond and the alkene double bond.

reminiscent of the helical structure Nozaki et al. found for their double-helical oligo esters.^[12] The configurations of diastereoisomers (*R,M*)-**7** and (*R,P*)-**7** (and of diastereoisomers (*S,P*)-**7** (major product) and (*S,M*)-**7** (minor product) obtained from (*S*)-**2**) were unequivocally established after removal of the chiral bridges of all obtained diastereoisomers ((*S,S,P*)-**5** (minor product), (*R,M*)-**7**, (*R,P*)-**7**, (*S,P*)-**7**, and (*S,M*)-**7**). The overcrowded alkenes were liberated from their chiral bridge by reduction with LiAlH_4 to provide enantiomers of thioxanthylidenes (*P*)-*cis*-**8** and (*M*)-*cis*-**8** with *ee* values of $96 \pm 1\%$ as determined by chiral HPLC (Scheme 3). Based on the X-ray analysis of (*S,S,P*)-**5** the overcrowded alkene part has a *P* configuration, which leads to (*P*)-*cis*-**8** after removal of the L-threitol moiety. The analytical data of (*P*)-*cis*-**8** (optical rotation, CD data, and retention times on chiral HPLC) obtained from (*S,S,P*)-**5** were correlated with those of the enantiomers of *cis*-**8** obtained by reductive cleavage of the four diastereoisomers (*R,M*)-**7**, (*R,P*)-**7**, (*S,P*)-**7**, and (*S,M*)-**7**. The results are outlined in Table 1.



Scheme 3. Cleavage of the chiral bridge (CB) from overcrowded alkenes **5** and **7**. *M* (left-handed helix) and *P* (right-handed helix) define the helicity at the hydroxymethyl-side of **8**.

Table 1. Stereochemical correlation and optical rotation data of **5**, **7**, and **8**.

Substrate	$[\alpha]_{\text{D}}^{20[\text{a}]}$	Product	$[\alpha]_{\text{D}}^{20[\text{a}]}$
(<i>S,S,P</i>)- 5 (minor)	+203 ^[b]	(<i>P</i>)- <i>cis</i> - 8	−92
(<i>R,M</i>)- 7 (major)	−101	(<i>M</i>)- <i>cis</i> - 8	+91
(<i>R,P</i>)- 7 (minor)	+120	(<i>P</i>)- <i>cis</i> - 8	−93
(<i>S,P</i>)- 7 (major)	+100	(<i>P</i>)- <i>cis</i> - 8	−92
(<i>S,M</i>)- 7 (minor)	−120	(<i>M</i>)- <i>cis</i> - 8	+91

[a] *c* = 1.00, CHCl_3 . [b] *c* = 0.50, CHCl_3 .

A racemization barrier ($\Delta^\ddagger G^\ominus$) of $26.7 \pm 0.5 \text{ kcal mol}^{-1}$ (polarimetry) was determined for *cis*-**8**, which is in accordance with the observation that the enantiomers of *cis*-**8** are stable at room temperature. A pair of identical CD spectra (except for the sign) were obtained for enantiomers (*P*)-*cis*-**8** and (*M*)-*cis*-**8**. Seven maxima were observed for (*M*)-*cis*-**8** (*n*-hexane/2-propanol 80/20) at wavelengths greater than 220 nm: λ_{max} ($\Delta\epsilon$) 230 nm (−3.5), 238 (+17.3), 252 (−6.2), 269 (+25.3), 291 (−38.6), 313 (+18.4), 342 (+10.7). The CD absorptions as well as the $\Delta\epsilon$ values are in good agreement with those obtained for related optically pure overcrowded alkenes that were obtained previously by preparative chiral HPLC.^[5]

In conclusion, an asymmetric synthesis method, which includes the transfer of axial single bond chirality to axial double bond chirality, for stable optically active overcrowded alkenes has been developed. The determination of the absolute configuration of the major stereoisomer revealed an appealing double-helical structure.

Experimental Section

(*R,M*)-**7** and (*R,P*)-**7** (the same procedure was used for (*S,P*)-**7** and (*S,M*)-**7**): Diester (*R*)-**6** (0.73 mmol) was refluxed overnight in oxalyl chloride (20 mL) under a nitrogen atmosphere. The excess of oxalyl chloride was evaporated under reduced pressure. The residue was dissolved in freshly distilled *p*-xylene (100 mL) and then activated Cu-bronze (15.90 mmol) was added. This mixture was refluxed overnight. After cooling, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2 /*n*-hexane 3/1) gave (*R,M*)-**7** (44% yield) and (*R,P*)-**7** (10% yield) as yellow solids. (*R,M*)-**7**: ^1H NMR (300 MHz, CDCl_3 , 25°C): δ = 8.02 (d, $^3J(\text{H,H})$ = 9.15 Hz, 2H; CH), 7.96 (d, $^3J(\text{H,H})$ = 8.42 Hz, 2H; CH), 7.49–7.29 (m, 12H; CH), 7.18 (d, $^3J(\text{H,H})$ = 8.42 Hz, 2H; CH), 7.07 (m, 2H; CH), 6.77 (m, 2H; CH), 6.42 (d,

$^3J(\text{H,H}) = 2.56 \text{ Hz}$, 2H; CH), 3.43 (s, 6H; CH_3); ^{13}C NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 164.11$, 158.00, 146.93, 142.18, 135.60, 134.91, 133.25, 131.30, 131.05, 129.12, 128.22, 127.97, 126.93, 126.88, 126.84, 126.62, 125.92, 125.74, 125.51, 123.41, 122.17, 115.09, 113.55, 54.99; HR-MS calcd for $\text{C}_{30}\text{H}_{30}\text{O}_6\text{S}_2$: 790.1484; found: 790.1494. (*R,P*)-**7**: ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 8.01$ (m, 4H; CH), 7.59–7.42 (m, 12H; CH), 7.30 (m, 2H; CH), 7.13 (d, $^3J(\text{H,H}) = 8.42 \text{ Hz}$, 2H; CH), 6.83 (dd, $^3J(\text{H,H}) = 2.56$, 8.42 Hz, 2H; CH), 6.42 (d, $^3J(\text{H,H}) = 2.56 \text{ Hz}$, 2H; CH), 3.43 (s, 6H; CH_3); ^{13}C NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 165.10$, 158.24, 146.76, 141.50, 136.38, 134.00, 133.34, 132.82, 131.54, 131.04, 129.51, 127.87, 127.65, 127.45, 127.33, 127.01, 126.83, 126.43, 125.51, 125.23, 123.09, 122.31, 115.55, 114.36, 55.02; HR-MS calcd for $\text{C}_{30}\text{H}_{30}\text{O}_6\text{S}_2$: 790.1484; found: 790.1494.

Compounds (*S,S,M*)-**5** and (*S,S,P*)-**5** were prepared analogously. A standard LiAlH_4 reduction afforded (*M*)-*cis*-**8** or (*P*)-*cis*-**8**. All new compounds were fully characterized.

The *ee* value of *cis*-**8** was determined by chiral HPLC (Daicel, Chiralcel OD column, flow rate 1.0 mL min⁻¹, *n*-hexane/*i*PrOH, 99/1): t_{ret} 98.1 min for (*M*)-*cis*-**8** and t_{ret} 125.1 min for (*P*)-*cis*-**8**.

The racemization barrier ($\Delta^\ddagger G^\circ$) of *cis*-**8** was determined by polarimetry (1,2-dibromoethane, $k = 7.22 \times 10^{-5}$ at 70.0 °C).

X-ray crystal structure analysis of (*R,M*)-**7**: Crystal dimensions 0.15 × 0.25 × 0.52 mm, monoclinic, space group $P2_1$, $a = 9.598(1)$, $b = 14.288(6)$, $c = 12.383(3)$ Å, $\beta = 110.77(1)^\circ$, $V = 1587.8(8)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.395 \text{ g cm}^{-3}$, $T = 130 \text{ K}$, $F(000) = 696$. Enraf-Nonius CAD-4 F^2 diffractometer, $\lambda(\text{MoK}\alpha) = 0.71073$ Å, $\mu = 2.2 \text{ cm}^{-1}$. The final refinement on F^2 carried out by full-matrix least-squares techniques converged at $wR(F^2) = 0.2108$ for 2909 reflections with $F_o^2 \geq 0$ and $R(F) = 0.0701$ for 2460 reflections obeying $F_o > 4.0\sigma(F_o)$ and 438 parameters. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-115682. 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).

Received: April 30, 1999 [Z13353IE]

German version: *Angew. Chem.* **1999**, *111*, 2902–2905

Keywords: alkenes • asymmetric synthesis • biaryls • chirality • helical structures

- [1] a) J. Sandström in *Topics in Stereochemistry*, Vol. 14 (Eds.: N. L. Allinger, E. L. Eliel, S. H. Wilen), Wiley, New York, **1983**; b) J. H. Day, *Chem. Rev.* **1963**, *63*, 65; c) W. T. Grubb, G. B. Kistiakowsky, *J. Am. Chem. Soc.* **1950**, *72*, 419; d) "Photochromism, Molecules and Systems" in *Studies in Organic Chemistry* 40 (Eds.: H. Dürr, H. Bouas Laurent), Elsevier, Amsterdam, **1990**; e) A. Schönberg, U. Sodtke, K. Praefcke, *Tetrahedron Lett.* **1968**, 3253; f) A. Schönberg, U. Sodtke, K. Praefcke, *Chem. Ber.* **1969**, *102*, 1453; g) R. Korenstein, K. A. Muszkat, E. Fisher, *Chem. Phys. Lett.* **1975**, *36*, 509; h) R. Korenstein, K. A. Muszkat, E. Fisher, *Mol. Photochem.* **1972**, *3*, 379; i) R. Korenstein, K. A. Muszkat, E. Fisher, *J. Photochem.* **1976**, *5*, 447; j) R. Korenstein, K. A. Muszkat, E. Fisher, *Helv. Chim. Acta* **1970**, *53*, 2102; k) Y. Tapuhi, O. Kalisky, I. Agranat, *J. Org. Chem.* **1979**, *44*, 1949; l) I. Agranat, Y. Tapuhi, J. Y. Lallemand, *Nouv. J. Chim.* **1979**, *3*, 59; m) I. Agranat, Y. Tapuhi, *Nouv. J. Chim.* **1977**, *1*, 361; n) I. Agranat, Y. Tapuhi, *J. Am. Chem. Soc.* **1978**, *100*, 5604; o) I. Agranat, Y. Tapuhi, *J. Am. Chem. Soc.* **1979**, *101*, 665; p) G. Kortüm, *Ber. Bunsen-Ges. Phys. Chem.* **1974**, *78*, 391.
- [2] For reviews on molecular switches, see a) B. L. Feringa, W. F. Jager, B. de Lange, *Tetrahedron* **1993**, *49*, 8267; b) B. L. Feringa, N. P. M. Huck, A. M. Schoevaars, *Adv. Mater.* **1996**, *8*, 681; c) W. F. Jager, J. C. de Jong, B. de Lange, N. P. M. Huck, A. Meetsma, B. L. Feringa, *Angew. Chem.* **1995**, *107*, 346; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 348.
- [3] a) B. L. Feringa, N. P. M. Huck, H. A. van Doren, *J. Am. Chem. Soc.* **1995**, *117*, 9929; b) N. P. M. Huck, W. F. Jager, B. de Lange, B. L. Feringa, *Science* **1996**, *273*, 1686.
- [4] M. L. C. M. Oosterling, A. M. Schoevaars, H. J. Haitjema, B. L. Feringa, *Isr. J. Chem.* **1996**, *36*, 341.

- [5] W. F. Jager, B. de Lange, A. M. Schoevaars, F. van Bolhuis, B. L. Feringa, *Tetrahedron: Asymmetry* **1993**, *4*, 1481.
- [6] a) S. Miyano, H. Fukushima, S. Handa, H. Ito, H. Hashimoto, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3249, and references therein; b) B. H. Lipshutz, Z. Liu, F. Kayser, *Tetrahedron Lett.* **1994**, *35*, 5567; c) M. Tanaka, H. Mitsunashi, M. Maruno, T. Wakamatsu, *Tetrahedron Lett.* **1994**, *35*, 3733; d) V. H. Rawal, A. S. Florjancic, S. P. Singh, *Tetrahedron Lett.* **1994**, *35*, 8985; e) K. S. Feldman, A. Sambandam, *J. Org. Chem.* **1995**, *60*, 8171; f) T. Sugimura, H. Yamada, S. Inoue, A. Tai, *Tetrahedron: Asymmetry* **1997**, *8*, 649.
- [7] a) Y. C. Yip, X. Wang, D. K. P. Ng, T. C. W. Mak, P. Chiang, T. Luh, *J. Org. Chem.* **1990**, *55*, 1881. b) X. Wang, T. Luh, *J. Org. Chem.* **1989**, *54*, 263.
- [8] Compound **3** was prepared from 4-methoxybenzenethiol and 4-bromoisophthalic acid in a two-step procedure.
- [9] a) A. Schönberg, S. Nickel, *Chem. Ber.* **1934**, *67*, 1795; b) A. Schönberg, W. Asker, *J. Chem. Soc.* **1942**, 272; c) A. Schönberg, A. Mustafa, M. E. El-Din Sobhy, *J. Am. Chem. Soc.* **1953**, *75*, 3377; d) A. Mustafa, M. E. El-Din Sobhy, *J. Am. Chem. Soc.* **1955**, *77*, 5124; e) A. Mustafa, W. Asker, M. E. El-Din Sobhy, *J. Org. Chem.* **1960**, *25*, 1519.
- [10] The chirality of this type of helical-shaped distorted alkenes is described by the helicity rule, with *P* (plus) for a right-handed helix and *M* (minus) for a left-handed helix, see for example, R. S. Cahn, C. K. Ingold, V. Prelog, *Angew. Chem.* **1966**, *78*, 413; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 385.
- [11] The model of (*R,M*)-**7** was constructed by using Quanta97/CHARMM, which is a product of Molecular Simulations Inc., San Diego, USA. Internet: <http://www.msi.com>. Dr. Franck Schoonbeek is acknowledged for his assistance.
- [12] K. Nozaki, T. Terakawa, H. Takaya, T. Hiyama, *Angew. Chem.* **1998**, *110*, 138; *Angew. Chem. Int. Ed.* **1998**, *37*, 131.

Influence of Perfluoroarene – Arene Interactions on the Phase Behavior of Liquid Crystalline and Polymeric Materials**

Marcus Weck, Alex R. Dunn, Kozo Matsumoto, Geoffrey W. Coates, Emil B. Lobkovsky, and Robert H. Grubbs*

Supramolecular chemistry, the chemistry of noncovalent intermolecular interactions such as hydrogen bonds, ionic interactions, metal–ion interactions, or the hydrophobic effect, is essential for processes in biological and synthetic systems, such as molecular recognition, catalysis, transport,

[*] Prof. R. H. Grubbs, Dr. M. Weck, A. R. Dunn, Dr. K. Matsumoto Arnold and Mabel Beckman Laboratories of Chemical Synthesis Division of Chemistry and Chemical Engineering California Institute of Technology Pasadena, CA 91125 (USA) Fax: (+1) 626-564-9297 E-mail: rhg@cco.caltech.edu

Prof. G. W. Coates, Dr. E. B. Lobkovsky Baker Laboratory Deptment of Chemistry & Chemical Biology Cornell University Ithaca, NY 14853-1301 (USA) Fax: (+1) 607-255-4137 E-mail: gc39@cornell.edu

[**] This work was supported by the United States Air Force. A.R.D. thanks Caltech for a Summer Undergraduate Research Fellowship (SURF).

and self-assembly.^[1–2] While systems based on hydrogen bonding and/or metal–ion interactions are widely studied and understood,^[1–5] there is growing interest in developing systems based on noncovalent interactions between aromatic molecules because of their responsibility for a wide array of phenomena in biology and chemistry.^[1, 2, 4, 6–13] Although supramolecular systems based on arene–arene interactions of benzene or its derivatives have attracted some attention,^[4, 6–13] there are only few reports on the use of electrostatic interactions between arenes and perfluoroarenes or their derivatives^[14–21] for the creation of such assemblies.

Experimental evidence for the strength and importance of the electrostatic interactions in these systems was found in the rotational barrier studies by Siegel, Cozzi et al. that were based on fluorinated 1,8-diarylnaphthalenes.^[17] Recently, Coates et al. used arene–perfluoroarene interactions in the solid state to pre-orient 1,3-diynes for photopolymerization.^[16] Herein we introduce the use of arene–perfluoroarene, in particular triphenylene–perfluorotriphenylene interactions, as a new supramolecular synthon to influence the phase behavior in liquid crystalline (LC) and polymeric materials.^[22–24]

In 1969 Smith and Massey found that a 1:1 mixture of perfluorotriphenylene (**2**) and triphenylene forms a complex with a higher melting point (250–252 °C) than the individual compounds (perfluorotriphenylene 109 °C and triphenylene 199 °C), suggesting a possible 1:1 interaction resulting from arene–perfluoroarene interactions.^[21] Based on these results, we grew crystals of a 1:1 perfluorotriphenylene–triphenylene mixture and determined their solid-state structure by X-ray diffraction. The structure analysis shows a stacked, columnar arrangement of perfluorotriphenylene–triphenylene (Figure 1).^[25] Pure perfluorotri-

phenylene and triphenylene have approximately 40° and 2° tilts in their skeletons.^[26] In the cocrystal, these tilts are 33° and 16°, respectively.^[25] It appears that the attraction between the triphenylene and perfluorotriphenylene is strong enough to induce marked conformational changes in both molecules. Building on these results, we investigated possible supramolecular 1:1 interactions between functionalized triphenylenes, in particular a chiral liquid crystalline triphenylene (**1**)^[26] and a polymer incorporating triphenylenes in its side chain (**4**) and perfluorotriphenylene **2**.

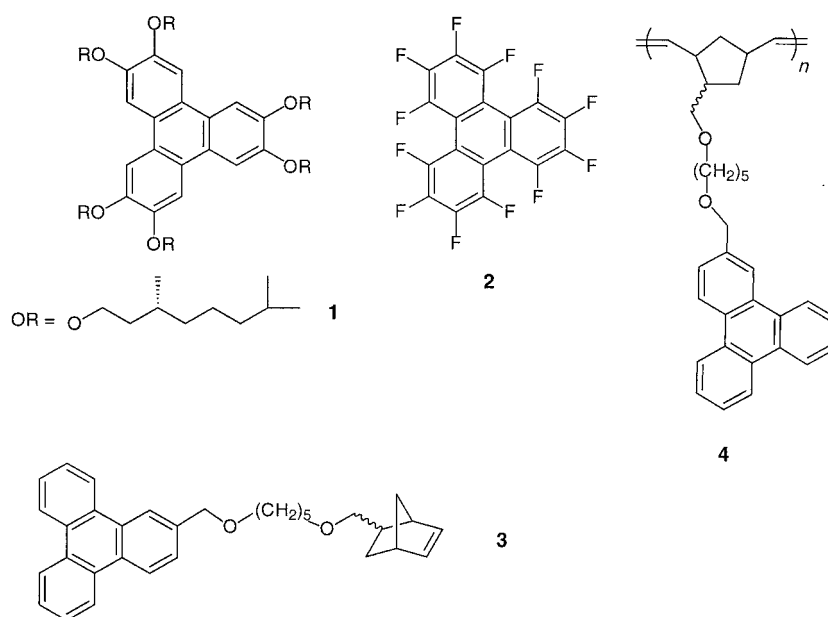


Figure 1. Single-crystal X-ray structure of a 1:1 mixture of triphenylene and perfluorotriphenylene. Atomic coordinates were determined by single-crystal X-ray diffraction. Centroid-to-centroid distance for the central rings of the triphenylenes is 3.698 Å. The shortest intermolecular C–C distance is 3.369 Å and the longest is 4.029 Å.

Triphenylenes **1** and **2** were synthesized by literature procedures.^[21, 27, 28] Polymer **4** was synthesized by ring-opening metathesis polymerization (ROMP) of monomer **3** using $[\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2]$ (**5**) (Cy = cyclohexyl) as catalyst; polymer **4** has a molecular weight (M_w) of 15000 and a polydispersity of 1.54.^[29] Monomer **3** was obtained in four steps from triphenylene through a Friedel–Crafts acylation followed by reduction of the aldehyde to produce the alcohol. After alkylation of norborn-5-ene-2-methanol with 1,5-dibromopentane, the product was treated with the triphenylene alcohol to give **3** in 62 % overall yield.^[30]

Solutions containing a 1:1 mixture of **2** with compounds **1** or **4** (based on triphenylene functionalities) in dichloromethane were rapidly evaporated to form solids. The first indication of an interaction between **1** and **2** was evident in the immediate color change from white for the pure compounds to light yellow for the 1:1 complex, which corresponds to a low, broad absorption around 360 nm not present in either **1** or **2** (Figure 2).^[31] By contrast, the mixture of **2** and **4** remained colorless. It seems likely that the complex of **1** and **2** has at least some charge transfer character, while the mixture of **2** and **4** is similar to other perfluoroarene–arene interactions.

To investigate the interaction of **2** with **1** or **4**, differential scanning calorimetry (DSC) measurements of all 1:1 complexes as well as the pure compounds were performed.^[28, 32] In

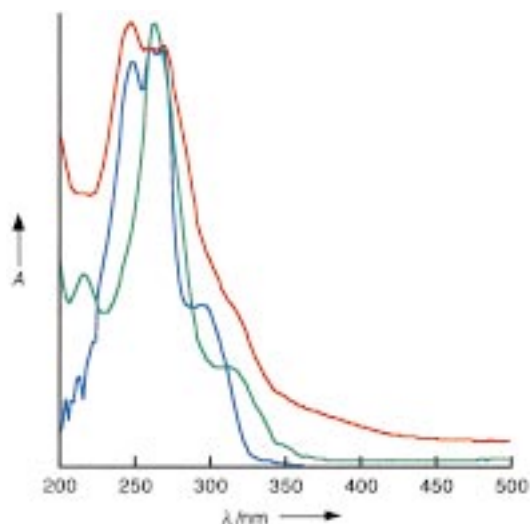


Figure 2. UV/Vis absorption spectra for **1** (green), **2** (blue), and a 1:1 mixture of the two compounds (red). Spectra were obtained using a Hewlett Packard 8452A Diode Array Spectrophotometer. Samples of **1** and the mixture of **1** and **2** were prepared as thin films deposited by spin-casting on quartz using CH_2Cl_2 as solvent. The spectrum for **2** was measured in CH_2Cl_2 , $\lambda_{\text{max}} = 268$, $\epsilon = 7.08 \times 10^{-6} \text{ cm}^{-1}\text{M}^{-1}$.

all 1:1 complexes we found that the peaks characteristic of the single compounds had vanished and new sets of peaks had appeared (Table 1). Figure 3 shows the DSC traces of **1**, **2**, and a 1:1 mixture of **1** and **2** as representative examples of the results obtained for 1:1 mixtures of the low molecular weight compounds **1** with **2**. The DSC trace of **1** exhibits two first-

Table 1. DSC analyses of compounds **1**, **2**, **4**, and the 1:1 mixtures of **2** and **1** as well as from **2** and **4** (the second heating scans are shown; scan rate [10 K min^{-1}])

Compound	Phase transition [$^{\circ}\text{C}$]	Compound	Phase transition [$^{\circ}\text{C}$]
1	K19D _{hd} 36i	1:2 (1:1)	D _{hd1} 21D _{hd2} 104i
2	k109i	2:4 (1:1)	k123i
4	g41i		

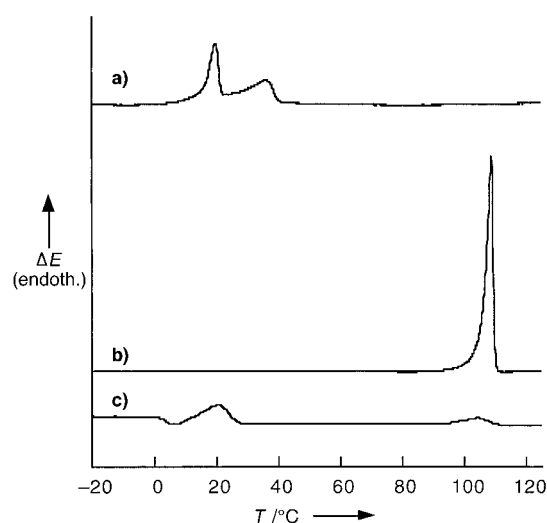


Figure 3. Normalized DSC thermograms for a) liquid crystal mesogen **1**, b) perfluorotriphenylene **2**, and c) a 1:1 mixture of **1** and **2** obtained at a scan rate of 10 K min^{-1} .

order transitions at 19°C and 36°C , while the DSC trace of **2** only shows one first-order endotherm at 109°C . In the 1:1 mixture of **1** and **2**, none of the first-order transitions observed for the single compounds were detected. By contrast, two new first-order transitions at 21°C and 104°C were observed.

To assign the mesophases of the 1:1 mixtures of **1** with **2**, optical polarized microscopy and powder X-ray diffraction were employed.^[32, 33] The 1:1 mixtures of **1** with **2** displayed fan-shaped textures characteristic of a discotic hexagonal (D_h) mesophase which were observed upon cooling from the isotropic melt (Figure 4). These results were substantiated by



Figure 4. Polarized optical micrograph (magnification $50\times$) of the fan-shaped texture observed at 90.8°C on cooling of a 1:1 mixture of **1** and **2** from the isotropic state.

powder X-ray diffraction spectroscopy results, which showed highly ordered columnar alignments of the mesogens in all cases, thereby demonstrating that no mesophase changes took place after mixing **1** with **2**, but that the columnar alignments of the mesogenic units are still present. This clearly shows that the LC mesophase is stabilized by the arene–perfluoroarene interaction with the stabilization resulting in an increase in the clearing temperature of 70°C .^[34, 35]

The trend toward phase stabilization is also evident in the 1:1 mixture of **2** and **4** (Figure 5). While polymer **4** displayed only a glass transition at 41°C , the 1:1 mixture of **4** and **2** clearly showed a first-order endotherm (crystallization peak) at 123°C . As in the above case, no signals characteristic of the individual compounds were observed in the 1:1 mixture. Thus, by adding an equal amount of the small molecule perfluoro-triphenylene **2** (based on triphenylene functionalities of **4**) to **4**, the polymer was driven to crystallization. This is, in contrast to the normal plastization of polymers, induced by small molecules.

In conclusion, we have introduced a new concept to modify phase behavior of compounds containing triphenylene moieties using arene–perfluoroarene interactions. The temperature range of the liquid crystalline discotic hexagonal mesophase was enlarged by adding a perfluoroarene. Furthermore, a polymeric material that in the absence of additives displays only a glass transition was driven to

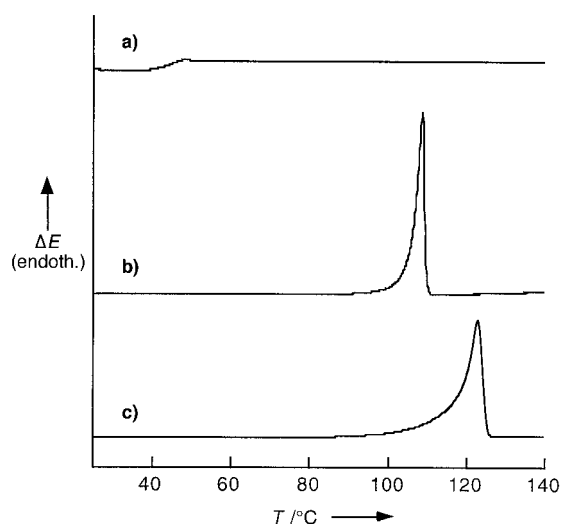


Figure 5. Normalized DSC thermograms for a) polymer **4**, b) perfluorotriphenylene **2**, and c) a 1:1 mixture of **4** and **2** obtained at a scan rate of 10 K min⁻¹.

crystallization through the addition of a small perfluorinated molecule. At present, experiments are underway to extend this concept to different classes of liquid crystals. If successful, this approach could lead to a general strategy to enhance liquid crystalline mesophases in liquid crystals, thereby overcoming a major obstacle for the technical use of such materials.

Received: January 18, 1999 [Z12928IE]

German version: *Angew. Chem.* **1999**, *111*, 2909–2912

Keywords: arenes • liquid crystals • polymerizations • stacking interactions • supramolecular chemistry

- [1] J. M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, **1995**, and references therein.
- [2] J. M. Lehn, *Angew. Chem.* **1988**, *100*, 91; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89.
- [3] G. R. Desiraju, *Angew. Chem.* **1995**, *107*, 2541; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2311.
- [4] D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154.
- [5] G. M. Whitesides, E. E. Simanek, J. P. Mathias, C. T. Seto, D. N. Chin, M. Mammen, D. M. Gordon, *Acc. Chem. Res.* **1995**, *28*, 37.
- [6] For an excellent contribution of the nature of π – π interactions as well as their use in chemistry and biology, see: C. A. Hunter, *Chem. Soc. Rev.* **1994**, *101*, and references therein.
- [7] a) S. C. Zimmerman, Z. Zeng, W. Wu, D. E. Reichert, *J. Am. Chem. Soc.* **1991**, *113*, 183; b) J. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **1992**, *114*, 9701; c) S. Paliwal, S. Geib, C. S. Wilcox, *J. Am. Chem. Soc.* **1994**, *116*, 4497.
- [8] G. Jones, B. J. Chapman, *Synthesis* **1995**, 475, and references therein.
- [9] D. Adam, P. Schuhmacher, J. Simmerer, L. Häussling, K. Siemensmeyer, K. Etzbach, H. Ringsdorf, D. Haarer, *Nature* **1994**, *371*, 141.
- [10] M. Luhmer, K. Batrik, A. Dejaegere, P. Bovy, J. Reisse, *Bull. Soc. Chim. Fr.* **1994**, *131*, 603.
- [11] J. C. Ma, D. A. Dougherty, *Chem. Rev.* **1997**, *97*, 1303.
- [12] V. Ramamurthy, D. F. Eaton, *Chem. Mater.* **1994**, *6*, 1128.
- [13] T. Dahl, *Acta Chem. Scand.* **1994**, *48*, 95.
- [14] A. P. West, Jr., S. Mecozzi, D. A. Dougherty, *J. Phys. Org. Chem.* **1997**, *10*, 347.
- [15] C. R. Patrick, G. S. Prosser, *Nature* **1960**, *187*, 1021.

- [16] a) G. W. Coates, A. R. Dunn, L. M. Henling, D. A. Dougherty, R. H. Grubbs, *Angew. Chem.* **1997**, *109*, 290; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 248; b) G. W. Coates, A. R. Dunn, L. M. Henling, J. W. Ziller, E. B. Lobkovsky, R. H. Grubbs, *J. Am. Chem. Soc.* **1998**, *120*, 3641.
- [17] F. Cozzi, F. Ponzini, R. Annunziata, M. Cinquini, J. S. Siegel, *Angew. Chem.* **1995**, *107*, 1092; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1019.
- [18] J. H. Williams, *Acc. Chem. Res.* **1993**, *26*, 593.
- [19] T. Dahl, *Acta Chem. Scand. A* **1988**, *42*, 1, and references therein.
- [20] a) J. Hernández-Trujillo, M. Costas, A. Vela, *J. Chem. Soc. Farad. Trans.* **1993**, *89*, 2441; b) J. H. Williams, J. K. Cockcroft, A. N. Fitch, *Angew. Chem.* **1992**, *104*, 1666; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1655; c) J. Vrbancich, L. D. Ritchie, *J. Chem. Soc. Farad. Trans. 2* **1980**, *76*, 648; d) J. M. Steed, T. A. Dixon, W. Klemperer, *J. Chem. Phys.* **1979**, *70*, 4940. e) R. E. Gillard, J. F. Stoddart, A. J. P. White, B. J. Williams, D. J. Williams, *J. Org. Chem.* **1996**, *61*, 4504.
- [21] a) V. B. Smith, A. G. Massey, *Tetrahedron* **1969**, *25*, 5495; b) M. B. Hursthouse, V. B. Smith, *J. Fluorine Chem.* **1977**, *10*, 145.
- [22] For a general review of the stabilization of liquid crystals through donor–acceptor interactions, see: a) K. Praefcke, J. D. Holbrey, *J. Inclusion. Phenom. Mol. Recognit. Chem.* **1996**, *24*, 19; b) D. Demus, J. Goodby, G. W. Gray, H. W. Spiess, V. Vill, *Handbook of Liquid Crystals Vol. 2B*, WILEY-VCH: Weinheim, **1998**, and references therein.
- [23] For phase stabilization in calamitic liquid crystals, see: a) G. Pelzl, D. Demus, H. Sackmann, *Z. Phys. Chem.* **1968**, *238*, 22; b) N. Homura, Y. Matsunaga, M. Suzuki, *Mol. Cryst. Liq. Cryst.* **1985**, *131*, 273; c) W. H. De Jeu, L. Longa, *J. Chem. Phys.* **1986**, *84*, 6410.
- [24] For examples of mesophase stabilization using trinitrofluorenes, see: a) H. Ringsdorf, R. Wüstefeld, E. Zerta, M. Ebert, J. H. Wendorff, *Angew. Chem.* **1989**, *101*, 934; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 914; b) K. Praefcke, D. Singer, B. Kohne, M. Ebert, A. Liebmann, J. H. Wendorff, *Liq. Cryst.* **1991**, *10*, 147; c) R. Lunkwitz, B. Neumann, C. Tschierske, *Liq. Cryst.* **1998**, *25*, 403.
- [25] a) Crystal structure data for the triphenylene cocrystal (single crystal from CH₂Cl₂): C₁₈H₆F₆, *M_r* = 336.23, crystal dimensions 0.4 × 0.2 × 0.05 mm, monoclinic, space group *C2/c*, *a* = 7.3899(7), *b* = 20.9871(19), *c* = 16.9977(15) Å, β = 95.255(1), *V* = 2625.1(4) Å³, *Z* = 8, ρ_{calc} = 1.701 g cm⁻³, $2\theta_{\text{max}}$ = 43.92°, SMART diffractometer (MoK α , λ = 0.71073 Å, graphite monochromator), ω scans, *T* = 295(2) K, 4971 measured reflections, 1603 reflections were used in the refinement. Lorentz and polarization factors were applied; μ = 1.58 cm⁻¹; structure and refinement: direct methods (SHELXS-97), full-matrix least-squares refinement of *F*² (SHELXL-97); 241 parameters. Hydrogen atoms were refined isotropically. *R* = 0.044 with *F*_o² > 2 σ (*F*_o²), *R* = 0.0685 with *F*_o² > 0, *wR* = 0.1101, $\Delta\rho_{\text{max}}$ = 0.164, $\Delta\rho_{\text{min}}$ = -0.229 e Å⁻³. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-120572. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). c) In this case, tilt is defined as the end-to-end twist of the central ring and the outer ring which is bisected by the C₂ axis of the molecule. The authors noted that different software packages gave slightly different values for these dihedral angles.
- [26] For the introduction of chirality in discotic hexagonal liquid crystals, see: a) K. Praefcke, A. Eckert, D. Blunk, *Liq. Cryst.* **1997**, *22*, 757; b) N. Boden, R. J. Bushby, A. N. Cammidge, G. Headdock, *J. Mater. Chem.* **1997**, *7*, 601; c) K. Praefcke, A. Eckert, D. Blunk, *Liq. Cryst.* **1997**, *22*, 113. In order to impart permanent chirality, perfluorotriphenylene would have to be chemically modified to prevent the rapid interconversion between stereoisomers.
- [27] For compound **1**, see: a) P. G. Schouten, J. F. Van der Pol, J. W. Zwicker, W. Drenth, S. J. Picken, *Mol. Cryst. Liq. Cryst.* **1991**, *195*, 291; b) N. Boden, R. C. Borner, R. J. Bushby, A. N. Cammidge, M. V. Jesudason, *Liq. Cryst.* **1993**, *15*, 851.
- [28] For compound **2**, see: a) M. B. Hursthouse, V. B. Smith, *J. Fluorine Chem.* **1977**, *10*, 145; b) C. S. Frampton, D. D. MacNicol, S. J. Rowan, *J. Mol. Struct.* **1997**, *405*, 169.
- [29] For a survey of catalysts and monomers used in ring-opening metathesis polymerization, see: K. J. Ivin, *Olefin Metathesis*, Academic Press: London, **1996**.

- [30] A detailed experimental description of the synthesis of **3** will be published elsewhere.
- [31] Unfortunately the small crystal size of the 1:1 complexes did not permit X-ray structure analysis.
- [32] Differential scanning calorimetry measurements were performed on a Perkin-Elmer DSC-7 with a 10 K min⁻¹ scan rate. GPC analyses were obtained on an HPLC system utilizing an Altex Model 110A pump, a Rheodyne model 7125 injector with a 100 µL injection loop, through two American Polymer Standards 10 micron mixed bed columns, and a Knauer differential-refractometer. The molecular weights and polydispersities are reported versus monodisperse polystyrene standards. Microscopic observations of the textures were made using a Zeiss Universal Polarizing Microscope equipped with a Minolta camera. Powder X-ray diffraction measurements were performed by using a SCINTAC INC., USA XDS-2000 instrument equipped with a high-temperature attachment.
- [33] Triphenylene **1** displayed discotic hexagonal liquid crystalline mesophase behavior. The polarized optical micrographs showed fan-shaped textures characteristic of discotic hexagonal mesophases.
- [34] If phase separation instead of mixing had taken place, signals characteristic of the single compounds would have been detected.
- [35] A small excess of a component can be detected in the DSC through the signals characteristic of the single compounds.

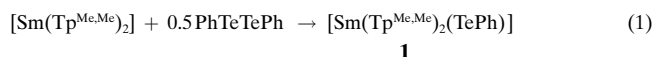
(PhTe)₃⁻: The Anionic Tellurium Analogue of I₃⁻**

Anna C. Hillier, Sung-Ying Liu, Andrea Sella,* and Mark R. J. Elsegood

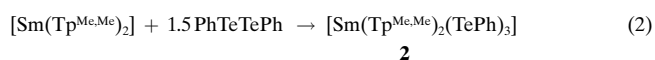
The chemistry of tellurium is an intriguing area for solid-state chemists, and numerous unexpected examples of structures not easily rationalized by simple models of bonding have come to light.^[1] Tritelluride units are a recurring motif in this chemistry, although these are often found as part of polymeric networks in which the interatomic interactions may be thought of as being supported by the network. Such structures are often related to those of the polyhalides, in particular I₃⁻; the direct analogue, the Te₃⁴⁻ ion, remains elusive.^[2, 3] The classic bent hypervalent Zintl ion Te₃²⁻ was first isolated by Corbett and Cisar in 1977.^[4-6] A cluster containing the linear selenium analogue Se₃⁴⁻ has been reported where the Se₃ unit

forms part of an overall Sm₃Se₁₁ cluster.^[7] A formal (but cationic) triiodide analogue, pentamethyltritellurium, was synthesized recently by addition of a Te₁ cation to a Te₂ unit.^[8] We now report the preparation of the corresponding *anionic* analogue of triiodide by the direct addition of diphenylditelluride to a tellurolate anion formed by reduction with divalent samarium.

Reductive cleavage of dichalcogenides RQQR (Q = S, Se, Te) is a convenient method for the synthesis of lanthanide chalcogenolates.^[9-13] Reaction of diphenylditelluride (0.5 molar equiv) with [Sm(Tp^{Me,Me})₂]^[14, 15] (Tp^{Me,Me} = hydrotris(3,5-dimethylpyrazolyl)borate) in toluene gave an orange solution, from which **1** could be isolated as a bright orange powder [Eq. (1)]. Complex **1** gives a simple ¹H NMR spectrum similar to that observed for [Sm(Tp^{Me,Me})₂(OTf)] (Tf = F₃CSO₂) at room temperature.^[16] The *ortho* hydrogen atoms of the phenyl group are significantly deshielded by the paramagnetic samarium center, suggesting a close interaction between the tellurium atom and the metal.



Addition of a 1.5-fold excess of PhTeTePh to [Sm(Tp^{Me,Me})₂] resulted in the formation of an orange solution, from which a moderately air sensitive deep red powder of stoichiometry [Sm(Tp^{Me,Me})₂(TePh)₃] (**2**) was isolated [Eq. (2)]. Compound **2** could also be prepared by addition of PhTeTePh to a solution of **1**.



The ¹H NMR spectrum of **2** was similar to that of **1**. The chemical shifts of the phenyl protons were, however, normal and apparently unaffected by the paramagnetic samarium center. The spectrum was temperature invariant, consistent with a symmetrical and nonfluxional coordination sphere around the metal. These observations are in agreement with a saltlike formulation, implying a six-coordinate metal center analogous to that in [Sm(Tp^{Me,Me})₂]BPh₄.^[17] The ¹²⁵Te spectrum of **2** at room temperature consists of a single peak at δ = 415, which is very similar to the chemical shift of diphenylditelluride (δ = 422). Although there was a considerable temperature dependence of the signal, no broadening of the signal was observed down to -80 °C.

Compound **2** was crystallized in both unsolvated (**2a**) and solvated forms (**2b**) from toluene. The structures show similar gross features, but only **2b** will be discussed here as the quality of the dataset for **2a** was marginal. The asymmetric unit consists of well-separated ions [Sm(Tp^{Me,Me})₂]⁺ and [Te₃Ph₃]⁻ (Figure 1) and half a molecule of toluene. No significant intermolecular or interionic contacts were noted. The cation is six-coordinate and similar to those in [Sm(Tp^{Me,Me})₂]I and [Sm(Tp^{Me,Me})₂]BPh₄.^[17] and the average Sm-N bond length (245(5) pm) is typical of this kind of system.

The [Te₃Ph₃]⁻ anion is very slightly bent (∠(Te-Te-Te) 172.92(3)°), consistent with the VSEPR prediction. This is in contrast to the diorganyltritellurides, which show significant

[*] Dr. A. Sella, Dr. A. C. Hillier, Dr. S.-Y. Liu
Christopher Ingold Laboratories
Department of Chemistry, University College London
20 Gordon Street, London WC1H0AJ (UK)
Fax: (+44) 171-380-7463
E-mail: a.sella@ucl.ac.uk
M. R. J. Elsegood
Department of Chemistry, Bedson Building
University of Newcastle
Newcastle upon Tyne NE1 7RU (UK)

[**] We are grateful to the EPSRC for a studentship to A.C.H. (GR/K11338) and for provision of the X-ray diffractometer (grant awarded to Prof. W. Clegg), and to the Formosa Chemical Company for a study leave to S.-Y.L. We thank Prof. W. Clegg for use of the SMART X-ray diffractometer and associated computer programs and facilities. We are grateful to Prof. Josef Takats, Prof. John G. Brennan, and Dr. Noemia Marques for helpful discussions, and to Prof. R. J. H. Clark for his interest and support.

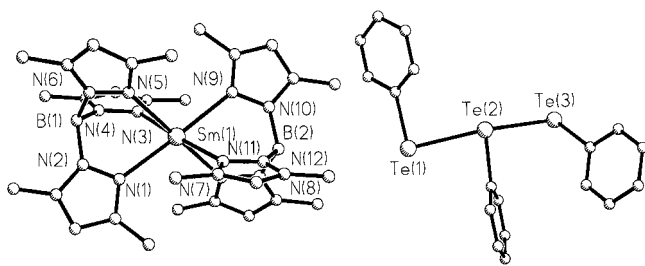


Figure 1. Ball-and-stick view of the cation and anion units in **2b**. Selected bond lengths [pm] and angles [°]: Te(1)–Te(2) 311.2(1), Te(2)–Te(3) 293.9(1); Te(1)–Te(2)–Te(3) 172.92(3).

bending at the central tellurium atom ($100\text{--}103^\circ$),^[18, 19] and the recently reported $[(\text{Mes})_2\text{Te}_2\text{Te}(\text{Mes})]^+$ cation ($159.51(3)^\circ$; Mes = 2,4,6-Me₃C₆H₂).^[8] The anion of **2** is unsymmetrical with Te–Te bond lengths of 293.9(2) and 311.3(1) pm. Both distances are significantly longer than in singly bonded compounds such as organoditellurides RTeTeR (typically 269–275 pm),^[11, 20–23] in the Te₂^{2–} bridging group of $[(\text{SmCp}^*_2)_2(\mu\text{-Te}_2)]$ (277.3(1) pm),^[24] in the tritellurides $[(\text{Me}_3\text{Si})_3\text{Si}]_2\text{Te}_3$ (271.0(1) pm)^[18] and $[(2\text{-pyrPh})_2\text{Te}_3]$ (277.6(1) pm, pyr = pyridyl),^[19] in the crown-shaped Te₈ rings of Cs₃Te₂₂ (280(2) pm),^[25] and in elemental tellurium itself (283.45(8) pm).^[26] Rather, the Te–Te distances are comparable to those observed in the pentamesitylditellurium cation (304.91(10) and 297.91(10) pm)^[8] and in the linear polyiodide analogue Te₅^{4–} present in NaTe (282–308 pm).^[27] A similarly long Te–Te distance is also found in the complex $[\text{Ru}_2(\eta\text{-C}_5\text{Me}_5)_2(\mu\text{-TePh})_2(\mu\text{-PhTeTePh})]$ with an intact bridging ditelluride moiety (290.1(3) pm).^[28]

The asymmetry of the ion, suggesting a neutral diphenylditelluride unit bound to a phenyltellurolate anion, is reminiscent of the triiodide ion, which has been isolated in both symmetrical^[29] and unsymmetrical structures,^[30] depending upon the counteranion. This analogy is further supported by the fact that we have also prepared the corresponding triiodide $[\text{Sm}(\text{Tp}^{\text{Me,Mes}})_2]\text{I}_3$ (**3**) by the reaction of $[\text{Sm}(\text{Tp}^{\text{Me,Mes}})_2]$ with excess iodine in toluene.

It is quite surprising to us that the (TePh)₃[–] anion has not been reported previously since it appears to be so easy to prepare in high yield. We assume that it is simply stabilized in the solid state by the presence of the large $[\text{Sm}(\text{Tp}^{\text{Me,Mes}})_2]^+$ cation. Experiments are in progress to verify whether the (TePh)₃[–] anion can be isolated after reduction with alkali metals in the presence of crown ethers. Preliminary experiments suggest, however, that sulfur and selenium analogues cannot be prepared analogously.

Experimental Section

1: $[\text{Sm}(\text{Tp}^{\text{Me,Mes}})_2]$ (100 mg, 0.13 mmol) and Te₂Ph₂ (27 mg, 0.065 mmol) were stirred in toluene at room temperature. The purple solid dissolved to give a red-orange, slightly turbid solution, which was filtered to give a clear deep red solution. The volume was reduced to 10 mL, and the solution cooled slowly to -20°C to give dark red crystals of **1**. Yield: 66 mg (54%). X-ray quality crystals were obtained by slow cooling of a solution in toluene. Elemental analysis calcd for C₃₆H₄₀N₁₂B₂SmTe: C 48.32, H 5.42, N 16.63; found: C 48.71, H 5.37, N 16.40; ¹H NMR (300 MHz, C₆D₆, 20°C ,

TMS): $\delta = -0.695$ (s, 18 H; 3-Me), 2.13 (s, 18 H; 5-Me), 5.465 (s, 6 H; CH), 7.35 (m, 2 H; *o*-Ph), 7.49 (m, 1 H; *p*-Ph), 9.47 (d, 2 H; *o*-Ph); IR (KBr): $\tilde{\nu} = 2554\text{ cm}^{-1}$ (BH).

2: Compound **2** was prepared according to a procedure analogous to that of **1** using Te₂Ph₂ (83 mg, 0.20 mmol). Yield: 72 mg (41%). X-ray quality crystals were obtained by slow cooling of a solution in toluene. Elemental analysis calcd for C₄₈H₅₀N₁₂B₂SmTe₃: C 42.33, H 4.38, N 12.37; found: C 43.28, H 4.36, N 12.50; ¹H NMR (300 MHz, C₆D₆, 20°C , TMS): $\delta = -0.99$ (s, 18 H; 3-Me), 3.08 (s, 18 H; 5-Me), 5.53 (s, 6 H; CH), 7.19 (m, 5 H; Ph); ¹³C NMR (100.16 MHz, C₆D₆, 20°C , TMS): $\delta = 11.3$ (q, 3 or 5 Me), 14.2 (q, 5 or 3 Me), 105.4 (d, C-H), 128.1 (d, Ph), 129.3 (s, Ph), 137.6 (d, Ph), 139.0 (d, Ph), 145.5 (s, C(3) or C(5)), 149.4 (s, C(5) or C(3)); ¹²⁵Te NMR (126.38 MHz, [D₈]toluene, 20°C , Me₂Te): $\delta = 415$ (s); IR (KBr): $\tilde{\nu} = 2554\text{ cm}^{-1}$ (BH).

3: To a purple slurry of $[\text{Sm}(\text{Tp}^{\text{Me,Mes}})_2]$ (100 mg, 0.13 mmol) in toluene at room temperature was added a solution of iodine (51 mg, 0.2 mmol). An immediate color change from purple to orange was observed along with the formation of an orange precipitate. The toluene was removed under reduced pressure, and the orange solid redissolved in dichloromethane. Addition of diethyl ether resulted in precipitation of the product. The mixture was allowed to settle for 1 h, the yellow supernatant was decanted, and the orange brown powder (**3**) was dried at room temperature under dynamic vacuum. Yield: 104 mg (71%). Elemental analysis calcd for C₃₆H₄₀N₁₂B₂SmI₃: C 32.02, H 3.94, N 14.93; found: C 31.73, H 3.83, N 14.59; ¹H NMR (300 MHz, CDCl₃, 20°C , TMS): $\delta = -2.57$ (s, 18 H; 3-Me), 4.03 (s, 18 H; 5-Me), 5.21 (s, 6 H; CH); ¹³C NMR (100.16 MHz, CDCl₃, 20°C , TMS): $\delta = 9.3$ (q; 3 or 5 Me), 15.3 (q; 5 or 3 Me), 102.1 (d; C-H), 144.0 (s; C(3) or C(5)), 147.6 (s; C(5) or C(3)); IR (KBr): $\tilde{\nu} = 2554\text{ cm}^{-1}$ (BH).

X-ray structure analysis: **2a:** C₄₈H₅₀N₁₂B₂SmTe₃, red crystal, $0.31 \times 0.23 \times 0.17$ mm, $M_r = 1358.84$, monoclinic, space group $P2_1/c$, $a = 8.7348(11)$, $b = 14.035(2)$, $c = 43.857(13)$ Å, $\beta = 88.751(2)^\circ$, $V = 5372.8(19)$ Å³, $Z = 4$, $F(000) = 2636$, $\rho_{\text{calcd}} = 1.680\text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 2.734\text{ mm}^{-1}$, $2\theta_{\text{max}} = 46^\circ$, $T = 160\text{ K}$. A total of 8941 reflections were collected on a Stoe-Siemens four-circle diffractometer using graphite-monochromated MoK α radiation ($\lambda = 0.71073$), ω/θ scans, and on-line profile fitting.^[31] Data were corrected for Lp effects and for absorption by ψ scans (transmission: 0.654–0.485). The structure was solved by direct methods and refined by full-matrix least squares on F^2 to $wR2 = 0.2637$ for 7343 independent data and 607 parameters; $R = 0.0884$. Hydrogen atoms were included in a riding model. The largest features in the final electron density map within $+2.35$ and -2.35 e Å^{-3} were close to heavy atoms. Programs: Bruker AXS SHELXTL (structure solution and refinement), Stoe DIF4 (data collection), and local programs.

2b: C₄₈H₅₀N₁₂B₂SmTe₃·0.5 C₇H₈, red crystal, $0.17 \times 0.16 \times 0.04$ mm, $M_r = 1404.91$, monoclinic, space group $P2_1/n$, $a = 8.6288(5)$, $b = 13.8812(8)$, $c = 46.185(3)$ Å, $\beta = 95.031(2)^\circ$, $V = 5510.6(6)$ Å³, $Z = 4$, $F(000) = 2736$, $\rho_{\text{calcd}} = 1.693\text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 2.668\text{ mm}^{-1}$, $2\theta_{\text{max}} = 50^\circ$, $T = 160\text{ K}$. A total of 38653 reflections were collected on a Bruker AXS SMART CCD area detector diffractometer with narrow frames (0.3°) using graphite-monochromated MoK α radiation ($\lambda = 0.71073$ Å). Data corrections as for **2a** (transmission: 0.901–0.660). The structure was solved by direct methods (refinement and treatment of hydrogen atoms as for **2a**). $wR2 = 0.1249$ (9707 unique data), 634 parameters, $R = 0.0788$. The largest features in the final electron density map within $+2.32$ and -2.32 e Å^{-3} were close to heavy atoms. Programs: Bruker AXS SMART and SAINT for data collection and reduction, SHELXTL, and local programs.

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-114734 (**2a**) and CCDC-114735 (**2b**). 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).

Received: March 5, 1999 [Z13117IE]
German version: *Angew. Chem.* **1999**, *111*, 2918–2920

Keywords: borates • iodine • lanthanides • samarium • tellurium

- [1] a) P. Böttcher, *Angew. Chem.* **1988**, *100*, 781–794; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 759–772; b) M. A. Ansari, J. A. Ibers, *Coord. Chem. Rev.* **1990**, *100*, 223–266.
- [2] M. G. Kanatzidis, *Angew. Chem.* **1995**, *107*, 2281–2283; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2109–2111.
- [3] Q. Liu, N. Goldberg, R. Hoffmann, *Chem. Eur. J.* **1996**, *2*, 390–397.
- [4] A. Cisar, J. D. Corbett, *Inorg. Chem.* **1977**, *16*, 623.
- [5] J. Shreeve Keyer, C. Warren, S. Dhingra, R. Haushalter, *Polyhedron* **1997**, *16*, 1193–1199.
- [6] R. Zagler, B. Eisenmann, H. Schafer, *Z. Naturforsch. B* **1987**, *42*, 151–156.
- [7] W. J. Evans, G. W. Rabe, M. A. Ansari, J. W. Ziller, *Angew. Chem.* **1994**, *106*, 2200–2201; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2110.
- [8] J. Jeske, W.-W. du Mont, P. G. Jones, *Angew. Chem.* **1997**, *109*, 2304; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2219–2221.
- [9] A. Strzelecki, C. Liker, B. Helsel, T. Utz, M. Lin, P. Bianconi, *Inorg. Chem.* **1994**, *33*, 5188–5194.
- [10] K. Mashima, Y. Nakayama, T. Shibahara, H. Fukumoto, A. Nakamura, *Inorg. Chem.* **1996**, *35*, 93.
- [11] J. Becker, J. Bernstein, M. Dayan, L. Shahal, *Chem. Commun.* **1992**, 1048–1049.
- [12] M. Berardini, J. Lee, D. Freedman, J. Lee, T. J. Emge, J. G. Brennan, *Inorg. Chem.* **1997**, *36*, 5772–5776.
- [13] D. Freedman, T. J. Emge, J. G. Brennan, *J. Am. Chem. Soc.* **1997**, *119*, 11114–11115.
- [14] G. H. Maunder, A. Sella, D. A. Tocher, *Chem. Commun.* **1994**, 885–886.
- [15] J. Takats, X. W. Zhang, V. W. Day, T. A. Eberspacher, *Organometallics* **1993**, *12*, 4286–4288.
- [16] S.-Y. Liu, G. H. Maunder, A. Sella, M. Stephenson, D. A. Tocher, *Inorg. Chem.* **1996**, *35*, 76–82.
- [17] J. Takats, personal communication.
- [18] F. Sladky, B. Bildstein, C. Rieke, A. Gieren, H. Betz, T. Hübner, *Chem. Commun.* **1985**, 1800–1801.
- [19] T. A. Hamor, N. Al Salim, A. A. West, W. R. McWhinnie, *J. Organomet. Chem.* **1986**, *310*, C5–C7.
- [20] G. Llabres, O. Dideberg, L. Dupont, *Acta Crystallogr. Sect. B* **1972**, *28*, 2438–2442.
- [21] M. R. Spirlet, G. Van de Bossche, O. Dideberg, L. Dupont, *Acta Crystallogr. Sect. B* **1979**, *35*, 1727–1735.
- [22] D. J. Sandman, L. Li, S. Tripathy, J. C. Starck, L. A. Acampora, B. M. Foxman, *Organometallics* **1994**, *13*, 348–353.
- [23] A. Edelmann, S. Brooker, N. Bertel, M. Noltemeyer, H. W. Roesky, G. M. Sheldrick, F. T. Edelmann, *Z. Naturforsch. B* **1992**, *47*, 305–309.
- [24] W. J. Evans, G. W. Rabe, J. W. Ziller, R. J. Doedens, *Inorg. Chem.* **1994**, *33*, 2719–2726.
- [25] W. S. Sheldrick, M. Wachhold, *Angew. Chem.* **1995**, *107*, 490; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 450–451.
- [26] P. Cherin, P. Unger, *Acta. Crystallogr.* **1967**, *23*, 670–675.
- [27] P. Böttcher, R. Keller, *J. Less-Common Met.* **1985**, *109*, 311–321.
- [28] H. Matsuzaka, T. Ogino, M. Nishio, Y. A. Noshibashi, S. Uemura, M. Hidai, *Chem. Commun.* **1994**, 223–224.
- [29] R. C. Mooney-Slater, *Acta Crystallogr. B* **1959**, *12*, 187–196.
- [30] H. A. Tasmin, K. H. Bozwijk, *Acta Crystallogr.* **1955**, *8*, 59–60.
- [31] W. Clegg, *Acta Crystallogr. Sect. A* **1981**, *37*, 22.

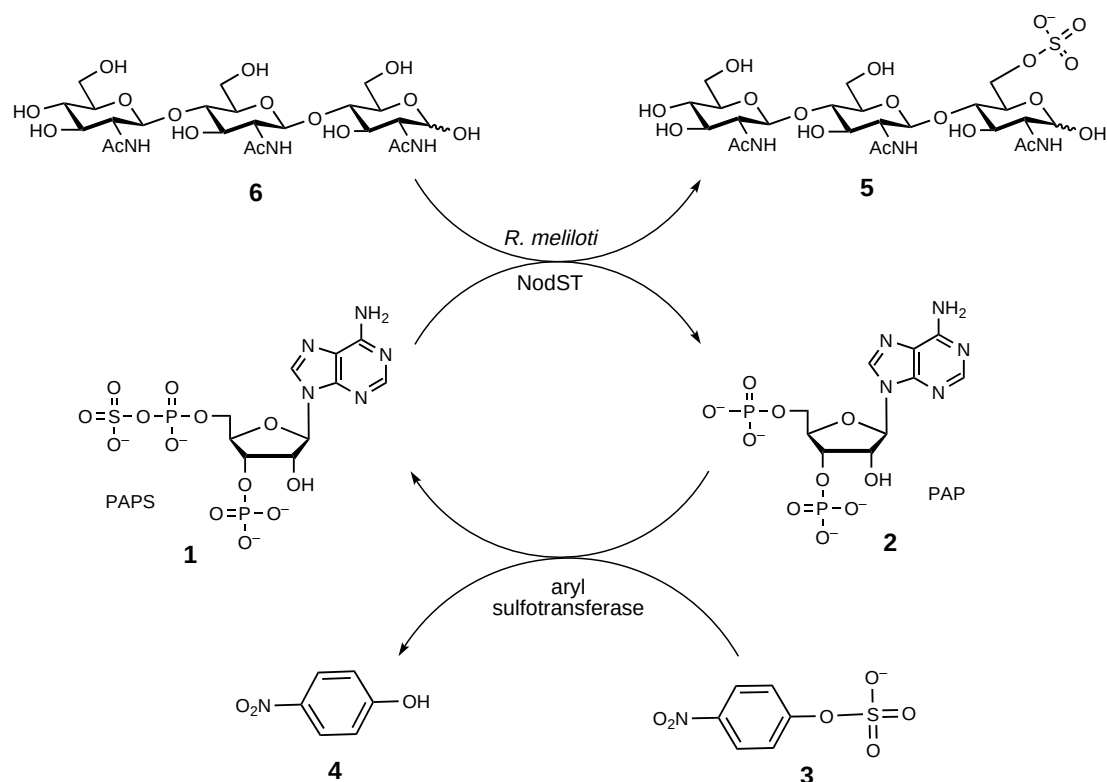
Enzymatic Regeneration of 3'-Phosphoadenosine-5'-Phosphosulfate Using Aryl Sulfotransferase for the Preparative Enzymatic Synthesis of Sulfated Carbohydrates

Michael D. Burkart, Masayuki Izumi, and Chi-Huey Wong*

Sulfotransferases comprise a family of enzymes that catalyze the transfer of a sulfo group (SO_3^-) from the cofactor 3'-phosphoadenosine-5'-phosphosulfate (PAPS, **1**) to an acceptor molecule. Sulfotransferases mediate the sulfation of different classes of substrates such as carbohydrates, proteins, and steroids for a variety of biological functions including signaling and modulation of receptor binding.^[1, 2] Within the past three years many new sulfotransferases have been identified and cloned.^[3] A facile means to produce large amounts of sulfated product and efficient sulfotransferase assays are essential for the biological study of these enzymes and their sulfated products.

The cofactor PAPS, the universal sulfate donor and source of sulfate for all sulfotransferases, is a highly expensive and unstable molecule that has been an obstacle to the large-scale production of enzymatically sulfated products.^[4] Product inhibition by adenosine 3',5'-diphosphate (PAP, **2**) has also been a limiting factor to large-scale applications.^[5, 6] We reported the first enzymatic regeneration of PAPS based on a multienzyme system coupled with *Rhizobium* Nod factor sulfotransferase (NodST) for the enzymatic synthesis of *N,N'*-diacetylchitobiose 6-sulfate.^[6] While application of the cloned enzymes used in this recycling system serve as a facile and efficient means to synthesize PAPS on a large scale, we have developed here a simpler, one-enzyme regeneration system using a recombinant rat liver aryl sulfotransferase IV (AST IV; Scheme 1). This enzyme, when coupled to a sulfotransferase of choice, transfers a sulfo group (SO_3^-) from *p*-nitrophenyl sulfate (**3**) to PAP.^[7] This system averts product inhibition by PAP while regenerating PAPS in situ and can be monitored quantitatively by measurement of the absorbance of released *p*-nitrophenol (**4**) at 400 nm. Additionally, this recycling system can be modified to serve as a continuous spectrophotometric assay for the activity of any sulfotransferase enzyme. The most common assay of sulfotransferase activity involves monitoring the transfer of radioisotopic sulfate from [^{35}S]PAPS to the product by thin-layer or paper chromatography using end-point methods.^[8] These assays are expensive and often imprecise.^[9] Demonstrated here is the use of this one-enzyme PAPS regeneration system for the synthesis of *N,N',N''*-triacylchitotriose 6-sulfate (**5**) and of a continuous, colorimetric, coupled-enzyme assay of NodST to determine the substrate specificity of this enzyme.

[*] Prof. C.-H. Wong, M. D. Burkart, M. Izumi
Department of Chemistry
and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2409
E-mail: wong@scripps.edu



Scheme 1. Regeneration of PAPS with recombinant aryl sulfotransferase and *p*-nitrophenyl sulfate.

The enzyme AST IV exists in two forms with different oxidation states^[10, 11] that can be easily resolved, and the isolated physiologically relevant form has been utilized to assay picomole quantities of PAPS and PAP.^[12] Since the bacterial expression of rat T IV has been demonstrated,^[13, 14] we cloned AST IV from a rat liver cDNA library and overexpressed the enzyme in *Escherichia coli*. To obtain the pure β form of the enzyme, in which PAP is not bound in the active site, conversion of the mixed enzyme forms was simply carried out during purification through nickel-agarose chromatography. The enzyme-bound nickel resin was incubated with alkaline phosphatase and β -mercaptoethanol (BME) prior to elution. The purified enzyme was then immediately available for PAPS regeneration. Capillary zone electrophoresis (CZE) was employed to distinguish between the ability of AST IV to form PAPS from PAP and *p*-nitrophenyl sulfate rather than effect mere hydrolysis of *p*-nitrophenyl sulfate, and it verified the production of PAPS from PAP.

N,N,N'-Triacetylchitotriose 6-sulfate (207 mg) was synthesized in 58 % yield from commercially available NodST and the β form of AST IV with 0.05 equivalents of PAP and 2.0 equivalents of *p*-nitrophenyl sulfate. The structure was confirmed by electrospray ionization (ESI) mass spectrometry, HPLC, and NMR spectroscopy. The same procedure was used in the synthesis of *N,N,N',N''*-tetraacetylchitotetraose 6-sulfate (150 mg, 95 % yield).

The continuous assay for kinetic analysis of sulfotransferases resembles the large-scale methodology with the exception that PAPS is added to the reaction in place of PAP, since the purpose of the assay is the continuous measurement of PAP production. The assay utilizes the β form of AST IV

described above. To demonstrate the application of this assay to the determination of enzymatic kinetic parameters, *N,N,N'*-triacetylchitotriose at concentrations of 10, 25, 50, 100, 250, and 500 μM was used as substrate. The data were fitted to the Michaelis–Menten equation with the nonlinear, least-squares program LineWeaver^[15] to yield $K_m = 103 \mu\text{M}$, $k_{\text{cat}} = 27.5 \text{ min}^{-1}$ (Figure 1). Specificity experiments for the acceptor sugar were also conducted to probe the substrate specificity of NodST with this assay. Table 1 contains the data for various *N*-acetylchitoses, *N*-acetylglucosamine (LacNAc), and an *N*-acetylglucosamine dimer (Gal(β 1-4)GlcNAc(β 1-

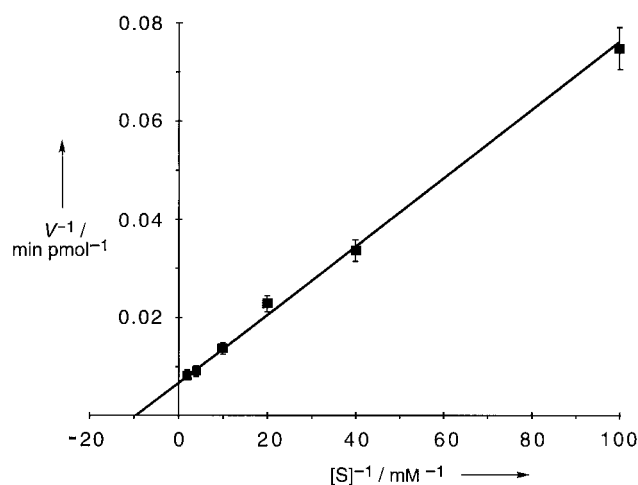


Figure 1. Lineweaver–Burke plot of kinetic data for the treatment of *N,N,N'*-triacetylchitotriose with NodST. $K_m = 20.4 \pm 3.6 \mu\text{M}$, $k_{\text{cat}} = 19.7 \pm 0.8 \text{ min}^{-1}$.

Table 1. Acceptor specificity for NodST.^[a]

Acceptor substrate	K_M [μM] ^[b]	k_{cat} [min^{-1}]
GlcNAc(β 1-4)GlcNAc	243 $\pm$ 40	23.6 $\pm$ 1.7
GlcNAc(β 1-4)GlcNAc(β 1-4)GlcNAc	103 $\pm$ 12	27.5 $\pm$ 2.9
GlcNAc(β 1-4)GlcNAc(β 1-4)GlcNAc(β 1-4)GlcNAc	20.4 $\pm$ 3.6	19.7 $\pm$ 0.8
GlcNAc(β 1-4)GlcNAc(β 1-4)GlcNAc(β 1-4)GlcNAc(β 1-4)GlcNAc	98.1 $\pm$ 12.4	25.9 $\pm$ 1.2
GlcNAc(β 1-4)GlcNAc(β 1-4)GlcNAc(β 1-4)GlcNAc(β 1-4)GlcNAc(β 1-4)GlcNAc	45.7 $\pm$ 6.0	22.7 $\pm$ 1.0
Gal(β 1-4)GlcNAc	> 5000	8.0 $\pm$ 1.3
Gal(β 1-4)GlcNAc(β 1-3)Gal(β 1-4)GlcNAc	87.0 $\pm$ 6.3	3.4 $\pm$ 0.1

[a] The acceptor sugar concentrations were chosen around their respective K_M values. The PAPS concentration was held constant at 20 μM . Kinetic constants were derived from the nonlinear, least-squares fit of the Michaelis–Menten equation with the LineWeaver program. [b] Apparent kinetic values.

3)Gal(β 1-4)GlcNAc).^[16] Not surprisingly, N,N',N'',N''' -tetra-acetylchitotetraose proved to be the best substrate ($k_{\text{cat}} = 19.7 \text{ min}^{-1}$, $K_M = 20.4 \mu\text{M}$), as it is the most similar to the natural substrate.^[17] Of particular interest is the 60-fold increase in acceptor specificity from LacNAc to the LacNAc dimer.

In summary, this new enzymatic regeneration of PAPS appears to be more practical and convenient than previously reported methods for the synthesis of carbohydrate sulfates and kinetic analysis of sulfotransferases. This regeneration system should be generally applicable to other sulfotransferases.

Experimental Section

Capillary zone electrophoresis was performed on a BioRad 3000 apparatus with a coated capillary (50 cm, 50 μm inner diameter) in 0.23M borate in running buffer (pH 7.8). The sample was injected at a pressure of 138 kPa $\cdot\text{s}^{-1}$, and electrophoresis was run with 20.0 kV (– to +) at 20 °C with detection at 260 nm. PAPS was detected at 5.53 min, and PAP at 5.98 min.

The AST IV gene was obtained by polymerase chain reaction as described^[11] from a cDNA library template (provided by W. E. Balch, The Scripps Research Institute). The clone, containing an engineered *NdeI* site preceding the 5' coding region and a *BamHI* site following the 3' stop codon, was digested with *BamHI* and *NdeI* and ligated with a similarly digested PET19b (Novagen, Madison, WI). The ligated plasmid was transformed into *E. coli* SURE (Stratagene, La Jolla, CA) for amplification. *E. coli* BL21(DE3) (Novagen) was transformed with the amplified plasmid, and a single colony was chosen to inoculate 100 mL of Luria–Bertani (LB) broth containing 50 $\mu\text{g mL}^{-1}$ of ampicillin. After overnight growth at 37 °C, the culture was distributed into four 1-L volumes of LB with ampicillin and grown at 37 °C to an optical density at 600 nm (OD_{600}) of 1.0. The cultures were induced with 50 μM diisopropyl- β -D-thiogalactopyranoside (IPTG), grown at 25 °C for 20 h, and centrifuged. The cell pellet was resuspended in 100 mM tris(hydroxymethyl)aminomethane (Tris, pH 7.6) with 5 mM 2-mercaptoethanol and disrupted by a French press. The supernatant was loaded onto a nickel–agarose column and washed with a solution of 100 mM Tris (pH 7.6), 5 mM 2-mercaptoethanol, 300 mM NaCl, 5 % glycerol, and 20 mM imidazole followed by equilibration with 100 mM Tris (pH 9.0), 50 mM NaCl, and 5 mM BME. Alkaline phosphatase (500 U) was added, and the resin was incubated at 20 °C for 15 h. After the resin was washed as described above, the β form of AST IV was eluted from the column with 100 mM Tris (pH 7.6) and 250 mM imidazole. Dialysis into 100 mM Tris (pH 7.6), concentration, and dilution to 50 % glycerol yielded 63 U of enzyme (15.8 U L^{-1}) in 14 mL (4.5 U mL^{-1}) of glycerol stock. One unit (U) is defined as the conversion of 1 μmol of PAP into PAPS per minute with *p*-nitrophenyl sulfate at pH 7.0, 25 °C.

5: N,N',N'' -triacylchitotriose (314 mg, 500 μmol) in a solution (100 mL) of bis[tris(hydroxymethyl)methylaminopropane] hydrochloride (bis-Tris-propane-HCl) (100 mM, pH 7.0) with 5 mM dithiothreitol and 10 mM *p*-nitrophenyl sulfate, 11 mg of PAP (25 μmol), 8.4 U of NodST (Calbiochem, La

Jolla, CA), and 18 U of β -AST IV were incubated at room temperature. Formation of N,N',N'' -triacylchitotriose 6-sulfate was monitored by TLC (*n*-propanol/30 % $\text{NH}_4\text{OH}/\text{H}_2\text{O}$ 7/1/2) and liberation of *p*-nitrophenol by the absorbance at 400 nm. After three days, the solution was passed through a column of LiChroPrep 18 (water). The void fraction was absorbed to a BioRad AG1-X8 column (HCO_2^- form) and eluted with a linear gradient (0 $\rightarrow$ 0.1M) of ammonium benzenesulfonate. Fractions containing N,N',N'' -triacylchitotriose 6-sulfate were concentrated and purified by size-exclusion chromatography (BioGel P-2, water) to yield 207 mg of **5** (290 μmol , 58 %). Positive-ion ESI MS: m/z : N,N',N'' -triacylchitotriose 6-sulfate 730 [$M+\text{Na}^+$], the degradation product N,N',N'' -triacylchitotriose 628 [$M+\text{H}^+$], 1-deoxy- N,N' -diacylchitobiose 407 [M^+], and 1-deoxy-*N*-acetylglucosamine 204 [M^+] (for comparison, see the original Nod signal characterization^[18]); HPLC (Spherisorb S5 SAX column (Waters 4.6 $\times$ 250 mm) with a linear gradient of 0.2 $\rightarrow$ 1.0M NaCl over 5 min in 10 mM KH_2PO_4 (pH 3.5), flow rate 1.0 mL min^{-1} , and detection at 220 nm): Two peaks (4.12, 4.37 min) correspond to the α and β anomer of the reducing end; ^1H NMR (500 MHz, D_2O): $\delta = 4.25$ (br, 0.4 H, $J = 10.3$ Hz, H6a β), 4.20 (dd, 0.6 H, $J = 1.8$, 11.0 Hz, H6a α), 4.16 (dd, 0.6 H, $J = 3.7$, 11.0 Hz, H6b α), 4.12 (dd, 0.4 H, $J = 3.7$, 9.6 Hz, H6b β); ^{13}C -NMR (125 MHz, D_2O): $\delta = 67.04$ (C6a), 66.97 (C6 β).

Assay of NodST: 100 mM bis-tris-propane-HCl (pH 7.0), 5 mM 2-BME, 20 μM PAPS, 2 mM *p*-nitrophenyl sulfate, 3.0 mU of NodST, 6.4 mU of β -AST IV, and substrate are combined to a total volume of 500 μL . The assay solution is incubated for 30 min at 20 °C prior to addition of substrate because commercial PAPS contains significant amounts of PAP. The evolution of *p*-nitrophenol is monitored at 400 nm for 10 min.

Received: April 26, 1999 [Z13317IE]
German version: *Angew. Chem.* **1999**, *111*, 2912–2915

Keywords: carbohydrates • cofactors • enzyme catalysis • sulfotransferases • synthetic methods

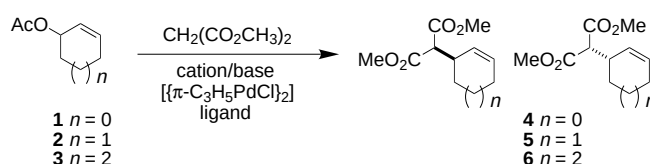
- [1] K. G. Bowman, C. R. Bertozzi, *Chem. Biol.* **1999**, *6*, R9–R22.
- [2] C. N. Falany, *FASEB J.* **1997**, *11*, 1–2.
- [3] a) J.-I. Aikawa, J. D. Esko, *J. Biol. Chem.* **1999**, *274*, 2690; b) T. P. Dooley, *Chem. Biol. Interact.* **1998**, *109*, 29; c) M. Fukuta, Y. Kobayashi, O. Habuchi, *Biochim. Biophys. Acta* **1998**, *1399*, 57; d) H. Habuchi, M. Kobayashi, K. Kimata, *J. Biol. Chem.* **1998**, *273*, 9208; e) K. D. Mazany, T. Peng, K. J. Williams, *Biochim. Biophys. Acta* **1998**, *1407*, 92; f) M. A. Nastuk, S. Davis, J. R. Fallon, *J. Neurosci.* **1998**, *18*, 7167; g) E. Ong, J.-C. Yeh, M. Fukuda, *J. Biol. Chem.* **1998**, *273*, 5190; h) Y.-B. Ouyang, K. L. Moore, *J. Biol. Chem.* **1998**, *273*, 24770; i) Y. Saeki, Y. Sakakibara, M. C. Liu, *J. Biochem.* **1998**, *124*, 55; j) K. Uchimura, H. Muramatsu, T. Muramatsu, *J. Biol. Chem.* **1998**, *273*, 22577; k) K. Yoshinari, K. Nagata, Y. Yamazoe, *J. Biochem.* **1998**, *123*, 740.
- [4] PAPS is available from Sigma Co. (US\$ 45.30 per mg). The half-life of PAPS in aqueous solution at pH 8.0 is approximately 20 h.
- [5] Inhibition of hydroxysteroid sulfotransferase by PAP was determined to be $K_i = 14 \mu\text{M}$. See C. J. Marcus, R. D. Sekura, W. B. Jakoby, *Anal. Biochem.* **1980**, *107*, 296.
- [6] C.-H. Lin, G.-J. Shen, E. Garcia-Junceda, C.-H. Wong, *J. Am. Chem. Soc.* **1995**, *117*, 8031.

- [7] *p*-Nitrophenyl sulfate is available from Sigma Co. (US\$ 18.90 per g).
 [8] S. G. Ramaswamy, W. B. Jakoby, *Methods Enzymol.* **1987**, *143*, 201–7.
 [9] [³⁵S]PAPS is available from NEN Life Science Products (US\$ 1013 per 100 mCi). The half-life of ³⁵S is 87.1 d. End-point methods of ³⁵S detection on TLC normally involve indirect qualitative determination of radioactivity.
 [10] a) A. D. Marshall, J. F. Darbyshire, W. B. Jakoby, *J. Biol. Chem.* **1997**, *272*, 9153; A. D. Marshall, J. F. Darbyshire, W. B. Jakoby, *Chem. Biol. Interact.* **1998**, *109*, 107; b) Y. S. Yang, S. W. Tsai, E. S. Lin, *Chem. Biol. Interact.* **1998**, *109*, 129; c) W.-X. A. Guo, Y.-S. Yang, X. Chen, P. McPhie, W. B. Jakoby, *Chem. Biol. Interact.* **1994**, *92*, 25–31; d) Y.-S. Yang, J.-J. Pan, J.-K. Hwang, *Protein Eng.* **1997**, *10*, 70.
 [11] Y.-S. Yang, A. D. Marshall, P. McPhie, W.-X. A. Guo, X. Xie, X. Chen, W. B. Jakoby, *Protein Expression Purif.* **1996**, *8*, 423–429.
 [12] E.-S. Lin, Y.-S. Yang, *Anal. Biochem.* **1998**, *264*, 111–117.
 [13] X. Chen, Y. S. Yang, Y. Zheng, B. M. Martin, M. W. Duffel, W. B. Jakoby, *Protein Expression Purif.* **1992**, *3*, 421–6.
 [14] S. Ozawa, K. Nagata, D. Gong, Y. Yamazoe, R. Kato, *Nucleic Acids Res.* **1990**, *18*, 4001.
 [15] LineWeaver, a graphical enzyme kinetics program for the Macintosh, was provided by Dr. Ian Ollmann, California Institute of Technology.
 [16] The *N*-acetylglucosamine dimer generously provided by Kathryn M. Koeller (Research group of Prof. Wong, Scripps Research Institute).
 [17] M. Schultze, C. Staehelin, H. Rohrig, M. John, J. Schmidt, E. Kondorosi, J. Schell, A. Kondorosi, *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 2706–2709.
 [18] P. Lerouge, P. Roche, C. Faucher, F. Maillet, G. Truchet, J. C. Promé, J. Dénarié, *Nature* **1990**, *344*, 781.

Proline-Based P,N Ligands in Palladium-Catalyzed Asymmetric π -Allyl Additions**

Scott R. Gilbertson* and Dejian Xie

The development of new ligands for use in asymmetric catalysis has undergone incredible growth in the last ten years. One of the reactions that has been investigated extensively is the palladium-catalyzed addition of nucleophiles to allyl acetates.^[1,2] One of the first substrates to yield to catalysis with high selectivity was 1,3-diphenylprop-2-enyl acetate.^[3–11] There are now a number of catalysts that have been developed that will catalyze the asymmetric addition of malonate to this substrate in greater than 90 % enantiomeric excess. A type of substrate that has been significantly more difficult to achieve high selectivity with has been the cyclic allyl acetates **1–3** (Scheme 1).^[12–15] To the best of our

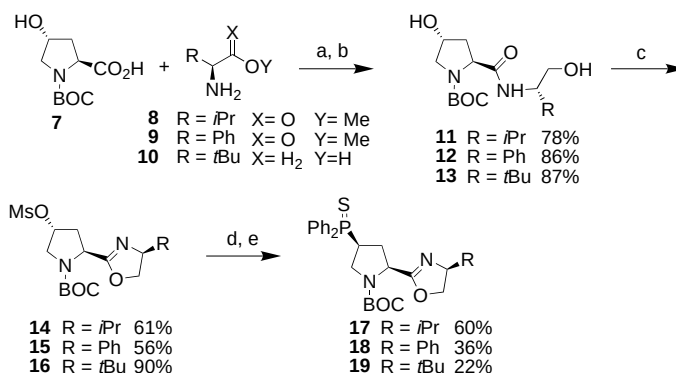


Scheme 1. Asymmetric addition of dimethylmalonate to cyclic allyl acetates **1–3**.

knowledge there are currently only two systems that give greater than 95 % *ee* with these types of substrates.^[16–22] Herein we report the synthesis of new phosphanyldihydrooxazole ligands that can be used to catalyze this substitution in high enantiomeric excess. The results obtained with these ligands are comparable to the most selective catalysts for the reaction of this substrate. Additionally, these ligands are readily accessible from common amino acids and are proving useful in the catalysis of a number of asymmetric transformations.

The design of this system was founded on the observation that ligands based on proline often result in reasonably high stereodifferentiation. There have been a number of examples of proline-based bisphosphane systems that have resulted in selective catalysis.^[23–27] For this reason a series of proline-based phosphanyldihydrooxazole ligands was synthesized.

The synthesis of this class of ligand begins with commercially available *tert*-butoxycarbonyl (BOC)-protected *trans*-4-hydroxy-*L*-proline (**7**) which could be coupled to either an amino acid ester or an amino alcohol (Scheme 2). The dihydrooxazole was formed through reduction of the ester

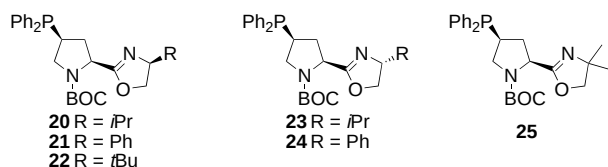


Scheme 2. Synthesis of the dihydrooxazole ligands **17–19**. EDC/HOBt, RT, CH₂Cl₂; b) when X = O, LiBH₄, THF, 0 °C to RT; c) MeSO₂Cl, Et₃N, CH₂Cl₂, RT; d) Ph₂P[–]Na⁺, THF, –78 °C to RT; e) S₈ or Na₂S₂O₈, CH₃OH/H₂O, 45 °C. EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole. Ms = mesyl.

to an alcohol and formation of a bis-mesylate by reaction with methanesulfonyl chloride. The primary mesylate then underwent cyclization to form the dihydrooxazole ring (**14–16**). After this reaction, the secondary mesylate was subjected to substitution by sodium diphenylphosphide. Following substitution the phosphane is protected as the phosphane sulfide. The ligands are purified as the phosphane sulfides and then converted to phosphanes (**20–25**) by reduction with Raney

[*] Prof. S. R. Gilbertson, Dr. D. Xie
 Department of Chemistry, Washington University
 Saint Louis, MO 63130 (USA)
 Fax: (+1) 314-935-4481
 E-mail: srg@wuchem.wustl.edu

[**] This work was partially supported by the National Institutes of Health (NIH) (grant no. R01 GM56490-01) and Washington University. We also gratefully acknowledge the Washington University High-Resolution NMR Facility, partially supported by the NIH (1S10R02004), and the Washington University Mass Spectrometry Resource Center, partially supported by the NIH (RR00954), for their assistance.



nickel before coordination to palladium. This route is appealing because it allows the synthesis of a wide variety of analogues. The R group on the dihydrooxazole ring is easily changed by simply coupling a different amino acid ester to *trans*-hydroxyproline. Another point of differentiation in this ligand system is at the nitrogen of the proline ring. Our initial studies have been with the nitrogen protected with a BOC group but there is clearly the possibility to make systematic changes to this portion of the molecule.

The reaction with cyclopent-2-enyl acetate (**1**) and dimethyl malonate, at 0 °C, using ligand **20** provided the desired substitution product in 94% yield and 90% *ee* (Table 1, entry 1). Reduction of the temperature to –20 °C resulted in an increase in selectivity to 94% *ee*. At –35 °C the selectivity improves to 96% *ee*. It was felt that modification of the R

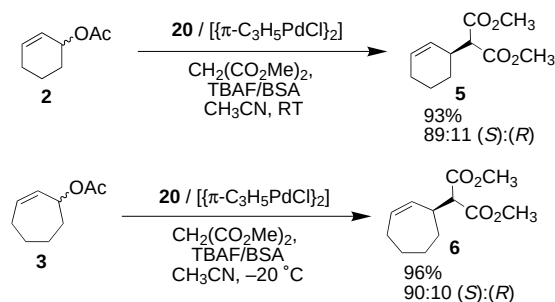
Table 1. Reactions of cyclic allyl acetate **1** with dimethylmalonate catalyzed by palladium complexes of ligands **20**–**25**.

Entry ^[a,b]	Ligand	<i>T</i> [°C]	solvent	Yield [%]	Ratio <i>S</i> : <i>R</i> ^[c]
1	20	0	CH ₃ CN	94	95:5
2	20	–20	CH ₃ CN	99	97:3
3	20	–35	CH ₃ CN	79	98:2
4 ^[d]	20	0	CH ₃ CN	96	93:7
5	20	20	CH ₃ CN	95	93:7
6	23	0	CH ₃ CN	93	84:16
7	21	0	CH ₃ CN	99	88:12
8	24	0	CH ₃ CN	91	88:12
9	25	0	CH ₃ CN	90	90:10
10 ^[e]	22	0	CH ₃ CN	92	84:16
11	20	0	CH ₂ Cl ₂	99	91:9
12	20	25	C ₆ H ₆	30	86:14
13	20	0	DMF	90	93:7
14	20	0	THF	86	90:10

[a] The phosphane ligand is generated by reduction of the phosphane sulfide with Raney nickel. [b] Reactions were run with 2 mol % Pd to 3 mol % ligand. [c] Enantiomeric ratios were determined by NMR spectroscopy using the [Eu(hfbc)] shift reagent (hfbc = 3-(heptafluorobutyl)-D-camphorate). The absolute stereochemistry was determined by comparison of optical rotations with the literature. [d] The ratio of Pd/ligand of 1/1 was used. [e] 2 mol % Pd was used.

group next to the dihydrooxazole nitrogen atom would result in an increase in the selectivity. In the phosphanyldihydrooxazole systems reported previously it has been shown that changing the stereochemistry of the group next to the nitrogen alters the selectivity of the catalysts in favor of the other enantiomer. In the proline-based system reported here this is not the case. Catalysis with the ligand where L-valine

(**20**) was replaced with D-valine (**23**) resulted in a significant decrease in the rate of the reaction as well as a decrease in the reaction's selectivity (entry 6); however, the major product is the same enantiomer in both cases. Catalysis by a variety of complexes with different R groups next to nitrogen resulted in variable results. Substitution of L-phenylalanine (**21**) for L-valine gives lower selectivity (76% *ee*, entry 7). Use of ligand **22** in the same stoichiometry as ligand **20** resulted in a decrease in selectivity (entry 10). Ligand **25**, which does not possess a chiral center next to the dihydrooxazole nitrogen, gives the product in 90% yield and 80% *ee* (entry 9). The effect of solvent on the reaction was also probed. It was found that acetonitrile gives the highest selectivity with DMF and methylene chloride giving selectivities above 80% *ee* (entries 13 and 11, respectively). When the reaction conditions found for cyclopent-2-enyl acetate (**1**) were used with cyclohex-2-enyl acetate (**2**) the reaction proceeded in high yield and with good selectivity. Catalysis of the addition to the cyclohept-2-enyl allyl acetate (**3**) proceeded in good selectivity and at a faster rate than for **2** (Scheme 3).



Scheme 3. Asymmetric addition of dimethylmalonate to cyclohex-2-enyl acetate **2** and cyclohept-2-enyl acetate **3** by using palladium complexes of the new phosphanyldihydrooxazole ligand **20**.

Figure 1 shows a model of the metal complex with an allyl group attached. It has been shown in other phosphanyldihydrooxazole systems that addition of the nucleophile to the allyl group takes place at the carbon that is *trans* to the phosphane on the metal center.^[4–7, 9, 28–30] To obtain the products observed with our catalyst the two methylenes of the five-membered ring must point down toward the BOC group. It is not obvious from this model what structural features are responsible for this preference in orientation, but given the high selectivity it is clearly favored. It is interesting that the configuration of the carbon center next to dihydrooxazole nitrogen does not have a stronger effect on the selectivity of the catalysis; the same enantiomer is obtained as the major product regardless of its stereochemistry.

Ligand **20** has proven to be very effective in the control of the addition of dimethyl malonate to allyl acetates **1**–**3**. This system differs from other phosphanyldihydrooxazole ligands in that the dominating chirality is not the chiral center next to the dihydrooxazole nitrogen but rather the chirality of the two hydroxyproline-derived chiral centers. We are currently looking at catalysis of the addition of other nucleophiles with this system. Derivatives of this ligand are also being developed for use in other transition metal catalyzed reactions.

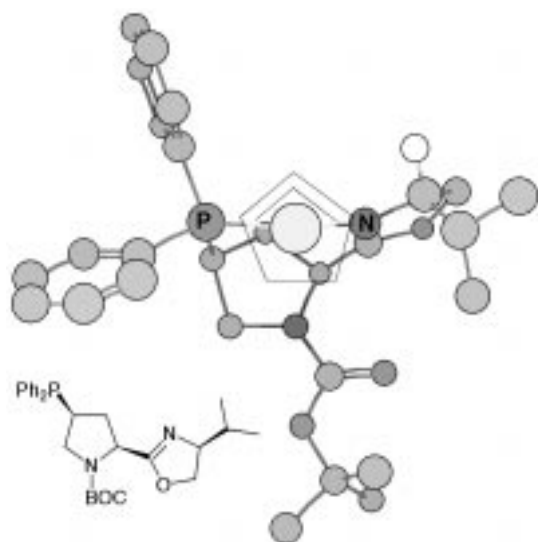


Figure 1. Model of the metal complex with an allyl group attached.

Experimental Section

Procedure for π -allyl alkylation: The phosphanyldihydrooxazole ligand was mixed with $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$ in degassed solvent, followed by addition of the cyclic allylic acetate. To this mixture a solution containing dimethyl malonate (3 equiv), tetrabutylammonium fluoride (TBAF) (3 equiv) and *N,O*-bis(trimethylsilyl)acetamide (BSA) (3 equiv) was added slowly through a addition funnel (30 min). After the reaction was complete, water was added to quench the reaction and the organic solvent was removed by evaporation. The water layer was then extracted with diethyl ether twice and the ether solution was washed with saturated NaHCO_3 , brine, and dried over Na_2SO_4 . Evaporation of solvent gave a residue that was chromatographed by using $\text{EtOAc}/n\text{-hexanes}$ (10/90, v/v) as an eluant to afford a colorless oil.

The enantiomeric purity was determined by integration of the NMR signals of the methyl residues on the dimethyl malonate, upon titration with europium chiral shift reagent $[\text{Eu}(\text{hfbc})_3]$.

The ligand with the opposite configuration can be synthesized from D-hydroxyproline, which is accessible from L-hydroxyproline.^[30]

Received: March 4, 1999 [Z13109IE]

German version: *Angew. Chem.* **1999**, *111*, 2915–2918

Keywords: alkylations • asymmetric catalysis • palladium • P,N ligands

- [1] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.
- [2] C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089–1122.
- [3] S. R. Gilbertson, C.-W. Chang, *Chem. Commun.* **1997**, 975–976.
- [4] P. von Matt, A. Pfaltz, *Angew. Chem.* **1993**, *105*, 614–615; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566–568.
- [5] J. Sprinz, M. Kiefer, G. Helmchen, M. Reggeline, G. Huttner, O. Walter, L. Zsolnai, *Tetrahedron Lett.* **1994**, *35*, 1523–1526.
- [6] H. Steinhagen, M. Reggeline, G. Helmchen, *Angew. Chem.* **1997**, *109*, 2199–2202; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2108–2110.
- [7] A. Togni, U. Burckhardt, V. Gramlich, P. S. Pregosin, R. Salzmann, *J. Am. Chem. Soc.* **1996**, *118*, 1031–1037.
- [8] M. Bovens, A. Togni, L. M. Venanzi, *J. Organomet. Chem.* **1993**, *451*, C28–C31.
- [9] J. V. Allen, S. J. Coote, G. J. Dawson, C. G. Frost, C. J. Martin, J. M. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2065–2071.
- [10] M. Yamaguchi, T. Shima, T. Yamagishi, M. Hida, *Tetrahedron Lett.* **1990**, *31*, 5049–5052.
- [11] S. R. Gilbertson, C.-W. Chang, *J. Org. Chem.* **1998**, *63*, 8424–8431.

- [12] T. Hayashi, M. Kawatsura, Y. Uozumi, *J. Am. Chem. Soc.* **1998**, *120*, 1681–1687.
- [13] T. Minami, Y. Okada, T. Otaguro, S. Tawarayama, T. Furuichi, T. Okauchi, *Tetrahedron: Asymmetry* **1995**, *6*, 2469–2474.
- [14] Y. Okada, T. Minami, Y. Umezumi, S. Nishikawa, R. Mori, Y. Nakayama, *Tetrahedron: Asymmetry* **1991**, *2*, 667–682.
- [15] U. Nettekoven, M. Widhalm, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron: Asymmetry* **1997**, *8*, 3185–3188.
- [16] B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1996**, *118*, 235–236.
- [17] B. M. Trost, R. C. Bunt, *Angew. Chem.* **1996**, *108*, 70–73; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 99–102.
- [18] B. M. Trost, M. G. Organ, G. A. O'Doherty, *J. Am. Chem. Soc.* **1995**, *117*, 9662–9670.
- [19] B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1994**, *116*, 4089–4090.
- [20] G. Helmchen, S. Kudis, P. Sennhenn, H. Steinhagen, *Pure Appl. Chem.* **1997**, *69*, 513–518.
- [21] G. Knühl, P. Sennhenn, G. Helmchen, *J. Chem. Soc. Chem. Commun.* **1995**, 1845–1846.
- [22] S. Kudis, G. Helmchen, *Angew. Chem.* **1998**, *110*, 3210–3212; *Angew. Chem. Int. Ed.* **1998**, *37*, 3047–3050.
- [23] G. Parrinello, J. K. Stille, *J. Am. Chem. Soc.* **1987**, *109*, 7122–7127.
- [24] M. Hodgson, D. Parker, *J. Organomet. Chem.* **1987**, *325*, C27–C30.
- [25] K. Tani, K. Suwa, E. Tanigawa, T. Ise, T. Yamagata, Y. Tatsuno, S. Otsuka, *J. Organomet. Chem.* **1989**, *370*, 203–221.
- [26] H. Brunner, E. Graf, W. Leitner, K. Wutz, *Synthesis* **1989**, 743–745.
- [27] H. Takeda, T. Tachinami, M. Aburatani, H. Takahashi, T. Morimoto, K. Achiwa, *Tetrahedron Lett.* **1989**, *30*, 367–370.
- [28] G. J. Dawson, J. M. J. Williams, *Tetrahedron: Asymmetry* **1995**, *6*, 2535–2546.
- [29] H. Kubota, K. Koga, *Tetrahedron Lett.* **1994**, *35*, 6689–6692.
- [30] G. L. Baker, S. J. Fritschel, J. R. Stille, J. K. Stille, *J. Org. Chem.* **1981**, *46*, 2954–2960.

DNA Responds to Ionizing Radiation as an Insulator, Not as a “Molecular Wire”**

Michael G. Debije, Michael T. Milano, and William A. Bernhard*

The understanding of electron and hole transfer in DNA is critical to predicting the biological consequences of exposure to ionizing radiation. These processes are biologically relevant since about 50 % of the consequential damage is produced by direct-type events,^[1] that is, from one-electron loss (holes) and one-electron gain directly by the DNA^[2] or by fast transfer of holes and electrons to the DNA from adjacent solvent.^[3] Transfer processes are chemically relevant since the distribu-

[*] Prof. W. A. Bernhard, M. G. Debije, M. T. Milano
Department of Biochemistry and Biophysics
University of Rochester
Rochester, NY 14642 (USA)
Fax: (+1) 716-275-6007
E-mail: william_bernhard@urmc.rochester.edu

[**] We thank Loren Williams and Gary Hu for providing crystals of d(CGATCG):anthracene, Tom Colby and Michael Strickler for assistance in verifying crystal structures, and Yuri Razskazovskii for his helpful discussions. The technical assistance of Kermit R. Mercer was invaluable. The investigation was supported by PHS Grant 2-R01-CA32546, awarded by the National Cancer Institute, DHHS. The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

tion of damage confronting the DNA repair enzymes is dependent on electron transfer events occurring within a fraction of a second following energy deposition. Over the past four decades, scientists working on the radiation physics and chemistry of DNA have given considerable attention to the question of DNA conductivity. This body of literature provides rather strong evidence, further discussed below, that the DNA polymer behaves as an insulator and not as a "molecular wire".

The possibility that DNA might possess properties of a molecular wire has been raised in recent years by a series of experiments using photochemistry to initiate and detect electron transfer. In 1993 Murphy et al. concluded that electron transfer was long range (>4.0 nm) and fast ($>10^9$ s $^{-1}$).^[14] In this and subsequent work (see reference [4] for a review), it was concluded that the dependence of the electron transfer rate on distance is relatively shallow; that is, the exponential factor $\beta^{[5]}$ is approximately $0.2 \text{ \AA}^{-1}$. The extremely small value of β was attributed to high electron and hole mobility through the " π -ways" of stacked bases. Other laboratories using photochemistry concluded that the value of β is much larger. For electron transfer, Meade and co-workers obtained $\beta \approx 1.0 \text{ \AA}^{-1}$,^[6] and for hole transfer Lewis et al. obtained $\beta \approx 0.6 \text{ \AA}^{-1}$.^[7] Thus, there is a debate with regard to range, rate, and mechanism of electron transfer in DNA.^[8–11]

Relatively absent from this debate has been discussion of earlier findings largely from the radiation research community, findings which are difficult to reconcile with unusually fast electron transfer rates over long distances (i.e., a β value an order of magnitude smaller than $1.0 \text{ \AA}^{-1}$). The absence is, in part, due to concern over the possibility that the mechanism of electron transfer through DNA might depend on the means by which electrons or holes are created. Chemistry initiated by electronic excitation often differs from that initiated by ionization. In the case of DNA conductivity, while there are indeed different artifacts that affect interpretation, electron and hole mobility through extended stacks of bases should be independent of the source of the electron and hole. The finding that electrons and holes migrate through the stacked bases of duplex DNA is not under debate; this was established decades ago.^[12, 13]

Here we show that DNA at 4 K is an extraordinarily efficient trap for both holes and electrons. Since the yield of trapped holes and electrons depends on the competition between electron–hole recombination and trapping reactions, the yield must also depend on electron transfer rate and distance. If the rate over long distances is fast, the yields of trapped radicals are small. This situation is analogous to that employed by Murphy et al., where a decreased yield in fluorescence was used to deduce a fast rate of electron transfer over a (presumably) known distance.^[14] Because their study lacks direct evidence of electron transfer, it is difficult to rule out other explanations.^[15, 16] What is needed are better defined samples. This shortcoming is overcome in the work presented here by employing crystalline deoxyoligonucleotides whose structures are known to angstrom resolution.

Crystals of the oligodeoxynucleotides d(CTCGAG) and d(CCCTAGGG) were grown following published procedures.^[17, 18] The crystals were verified to conform to the

published structures using a MSC R-Axis II X-ray detector with a cooling device that maintained the crystals at 77 K. Crystalline samples were irradiated at 4 K by 70-keV X-rays,^[19] and EPR spectra recorded at the same temperature. Examples of first-derivative spectra are provided in Figure 1. To our knowledge, these are the first published EPR spectra of drug-free single crystals of oligonucleotide DNA. The qualitative features of the spectra are consistent with a radical population dominated by one-electron-reduced cytosine and one-electron -oxidized guanine.^[20, 21] Here we focus on the total yield of trapped radicals in DNA.

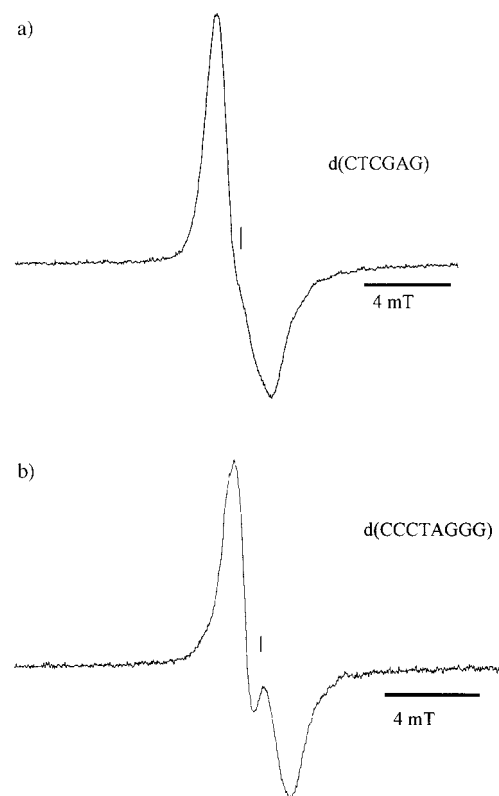


Figure 1. Single-scan 20-mT Q-band EPR spectrum of a) a single crystal of d(CTCGAG) taken at 4 K after a 12-kGy dose (crystal orientation undetermined) and b) a single crystal of d(CCCTAGGG) taken at 4 K after a 20-kGy dose (orientation is B_0 parallel to the crystallographic a axis). The position of $g = 2.0023$ is indicated by the vertical line.

The free radical yields were calculated from the initial slope of the dose-response curves (the presaturation linear region, dose <5 kGy) that are presented in Figures 2 and 3. To measure the concentration of free radicals trapped by DNA, the intensity of each spectrum was compared to the intensity of a ruby standard.^[19]

The yield of the d(CTCGAG) system was obtained from six different single-crystal or polycrystalline samples weighing from 28 to 209 μg . The oligonucleotide molecules stack pseudo-continuously in an end-to-end fashion, maintaining π -bond overlap. The duplex is in a B-form conformation. The measured free radical yield (FRY) is $G(\text{fr}) = 0.75 \pm 0.14 \mu\text{mol}$ of free radicals per Joule of absorbed energy (fr = free radical). The yield of the d(CCCTAGGG) system was

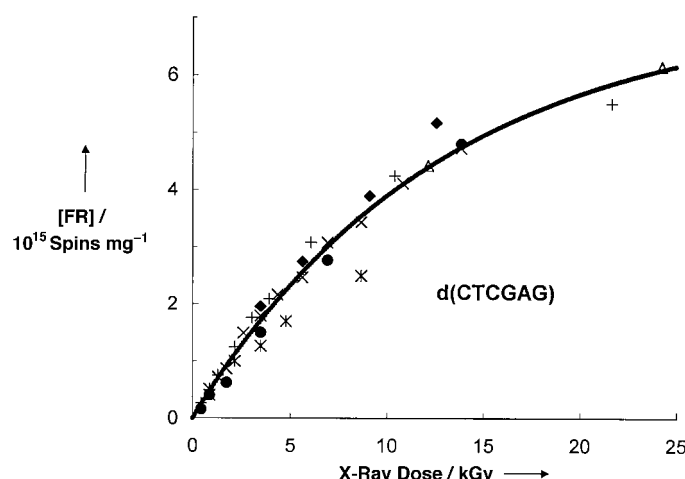


Figure 2. Plot of the free radical concentration versus the X-ray dose for six different crystalline samples of d(CTCGAG) irradiated and measured at 4 K. The solid curve represents the least-squares fit by the equation $C = C_i(1 - e^{-\sigma D})$, where C is the free radical concentration at dose D , C_i is the concentration at dose saturation, and σ is the cross-section for radical destruction; $C_i = 7.2 \times 10^{18} \text{ fr g}^{-1}$ and $\sigma = 0.078 \text{ kGy}^{-1}$. From this we conclude that the maximum trapping capacity of d(CTCGAG) at high doses is $7.2 \times 10^{18} \text{ fr g}^{-1}$.

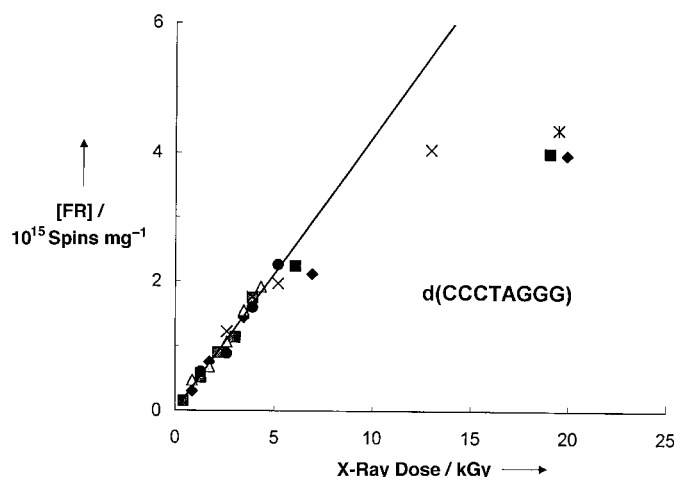


Figure 3. Plot of the free radical concentration versus the X-ray dose for six different crystalline samples of d(CCCTAGGG) irradiated and measured at 4 K. The linear region of the data below 5 kGy has been fitted with a least-squares curve. From the slope of this line we may determine the free radical yield of the d(CCCTAGGG) crystal samples. The same fitting procedure was followed in determining the free radical yield of the d(CTCGAG) samples.

determined from six different crystalline or polycrystalline samples weighing between 71 and 230 μg . The terminal base pair of one helix contacts the sugar phosphate backbone of its lattice neighbor; there is no continuity in base stacking between adjacent octamers. The duplex is A-form, and the resultant yield is $G(\text{fr}) = 0.70 \pm 0.04 \mu\text{mol J}^{-1}$. The $G(\text{fr})$ values are revealing in three ways: 1) the absolute magnitude is large, 2) the magnitude for a given crystal type is independent of crystal size, and 3) the two different types of crystals give values of the same magnitude.

The measured yield of trapped radicals in crystalline DNA corresponds to about 60% ($\approx 0.7/1.2$) of the radicals initially formed by the radiation (the initial radical yield of liquid

water, which has a stopping power comparable to that of DNA,^[22] is $G(\text{fr}) = 1.2 \mu\text{mol J}^{-1}$ ^[23]). This is an exceptionally high yield given that a large fraction of the initial radicals must be lost by geminate ion recombination. Furthermore, high yields can only occur if the conductivity of the DNA crystals is very low. In a conductor, there are effectively no barriers to prevent the electrons and holes from combining. For example, it is well known that a three-dimensional conductor like metallic copper has a radical yield of zero. A solid with two-dimensional conductivity provides a matrix that could trap one electron or hole per conducting plane. To provide a comparison with a two-dimensional conductor, we measured $G(\text{fr})$ for graphite at 4 K by using a 0.5-mm pencil lead with a room-temperature conductivity of 1 S cm^{-1} . The $G(\text{fr})$ value of graphite ($< 0.005 \mu\text{mol J}^{-1}$) is too small to detect in the presence of the quartz sample holder.

In sharp contrast, crystals of α -methylmannoside (a lattice of sugar molecules that is an insulator) give a yield of $0.5 \mu\text{mol J}^{-1}$ at 4 K. As shown in Table 1, this is comparable to

Table 1. Free radical yields at 4 K of various materials exposed to ionizing radiation, and comparison of DNA samples against known conductors and insulators.

Material	Form	Yield [$\mu\text{mol J}^{-1}$]
copper	wire	0
graphite rod	pressed powder	< 0.005
α -methylmannoside	crystalline	0.44 ± 0.03 ^[a]
lysozyme	crystalline	0.57 ± 9.04 ^[a]
calf thymus DNA	film	$0.4 - 0.5$ ^[b]
calf thymus DNA	lyophilized powder	$0.5 - 0.6$ ^[b]
d(CCCTAGGG)	crystalline	0.70 ± 0.04 ^[a]
d(CTCGAG)	crystalline	0.75 ± 0.14 ^[a]
d(CGATCG):anthracycline	crystalline	0.24 ± 0.03 ^[a]

[a] Quoted errors are relative errors; absolute errors are higher ($\pm 25\%$).^[46]
 [b] Hydration state of 16 waters per nucleotide.^[46]

DNA irradiated in the form of films, powders, and crystals. Also, given the large body of work on electron transfer in proteins (see for example reference [24]), we measured the free radical yield of lysozyme crystals at 4 K. The $G(\text{fr})$ value of lysozyme ($0.57 \pm 0.03 \mu\text{mol J}^{-1}$) shows that the probability of electron-hole combination within this protein lattice is essentially the same as observed for DNA. The range of electrons and holes in lysozyme crystals, therefore, is comparable to the range in DNA.

If π -ways in DNA exist, the d(CTCGAG) hexamer crystal is optimized to detect them. Assuming base stacking continuity results in electrical continuity, the hexamer crystal would be unable to trap more than two free radicals per continuous duplex column (i.e., one electron or hole per "strand"). Since each strand of stacked bases extends the length of the crystal, strand length depends on crystal size and shape. Assuming one radical per strand of stacked bases in a cubic crystal containing 100 μg of d(CTCGAG),^[25] the calculated free radical concentration is less than $10^{15} \text{ fr g}^{-1}$. Observed concentrations exceed this value by more than three orders of magnitude. The maximum measured concentration at free radical saturation is $7.2 \times 10^{18} \text{ fr g}^{-1}$. Each strand of approximately 10^6 bases traps, on average, around 6000 free

radicals. Viewed another way, the free radical density at dose saturation, assuming uniform trapping across the entire crystal, is about one free radical per 57 bp, a through-base-stack distance of 17 nm. Since energy deposition is not uniform,^[26] the mean interrads distance is smaller.

The high density of holes and electrons trapped by d(CTCGAG) at dose saturation is compelling evidence that no conductive states exist in the B-form helix. Indeed, if electron or hole transfer is long-range, then the FRY in d(CTCGAG) crystals should depend on crystal size. Reducing the size of a cubic crystal by 10-fold should increase the FRY by a factor of 2.154. Variations in crystal size, from less than 10 μg to greater than 100 μg , give FRYs within the observed standard deviation of $\pm 20\%$, further indicating that the range at 4 K is limited.

A comparison between the two crystals provides an estimate of the electron range. The largest run of stacked bases in d(CCCATGGG) is 8 bp, and yet $G(\text{fr})$ is the same as for d(CTCGAG), where base stacking is continuous. This observation of limited range is consistent with a number of studies that indicate the mean range of a thermalized electron through DNA is short. EPR measurements at 4–77 K have provided evidence that the range of thermalized electrons and holes in DNA is at least 2 bp^[19] with a mean between 3–11 bp.^[27, 28]

Further support of a short range comes from EPR measurements on single crystals of a hexamer anthracycline complex.^[19] The complex contains two intercalated anthracyclines per d(CGATCG) with intercalation occurring between each of the tandem CG base pairs. Base stacking is continuous through the crystal.^[29] It is known from single-crystal EPR that holes and electrons trap only at anthracycline. No DNA-centered radicals are observed. This is expected given the redox properties of anthracycline, which make it the deepest trapping site for both electrons and holes. It also proves that holes migrate through the stacked bases. We have measured the FRY of these crystals at 4 K and find that $G(\text{fr}) = 0.27 \pm 0.03 \mu\text{mol J}^{-1}$.^[30] Thus, the high density of anthracycline traps does not increase yields. This can be understood if pure duplex DNA contains, inherently, a high density of traps such that the range of thermalized electrons and holes is limited to very short distances.

If DNA had a metallike band structure, one should expect an increased conductivity at low temperatures. This phenomenon has not been observed: in fact, the opposite is true. To date, we have measured $G(\text{fr})$ values and temperature effects on 12 different types of crystals, representing a wide range of conformation, packing, and sequence. We have observed that $G(\text{fr})$ of crystalline DNA irradiated at 4 K and annealed to 240 K has 20–40 % of the yield obtained at 4 K.^[31, 32] The EPR spectrum qualitatively changes in a manner consistent with an initial set of radicals that are shallowly trapped, accompanied by reversible protonation/deprotonation. These low-temperature radicals convert into a set of more deeply trapped species at higher temperatures, and these are typically irreversibly protonated/deprotonated.^[33] A minimum and maximum distance for the thermally activated migration has been estimated. The minimum is about 2 nm based on the absence of spectral features due to radical pairs.^[27] The

maximum is on the order of 20 nm based on the free radical concentration remaining after annealing at 240 K. Both boundaries are compatible with the results of Razskazovskii et al.^[28] With track structure calculations (currently underway), it should be possible to determine the distribution of migration distances from our measurements on crystalline DNA. As with other EPR studies that show a decrease in radical concentration upon annealing,^[34–36] there is no doubt that electron transfer occurs through the stacked bases of duplex DNA and that electrons migrate by thermally activated hopping.

The migration of charge through DNA is supported by experiments with solid-state EPR,^[33] pulse radiolysis,^[37] and product analysis.^[38, 39] In a paper by Razskazovskii et al., it is concluded that the mean distance of electron migration at 77 K is 11 bp and that above 150 K thermally activated migration extends to 30 bp or more.^[28] Their results are consistent with a base-to-base hopping mechanism.

Our observations on crystalline DNA are well explained by a model in which the migration of electrons and holes is propagated primarily by hopping between shallow traps. At temperatures less than 80 K, the deepest electron trap is cytosine (C),^[20, 40] where the rate of proton transfer from N1 of guanine (G) to N3 of C^{•-} (forming C(N3 + H)•)^[41] competes effectively with the rate of electron transfer.^[42] Likewise, the deepest hole trap is guanine,^[20, 43] where proton transfer away from N1 of G^{•+} to N3 of C (forming G(N1 – H)•)^[44] competes with hole transfer.^[45] Steenken has written an excellent review of the role of proton transfer in moderating electron transfer.^[42] Proton transfer separates the charge from the unpaired electron, leaving a neutral radical on one strand and a diamagnetic ion on the conjugate base of the opposing strand and reduces the probability of electrons and holes combining.

In conclusion, crystalline oligodeoxynucleotides serve as well-defined samples that give improved precision in the measurement of free radical yields. Increased length of base stacking beyond eight base pairs has no effect on free radical yields, and the yields are markedly high ($0.7 \mu\text{mol J}^{-1}$). The high yields coupled with the absence of a dependence on long-range base stacking supports the conclusion that the range of holes and electrons at 4 K is short (2–8 bp). It follows that DNA is effectively an insulator.

Received: January 29, 1999

Revised version: May 18, 1999 [Z12977IE]

German version: *Angew. Chem.* **1999**, *111*, 2926–2930

Keywords: DNA structures • electron transfer • EPR spectroscopy • nucleotides • radicals

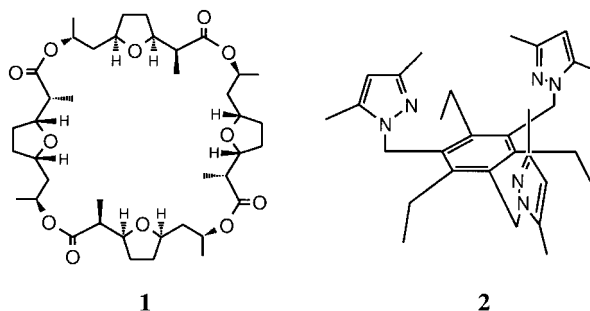
- [1] R. E. Krisch, M. B. Flick, C. N. Trumbore, *Radiat. Res.* **1991**, *126*, 251.
- [2] W. Wang, M. Yan, D. Becker, M. D. Sevilla, *Radiat. Res.* **1994**, *137*, 2.
- [3] N. Mroczka, W. A. Bernhard, *Radiat. Res.* **1993**, *135*, 155.
- [4] R. Holmlin, P. Dandliker, J. Barton, *Angew. Chem.* **1997**, *109*, 2830; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2714.
- [5] At long distances, the tunneling electron transfer reactions are expected to drop off exponentially, that is, $k_{\text{ET}} \propto \exp[-\beta(R - R_0)]$, where R_0 is the donor–acceptor separation at the van der Waals contact.
- [6] T. J. Meade, J. F. Kayyem, *Angew. Chem.* **1995**, *107*, 358; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 352.

- [7] F. D. Lewis, W. Wu, Y. Zhang, R. L. Letsinger, S. R. Greenfield, M. R. Wasielewski, *Science* **1997**, 277, 673.
- [8] A. Harriman, *Angew. Chem.* **1999**, 111, 996; *Angew. Chem. Int. Ed.* **1999**, 38, 945.
- [9] P. Barbara, E. Olson in *Electron Transfer: From Isolated Molecules, Part Two* (Eds.: J. Jortner, M. Bixon), Wiley, New York, **1999**, ch. 13.
- [10] S. Priyadarshy, S. Risser, D. Beratan, *J. Biol. Inorg. Chem.* **1998**, 3, 196.
- [11] N. Turro, J. Barton, *J. Biol. Inorg. Chem.* **1998**, 3, 201.
- [12] M. Sevilla in *Excited States in Organic and Biochemistry* (Eds.: B. Pullman, N. Goldblum), Reidel, Boston, **1977**, p. 15.
- [13] S. Gregoli, M. Olast, A. Bertinchamps, *Radiat. Res.* **1982**, 89, 238.
- [14] C. Murphy, M. Arkin, Y. Jenkins, N. Ghatlia, S. Bossmann, N. Turro, J. Barton, *Science* **1993**, 262, 1025.
- [15] E. Krider, T. Meade, *J. Biol. Inorg. Chem.* **1998**, 3, 222.
- [16] D. N. Beratan, S. Priyadarshy, S. M. Risser, *Chem. Biol.* **1997**, 4, 3.
- [17] M. Wahl, S. Rao, M. Sundaralingam, *Biophys. J.* **1996**, 70, 2857.
- [18] D. B. Tippin, M. Sundaralingam, *Acta Crystallogr. Sect. D* **1996**, 52, 997.
- [19] M. T. Milano, G. G. Hu, L. D. Williams, W. A. Bernhard, *Radiat. Res.* **1998**, 150, 101.
- [20] M. Sevilla, D. Becker, M. Yan, S. Summerfield, *J. Phys. Chem.* **1991**, 95, 3409.
- [21] W. A. Bernhard in *The Early Effects of Radiation on DNA, Ser. H 54* (Eds.: E. M. Fielden, P. O'Neill), Springer, Berlin, **1991**, p. 141.
- [22] J. A. La Verne, S. M. Pimblott, *Radiat. Res.* **1995**, 141, 208.
- [23] W. R. Holley, A. Chatterjee in *The Early Effects of Radiation on DNA* (Eds.: E. M. Fielden, P. O'Neill), Springer, Berlin, **1991**, p. 195.
- [24] C. Moser, J. Keske, K. Warncke, R. Ford, P. Dutton, *Nature* **1992**, 355, 796.
- [25] The crystal habit of d(CTCGAG) is rodlike with no one dimension greater than five times the smallest dimension.
- [26] S. M. Pimblott, J. A. L. Verne, A. Mozumder, N. J. Green, *J. Phys. Chem.* **1990**, 94, 488.
- [27] R. A. Spalletta, W. A. Bernhard, *Radiat. Res.* **1992**, 130, 7.
- [28] Y. Razskazovskii, S. Swarts, J. Falcone, C. Taylor, M. Sevilla, *J. Phys. Chem.* **1997**, 101, 1460.
- [29] L. A. Lipscomb, M. E. Peek, F. X. Zhou, J. A. Bertrand, D. van Derveer, L. D. Williams, *Biochemistry* **1994**, 33, 3649.
- [30] M. Milano, PhD Thesis, University of Rochester, Rochester, New York, **1998**, p. 278.
- [31] M. G. Debije, unpublished results.
- [32] There are two general mechanisms by which the trapped electrons and holes are lost upon annealing. One is by free radical conversions, which require higher thermal energy and are activated at $T > 150$ K. The other is by free radical combination reactions, which require lower thermal energy and are activated over a wide range of temperatures ($50 < T < 160$ K). Radical combination reactions occur by detrapping the electron and/or hole.
- [33] D. Becker, M. D. Sevilla, *Adv. Radiat. Biol.* **1993**, 17, 121.
- [34] W. A. Bernhard, N. Mroczka, J. Barnes, *Int. J. Radiat. Biol.* **1994**, 66, 491.
- [35] W. Wang, M. Sevilla, *Radiat. Res.* **1994**, 138, 9.
- [36] N. E. Mroczka, W. A. Bernhard, *Radiat. Res.* **1995**, 144, 251.
- [37] R. F. Anderson, K. B. Patel, W. R. Wilson, *J. Chem. Soc. Faraday Trans.* **1991**, 87, 3739.
- [38] A. F. Fuciarrelli, E. C. Sisk, J. H. Miller, J. D. Zimbrick, *Int. J. Radiat. Biol.* **1994**, 66, 505.
- [39] S. G. Swarts, M. D. Sevilla, D. Becker, C. J. Tokar, K. T. Wheeler, *Radiat. Res.* **1992**, 129, 333.
- [40] W. A. Bernhard, *J. Phys. Chem.* **1989**, 93, 2187.
- [41] J. Barnes, W. Bernhard, *J. Phys. Chem.* **1994**, 98, 887.
- [42] S. Steenken, *Biol. Chem.* **1997**, 378, 1293.
- [43] S. Steenken, S. V. Jovanovic, *J. Am. Chem. Soc.* **1997**, 119, 617.
- [44] D. Close, *Radiat. Res.* **1993**, 135, 1.
- [45] B. Giese, S. Wessely, M. Spormann, U. Lindemann, E. Meggers, M. E. Michel-Beyerle, *Angew. Chem.* **1999**, 111, 1050; *Angew. Chem. Int. Ed.* **1999**, 38, 996.
- [46] M. T. Milano, W. A. Bernhard, *Radiat. Res.* **1999**, 151, 39.

A Rational Approach to Selective Recognition of NH_4^+ over K^+ **

Jik Chin,* Christian Walsdorff, Brent Stranix, Jinho Oh, Hyun Jeil Chung, Su-Moon Park,* and Kimoon Kim*

Over the past several decades there has been considerable interest in developing receptors for NH_4^+ . Such receptors are desirable as sensors in clinical analysis and in environmental chemistry.^[1] For example, concentrations of urea or creatinine in biological samples can be determined indirectly by measuring the amount of NH_4^+ released upon enzyme-catalyzed hydrolysis of the substrates. These receptors are also useful for determining the concentrations of NH_4^+ or ammonia in drinking water and in the air. One of the most effective NH_4^+ receptors is nonactin (**1**), a natural antibiotic agent that is currently used commercially in ion-selective electrodes (ISE).^[1, 2] However, a serious drawback of nonactin is that it binds only about ten times more tightly to NH_4^+ than to K^+ . Similarly, crown ethers show little or no selectivity for binding NH_4^+ over K^+ .^[3] Here we report a rationally designed receptor (**2**) that is highly selective for binding NH_4^+ over K^+ .



[*] Prof. K. Kim, Dr. C. Walsdorff, J. Oh
National Creative Research Initiative Center
for Smart Supramolecules
and
Department of Chemistry
Pohang University of Science and Technology (Postech)
San 31 Hyojadong, Pohang 790-784 (Republic of Korea)
Fax: (+82) 562-279-8129
E-mail: kkim@postech.ac.kr
Prof. S.-M. Park, H. J. Chung
Department of Chemistry
Pohang University of Science and Technology
San 31 Hyojadong, Pohang 790-784 (Republic of Korea)
Fax: (+82) 562-279-8129
E-mail: smpark@postech.ac.kr
Prof. J. Chin, Dr. B. Stranix
Department of Chemistry
McGill University
801 Sherbrooke Street West, Montreal, Quebec H3A 2K6 (Canada)
Fax: (+1) 514-398-3797
E-mail: chin@musica.mcgill.ca

[**] This work was supported by the Creative Research Initiative Program of the Korean Ministry of Science and Technology, the Korea Science and Engineering Foundation (96-051-05-01-3), and the National Science and Engineering Council of Canada. This collaboration began during the sabbatical leave of J. C. at the Center of Biofunctional Molecules, Postech.

The main reason why it has been difficult to design receptors that are highly selective for binding NH_4^+ over K^+ is that the sizes of the two monocations are closely matched. However, NH_4^+ and K^+ are clearly distinct in terms of their symmetry. K^+ has a closed valence electron shell with spherical symmetry and prefers ionic bonds with coordination numbers of six or more. In contrast, NH_4^+ has tetrahedral symmetry and allows four specifically positioned hydrogen bonds in addition to ionic interactions. Our goal was thus to develop a receptor with lone pair electrons that are rigidly held at the correct geometry for binding NH_4^+ by hydrogen bonds.^[4] We avoided additional functional groups that may stabilize NH_4^+ by dipole interactions since these groups may lower the selectivity.

Molecular mechanics computation^[5] showed that the three imine nitrogen atoms in **2** are ideally positioned for hydrogen bonding to NH_4^+ with $\text{N}_R \cdots \text{N}_A$ distances of about 3 Å and $\text{N}_R \cdots \text{N}_A \cdots \text{N}_R$ angles of about 110° (where N_R represents a receptor imine nitrogen atom, and N_A represents the NH_4^+ nitrogen atom). Whereas this expected bite is perfect for NH_4^+ , the bite angle (110°) is too wide to favor higher coordination numbers for metal ions like K^+ , and the bite distance (3 Å) is too long for metal ions with a smaller radius.^[6] The three ethyl groups in **2** are expected to assist in directing the three pyrazole rings to the same side of the benzene ring by steric interactions (forming *ababab* structures).^[7] The three methyl groups in the 5-position of the pyrazole rings were intended to converge the imine nitrogen atoms for binding NH_4^+ , and the three methyl groups in the 3-position of the pyrazole rings were intended to block ligands from coordinating to K^+ .

Figures 1 and 2 show the crystal structures of **2** and its $\text{NH}_4^+ \cdot \text{PF}_6^-$ complex (**3**), respectively.^[8] The structure of **2** reveals that the three pyrazole groups are not all on the same side of the benzene ring. Consistent with the solid-state structure, low-temperature ^1H NMR spectra of **2** in CD_2Cl_2 reveal that the receptor lacks C_3 symmetry in solution.^[9] It may be that the repulsion between the three lone pair electrons on the pyrazole imine nitrogen atoms prevents the formation of the above-mentioned *ababab* structure. However, all three pyrazoles of **3** are on the same side of the benzene rings and are hydrogen bonded to NH_4^+ as predicted. Additionally the counterion (PF_6^-) is located close to the NH_4^+ ion with a $\text{N}_A \cdots \text{F6}$ distance of about 3.0 Å. The $\text{N}_R \cdots \text{N}_A$ distances

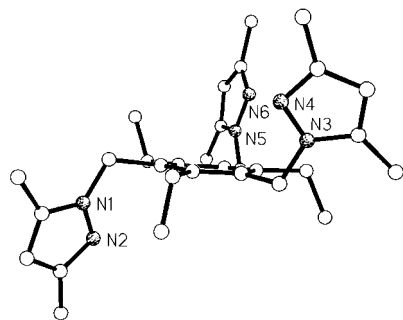


Figure 1. The structure of **2** in the solid state. The asymmetric unit contains two independent molecules with enantiomeric conformations that are related by near noncrystallographic inversion symmetry. Only one of them is depicted.

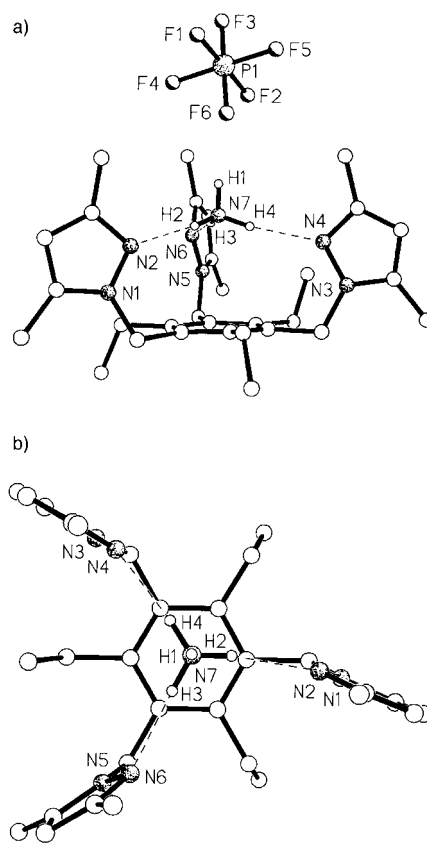


Figure 2. a) Side and b) top views of **3** in the solid state. Except for the four NH_4^+ hydrogen atoms that have been located in the differential Fourier density map and refined without constraints, hydrogen atoms have been omitted for clarity. In (b) the PF_6^- ion has been omitted. Selected interatomic distances [Å] and angles [$^\circ$]: $\text{N2} \cdots \text{N7}$ 2.949(4), $\text{N4} \cdots \text{N7}$ 3.001(4), $\text{N6} \cdots \text{N7}$ 3.053(4), $\text{P6} \cdots \text{N7}$ 3.031(4); N2-N7-N4 125.2(3), N2-N7-N6 105.8(1), N4-N7-N6 111.9(1).

range from 2.95 Å to 3.05 Å for **3**, typical of hydrogen bonded N-H-N units.^[10] The value of the $\text{N}_R \cdots \text{N}_A \cdots \text{N}_R$ angles range from 105° to 125° for **3**, in good agreement with molecular modeling. It is evident from the crystal structures that the match between the NH_4^+ and the receptors is excellent with no major deformations (Figure 1).^[11]

Figure 3 shows that an ISE based on receptor **2** is highly selective for binding NH_4^+ over K^+ ($\lg K_{\text{NH}_4^+/\text{K}^+} = -2.6$).^[12] In reasonable agreement with this data, the equilibrium constant for binding of the NH_4^+ to **2** ($1.4 \times 10^6 \text{ M}^{-1}$) as determined by the extraction method^[3] is over two orders of magnitude greater than that for binding of K^+ to **2** ($8.8 \times 10^3 \text{ M}^{-1}$). The selectivity of the electrode for binding NH_4^+ over Na^+ is even greater ($\lg K_{\text{NH}_4^+/\text{Na}^+} = -2.8$).^[13] By comparison, a nonactin-based ISE, prepared the same way as the **2**-based ISE, is only about ten times more selective for binding NH_4^+ over K^+ ($\lg K_{\text{NH}_4^+/\text{K}^+} = -1.0$ and $\lg K_{\text{NH}_4^+/\text{Na}^+} = -2.6$).^[14]

Experimental Section

2: 3,5-Dimethyl pyrazole is dissolved in THF, deprotonated with solid NaH, and allowed to react with 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene.^[15] The mixture is poured into water, and extracted with CHCl_3 . The organic phase is washed with aqueous NaOH and evaporated, and the residue is recrystallized from ethanol to give **2** as colorless crystals in 73% yield. Elemental analysis calcd for $\text{C}_{30}\text{H}_{42}\text{N}_6$: C 74.03, H 8.70, N 17.27; found: C

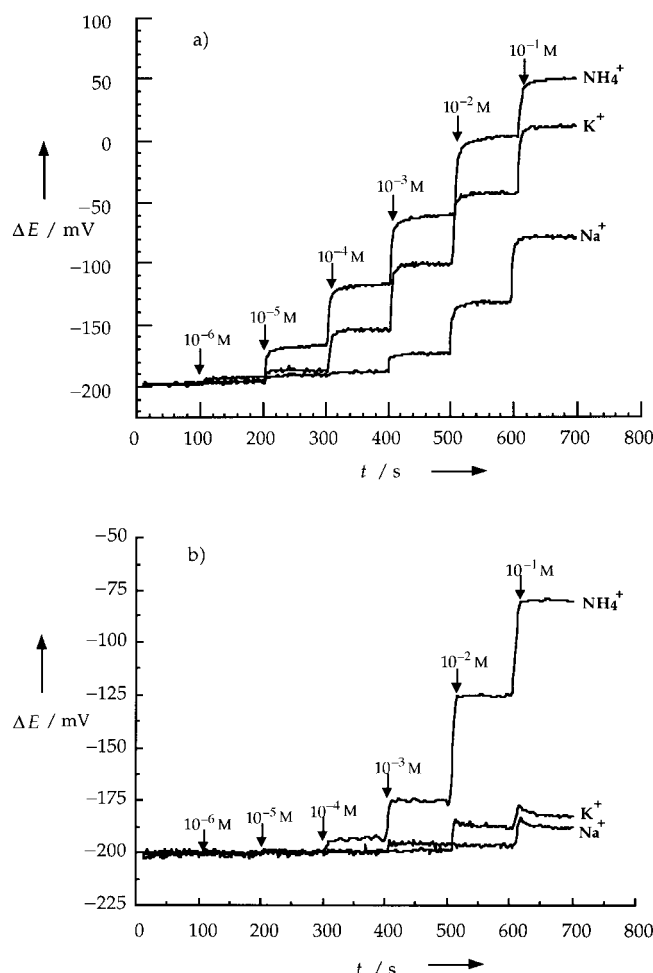


Figure 3. Responses of ISEs to NH_4^+ , Na^+ and K^+ . a) ISE based on **1**. b) ISE based on **2**.

73.79, H 8.71, N 17.04; ^1H NMR (CDCl_3 , 300 MHz): δ = 0.86 (9H, t, Me), 2.14 (9H, s, Me), 2.15 (9H, s, Me), 2.77 (6H, q, CH_2), 5.18 (6H, s, CH_2), 5.76 (3H, s, pyrazol-4-yl-H); ^{13}C NMR (CDCl_3 , 75 MHz): δ = 11.85, 13.75, 15.09, 24.12, 47.59, 106.03, 130.83, 139.85, 145.62, 147.38.

3: Colorless crystals of $[\text{2} \cdot \text{NH}_4]\text{PF}_6$ (**3**) were obtained by recrystallizing stoichiometric amounts of **2** and NH_4PF_6 from hot ethanol in 70% yield. Elemental analysis calcd for $\text{C}_{30}\text{H}_{46}\text{F}_6\text{N}_7\text{P}$: C 55.46, H 7.14, N 15.09; found: C 55.83, H 7.26, N 15.29; ^1H NMR (CDCl_3 , 300 MHz): δ = 1.11 (9H, t, Me), 2.11 (9H, s, Me), 2.38 (9H, s, Me), 2.47 (6H, q, CH_2), 5.05 (6H, s, CH_2), 5.85 (3H, s, pyrazol-4-yl-H), 6.79 (3 or 4H, somewhat broad, NH_4).

Received: March 18, 1999 [Z13183IE]
German version: *Angew. Chem.* **1999**, *111*, 2923–2926

Keywords: ammonium ions • cations • electrodes • receptors

- [1] P. Bühlmann, E. Pretsch, E. Bakker, *Chem. Rev.* **1998**, *98*, 1593–1687.
- [2] M. Dobler in *Comprehensive Supramolecular Chemistry*, Vol. 1 (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle), Pergamon, Oxford, **1996**, pp. 276–313.
- [3] S. S. Moore, T. L. Tarnowski, M. Newcomb, D. J. Cram, *J. Am. Chem. Soc.* **1977**, *99*, 6398–6405.
- [4] Cation- π interaction between the benzene ring of the receptor and NH_4^+ may also contribute to the overall binding energy. However, this is not expected to affect the selectivity. Experimental ΔH° values for the complexation of K^+ and NH_4^+ to a benzene ring are -19.2 and -19.3 kcal mol $^{-1}$, respectively: J. Sunner, K. Nishizawa, P. Kébarle, *J.*

Phys. Chem. **1981**, *85*, 1814–1820; C. A. Deakyne, M. Meot-Ner, *J. Am. Chem. Soc.* **1985**, *107*, 474–479.

- [5] The energy minimum of the NH_4^+ -bound receptor was obtained by molecular mechanics computation using Quantum Cache (version 3.11) from the Oxford Molecular Group. Preliminary ab initio computation also shows that the minimized structure is in good agreement with that obtained from X-ray crystallography.
- [6] Tris(pyrazol-1-ylmethyl)benzenes have been studied in metal-coordination chemistry. In line with our argument they do not act as mononucleating tridentate ligands of a single metal each, but rather bridge different metal centers: a) W.-K. Chang, S.-C. Sheu, G.-H. Lee, Y. Wang, T.-I. Ho, Y.-C. Lin, *J. Chem. Soc. Dalton Trans.* **1993**, 687–694; b) C. M. Hartshorn, P. J. Steel, *Chem. Commun.* **1997**, 541–542. An exception is found in a complex with ruthenium that is η^6 -bound to the benzene ring and further coordinated by the three pyrazole nitrogen atoms. The benzene ring is deformed and the pyrazolylmethyl units are bent inwards: c) C. M. Hartshorn, P. J. Steel, *Angew. Chem.* **1996**, *108*, 2818–2820, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2655–2657. However, such a mode is hardly expected with alkaline metals.
- [7] D. J. Iverson, G. Hunter, J. F. Blount, J. R. Damewood, Jr., K. Mislow *J. Am. Chem. Soc.* **1981**, *103*, 6073–6083; for other interesting examples, see T. D. P. Stack, J. A. Weigel, R. H. Holm, *Inorg. Chem.* **1990**, *29*, 3745–3760; C. Walsdorff, W. Saak, S. Pohl, *J. Chem. Soc. Dalton Trans.* **1997**, 1857–1861; C. Walsdorff, W. Saak, D. Haase, S. Pohl, *Chem. Commun.* **1997**, 1931–1932; Z. Hou, T. D. P. Stack, C. J. Sunderland, K. N. Raymond, *Inorg. Chim. Acta* **1997**, *263*, 341–355; A. Metzger, V. M. Lynch, E. V. Anslyn, *Angew. Chem.* **1997**, *109*, 911–914, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 862–865; A. P. Bisson, V. M. Lynch, M.-C. K. Monahan, E. V. Anslyn, *Angew. Chem.* **1997**, *109*, 2435–2437, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2340–2342; B. F. Hoskins, R. Robson, D. A. Slizys, *Angew. Chem.* **1997**, *109*, 2861–2863, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2752–2755; T. Szabo, B. M. O’Leary, J. Rebek, Jr., *Angew. Chem.* **1998**, *110*, 3606–3609, *Angew. Chem. Int. Ed.* **1998**, *37*, 3410–3413; C. Walsdorff, S. Park, J. Kim, J. Heo, K.-M. Park, J. Oh, K. Kim, *J. Chem. Soc. Dalton Trans.* **1999**, 923–929.
- [8] Crystal data for **2**: $0.3 \times 0.3 \times 0.2$ mm, $\text{C}_{30}\text{H}_{42}\text{N}_6$, M_r = 486.70, monoclinic, space group *Cc*, a = 11.2859(2), b = 20.8673(4), c = 24.1688(5) Å, β = 97.303(1)°, V = 5645.7(2) Å ^{3} , Z = 8, T = 296 K, ρ_{calcd} = 1.145 g cm $^{-3}$, Siemens SMART CCD diffractometer, $\text{MoK}\alpha$ radiation, 11730 reflections collected, 5567 independent reflections, R_1 = 0.0592, wR_2 = 0.1525 [$I > 2\sigma(I)$], R_1 = 0.0732, wR_2 = 0.1697 (all data), GOF = 1.105. Crystal data for **3**: $0.7 \times 0.3 \times 0.3$ mm, $\text{C}_{30}\text{H}_{46}\text{F}_6\text{N}_7\text{P}$, M_r = 649.71, triclinic, space group $P\bar{1}$, a = 10.927(4), b = 11.302(3), c = 15.464(4) Å, α = 95.27, β = 95.99(3), γ = 112.66(3)°, V = 1734.5(9) Å ^{3} , Z = 2, ρ_{calcd} = 1.244 g cm $^{-3}$, 5198 independent reflections, R_1 = 0.0631, wR_2 = 0.1709 [$I > 2\sigma(I)$], R_1 = 0.0729, wR_2 = 0.1822 (all data), GOF = 1.062. 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-115195 (**2**) and CCDC-115196 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] For example, the ^1H NMR signals due to the three methyl groups (δ = 0.8, t, 9H) of the ethyl groups in **2** are equivalent at 297°K. However, this signal splits into two (δ = 1.2, br, 3H; δ = 0.3, br, 6H) at 180°K.
- [10] L. N. Kuleshova, P. M. Zorkii, *Acta Crystallogr. Sect. B* **1981**, *37*, 1363–1366.
- [11] We expected the three ethyl groups in ammonium-bound **2** to point away from the three pyrazole groups. It appears that crystal packing between two molecules of the complex within the unit cell forces one of the ethyl groups to point in the direction of the pyrazole rings: C. Walsdorff, K.-M. Park, J. Oh, K. Kim, *Acta Crystallogr. Sect. C* **1999**, *55*, 108–110.
- [12] The ion-selective membranes were prepared by slow evaporation of a solution in THF containing 1% ionophore, 33% polyvinyl chloride, and 66% bis(2-ethylhexyl)adipate (by weight). A 0.10 M NH_4Cl solution was used as filling solution with an AgCl-coated silver wire in the standard compartment of the ISE. Selectivity constants for each electrode were determined by the two solution method at 0.010 M

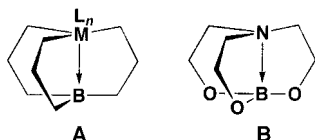
concentrations of NH_4^+ (pH 7.2 with 0.10 M Tris buffer): Y. Umezawa, K. Umezawa, H. Sato, *Pure. Appl. Chem.* **1965**, 67, 507–518.

- [13] An elegantly designed cryptand that is highly sensitive and selective for binding NH_4^+ has been reported. However, the cryptand is much too basic (more basic than ammonia) and hydrophilic for use as an ISE: E. Graf, J.-P. Kintzinger, J.-M. Lehn, J. LeMoigne, *J. Am. Chem. Soc.* **1982**, 104, 1672–1678.
- [14] However, nonactin binds more tightly to NH_4^+ than does **2**.
- [15] 1,3,5-Tris(bromomethyl)-2,4,6-triethylbenzene was prepared as previously described: C. Walsdorff, W. Saak, S. Pohl, *J. Chem. Res. (S)* **1996**, 282–283, *J. Chem. Res. (M)* **1996**, 1601–1618.

The Sting of the Scorpion: A Metallaboratrane**

Anthony F. Hill,* Gareth R. Owen,
Andrew J. P. White, and David J. Williams

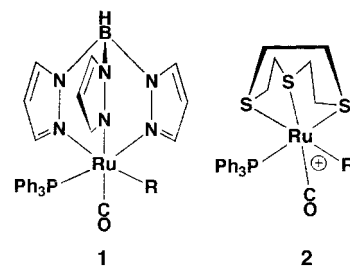
Bis(azolyl)borate chelates are often referred to as “scorpionates” because their coordination geometry can place a hydrogen substituent on boron in close proximity to a metal center constrained within the claws.^[1] This arrangement leads in some cases to agostic interactions, however to date none of these situations have involved direct formation of a metal–boron bond (B–H oxidative addition). By extending this conceptual arthropomorphism and in deference to the parable, we confirm that it is indeed “in the nature of the scorpion to sting”. Herein we report the first example of a poly(azolyl)borate ligand that undergoes B–H activation (stinging) at one metal center to provide the unprecedented metallaboratrane structural motif (**A**), akin to the more familiar boratrane cages (**B**).^[2]



We have previously described the chemistry of the isoelectronic σ -organyl complexes $[\text{Ru}(\text{R})(\text{CO})\{\text{HB}(\text{pz})_3\}(\text{PPh}_3)]$ (**1**, pz = pyrazol-1-yl; R = vinyl, aryl),^[3] and $[\text{Ru}(\text{R})(\text{CO})(\text{PPh}_3)_2\{[9]\text{aneS}_3\}]^+$ (**2**, [9]aneS₃ = 1,4,7-trithiacyclononane),^[4] which feature facially tridentate triaza-scorpionate or trithia macrocyclic coligands. The recent report of the new ligand “HB(mt)₃” (mt = 2-sulfanyl-1-methylimidazole)^[5] suggested to us that the complexes $[\text{Ru}(\text{R})(\text{CO})(\text{PPh}_3)\{\text{HB}(\text{mt})_3\}]$ (**3**)

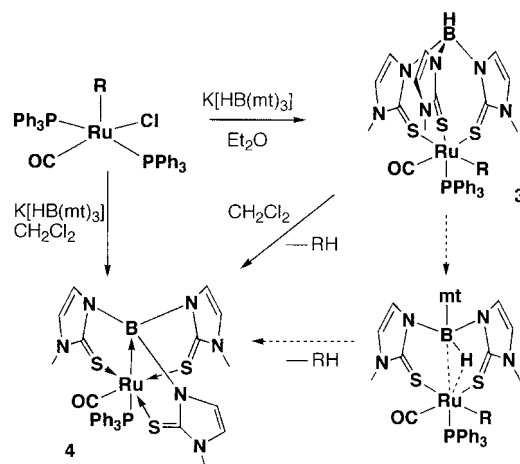
[*] Dr. A. F. Hill, G. R. Owen, Dr. A. J. P. White, Prof. D. J. Williams
Department of Chemistry
Imperial College of Science, Technology, and Medicine
South Kensington, London SW72AY (UK)
Fax: (+44) 171-5945804
E-mail: a.hill@ic.ac.uk

[**] Poly(azolyl)chelate Chemistry, Part 9. A.F.H. gratefully acknowledges the award of a Senior Research fellowship from The Leverhulme Trust and The Royal Society. Ruthenium salts were generously provided by Johnson Matthey Chemicals Ltd. – Part 8: A. F. Hill, A. J. P. White, D. J. Williams, J. D. E. T. Wilton-Ely, *Organometallics* **1998**, 17, 4249.



should be readily accessible, and that the HB(mt)₃ ligand in such complexes would effectively serve as a hybrid of the HB(pz)₃ and [9]aneS₃ ligands. In our initial attempts to prepare the complexes **3** we have encountered an unprecedented class of reaction for tris(azolyl)borates, namely the intramolecular activation of the bridgehead B–H bond to provide the first example **4** of a metallaboratrane.

The treatment of the complex $[\text{Ru}(\text{CH}=\text{CHCPh}_2\text{OH})\text{Cl}(\text{CO})(\text{PPh}_3)_2]$ ^[6] with Na[HB(mt)₃] (dichloromethane, room temperature) provides high yields of the novel ruthenaboratrane complex $[\text{Ru}\{\text{B}(\text{mt})_3\}(\text{CO})(\text{PPh}_3)]$ (**4**, Scheme 1). The



Scheme 1. Synthesis of **4**. R = CH=CH₂, CH=CHCPh₂OH, CH=CH(4-MeC₆H₄), C₆H₅.

formulation of the yellow complex follows from spectroscopic data and was confirmed by a crystallographic study.^[7] The gross composition is reflected in the positive-ion FAB mass spectrum, which includes a molecular ion as the base peak and fragmentations arising from the loss of the carbonyl and phosphane ligands. One singlet resonance ($\delta = 17.1$) is observed for the bridgehead boron atom in the ¹¹B NMR spectrum. The ¹H NMR and ¹³C{¹H} NMR spectra are solvent dependent: Thus in CDCl₃ a static structure is suggested by the appearance of sharp peaks arising from two mt environments. However, the operation of a fluxional process is apparent in C₆D₆ at room temperature. The infrared spectrum reveals one carbonyl absorption at $\tilde{\nu} = 1888 \text{ cm}^{-1}$ (Nujol), a frequency which is suggestive of zero-valent ruthenium (see below).

The structure of the complex **4**, as revealed from an X-ray diffraction study, is shown in Figure 1.^[7] The ruthenium atom adopts a distorted octahedral coordination despite the constraints of bis-chelation, with *cis*-interligand angles in the

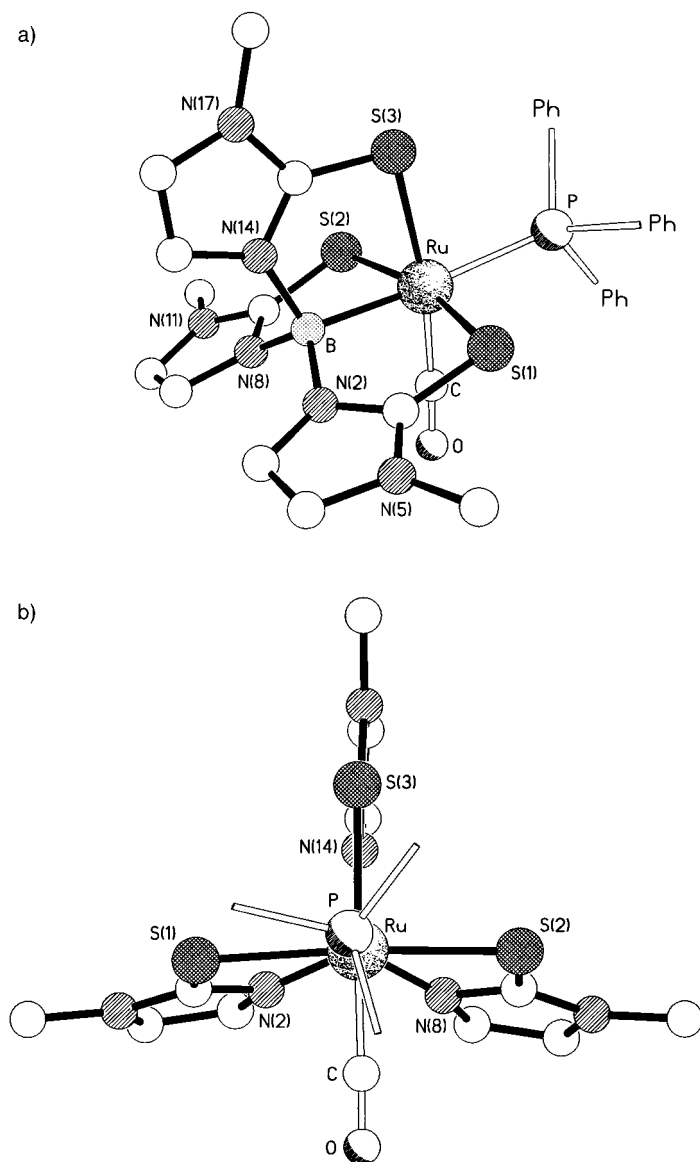


Figure 1. a) Molecular Structure of **4**. Hydrogen atoms and phenyl groups are omitted for clarity. b) Simplified view of **4** normal to the plane defined by N(2), N(8), and N(14).

range $82.7(2)–100.89(5)^\circ$. One of the three Ru–S bond lengths, the one that is *trans* to the carbonyl group (that is, adjacent to the bulky phosphane) is, as expected, significantly longer ($2.4857(14)$ Å) than the pair of mutually *trans* Ru–S bonds (Ru–S(1) $2.4066(14)$, Ru–S(2) $2.4112(14)$ Å). The coordination at the boron center naturally provides the focus of structural interest: The boron atom is tetrahedrally coordinated with angles in the range $105.5(4)–113.9(4)^\circ$, the largest of these (N(8)–B–N(2)) being associated with the *mer*-bis-chelate unit. Distinct foldings of two of the five-membered chelate rings are immediately apparent if the structure is viewed normal to the plane of the three boron-coordinated nitrogen atoms (Figure 1b). Thus, whereas the N(14)-based ring is essentially planar, with a fold of 3° about the S(3)⋯B vector, the S(1)- and S(2)-containing rings are distinctly folded (20 and 27° , respectively). In simplistic terms, this geometry is the most “relaxed” for accommodating linked

tetrahedral (B) and octahedral (Ru) centers. The ruthenium–boron bond of $2.161(5)$ Å is without precedent for comparison, but falls within the range ($2.046(7)–2.20(2)$ Å) found in osmium– σ -boryl complexes,^[8, 9] which contain an Os–B π -bonding component, but none of the ring strain that must be accommodated in the tricyclic structure of **4**. Very recently a ruthenium– σ -boryl complex $[\text{Ru}\{\text{B}(\text{NMe}_2)\text{BBr}(\text{NMe}_2)\}(\text{CO})_2(\eta\text{-C}_5\text{H}_5)]$ has also been structurally characterized (Ru–B $2.173(3)$ Å).^[10] Thus it must be concluded that the Ru–B bond in **4** represents a comparatively strong interaction. These results taken together with the observed stereochemistry at the ruthenium atom, which places the boron center in a position *trans* to the stronger donor, lead us to suggest that the canonical representation based on zero-valent ruthenium (Scheme 1) contributes significantly, though probably not exclusively, to the bonding. This type of interaction is clearly novel, but finds loose analogy in the salt $[\text{Et}_4\text{N}][\text{Fe}(\text{BPh}_3)(\text{CO})_2(\eta\text{-C}_5\text{H}_5)]$, which has been characterized on the basis of spectroscopic data ($\delta(^{11}\text{B})=28.8$; $\tilde{\nu}(\text{CO})=1991, 1920\text{ cm}^{-1}$), and is an intermediate in the reaction of $[\text{Et}_4\text{N}][\text{Fe}(\text{CO})_2(\eta\text{-C}_5\text{H}_5)]$ with BPh_3 to provide $[\text{Et}_4\text{N}][\text{Fe}_2(\text{CO})_4(\eta\text{-C}_5\text{H}_5)(\eta\text{-C}_5\text{H}_4\text{BPh}_3)]$.^[11]

Although the structure and bonding in complex **4** is novel, in retrospect the likely mechanism by which **4** forms is straightforward. The reaction of $[\text{Ru}(\text{R})\text{Cl}(\text{CO})(\text{PPh}_3)_2]$ (R = vinyl, aryl) with $\text{K}[\text{HB}(\text{pz})_3]$ is known to provide $[\text{Ru}(\text{R})(\text{CO})\{\text{HB}(\text{pz})_3\}(\text{PPh}_3)]$,^[3] which supports the initial formation of $[\text{Ru}(\text{CH}=\text{CHCPh}_2\text{OH})(\text{CO})(\text{PPh}_3)\{\text{HB}(\text{mt})_3\}]$ (**3a**). In contrast to the rigid chelation of the $\text{HB}(\text{pz})_3$ ligand, the more expansive chelation of $\text{HB}(\text{mt})_3$ might be expected to be more flexible and labile. Dissociation of one mt arm followed by agostic B–H coordination and ultimate oxidative addition of the B–H bond could provide a *cis*-hydrido–vinyl complex that undergoes alkene reductive elimination with formation of **4**. In this context, the elegant synthesis of ruthenium– σ -boryl complexes by Roper and Wright et al. through the reactions of $[\text{Ru}(\text{C}_6\text{H}_5)\text{Cl}(\text{CO})(\text{PPh}_3)_2]$ with boranes^[8, 9] provides compelling support for the proposed mechanism. Given the surprisingly mild conditions under which **4** is formed, this mechanistic conjecture begs the isolation of complexes of the form **3**. The complexes $[\text{Ru}(\text{R})\text{Cl}(\text{CO})(\text{PPh}_3)_2]$ (R = $\text{CH}=\text{CHCPh}_2\text{OH}$, $\text{CH}=\text{CH}_2$, $\text{CH}=\text{CH}(4\text{-MeC}_6\text{H}_4)$, C_6H_5) were all found to react with $\text{Na}[\text{HB}(\text{mt})_3]$ in dichloromethane to provide **4**. However, high yields of the complexes $[\text{Ru}(\text{R})(\text{CO})(\text{PPh}_3)\{\text{HB}(\text{mt})_3\}]$ (R = $\text{CH}=\text{CHCPh}_2\text{OH}$ (**3a**), $\text{CH}=\text{CH}_2$ (**3b**), $\text{CH}=\text{CH}(4\text{-MeC}_6\text{H}_4)$ (**3c**), C_6H_5 (**3d**)) were obtained if the reactions were carried out as a suspension in diethyl ether. Dissolution of the isolated complexes **3** in dichloromethane or chloroform resulted in the smooth and rapid conversion into **4** without liberation of phosphane (^{31}P NMR). This confirms that the complexes bear only one phosphane ligand, in contrast to the recently reported bis(phosphane) complexes $[\text{MR}(\text{CO})\{\eta^2\text{-HB}(\text{pz})_3\}(\text{PPh}_3)_2]$ (MR = RuH, OsPh), which are isolable intermediates en route to $[\text{MR}(\text{CO})\{\eta^3\text{-HB}(\text{pz})_3\}(\text{PPh}_3)]$.^[12]

Our initial investigations developed from a presumed simple analogy between the coordination chemistry of the $\text{HB}(\text{pz})_3$ and $\text{HB}(\text{mt})_3$ ligands. The results obtained clearly indicate that both parallels and divergencies may be antici-

pated in the chemistry of these ligands. The remarkable facility with which the ruthenaboratrane forms may presumably be traced to both the lability of HB(mt)₃ chelation and the increased ring size of the chelates, which allows the scorpion's sting to more closely approach the metal center.

Experimental Section

Na[HB(mt)₃]: Finely and intimately ground Na[BH₄] (2.08 g, 60 mmol) and 1-methylimidazole-2-thiol (Hmt, 25.0 g, 220 mmol) were suspended in xylene (30 mL) and heated under reflux for 2 h. The crude product was filtered off, washed with hot toluene and hexane, and dried in vacuo. Yield 19.17 g (94 %).

4: A mixture of [Ru(CH=CHCPh₂OH)Cl(CO)(PPh₃)₂] (0.36 g, 0.40 mmol) and Na[HB(mt)₃] (0.15 g, 0.40 mmol) in dichloromethane (50 mL) was stirred for 30 min and then filtered through diatomaceous earth and freed of volatiles. The residue was crystallized from a mixture of dichloromethane and hexane to provide yellow crystals. Yield 0.24 g (81 %). IR (Nujol): $\tilde{\nu}$ = 1888 cm⁻¹ (vs; CO); IR (CH₂Cl₂): $\tilde{\nu}$ = 1894 cm⁻¹ (vs; CO); ¹H NMR (270 MHz, CDCl₃, 25 °C): δ = 3.43 (s, 6H; NCH₃), 3.60 (s, 3H; NCH₃), 6.39, 6.70 (AB, ³J_{AB} = 2.1 Hz, 2H; CH=CH), 6.98 and 7.35 ((AB)₂, ³J_{AB} = 2.0 Hz, 4H; CH=CH), 7.25–7.35 and 7.55–7.61 (m × 2, 15H; C₆H₅); ¹³C NMR (68 MHz, CDCl₃, 25 °C): δ = 206.5 (RuCO), 170.5, 170.4 (CS), 138.5 (d, ¹J_{PC} = 21.8 Hz; C1 (C₆H₅)), 133.6 (d, ²J_{PC} = 13.4 Hz; C2, C6 (C₆H₅)), 128.4 (C4 (C₆H₅)), 127.8 (d, ³J_{PC} = 8.9 Hz; C3, C5 (C₆H₅)), 122.0 (2C), 119.2 (1C), 116.3 (2C), 113.7 (1C; CH=CH), 34.2 (1C; NCH₃), 33.7 (2C; NCH₃); ¹B NMR (CDCl₃, 25 °C, BF₃OEt₂): δ = 17.1; ³¹P{¹H} NMR (109 MHz, CDCl₃, 25 °C, 85 % H₃PO₄): δ = 26.6 (br s); FAB-MS: *m/z* (%): 743 (4) [*M*⁺], 714 (3) [*M*⁺ – CO], 452 (19) [*M*⁺ – COPPh₃]. The complex crystallized from chloroform as a bis-solvate and was also characterized crystallographically.^[7]

Received: March 22, 1999 [Z13198IE]
German version: *Angew. Chem.* **1999**, *111*, 2920–2923

Keywords: boratrane • boron • N ligands • ruthenium

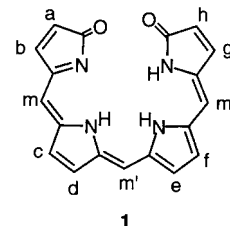
- [1] S. Trofimenko, *Chem. Rev.* **1993**, *93*, 943.
- [2] H. C. Brown, E. A. Fletcher, *J. Am. Chem. Soc.* **1951**, *73*, 2808.
- [3] A. F. Hill, *J. Organomet. Chem.* **1990**, *395*, C35; N. W. Alcock, A. F. Hill, R. P. Mellings, *Organometallics* **1991**, *10*, 3898.
- [4] J. C. Cannadine, A. L. Hector, A. F. Hill, *Organometallics* **1992**, *11*, 2323; J. C. Cannadine, A. F. Hill, A. J. P. White, D. J. Williams, J. D. E. T. Wilton-Ely, *Organometallics* **1996**, *15*, 5409.
- [5] M. Garner, J. Reglinski, I. Cassidy, M. D. Spicer, A. R. Kennedy, *Chem. Commun.* **1996**, 1975.
- [6] K. J. Harlow, A. F. Hill, T. Welton, A. J. P. White, D. J. Williams, *Organometallics* **1998**, *17*, 1916.
- [7] Crystal data for **4**: C₃₁H₃₀N₆O₆BP₃Ru · 2CHCl₃, *M*_r = 980.4, yellow blocks, 0.93 × 0.77 × 0.53 mm, triclinic, space group *P* $\bar{1}$ (no. 2), *a* = 11.932(1), *b* = 13.329(3), *c* = 14.484(2) Å, α = 68.75(1), β = 74.55(1), γ = 81.67(1)°, *V* = 2066.3(5) Å³, *Z* = 2, ρ_{calc} = 1.576 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 9.94 cm⁻¹, *F*(000) = 988, *T* = 293 K; Siemens P4/PC diffractometer, graphite-monochromated MoK α radiation, ω -scans, 7128 independent reflections. The structure was solved by direct methods and the non-hydrogen atoms of the complex, and the major occupancy non-hydrogen atoms of the disordered chloroform solvent molecules, were refined anisotropically (the others isotropically) with full matrix least-squares based on *F*² to give *R*₁ = 0.049, *wR*₂ = 0.113 for 5475 independent observed reflections [*F*_o > 4σ(*F*_o)], 2θ ≤ 50° and 453 parameters. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-116432. 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).

- [8] G. J. Irvine, M. J. G. Lesley, T. B. Marder, N. C. Norman, C. R. Rice, E. G. Robins, W. R. Roper, G. R. Whittell, L. J. Wright, *Chem. Rev.* **1998**, *98*, 2685.
- [9] G. J. Irvine, W. R. Roper, L. J. Wright, *Organometallics* **1997**, *16*, 2291; G. R. Clark, G. J. Irvine, W. R. Roper, L. J. Wright, *Organometallics* **1997**, *16*, 5499; C. E. F. Rickard, W. R. Roper, A. Williamson, L. J. Wright, *Organometallics* **1998**, *17*, 4869.
- [10] H. Braunschweig, M. Koster, R. Wang, *Inorg. Chem.* **1999**, *38*, 415.
- [11] J. M. Burlitch, J. H. Burk, M. E. Leonowicz, R. E. Hughes, *Inorg. Chem.* **1979**, *18*, 1702.
- [12] I. D. Burns, A. F. Hill, A. J. P. White, D. J. Williams, J. D. E. T. Wilton-Ely, *Organometallics* **1998**, *17*, 1552.

Tetrapyrroles as π Donors: A Pd₂²⁺ Unit Sandwiched between Two Helical Bilindione–Palladium Moieties**

Pamela Lord, Marilyn M. Olmstead, and Alan L. Balch*

The linear tetrapyrroles of the bilindione family **1**^[1] are metabolites of heme degradation which show biological activity (antioxidant^[2] and antiviral activity^[3]) that is poorly understood at the molecular level. Like porphyrins bilindiones form four-coordinate metal complexes that undergo a variety of changes in redox state, electronic structure, and axial ligation.^[4–6] The general mode of coordination of both the bilindiones and porphyrins involves bonding of the four nitrogen atoms to a central metal ion. With the bilindione ligand, the four nitrogen atoms cannot be coplanar when bonded to a relatively small first-row transition metal ion. Consequently, helical complexes result.



Here we report on the formation of complexes that involve a larger second-row transition metal ion and in which the metalation of the linear tetrapyrrole results in an unusual sandwich structure.

Treatment of octaethylbilindione H₃OEB (**1**, a–h = Et) with palladium(II) acetate in chloroform/ethanol followed by chromatography on silica gave dark green crystals of [Pd₄(OEB)₂] in 66 % yield. The electronic spectrum of the complex which displays bands at 831 nm (ϵ = 2.2 × 10⁴), 358 nm (ϵ = 4.6 × 10⁴), and 284 nm (ϵ = 3.7 × 10⁴), resembles that of [Zn^{II}(OEBOMe)]^[7] rather than those of other complexes in which the tetrapyrrole is coordinated to the metal center simply through four M–N bonds, such as [Co(OEB)]^[4] and

[*] Prof. Dr. A. L. Balch, P. Lord, Dr. M. M. Olmstead
Department of Chemistry
University of California, Davis
Davis, CA 95616 (USA)
Fax: (+1) 530-752-8995
E-mail: albalch@ucdavis.edu

[**] This work was supported by the US National Institutes of Health (Grant GM 26226).

[Ni(OEB)].^[5] Consequently, an additional bond to one of the oxygen atoms of the OEB ligand was expected.

The structure of [Pd₄(OEB)₂]·THF, as determined by a single-crystal X-ray diffraction study, is shown in Figure 1. The complex, which has no crystallographically imposed symmetry, consists of two helical Pd^{II}(OEB) units that are joined

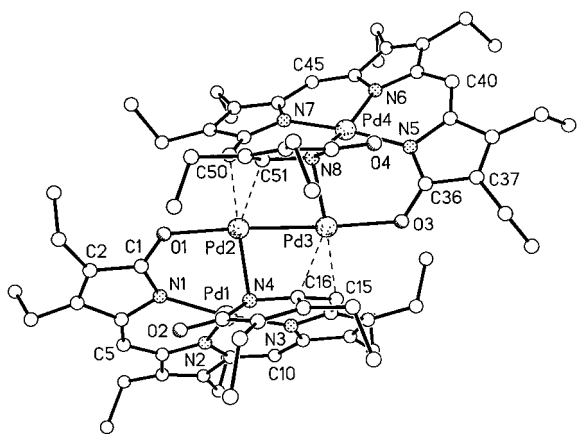


Figure 1. Perspective view of [Pd₄(OEB)₂]. Selected bond lengths [Å] and angles [°]: Pd1–N1 2.051(8), Pd1–N2 2.011(9), Pd1–N3 2.017(8), Pd1–N4 2.082(9), Pd3–N8 2.091(8), Pd4–N5 2.007(10), Pd4–N6 2.017(9), Pd4–N7 2.036(10), Pd4–N8 2.094(8), Pd2–N4 2.107(8), Pd2–C50 2.183(10), Pd2–C51 2.223(11), Pd3–C15 2.185(9), Pd3–C16 2.202(9), Pd2–O1 2.108(7), Pd3–O(3) 2.126(7), Pd2–N3 2.4725(11); N2–Pd1–N1 89.3(3), N2–Pd1–N3 90.4(3), N3–Pd1–N4 88.8(3), N1–Pd1–N4 93.4(3), N3–Pd1–N1 171.0(3), N2–Pd1–N4 167.5(3), N5–Pd4–N6 88.1(4), N6–Pd4–N7 89.8(4), N7–Pd4–N8 91.3(4), N5–Pd4–N8 93.1(4), N5–Pd4–N7 170.0(4), N6–Pd4–N8 165.8(3), O1–Pd2–Pd3 172.12(19), N4–Pd2–O1 94.6(3), N4–Pd2–Pd3 81.8(2), N8–Pd3–O3 94.6(3), N8–Pd3–Pd2 80.5(3).

through a (Pd₂)²⁺ unit. Remarkably, each OEB ligand donates seven pairs of electrons to the two palladium atoms to which it is bound. While the coordination geometry within the two Pd^{II}(OEB) portions of the tetranuclear complex is similar to those of a number of mononuclear complexes of the OEB ligand, the mode of interaction with the central Pd₂²⁺ portion is not.

The coordination environment of the central (Pd₂)²⁺ moiety, which is suspended between the two Pd(OEB) units, has several novel features. Each palladium atom of the (Pd₂)²⁺ unit is coordinated to an olefinic bond of one of the two Pd(OEB) units. Such η^2 coordination of a transition metal center to the π system at one of the *meso* carbon atoms of the OEB ligand is unprecedented in the chemistry of linear tetrapyrroles and porphyrins.^[8] Coordination of transition and alkali metal ions to individual pyrrole rings of porphyrins^[9, 10] and porphyrinogens^[11, 12] (which are nonconjugated) has been observed, but in the present example, the coordination is to a π bond that is exocyclic to the adjacent pyrrole ring. Two of the nitrogen atoms (N4 and N8), that is, one from each tetrapyrrole ring, are also coordinated to the central (Pd₂)²⁺ unit. These nitrogen atoms act as direct bridging links between Pd1 and Pd2 and between Pd3 and Pd4. The Pd–N distances that involve the bridging nitrogen atoms (Pd1–N4 2.082(9), Pd2–N4 2.107(8), Pd3–N8 2.091(8), Pd4–N8 2.094(8) Å) are longer than the strictly terminal Pd–N distances (2.007(10)–2.051(8) Å). Such bridging by pyrrole nitrogen atoms in transition metal complexes of porphyrins

and related tetrapyrroles is uncommon. However, bridging pyrrole nitrogen atoms were observed in the tetraphenylporphyrin (H₂tpp) complexes [(tpp){Re(CO)₃}]₂ and [(tpp){Re(CO)₃}[Re(CO)₃Cl]][SbCl₆].^[13, 14] In these complexes the two rhenium atoms are bound to opposite sides of the porphyrin by coordination to three pyrrole nitrogen atoms, and two of the four pyrrole nitrogen atoms bridge the two rhenium centers. In these rhenium complexes, the Re–N distances are also longer for the bridging nitrogen atoms than for the terminal nitrogen atoms. Finally, one of the oxygen atoms of each Pd^{II}(OEB) unit is coordinated to the (Pd₂)²⁺ moiety.

The overall structure at the center of [Pd₄(OEB)₂] conforms to that seen in other dinuclear Pd^I complexes. These dinuclear complexes generally involve six donor centers that are arranged about the Pd–Pd bond to give planar coordination at each metal atom. In the (Pd₂)²⁺ unit the Pd–Pd distance of 2.4725(11) Å is indicative of a Pd–Pd single bond. In comparison, the lengths of the unsupported Pd–Pd single bonds in [Pd₂(CNMe)₆]²⁺ and [Pd₂(CNMe)₄I₂] are 2.5310(9)^[15] and 2.533(1) Å, respectively.^[16] Other Pd–Pd single bonds have bond lengths in the range 2.5–2.7 Å.^[17] The remaining Pd···Pd separations (Pd1···Pd2 3.1298(11), Pd3···Pd4 3.1224(11) Å) are much longer and are inconsistent with any direct bonding between them. The diamagnetism of [Pd₄(OEB)₂] is readily explained: two diamagnetic (OEB)³⁻ ligands chelate two diamagnetic Pd^{II} centers (Pd1 and Pd4), and the d⁹ Pd^I centers (Pd2 and Pd3) are spin-coupled through the direct Pd–Pd bond, as in many dinuclear Pd^I complexes.

Each Pd(OEB) unit in [Pd₄(OEB)₂] is chiral and has a *p*-helical configuration. Thus, each individual tetranuclear complex is chiral. However, the space group *P* $\bar{1}$ is centrosymmetric, and consequently crystals of [Pd₄(OEB)₂] contain a racemate of the two enantiomeric helices.

Treatment of [Pd₄(OEB)₂] with pyridine/ethanol leads to the precipitation of black crystals of the odd-electron complex [Pd(OEB)], which shows an intense EPR spectrum with *g* = 2.003 in toluene at 23 °C and no NMR spectrum. The structure of this complex, as determined by X-ray diffraction, is shown in Figure 2. The complex has the helical geometry that is typical of other [M(OEB)] complexes and similar to that of

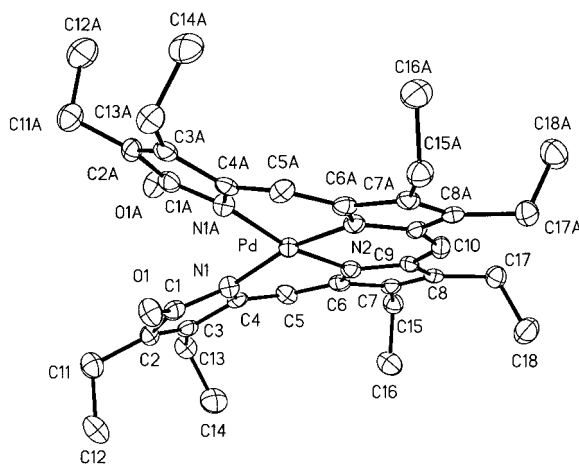


Figure 2. Perspective view of [Pd(OEB)]. Selected bond lengths [Å] and angles [°]: Pd–N1 2.012(4), Pd–N2 2.011(4); N1–Pd–N2 89.42(14), N1–Pd–N1A 93.5(2), N1–Pd–N2A 167.03(16), N2–Pd–N2A 90.6(2).

the two end units of $[\text{Pd}_4(\text{OEB})_2]$. The formation of $[\text{Pd}(\text{OEB})]$ from the pyridine/ethanol solution is governed by the ability of pyridine to coordinate to the central Pd_2 unit and thus to facilitate its dissociation from $[\text{Pd}_4(\text{OEB})_2]$.

The η^2 coordination of the bilindione by a palladium center not only produces the novel structure shown in Figure 1, but also alters the chemical reactivity of the ligand. We will describe the rearrangement of the ligand core in $[\text{Pd}_4(\text{OEB})_2]$ elsewhere.^[18]

Experimental Section

$[\text{Pd}_4(\text{OEB})_2]$: Under a dinitrogen atmosphere, a solution of palladium(II) acetate (115 mg, 0.512 mmol) in chloroform (5 mL) was added to a solution of octaethylbiliverdin (30 mg, 0.054 mmol) in ethanol (25 mL). (Ethanol is critical for the success of the reaction and serves as reductant.) After the mixture was heated to 65 °C for 5 min and stirred for 1.5 h at 25 °C, the solvent was evaporated. The residue was subjected to chromatography on silica with chloroform as the eluant. The first dark green fraction was collected and evaporated to dryness (yield: 27.5 mg, 66.5%). Crystals suitable for X-ray crystallography were grown by slow diffusion of water into a solution of the complex in THF. ^1H NMR (300 MHz, CDCl_3): δ = 6.759 (s, *meso*-CH), 6.007 (s, *meso*-CH), 5.156 (s, *meso*-CH), 2.575–1.892 (m, CH_2), 1.340–0.863 (m, CH_3). UV/Vis: λ_{max} [nm] (ϵ [$\text{M}^{-1}\text{cm}^{-1}$]) = 831 (2.2×10^4), 358 (4.6×10^4), 284 (3.7×10^4). MALDI MS (positive ion): parent cluster at 1527.00 amu.

Crystal data for $[\text{Pd}_4(\text{OEB})_2] \cdot \text{THF}$: Dark green plate, dimensions $0.22 \times 0.16 \times 0.02$ mm, triclinic, space group $P\bar{1}$, $a = 14.7685(15)$, $b = 14.935(2)$, $c = 16.328(2)$ Å, $\alpha = 87.407(9)^\circ$, $\beta = 83.278(8)^\circ$, $\gamma = 76.132(8)^\circ$, $V = 3472.0(6)$ Å³, $\lambda = 1.54178$ Å, $Z = 2$, $\rho_{\text{calcd}} = 1.532$ Mg m⁻³; $\mu(\text{CuK}\alpha) = 8.665$ mm⁻¹; Siemens P4 diffractometer, rotating anode; $2\theta - \omega$ scans, $2\theta_{\text{max}} = 113$; $T = 130$ K; 9187 reflections collected; 9187 independent reflections; min./max. transmission 0.2516/0.8458; solution by direct methods (SHELXS-97; G. M. Sheldrick, 1990); refinement by full-matrix least-squares methods on F^2 (SHELXL-97; G. M. Sheldrick, 1997); 806 parameters, $R1 = 0.0893$, $wR2 = 0.1772$ for all data; $R1 = 0.0649$ for 6915 observed data ($I > 2\sigma(I)$). An empirical absorption correction was applied.^[19]

Crystal data for $[\text{Pd}(\text{OEB})]$: Black needle, dimensions $0.44 \times 0.08 \times 0.08$ mm, monoclinic, space group $I2/a$, $a = 13.274(3)$, $b = 18.655(4)$, $c = 14.144(3)$ Å, $\beta = 116.00(3)^\circ$, $V = 3141.3(11)$ Å³, $\lambda = 0.71073$ Å, $Z = 4$, $\rho_{\text{calcd}} = 1.392$ Mg m⁻³; $\mu(\text{MoK}\alpha) = 0.628$ mm⁻¹; Siemens R3m/V diffractometer; $2\theta - \omega$ scans, $2\theta_{\text{max}} = 45$; $T = 140(2)$ K; 2198 reflections collected; 2030 independent reflections; min./max. transmission 0.770/0.952; solution by direct methods (SHELXS-97; G. M. Sheldrick, 1990); refinement by full-matrix least-squares methods on F^2 (SHELXL-97; G. M. Sheldrick, 1997); 195 parameters, $R1 = 0.055$, $wR2 = 0.0900$ for all data; $R1 = 0.042$ for 1715 observed data ($I > 2\sigma(I)$). An empirical absorption correction was applied. 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-113559 and CCDC-114918. 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).

Received: February 23, 1999 [Z 130751E]

German version: *Angew. Chem.* **1999**, *111*, 2930–2932

Keywords: N ligands • oligopyrroles • palladium • pi interactions

- [1] H. Falk, *The Chemistry of Linear Oligopyrroles and Bile Pigments*, Springer, Vienna, **1989**.
- [2] R. Stocker, Y. Yamamoto, A. F. McDonagh, A. N. Glazer, B. N. Ames, *Science* **1987**, *235*, 1043.
- [3] T. Nakagami, S. Tajiri, M. Takahashi, K. Yamanishi, *Microbiol. Immunol.* **1992**, *36*, 381; H. Mori, T. Otake, M. Morimoto, N. Ueba, N. Kunita, T. Nakagami, N. Yamasaki, S. Tajiri, *Jpn. J. Cancer Res.* **1991**, *82*, 755.

- [4] A. L. Balch, M. Mazzanti, B. C. Noll, M. M. Olmstead, *J. Am. Chem. Soc.* **1994**, *116*, 9114.
- [5] J. V. Bonfiglio, R. Bonnett, D. G. Buckley, D. Hamzesh, K. M. Hursthouse, K. M. A. Malik, A. F. McDonagh, J. Trotter, *Tetrahedron* **1983**, *39*, 1865.
- [6] a) A. L. Balch, M. Mazzanti, B. C. Noll, M. M. Olmstead, *J. Am. Chem. Soc.* **1993**, *115*, 12206; b) S. Attar, A. L. Balch, P. M. Van Calcar, K. Winkler, *J. Am. Chem. Soc.* **1997**, *119*, 3317; c) S. Attar, A. Ozarowski, P. M. Van Calcar, K. Winkler, A. L. Balch, *Chem. Commun.* **1997**, 1115; d) A. L. Balch, L. Latos-Grażyński, B. C. Noll, M. M. Olmstead, N. Safari, *J. Am. Chem. Soc.* **1993**, *115*, 9056.
- [7] a) L. Latos-Grażyński, J. A. Johnson, S. Attar, M. M. Olmstead, A. L. Balch, *Inorg. Chem.* **1998**, *37*, 4493; b) R. Koerner, L. Latos-Grażyński, A. L. Balch, *J. Am. Chem. Soc.* **1998**, *120*, 9246.
- [8] A compound in which two lithium ions are sandwiched between two anionic porphyrins has been structurally characterized: C. S. Alexander, S. J. Retig, B. R. James, *Organometallics* **1994**, *13*, 2542.
- [9] K. K. Dailey, G. P. A. Yap, A. L. Rheingold, T. B. Rauchfuss, *Angew. Chem.* **1996**, *108*, 1985; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1833.
- [10] M. Senge, *Angew. Chem.* **1996**, *108*, 2051; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1923.
- [11] C. Floriani, E. Solari, G. Solari, A. Chiesi-Villa, C. Rizzoli, *Angew. Chem.* **1998**, *110*, 2367; *Angew. Chem. Int. Ed.* **1998**, *37*, 2245.
- [12] C. Floriani, *Chem. Commun.* **1996**, 1257.
- [13] D. Cullen, E. Meyer, T. S. Srivastava, M. Tsutsui, *J. Am. Chem. Soc.* **1972**, *94*, 7603.
- [14] S. Kato, M. Tsutsui, D. Cullen, E. Meyer, Jr., *J. Am. Chem. Soc.* **1977**, *99*, 620.
- [15] D. J. Doonan, A. L. Balch, S. Z. Goldberg, R. Eisenberg, J. S. Miller, *J. Am. Chem. Soc.* **1975**, *97*, 1961.
- [16] N. M. Rutherford, M. M. Olmstead, A. L. Balch, *Inorg. Chem.* **1984**, *23*, 2833.
- [17] A. L. Balch, *Comments Inorg. Chem.* **1984**, *3*, 51.
- [18] P. Lord, M. M. Olmstead, A. L. Balch, unpublished results.
- [19] S. Parkin, B. Moezzi, H. Hope, *J. Appl. Crystallogr.* **1995**, *28*, 53.

The Concept of Docking/Protecting Groups in Biohydroxylation**

Gerhart Braunnegg, Anna de Raadt,
Sabine Feichtenhofer, Herfried Griengl,*
Irene Kopper, Antje Lehmann, and Hans-Jorg Weber

The application of enzymes and microorganisms in organic synthesis has become a valuable and indispensable tool of synthetic chemistry within the last ten to fifteen years.^[1] Since, in general, nonnatural substrates are transformed, it is not surprising that these compounds are not always well accepted by the biocatalysts in question. With regard to biohydroxylation, it was recognized at an early stage that the presence of

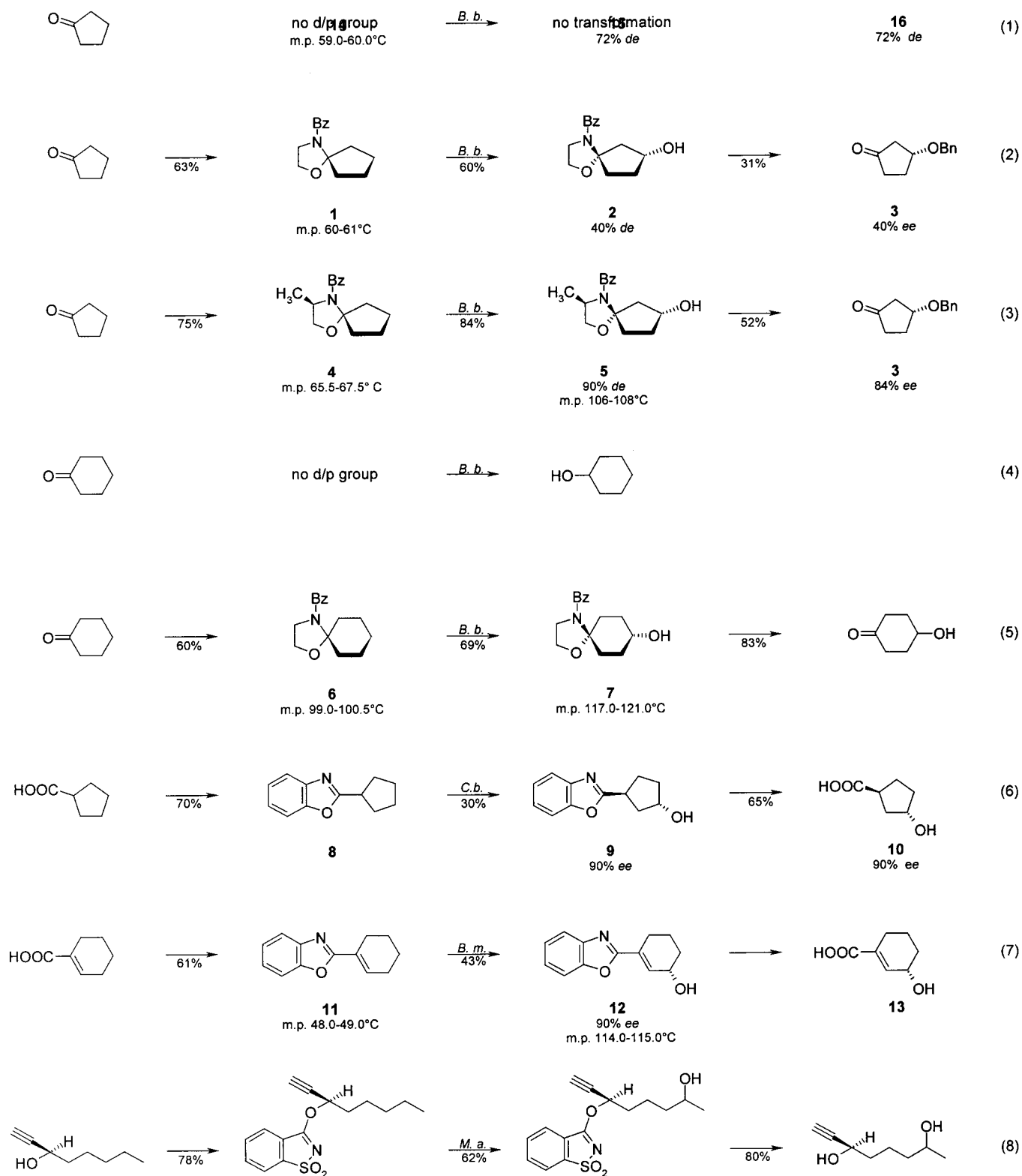
[*] Prof. Dr. H. Griengl, Prof. Dr. G. Braunnegg, Dr. A. de Raadt, S. Feichtenhofer, I. Kopper, Dr. A. Lehmann, Dr. H.-J. Weber
Spezialforschungsbereich F01 Biokatalyse
Institut für Organische Chemie der Technischen Universität Graz
Stremayrgasse 16, A-8010 Graz (Austria)
Fax: (+43) 316-873-8740
E-mail: sekretariat@orgc.tu-graz.ac.at

[**] We thank Prof. K. Kieslich for performing initial screening experiments, C. Illaziewicz for the measurement of NMR spectra, and M. Kaube for help with preparing this manuscript.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

certain functional groups has a positive influence on substrate acceptance.^[2] On the basis of this observation and extending a strategy first suggested by Furstoss et al. for the hydroxylation of compounds such as alcohols and alkenes,^[3] we developed a general concept which can be successfully applied for biohydroxylation. Similar to the common practice of using

protective groups in organic chemistry, a docking/protecting (d/p) group is first introduced, ideally under mild conditions and in high yield, and subsequently the biotransformation is performed. Under the conditions employed in this work, without the d/p group hydroxylation did not take place or side reactions occurred [Eq. (1) and (4)].^[4] After the biotransfor-



mation, the d/p group is removed. Besides promoting interaction of the substrate with the active site of the hydroxylating enzyme, the d/p group should be UV-active to facilitate detection (TLC, HPLC). In some cases, it would also be beneficial to reduce the volatility of the parent substance by the introduction of the d/p group to avoid substrate losses during the fermentation. In accordance with these criteria, a number of compounds were prepared and their suitability as d/p groups experimentally accessed. This was achieved by screening these substrates with a range of microorganisms which were known to hydroxylate similar organic compounds.

As can be seen from the selected entries presented (further examples will be published in a forthcoming paper), this concept could be successfully applied to a number of different substrate classes.

The fungus *Beauveria bassiana* ATCC 7159^[5] (*B. b.*) is a microorganism with broad substrate acceptance.^[6] In particular, the presence of a benzamide group proved to be beneficial for substrate acceptance.^[2, 7] Taking this into account for the biohydroxylation of aldehydes and ketones, the transformation of these substrates into *N*-benzoyloxazolidines and *N*-benzoylspirooxazolidines, respectively, was carried out as an application of the d/p group concept. Unlike cyclopentanone which is not accepted by *B. b.* [Eq. (1)], after introduction of the d/p group (one-pot reaction: 1) $\text{NH}_2\text{CH}_2\text{CH}_2\text{OH}$ (1 equiv), K_2CO_3 (2 equiv), CH_2Cl_2 , RT, 48 h; 2) BzCl (1 equiv), RT, 24 h) to give *N*-benzoylspirooxazolidine **1**, biohydroxylation took place and (5*R*,7*S*)-4-benzoyl-1-oxa-4-azaspiro[4.4]nonan-7-ol (**2**) was obtained in 60% yield and 40% *de*. This compound was then benzylated (BnBr , NaH , THF/DMF , 20 °C) prior to the last deprotection step (IR 120 (H^+), CH_3CN , 20 °C) to avoid elimination. Consequently, ketone **3** was afforded as the final product (40% *ee*). The optical purity and yield of the hydroxylated product improved dramatically when a chiral d/p group was used. This is illustrated with one of the chiral derivatives from this group of ketones, substrate **4** [Eq. (3)]. After fermentation, spirononanol **5** was isolated in 84% yield and 90% *de*. Since the benzyl derivative of **5** is crystalline it is possible to further raise the enantiopurity by recrystallization.

In a similar manner, cyclohexanone was also hydroxylated to give **7** [Eq. (5)]. The benefits of chiral derivatives, such as **4**, may not be restricted to the improvement of product optical purity and yield. These compounds may also be valuable as "active site" probes by changing the substitution on the d/p group. Such minor variations in substrate structure and the effect on the site of hydroxylation would give valuable information on substrate structure requirements. In this context, in an extension of work by Fonken et al.,^[8] Furstoss et al.,^[9] and Haufe et al.,^[10] we are currently carrying out molecular modeling investigations.

This d/p group concept has also been applied to the hydroxylation of cycloalkane carboxylic acids. Here, the parent acid is transformed into a benzoxazole.^[11] As can be seen from Equation (6), benzoxazole **8** was hydroxylated by *Cunninghamella blakesleeana* DSM 1906^[11] (*C. b.*) and deprotected (4*N* aq. HCl/EtOH (1:1, v/v), ZnCl_2 (2 equiv), reflux) to afford (1*S*,3*S*)-3-hydroxycyclopentanecarboxylic

acid (**10**) in acceptable chemical yield and enantiopurity. In an analogous manner, cyclohexenecarboxylic acid derivative **11** [Eq. (7)], after treatment with *Bacillus megaterium* DSM 32 (*B. m.*),^[11] furnished a mixture of alcohol **12** (43%, *ee* > 90%, absolute configuration was determined by X-ray structure analysis) and the corresponding ketone (28%). Suitable conditions to deprotect alcohol **12** and afford derivative **13** are currently under investigation.

The biohydroxylation of alcohols according to this concept was accomplished by the preparation of isosaccharine derivatives, as shown with Equation (8). Derivative **14**, obtained from (*R*)-3-octynol ($\text{C}_8\text{H}_{13}\text{OH}$ (1 equiv), $\text{C}_3\text{H}_5\text{N}$ (2 equiv) 3-chloro-1,2-benzisothiazole-1,1-dioxide (2 equiv), CH_2Cl_2 , RT, 24 h) was hydroxylated regioselectively by *Mortierella alpina* ATCC 8979^[12] (*M. a.*) to give **15** (72% *de*) which was deprotected (NaOCH_3 (0.5 equiv), CH_3OH (absolute), RT, 3 h) to yield diol **16**. The absolute configuration of the second hydroxy group in the molecule is currently under investigation.

To date, biohydroxylation of nonactivated C–H bonds of alkyl or cycloalkyl moieties has been mainly applied in the area of steroids with considerable success regarding yield and regio- and enantioselectivity. In comparison, biohydroxylation of other substrates is far removed from being a method of general use in preparative organic chemistry. However, the use of the d/p group concept broadens the applicability of biohydroxylations in synthetic organic chemistry. Details of this work, experimental methods, and the assignment of the absolute configurations will be discussed in a forthcoming full paper.

Experimental Section

As a representative example of this d/p concept, the biohydroxylation of cyclopentanone is described [Eq. (3)].

By employing (*R*)-1-amino-2-propanol (Aldrich, 98% *ee*) as the d/p group, **4** was prepared in a manner similar to that given for **1**, the procedure being based on a procedure published by Saavedra.^[13] Yield 75%; 98% *ee*; m.p. 65.5–67.5 °C; $[\alpha]_D^{20} = -79.8$ ($c = 2.1$ in CH_2Cl_2); ^1H NMR (200 MHz, CDCl_3 , 25 °C): $\delta = 0.96$ (d, $J = 6.5$ Hz, 3H; Me), 1.64–1.98, 2.37–2.71 (2 × m, 6H, 2H; H6, 7, 8, 9), 3.60 (m, 1H; H2), 4.00 (m, 2H; H2,3), 7.40 (s, 5H; benzoyl); GC-MS: m/z (%): 245 (8) [M^+].

5: After exposure of **4** to *B. bassiana* ATCC 7159^[5] and chromatographic isolation, the crystalline compound **5** was obtained as the major diastereoisomer in 84% yield and with 90% *de*; m.p. 106–108 °C; $[\alpha]_D^{20} = -78.4$ ($c = 0.9$ in CH_2Cl_2); ^1H NMR (200 MHz, CDCl_3 , 25 °C, minor diastereoisomer given in italics; * implies that the assignment could be interchanged): $\delta = 0.93$ (d, $J = 5.7$ Hz, 3H; Me); 1.73–2.41 (m, 4H; H6, 8, 9*, 9), 2.57–2.69 (m, 2H; H8*, OH), 2.75, 2.94 (2 × dd; $J = 5.7$ Hz, $J' = 14.0$ Hz, 1H ratio: 20:1; H6), 3.63 (dd, $J = 5.1$ Hz, $J' = 11.3$ Hz, 1H; H2), 3.98 (m, 2H; H2, H3), 4.42 (br.s, 1H; H7), 7.37 (s, 5H, benzoyl); GC-MS: m/z (%): 261 (2) [M^+].

3: Benzoylation of **5** under standard conditions^[14] and d/p group removal afforded **3** as a syrup. Yield (over two steps) 52%; 84% *ee*; $[\alpha]_D^{20} = -43.0$ ($c = 1.0$ in CH_2Cl_2); NMR data in agreement with literature values.^[15]

Received: December 30, 1998

Revised version: May 3, 1999 [Z12851 IE]

German version: *Angew. Chem.* **1999**, *111*, 2946–2949

Keywords: asymmetric synthesis • bioorganic chemistry • enzyme catalysis • hydroxylations • synthetic methods

- [1] a) *Biotechnology: Biotransformations I*, Vol. 8a (Ed.: D. Kelly), Wiley-VCH, Weinheim, **1998**; b) K. Faber, *Biotransformations in Organic Chemistry*, 3rd ed., Springer, Berlin, **1997**; c) *Enzyme Catalysis in Organic Synthesis* (Eds.: K. Drauz, H. Waldmann), VCH, Weinheim, **1995**.
- [2] G. S. Fonken, R. A. Johnson, *Chemical Oxidations with Microorganisms*, Marcel Dekker, New York, **1972**.
- [3] R. Furstoss, A. Archelas, J. D. Fourneron, B. Vigne in *Organic Synthesis: an interdisciplinary challenge, IUPAC* (Eds.: J. Streith, H. Prinzbach, G. Schill), Blackwell, Oxford, **1985**, pp. 215–226.
- [4] A. Kergomard, M. F. Renard, H. Veschambre, *J. Org. Chem.* **1982**, *47*, 792–798.
- [5] In this work, *B. bassiana* ATTC 7159 was cultivated in a manner similar to that reported in reference [7c].
- [6] H. L. Holland, *Organic Synthesis with Oxidative Enzymes*, VCH, New York, **1992**, pp. 72–76.
- [7] For recent examples of the application of benzamide groups in biohydroxylation: a) R. A. Johnson, M. E. Herr, H. C. Murray, C. G. Chidester, F. Han, *J. Org. Chem.* **1992**, *57*, 7209–7212; b) C. R. Davis, R. A. Johnson, J. I. Cialdella, W. F. Liggett, S. A. Mizesak, F. Han, V. P. Marshall, *J. Org. Chem.* **1997**, *62*, 2252–2254; c) H. F. Olivo, M. S. Hemenway, M. H. Gezinci, *Tetrahedron Lett.* **1998**, *39*, 1309–1312.
- [8] R. A. Johnson, M. E. Herr, H. C. Murray, G. S. Fonken, *J. Org. Chem.* **1968**, *33*, 3217–3221.
- [9] R. Furstoss, A. Archelas, J. D. Fourneron, B. Vigne in *Enzymes as Catalysts in Organic Synthesis* (Ed.: M. P. Schneider), D. Reidel, **1986**, pp. 361–370.
- [10] S. Peitz, D. Wolker, G. Haufe, *Tetrahedron* **1997**, *53*, 17067–17078.
- [11] A. de Raadt, H. Griengl, M. Petsch, P. Plachota, N. Schoo, H. Weber, G. Braunegg, I. Kopper, M. Kreiner, A. Zeiser, K. Kieslich, *Tetrahedron: Asymmetry* **1996**, *7*, 467–496.
- [12] *M. alpina* ATCC 8979 was cultured in the same manner as that described for *C. blakesleeana* DSM 1906, reference [11].
- [13] J. E. Saavedra, *J. Org. Chem.* **1985**, *50*, 2379–2380.
- [14] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, New York, **1991**.
- [15] T. H. Eberlein, F. G. West, R. W. Tester, *J. Org. Chem.* **1992**, *57*, 3479–3482.

The Mixed-Valent (μ -Nitrido)dimanganese Complex Anion $[(\text{CN})_5\text{Mn}^{\text{V}}(\mu\text{-N})\text{Mn}^{\text{II}}(\text{CN})_5]^{6-}$

Jesper Bendix,* Thomas Weyhermüller, Eckhard Bill, and Karl Wieghardt*

The synthesis and reactivity of complexes of the first-row transition metals with terminal and bridging nitrido ligands is a rapidly expanding area of research. Complexes with terminal nitrido ligands are known for V, Cr, and Mn,^[1] whereas nitride-bridged complexes have been described for V, Cr, and Fe but not for Mn.^[2] Interest in these systems derives from their unique molecular structures with very short

covalent M–N bonds (1.50–1.60 Å), their electronic structures with strong axial ligand fields from the bound nitride, and from the ability of these systems to engage in N-atom transfer reactions. To date such reactions have been most thoroughly investigated for nitridomanganese(v) complexes containing tetrapyrrole or Schiff-base auxiliary ligands, where transfer of the nitrogen atom to olefins has been demonstrated.^[3] N-transfer reactions between two metal ions, for example, from nitrido(porphyrinato)manganese(v) to porphyrinatochromium(III) has been demonstrated by Bottomley and Neely.^[4] The homometallic N-transfer reaction from a nitridomanganese(v) complex to a different manganese(III) species has also been observed.^[5] Thus, it is remarkable that no nitrido-bridged manganese complexes have been described to date. Here we report the synthesis and characterization of the (μ -nitrido)dimanganese complex $[\text{Mn}_2(\mu\text{-N})(\text{CN})_{10}]^{6-}$.

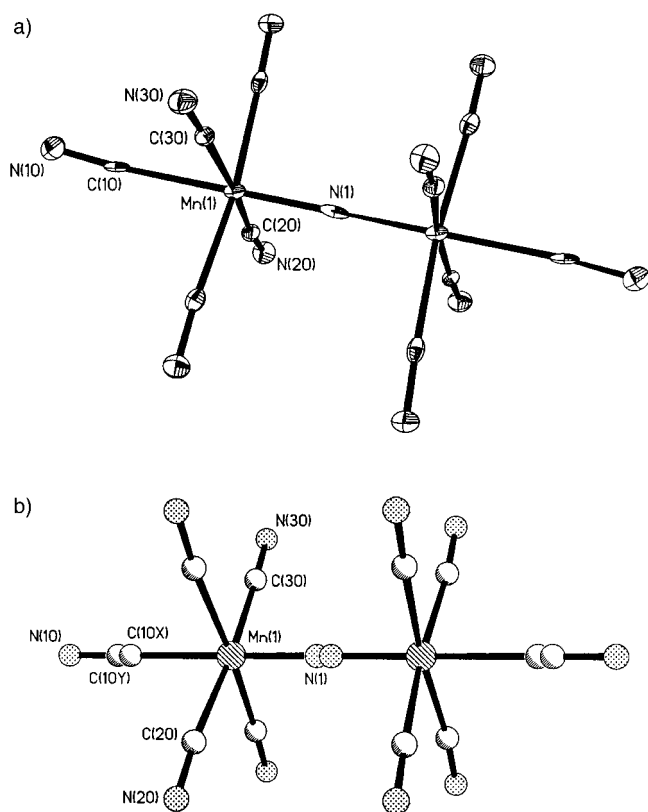
Treatment of solutions containing $[\text{Mn}^{\text{V}}(\text{N})(\text{salen})]^{3-}$ (H_2salen = bis(salicylidene)ethylenediamine) and KCN with reductants such as hydrazine or methanol produced intensely colored red-purple solutions from which the salt $\text{K}_5\text{H}[\text{Mn}_2(\mu\text{-N})(\text{CN})_{10}] \cdot 2\text{H}_2\text{O}$ (**1**) was isolated in low yield. The same compound was obtained in high yield from the reaction of an Mn^{II} salt with an aqueous KCN solution of $[\text{NMe}_4]_2\text{Na}[\text{Mn}^{\text{V}}(\text{N})(\text{CN})_5] \cdot \text{H}_2\text{O}$.^[1b] The stability of aqueous solutions of **1** depends strongly on the cyanide concentration. With no added cyanide, the complex decomposes in seconds, whereas it is stable for more than 30 min in 1M NaCN. From such solutions the mixed sodium–rubidium salt $\text{Na}_2\text{Rb}_4[\text{Mn}_2(\mu\text{-N})(\text{CN})_{10}] \cdot 6\text{H}_2\text{O}$ (**2**) and $[\text{Rh}(\text{tn})_3]_2[\text{Mn}_2(\mu\text{-N})(\text{CN})_{10}] \cdot 10\text{H}_2\text{O}$ (**3**) (tn = propane-1,3-diamine) were isolated by addition of RbCl or $[\text{Rh}(\text{tn})_3]\text{Cl}_3$.

The structure of the anion in **2** is shown in Figure 1.^[6] It consists of an eclipsed $[\text{Mn}_2(\mu\text{-N})(\text{CN})_{10}]^{6-}$ ion,^[7] which possesses crystallographic $2/m$ symmetry; the center of the complex resides on an inversion center. Inspection of the thermal parameters of the atoms C(10) and N(1) (Figure 1a) reveals that these atoms are severely disordered. This disorder was successfully modeled by using a split-atom model for these atoms with isotropic thermal parameters (Figure 1b). The refinement converged smoothly to give two equally populated sites for each of these atoms. Thus, the anion in **2** is asymmetric with a short $\text{Mn}=\text{N}$ bond (1.58(1) Å) and a long $\text{Mn}-\text{N}$ bond (1.84(1) Å). The shorter $\text{Mn}=\text{N}$ bond is only 0.05–0.08 Å longer than the $\text{Mn}=\text{N}$ bond in monomeric nitridocyanomanganates(v).^[1b] The $\text{Mn}-\text{C}$ bond *trans* to the short $\text{Mn}=\text{N}$ bond is then considered to be the long one (2.19(2) Å) due to a *trans* influence and the short $\text{Mn}-\text{C}$ bond (1.95(2) Å) is *trans* to the longer $\text{Mn}-\text{N}$ bond. Interestingly, the four equatorial $\text{Mn}-\text{C}$ distances in $[\text{Mn}^{\text{II}}(\text{CN})_6]^{4-}$ and $[\text{Mn}^{\text{V}}(\text{N})(\text{CN})_5]^{3-}$ (1.95(1) Å and 1.985(8)–2.001(8) Å,^[8] respectively) are nearly equidistant despite the fact that these Mn ions differ in formal oxidation states by three.^[9] In **2** the equatorial average $\text{Mn}-\text{C}$ distance is 2.005(4) Å. This interpretation of the structure of **2** renders the anion $[\text{Mn}_2(\mu\text{-N})(\text{CN})_{10}]^{6-}$ a mixed-valent $\text{Mn}^{\text{V}}-\text{Mn}^{\text{II}}$ species which is statistically disordered over two sites in the crystal.

The effective magnetic moment of solid **3** increases from 1.72 μ_{B} at 4 K to 2.03 μ_{B} at 300 K. The salts **1** and **2** also have magnetic moments in this range, but they are less temper-

[*] Dr. J. Bendix, Prof. Dr. K. Wieghardt, Dr. T. Weyhermüller, Dr. E. Bill
 Max-Planck-Institut für Strahlenchemie
 Stiftstrasse 34–36, D-45470 Mülheim an der Ruhr (Germany)
 Fax: (+49) 208-306-3952
 E-mail: wieghardt@mpi-muelheim.mpg.de

[**] This work was supported by the Fonds der Chemischen Industrie. J.B. acknowledges support from the Danish Research Councils. We thank Dr. K. P. Simonsen for supplying the $[\text{Rh}(\text{tn})_3]\text{Cl}_3$.



ature-dependent. The μ_{eff} value corresponds to one unpaired electron per manganese dimer and can then be rationalized either as an antiferromagnetically coupled $\text{Mn}^{\text{III}}-\text{Mn}^{\text{IV}}$ system or as a low-spin $\text{Mn}^{\text{II}}-\text{low-spin Mn}^{\text{V}}$ system. In the latter formulation low-spin Mn^{V} refers to the spin-paired configuration $(d_{xy})^2$ found for all monomeric nitridomanganese(v) complexes including $[\text{Mn}(\text{N})(\text{CN})_5]^{3-}$.^[1b]

The EPR spectra of powdered samples of **1** and **2** at 10 K show a broad axial signal with $g_{\parallel} \cong 1.96$ and $g_{\perp} \cong 2.18$ without discernible hyperfine coupling. However, a frozen solution (1M aqueous NaCN) of either compound shows an axial spectrum with a distinct ^{55}Mn hyperfine splitting of the $g_{\parallel}$ signal with coupling to *one* manganese nucleus (Figure 2). Importantly, the solid-state EPR spectrum of the magnetically more dilute salt, **3**, is almost indistinguishable from the spectrum obtained from the frozen solution of **1** or **2**. Taken in combination with the magnetism of **3**, this strongly supports that the frozen solution EPR spectrum stems from the dinuclear anion. We have also quantified the EPR signal, and could show that the signal intensity is >60% of the expected value and is thus not attributable to an impurity. The frozen solution EPR spectrum of **2** was satisfactorily fitted for an $S_1 = \frac{1}{2}$ system where an electron spin of $\frac{1}{2}$ is coupled to one nuclear spin of $\frac{5}{2}$ (see Figure 2). Thus, the EPR signal cannot originate from an antiferromagnetically coupled $\text{Mn}^{\text{III}}-\text{Mn}^{\text{IV}}$ system. For such a system with $S_1 = \frac{1}{2}$, the coupling coefficients require that hyperfine coupling to both manganese

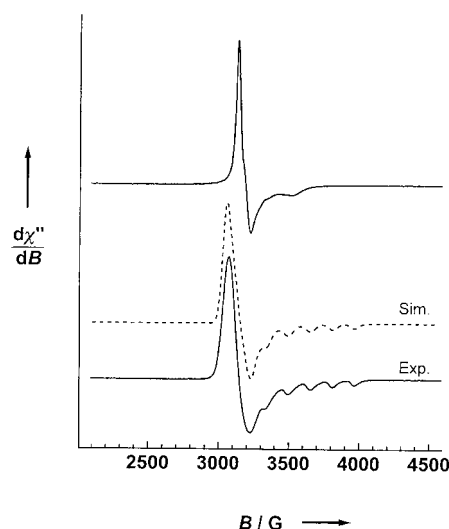


Figure 2. EPR spectra ($T = 10\text{ K}$, $\tilde{\nu} = 9.64396\text{ GHz}$) of a solid powder sample of **2** (top) and a frozen aqueous solution of **2** (bottom). The simulation of the frozen-solution spectrum (dotted) employed the following parameters: $g_{\parallel} = 1.924$, $g_{\perp} = 2.181$, $A_{\parallel} = 141 \times 10^{-4}\text{ cm}^{-1}$, $A_{\perp} = 20(5) \times 10^{-4}\text{ cm}^{-1}$, and Gaussian derivative lineshapes ($W = 36\text{ G}$).

centers will be observed as is experimentally borne out by numerous 11–16-line spectra observed for such dimers.^[10] The axial EPR spectrum of $[\text{Mn}_2(\mu\text{-N})(\text{CN})_{10}]^{6-}$ with $g_{\parallel}$ split by ^{55}Mn -hyperfine interaction resembles that of *trans*- $[\text{Mn}(\text{pc})(\text{NEt}_3)_2]$ ($\text{H}_2\text{pc} = \text{phthalocyanine}$) a low-spin manganese(II) complex.^[11]

The UV/Vis spectrum of $[\text{Mn}_2(\mu\text{-N})(\text{CN})_{10}]^{6-}$ in aqueous cyanide solution (Figure 3) is distinctly different from those of known cyanomanganate complexes; it is dominated by a very

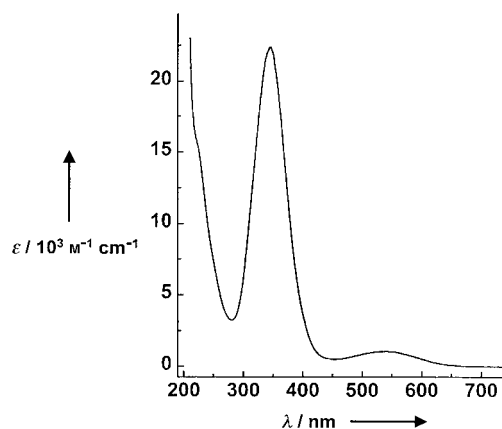


Figure 3. UV/Vis spectrum of an aqueous solution (1M NaCN) of **2**.

intense band at 345 nm ($\epsilon = 2.25 \times 10^4\text{ M}^{-1}\text{cm}^{-1}$), and it has an additional less intense band at 543 nm. The band at 345 nm is more intense by an order of magnitude than the CT band at similar energy found in $[\text{Mn}^{\text{V}}(\text{N})(\text{CN})_5]^{3-}$ and it is also much more intense than any CT band found above 250 nm in the $[\text{Mn}(\text{CN})_6]^{4-}/[\text{Mn}(\text{CN})_6]^{3-}$ complexes. Therefore, we tentatively assign this band as an intervalence band. The 543 nm absorption is located at an energy similar to that of the $^1A_1(d_{xy})^2 \rightarrow ^1E(d_{xy})^1(d_{zx}, d_{yz})^1$ transition in $[\text{Mn}^{\text{V}}(\text{N})(\text{CN})_5]^{3-}$ (516 nm). Accordingly, we assign the 543 nm band to a

manganese(v)-centered d–d transition; it “borrows” intensity from the 345 nm band (neither $[\text{Mn}(\text{CN})_6]^{4-}$ nor $[\text{Mn}(\text{CN})_6]^{3-}$ have absorptions above 360 nm).

In the IR spectra of the salts **1**, **2**, and **3** the $\nu_{\text{as}}(\text{Mn-N-Mn})$ valence stretch is observed in the range 935–976 cm^{-1} . This band, although not as sharp and intense as $\nu(\text{Mn}\equiv\text{N})$ in Mn complexes with terminal nitrido groups, is more pronounced than the asymmetric bridge stretching frequency at 880 cm^{-1} in the genuinely symmetric oxo-bridged dimer $[\text{Mn}^{\text{III}}(\mu\text{-O})\text{-(CN)}_{10}]^{6-}$.^[12] It is noteworthy that $\nu_{\text{as}}(\text{Mn-N-Mn})$ band in **1**, **2**, and **3** falls only slightly below the range, 983–1043 cm^{-1} , found for $\nu(\text{Mn}\equiv\text{N})$ in octahedral mononuclear nitridomanganese(v) complexes.^[1]

In conclusion, the X-ray structure, and especially the EPR spectrum in conjunction with the magnetic data strongly suggest that $[\text{Mn}_2(\mu\text{-N})(\text{CN})_{10}]^{6-}$ is a Class II (Robin and Day) valence-localized $\text{Mn}^{\text{V}}\text{--Mn}^{\text{II}}$ system. Although examples of such large difference in oxidation states in mixed-valent homodimetallic complexes are well established when the coordination environment at the two metal sites is very asymmetric, this is to our knowledge unprecedented in systems where a single atom bridge induces the asymmetry. One related, but less extreme example is known in $[\text{V}^{\text{V}}\text{Cl}_2(\text{L})(\mu\text{-N})\text{V}^{\text{III}}\text{Cl}_3(\text{L})]$ (L = tetramethylethylenediamine) where the coordination numbers at the two vanadium centers differ.^[13]

Experimental Section

1: Method 1: To an Ar-degassed suspension of $[\text{Mn}(\text{N})(\text{salen})]$ (1.3 g, 3.9 mmol) in $\text{H}_2\text{O}/\text{MeOH}/\text{DMF}$ (1/1/1; 40 mL) an excess of KCN (3.4 g, 52 mmol) and $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ (0.8 g, 16 mmol) were added. The suspension was refluxed until no more solid $[\text{Mn}(\text{N})(\text{salen})]$ was visible and cooled. A brown-purple crystalline precipitate was collected by filtration and washed with $\text{H}_2\text{O}/\text{MeOH}$ (1/1) (3 $\times$). The product was air-stable. Yield: 0.31 g (26%); IR (KBr) [cm^{-1}]: $\tilde{\nu}$ = 2098(s), 2083(s), ($\nu(\text{CN})$), 936(m, br) ($\nu_{\text{as}}(\text{Mn-N-Mn})$); UV/Vis: (1.0 M NaCN/ H_2O): λ_{max} [nm] (ϵ [$\text{M}^{-1}\text{cm}^{-1}$]) = 543 (1.16×10^3), 345 (2.45×10^4), 223 sh (1.72×10^4); μ_{eff} = 1.65 μ_{B} (10 K)–1.88 μ_{B} (300 K); elemental analysis (%) calcd for $\text{C}_{10}\text{H}_5\text{K}_5\text{Mn}_2\text{N}_{11}\text{O}_2$: C 19.48, H 0.82, K 31.78, Mn 17.82, N 24.99; found: C 19.29, H 0.77, K 30.08, Mn 17.72, N 24.81.

Method 2: To an Ar-degassed solution of $(\text{NMe}_4)_2\text{Na}[\text{Mn}(\text{N})(\text{CN})_5] \cdot \text{H}_2\text{O}$ (390 mg, 1.00 mmol) in 1 M aqueous KCN (15 mL), a solution of $\text{Mn}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$ (245 mg, 1.00 mmol) in degassed water (3 mL) was added. Immediately the color changed from pink to dark red-purple. After the mixture was stirred for 10 min, solid KCN (2.5 g, 38 mmol) was added batchwise. The product was isolated as above. Yield: 0.51 g (83%).

2: To a solution of **1** (150 mg, 0.244 mmol) in 0.5 M aqueous NaCN (3.5 mL) solid RbCl (0.5 g, 4.1 mmol) was added. Small intergrown purple rhombohedra of **2** were collected after 2 h. Yield: 116 mg (54%); IR (KBr) [cm^{-1}]: $\tilde{\nu}$ = 2108(s), 2084(s) ($\nu(\text{CN})$), 1623(s) ($\delta(\text{H}_2\text{O})$), 940(m, br.) ($\nu_{\text{as}}(\text{Mn-N-Mn})$); μ_{eff} = 1.81 μ_{B} (4.2 K)–2.02 μ_{B} (300 K); elemental analysis (%) calcd for $\text{C}_{10}\text{H}_{12}\text{Mn}_2\text{N}_{10}\text{Na}_2\text{O}_6\text{Rb}_4$: C 13.65, H 1.37, Mn 12.41, N 17.51; found: C 13.68, H 1.48, Mn 12.00, N 17.69.

3: To a solution of **1** (120 mg, 0.195 mmol) in 0.5 M aqueous NaCN (20 mL) a solution of $[\text{Rh}(\text{tn})_3]\text{Cl}_3$ (100 mg, 0.232 mmol) in H_2O (10 mL) was added very slowly. Flat purple needles were isolated. Yield: 125 mg (89%). IR (KBr) [cm^{-1}]: $\tilde{\nu}$ = 2118(s), 2100(s), 2083(s) ($\nu(\text{CN})$), 976(m) ($\nu_{\text{as}}(\text{Mn-N-Mn})$); μ_{eff} = 1.72 μ_{B} (4.2 K)–2.03 μ_{B} (300 K); elemental analysis (%) calcd for $\text{C}_{28}\text{H}_{80}\text{Mn}_2\text{N}_{25}\text{O}_{10}\text{Rh}_2$: C 27.68, H 6.64, Mn 9.04, N 26.52; found: C 27.92, H 6.58, Mn 8.18, N 26.39.

Keywords: manganese • mixed-valent compounds • multiple bonds • nitrides

- [1] a) A. Niemann, U. Bossek, G. Haselhorst, K. Wieghardt, B. Nuber, *Inorg. Chem.* **1996**, 35, 906–915; b) J. Bendix, K. Meyer, T. Weyhermüller, E. Bill, N. Metzler-Nolte, K. Wieghardt, *Inorg. Chem.* **1998**, 37, 1767–1775; c) K. Meyer, J. Bendix, N. Metzler-Nolte, T. Weyhermüller, K. Wieghardt, *J. Am. Chem. Soc.* **1998**, 120, 7260–7270.
- [2] a) S. C. Critchlow, M. E. Lerchen, R. C. Smith, N. M. Doherty, *J. Am. Chem. Soc.* **1988**, 110, 8071–8075; b) A. L. Odom, C. C. Cummins, *Organometallics* **1996**, 15, 898–900; c) W. R. Scheidt, D. A. Summerville, I. A. Cohen, *J. Am. Chem. Soc.* **1976**, 98, 6623–6628.
- [3] a) J. T. Groves, T. Takahashi, *J. Am. Chem. Soc.* **1983**, 105, 2073–2074; b) J. DuBois, J. Hong, E. M. Carreira, M. W. Day, *J. Am. Chem. Soc.* **1996**, 118, 915–916.
- [4] L. A. Bottomley, F. L. Neely, *Inorg. Chem.* **1997**, 36, 5435–5439.
- [5] a) L. K. Woo, *Chem. Rev.* **1993**, 93, 1125–1136; b) C. J. Chang, D. W. Low, H. B. Gray, *Inorg. Chem.* **1997**, 36, 270–271.
- [6] Crystal data for **2** ($\text{C}_{10}\text{H}_{12}\text{Mn}_2\text{N}_{10}\text{Na}_2\text{O}_6\text{Rb}_4$): orthorhombic, *CmCa*, $a = 17.102(2)$, $b = 16.662(2)$, $c = 9.0070(8)$ Å, $V = 2566.6(5)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 2.278$ g cm^{−3}; crystal size: $0.35 \times 0.24 \times 0.06$ mm. Of 6411 reflections with $2.38^\circ < \theta < 23.31^\circ$, 966 were independent, and 955 observed ($I > 2\sigma(I)$); 102 parameters; $R(F) = 0.0263$, $wR(F^2) = 0.0614$. The data were collected on a Siemens SMART CCD detector system with MoK_α irradiation ($\lambda = 0.71073$ Å) at 100(2) K. Absorption correction was performed with the SADABS program (G. M. Sheldrick, Universität Göttingen, 1994). The structure was solved by direct methods and refined by full-matrix least-squares methods against F^2 (SHELXTL program packet; version 5.1). Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-410749.
- [7] In crystals of **2** all of the cyanide ligands *cis* to the bridge interact with the Rb^+ counterions. It is accordingly not possible to conclude if the eclipsed conformation of the anion results from electronic or crystal packing effects.
- [8] a) A. Tullberg, N.-G. Vannerberg, *Acta Chem. Scand. Ser. A* **1974**, A28, 551–562; b) J. Bendix, T. Weyhermüller, E. Bill, K. Wieghardt, unpublished results.
- [9] For $[\text{Mn}^{\text{V}}(\text{N})(\text{CN})_5]^{3-}$: J. Bendix, T. Weyhermüller, E. Bill, K. Wieghardt, *Inorg. Chem.* submitted. For $[\text{Mn}^{\text{II}}(\text{CN})_6]^{4-}$: A. Tullberg, N.-G. Vannerberg, *Acta Chem. Scand. Ser. A* **1974**, A28, 551–562.
- [10] a) K.-O. Schäfer, R. Bittl, W. Zweggart, F. Lendzian, G. Haselhorst, T. Weyhermüller, K. Wieghardt, W. Lubitz, *J. Am. Chem. Soc.* **1998**, 120, 13104–13120.
- [11] J. Livoriness, T. D. Smith, J. R. Pilbrow, G. R. Sinclair, *J. Chem. Soc. Faraday Trans.* **1984**, 80, 425–436.
- [12] R. F. Ziolo, R. H. Stanford, G. R. Rossman, H. B. Gray, *J. Am. Chem. Soc.* **1974**, 96, 7910–7915.
- [13] K. L. Sorensen, M. E. Lerchen, J. W. Ziller, N. M. Doherty, *Inorg. Chem.* **1992**, 31, 2678–2679.

Received: March 18, 1999 [Z 13182IE]

German version: *Angew. Chem.* **1999**, 111, 2932–2935

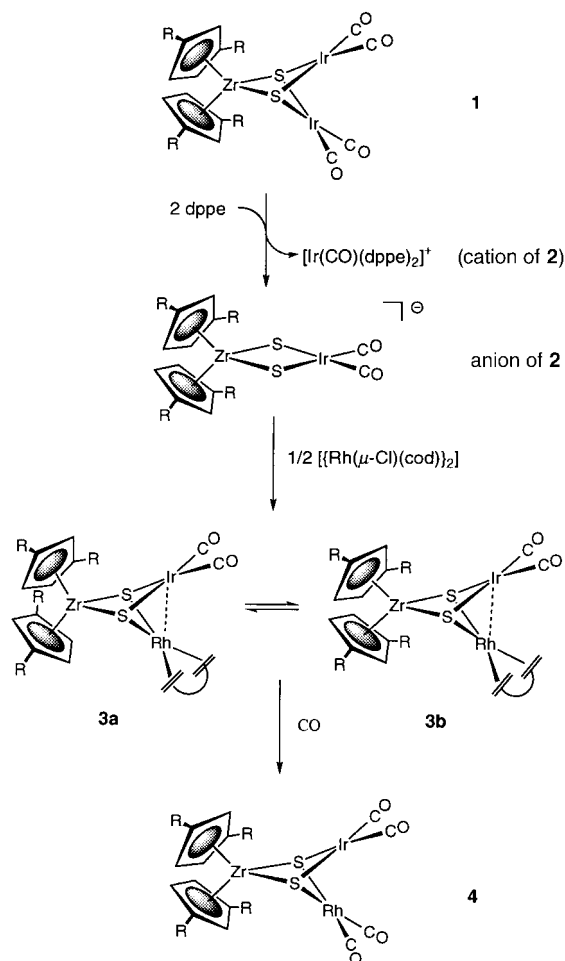
Controlled Synthesis of Early–Late Zr–Ir–Rh Heterotrimetallic Compounds by Metal Exchange Reactions**

Marc A. F. Hernandez-Gruel, Jesús J. Pérez-Torrente, Miguel A. Ciriano,* Fernando J. Lahoz, and Luis A. Oro*

Transition metal sulfide clusters have received wide attention because of their relevance to biological systems and industrial solid-surface catalysis.^[1] However, the chemistry of metal–sulfur polynuclear compounds containing widely divergent transition metals—that is, early–late heterometallic complexes—is still poorly developed^[2] despite their potential for new reactivity patterns in both catalytic^[3] and stoichiometric reactions.^[4] A goal is still to find ways to accommodate the differing electronic and coordination environments required by the metals in close proximity but still obtain stable compounds.^[5] In this context, we recently reported that additive deprotonation reactions of $[\text{Cp}_2\text{Ti}(\text{SH})_2]$ ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5$) with methoxo-bridged dinuclear rhodium complexes make accessible the early–late heterobimetallic complexes $[\text{CpTi}(\mu_3\text{-S})_3\{\text{Rh}(\text{tfbb})\}_3]$ (tfbb = tetrafluorobenzobarralene) and $[\{\text{CpTi}\}_2(\mu_4\text{-O})(\mu_3\text{-S})_4\{\text{Rh}_4(\text{CO})_4(\text{PR}_3)_2\}]$.^[6] Here we report on the controlled synthesis of novel trinuclear early–late heterotrimetallic (ELHT) complexes driven by the zirconium metalloligand $[\text{Cp}_2^*\text{Zr}(\text{SH})_2]$, as well as some aspects of the reactivity of the early–late heterobimetallic (ELHB) precursors.

The new complex $[\text{Cp}_2^*\text{Zr}(\text{SH})_2]$ ($\text{Cp}^* = \eta^5\text{-1,3-di-tert-butylcyclopentadienyl}$), prepared analogously to the related pentamethylcyclopentadienyl complex,^[7] reacts with two molar equivalents of $[\text{IrCl}_2(\text{CO})_2]^-$ in dichloromethane/methanol in the presence of triethylamine to give the trinuclear ELHB complex **1**, which was isolated in good yield (70%) as an apple-green solid.^[8] Reaction of **1** with two molar equivalents of 1,2-bis(diphenylphosphanyl)ethane (dppe) in dichloromethane gave the ion-pair product **2** (Scheme 1), which was precipitated quantitatively with *n*-hexane as a highly air- and moisture-sensitive pale orange solid. A related precedent of this anion is the heterobimetallic complex $[\text{Cp}_2^*\text{Zr}(\mu\text{-S})\text{-Rh}(\text{CO})_2]^-$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$).^[9]

Interestingly, the heterodinuclear anion $[\text{Cp}_2^*\text{Zr}(\mu\text{-S})_2\text{-Ir}(\text{CO})_2]^-$ behaves as a metalloligand towards d^8 metal centers and allows the synthesis of unprecedented Zr–Ir–Rh heterotrimetallic complexes. Reaction of **2** with 0.5 equivalents of



Scheme 1. Synthesis of heterotrimetallic complexes. R = *t*Bu.

$[\{\text{Rh}(\mu\text{-Cl})(\text{cod})\}_2]$ (cod = 1,5-cyclooctadiene) in dichloromethane gave **3** (Scheme 1), which was isolated as brown-orange microcrystals in 70% yield.

The molecular structure of **3** (Figure 1) shows a triangular ZrIrRh core capped on both sides by symmetrical μ_3 -sulfido

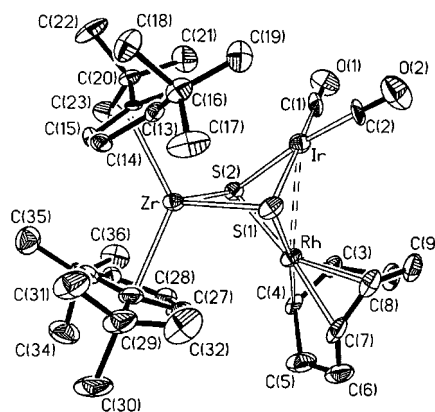


Figure 1. Molecular structure of **3**. Selected bond lengths [Å] and angles [°]: Zr–S(1) 2.506(3), Zr–S(2) 2.519(3), Zr–G(1) 2.290(9), Zr–G(2) 2.290(13), Ir–S(1) 2.417(3), Ir–S(2) 2.410(3), Ir–C(1) 1.838(13), Ir–C(2) 1.843(14), Rh–S(1) 2.411(3), Rh–S(2) 2.413(3), Rh–C(cod) 2.146–2.171(10); S(1)–Zr–S(2) 79.84(10), S(1)–Ir–S(2) 83.83(10), C(1)–Ir–C(2) 94.1(6), S(1)–Rh–S(2) 83.90(9), Zr–S(1)–Ir 87.41(9), Zr–S(2)–Ir 87.26(8), Zr–S(1)–Rh 84.02(9), Zr–S(2)–Rh 83.71(8), Ir–S(1)–Rh 71.50(8), Ir–S(2)–Rh 71.58(8). G(1) and G(2) are the centroids of the cyclopentadienyl rings.

[*] Prof. Dr. L. A. Oro, Dr. M. A. Ciriano, Dr. M. A. F. Hernandez-Gruel, Dr. J. J. Pérez-Torrente, Dr. F. J. Lahoz
Departamento de Química Inorgánica
Instituto de Ciencia de Materiales de Aragón
Universidad de Zaragoza – CSIC
E-50009 Zaragoza (Spain)
Fax: (+34) 976761143
E-mail: oro@posta.unizar.es
mciriano@posta.unizar.es

[**] Financial support from Dirección General de Enseñanza Superior (DGES, Projects PB95-221-C1 and PB94-1186) and a fellowship from the Ministerio de Educación y Cultura (to M.A.F.H.-G.) are gratefully acknowledged. We also thank Dr. E. Gutierrez Puebla (ICMM–CSIC) for facilities and infrastructure to carry out X-ray data collection.

ligands.^[10] If the metal–metal interactions are neglected, the d⁸ rhodium and iridium centers exhibit square-planar coordination environments and the zirconium center has a distorted pseudo-tetrahedral geometry. Although no significant d⁰–d⁸ bonding interactions are present (Zr⋯Rh 3.2913(14), Zr⋯Ir 3.4018(15) Å), the Rh⋯Ir distance of 2.8205(10) Å lies in the expected range for a metal–metal bond. Slightly shorter Rh–Ir separations were found in [Cp*IrRhCl(CO)₂][P(OiPr)₃]₂ (2.797(1) Å)^[11] with an unsupported metal–metal bond and in the heterodinuclear complexes [RhIr(CH₃)(CO)₃-(μ-dppm)₂]⁺ (2.743(1) Å)^[12] and [RhIr(CO)₃(μ-dppm)₂]⁺ (2.7722(7) Å)^[13] supported by two bis(diphenylphosphanyl)-methane (dppm) ligands. Longer metal–metal distances were found in the related cluster [(Cp*Ir)₂(μ₃-S)₂Rh(cod)][RhCl₂(cod)] (2.906(1) and 2.913(9) Å).^[14] The presence of a d⁸–d⁸ metal–metal interaction in **3** is also supported by the Rh–S–Ir angles (mean 71.54(6)°), which are smaller than the M–S–Zr angles (83.7–87.4°; M = Rh, Ir).

A remarkable feature of **3** is the fully staggered relative disposition of the Cp^{tt} ligands (Figure 2; G(1)–Zr–G(2) 129.8(4)°) in the Zr sandwich moiety, which results in C_s symmetry. This conformation differs greatly from the nearly

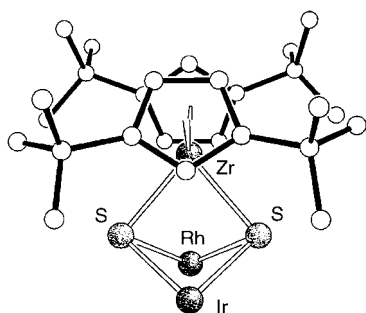


Figure 2. View of the Cp^{tt}Zr moiety of **3** perpendicular to the plane defined by Zr and the sulfido ligands. The staggered disposition of the Cp^{tt} ligands is evident.

eclipsed and straddle dispositions of [Cp^{tt}TiCl₂]^[15a] and [Cp^{tt}ZrI₂]^[15b] respectively, probably as a consequence of the location of the bulky *tert*-butyl groups of the Cp^{tt} rings in the sterically least congested regions of the molecule. Complex **3** exists in CDCl₃ as two interconverting rotamers **3a** and **3b** (Scheme 1) in a 3:1 ratio, as shown by the negative cross-peaks in the phase-sensitive NOESY spectrum. Both C_s rotamers were unambiguously characterized by ¹H and ¹³C{¹H} NMR spectroscopy and two-dimensional NMR techniques, in particular, ¹H COSY, ¹³C–¹H HETCOR, and NOESY. The major rotamer **3a** has a staggered arrangement of the *tert*-butyl groups, as is found in the solid state, whilst the spectroscopic data for the minor isomer **3b** suggest an eclipsed conformation. The Cp^{tt} ligand close to the Rh(cod) fragment in **3a** is easily distinguishable since the ring protons have unusual chemical shifts. Moreover, the observed NOE between two of the olefinic cod protons and the H4 and H5 protons of this Cp^{tt} ring corroborates their close proximity.

A restricted rotation of the Cp^{tt} ligand close to the more sterically demanding Rh(cod) fragment in **3** could account for the observation of the two rotamers in solution. However,

neither a change in the ratio of the rotamers nor coalescence of the signals was observed in the ¹H NMR spectrum between 183 and 363 K in [D₈]toluene, although line-broadening effects are noticeable above room temperature. The activation parameters for the rotation of the Cp^{tt} ligand, obtained by the NMR spin-saturation transfer method in the range 308–276 K in CDCl₃, are ΔH[‡] = 19.2 ± 1.5 kcal mol^{−1} and ΔS[‡] = 6.7 ± 2.6 e.u. Energy barriers associated with the hindered rotation of η⁵-cyclopentadienyl complexes are generally less than 13 kcal mol^{−1}.^[16] Rotational barriers of 8.9 ± 0.5 kcal mol^{−1} were observed for the metallocene complexes [Cp^{tt}TiCl₂]^[17a] and [Cp^{tt}TiF₂]^[17b] (Cp^{tt} = 1,3-bis(trimethylsilyl)cyclopentadienyl). The larger value found for **3** (ΔG₂₉₈[‡] = 17.2 kcal mol^{−1}) relative to the above-mentioned compounds is consistent with the larger steric hindrance of the metal fragments.

Carbonylation of **3** under atmospheric pressure in diethyl ether gives quantitatively the new ELHT complex **4** (Scheme 1), which was isolated as a green microcrystalline solid. Compound **4** can also be obtained in 70 % yield in a one-pot synthesis starting from **1** by successive addition of dppe and the anion [RhCl₂(CO)₂][−].

Received: March 29, 1999 [Z13225 IE]

German version: *Angew. Chem.* **1999**, *111*, 2935–2938

Keywords: iridium • rhodium • S ligands • zirconium

- [1] a) *Transition Metal Sulfur Chemistry: Biological and Industrial Significance* (Eds: E. I. Stiefel, K. Matsumoto), American Chemical Society, Washington, DC, **1996**; b) A. N. Startsev, *Catal. Rev. Sci. Eng.* **1995**, *37*, 353; c) J. B. Howard, D. C. Rees, *Chem. Rev.* **1996**, *96*, 2965; d) B. K. Burgess, D. J. Lowe, *Chem. Rev.* **1996**, *96*, 2983.
- [2] a) T. Ikada, S. Kuwata, Y. Mizobe, M. Hidai, *Inorg. Chem.* **1999**, *38*, 64; b) T. Ikada, S. Kuwata, Y. Mizobe, M. Hidai, *Inorg. Chem.* **1998**, *37*, 5793; c) D. W. Stephan, T. T. Nadasdi, *Coord. Chem. Rev.* **1996**, *147*, 147; d) D. W. Stephan, *Coord. Chem. Rev.* **1989**, *95*, 41.
- [3] a) W. A. Herrmann, B. Cornils, *Angew. Chem.* **1997**, *109*, 1074; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1049; b) T. Wakabayashi, Y. Ishii, T. Murata, Y. Mizobe, M. Hidai, *Tetrahedron Lett.* **1995**, *36*, 5585.
- [4] a) S. H. Druker, M. D. Curtis, *J. Am. Chem. Soc.* **1995**, *117*, 6366; b) U. Riaz, O. Curnow, M. D. Curtis, *J. Am. Chem. Soc.* **1991**, *113*, 1416.
- [5] A. Spannenberg, M. Oberthür, H. Noss, A. Tilac, P. Arndt, R. Kempe, *Angew. Chem.* **1998**, *110*, 2190; *Angew. Chem. Int. Ed.* **1998**, *37*, 2079.
- [6] R. Atencio, M. A. Casado, M. A. Ciriano, F. J. Lahoz, J. J. Pérez-Torrente, A. Tiripicchio, L. A. Oro, *J. Organometal. Chem.* **1996**, *514*, 103; M. A. Casado, M. A. Ciriano, A. J. Edwards, F. J. Lahoz, J. J. Pérez-Torrente, L. A. Oro, *Organometallics* **1998**, *17*, 3414.
- [7] W. A. Howard, G. Parkin, *Organometallics* **1993**, *12*, 2363.
- [8] Selected spectroscopic data for the new compounds: **1**: ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 6.74 (t, J(H,H) = 2.6 Hz, 2H, H2), 6.24 (d, J(H,H) = 2.6 Hz, 4H, H4 and H5), 1.31 (s, 36H, Cp^{tt}); ¹³C{¹H} NMR (75 MHz, CDCl₃, 25 °C): δ = 174.7 (CO), 150.0 (C1 and C3), 127.5 (C2), 111.0 (C4 and C5), 35.1 (CMe₃), 32.1 (CH₃, Cp^{tt}); MS (FAB⁺, CH₂Cl₂): m/z (%): 1006 (93) [M⁺], 487 (100) [M⁺ – Cp^{tt}]; IR (CH₂Cl₂): ν̄(CO) = 2056 (s), 2027 (s), 1979 cm^{−1} (s). **2**: ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.70–6.80 (m, 40H, dppe), 5.57 (d, J(H,H) = 2.4 Hz, 4H, H4 and H5, Cp^{tt}), 4.76 (t, J(H,H) = 2.4 Hz, 2H, H2, Cp^{tt}), 2.1 (m, 8H, CH₂, dppe), 1.21 (s, 36H, Cp^{tt}); ³¹P{¹H} NMR (121 MHz, CDCl₃, 25 °C): δ = 25.6 (s); ¹³C{¹H} NMR (75 MHz, CDCl₃, 25 °C): δ = 186.3 (CO, [Ir(CO)(dppe)₂]⁺), 179.6 (CO, [Cp^{tt}Zr(μ-S)₂Ir(CO)₂][−]), 140.0 (C1 and C3, Cp^{tt}), 132.6 (m), 131.1 (brs), 128.6 (m, dppe), 108.0 (C₂), 99.8 (C4 and C5), 33.3 (CMe₃), 31.6 (CH₃, Cp^{tt}), 30.8 (m, CH₂, dppe); MS (FAB⁺, CDCl₃): m/z (%): 989 (100) [M⁺ – CO]; MS (FAB[−], CDCl₃): m/z (%): 757 (100) [M[−]]; IR

(CH₂Cl₂): $\bar{\nu}(\text{CO}) = 2004$ (vs), 1947 (sh), 1931 cm⁻¹ (vs). **3**: MS (FAB⁺, CH₂Cl₂): m/z (%): 968 (100) [M^+], 791 (92) [$M^+ - \text{Cp}^{\text{II}}$]; IR (CH₂Cl₂): $\bar{\nu}(\text{CO}) = 2023$ (vs), 1954 cm⁻¹ (vs); ¹H NMR (300 MHz, CDCl₃, 25 °C): rotamer **3a**: $\delta = 7.18$ (d, $J(\text{H,H}) = 2.4$ Hz, 2H, H4 and H5), 6.60 (t, $J(\text{H,H}) = 2.4$ Hz, 1H, H2), 5.94 (d, $J(\text{H,H}) = 2.4$ Hz, 2H, H4 and H5), 5.83 (t, $J(\text{H,H}) = 2.4$ Hz, 1H, H2, Cp^{II}), 4.42 and 4.19 (m, 2H each, =CH, cod), 2.7–2.4 (m, 2H), 1.9–2.2 (m, 4H), 1.8–1.6 (m, 2H, CH₂, cod), 1.32 and 1.26 (s, 18H each, Cp^{II}); rotamer **3b**: $\delta = 6.69$ and 6.38 (t, $J(\text{H,H}) = 2.4$ Hz, 1H each, H2), 6.03 and 5.90 (d, $J(\text{H,H}) = 2.4$ Hz, 2H each, H4 and H5, Cp^{II}), 4.42 and 4.19 (m, 2H each, =CH, cod), 2.7–2.4 (m, 2H), 2.2–1.9 (m, 4H), 1.8–1.6 (m, 2H, CH₂, cod), 1.31 and 1.30 (s, 18H each, Cp^{II}); ¹³C{¹H} NMR (75 MHz, CDCl₃, 25 °C): rotamer **3a**: $\delta = 177.7$ (CO), 150.0 and 142.2 (C1 and C3), 127.6 (C2), 119.7 (C4 and C5), 110.0 (C2), 105.5 (C4 and C5, Cp^{II}), 84.0 and 80.6 (d, $J(\text{Rh-C}) = 11.5$ Hz, =CH, cod), 34.8 and 34.0 (CMe₃), 32.7 and 31.8 (CH₃, Cp^{II}), 31.7 and 30.6 (CH₂, cod); rotamer **3b**: $\delta = 178.3$ (CO), 147.2 and 147.1 (C1 and C3), 123.8 and 120.7 (C2), 109.5 and 108.8 (C4 and C5, Cp^{II}), 85.9 and 80.6 (d, $J(\text{Rh-C}) = 11.5$ Hz, =CH, cod), 34.5 and 34.4 (CMe₃), 32.3 and 32.2 (CH₃, Cp^{II}), 31.6 and 30.2 (CH₂, cod). **4**: ¹H NMR (300 MHz, CDCl₃, 25 °C): $\delta = 6.72$ and 6.62 (t, $J(\text{H,H}) = 2.5$ Hz, 1H each, H2), 6.16 and 6.11 (d, $J(\text{H,H}) = 2.5$ Hz, 2H each, H4 and H5), 1.31 and 1.30 (s, 18H each, Cp^{II}); ¹³C{¹H} NMR (75 MHz, CDCl₃, 25 °C): $\delta = 184.9$ (d, $J(\text{Rh-C}) = 74$ Hz, CO), 175.4 (CO), 149.4 and 149.1 (C1 and C3), 126.2 and 122.5 (C2), 110.1 and 110.0 (C4 and C5), 34.9 and 34.8 (CMe₃), 32.2 (CH₃, Cp^{II}); MS (FAB⁺, CH₂Cl₂): m/z (%): 916 (46) [M^+], 860 (100) [$M^+ - 2\text{CO}$], 739 (49) [$M^+ - \text{Cp}^{\text{II}}$]; IR (CH₂Cl₂): $\bar{\nu}(\text{CO}) = 2062$ (s), 2031 (s), 1996 (m), 1971 cm⁻¹ (m).

- [9] P. Kalck, C. Serra, C. Machet, R. Broussier, B. Gautheron, G. Delmas, G. Trouvé, M. Kubicki, *Organometallics* **1993**, *12*, 1021.
- [10] Crystal data for **3**: C₃₆H₃₄IrO₂RhS₂Zr, $M_r = 969.24$, monoclinic, space group $P2_1/c$; $a = 11.9123(9)$, $b = 21.5742(17)$, $c = 15.0796(12)$ Å, $\beta = 105.526(2)^\circ$, $V = 3734.0(5)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.724$ g cm⁻³, $\mu = 4.407$ mm⁻¹. Crystal dimensions 0.12 × 0.16 × 0.18 mm. Bruker SMART CCD diffractometer, $T = 153(1)$ K, graphite-monochromated MoK α radiation ($\lambda = 0.71073$). A complete hemisphere of data was scanned on ω (0.30° per frame) with a run time of 20 s at the detector resolution of 512 × 512 pixel. Reflections were extracted by using the SAINT program, and Lorentzian, polarization, and absorption corrections were applied. Of 9398 reflections measured, 4506 were unique ($R_{\text{int}} = 0.0657$). The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least squares on F^2 (SHELXL-97). Anisotropic displacement parameters were used for all non-hydrogen atoms. Hydrogen atoms were included in calculated positions. 403 parameters, 18 restraints; $R = 0.0509$ (3512 reflections, $F \leq 4\sigma(F_o)$), $R_w(F^2) = 0.1007$ (all reflections), and $S = 1.076$. Max. residual electron density 1.05 e Å⁻³ close to the Ir atom. 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-116623. 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).
- [11] A. A. Del Paggio, E. L. Muettterties, D. M. Heinekey, V. W. Day, C. S. Day, *Organometallics* **1986**, *5*, 575.
- [12] F. H. Antwi-Nsiah, O. Oke, M. Cowie, *Organometallics* **1996**, *15*, 1042.
- [13] R. McDonald, M. Cowie, *Inorg. Chem.* **1990**, *29*, 1564.
- [14] Z. Tang, Y. Nomura, Y. Ishii, Y. Mizobe, M. Hidai, *Organometallics* **1997**, *16*, 151.
- [15] a) I. F. Urazowski, V. I. Ponomaryov, O. G. Ellert, I. E. Nifant'ev, D. A. Lemenovskii, *J. Organomet. Chem.* **1988**, *356*, 181; b) W. A. King, S. Di Bella, A. Gulino, G. Lanza, I. L. Fragalà, C. L. Stern, T. Marks, *J. Am. Chem. Soc.* **1999**, *121*, 355.
- [16] C. H. Winter, D. A. Dobbs, X.-X. Zhou, *J. Organomet. Chem.* **1991**, *403*, 145.
- [17] a) J. Okuda, *J. Organomet. Chem.* **1988**, *35b*, C43; b) C. H. Winter, X.-X. Zhou, M. J. Heeg, *Inorg. Chem.* **1992**, *31*, 1808.

Photomodulation of the Conformation of Cyclic Peptides with Azobenzene Moieties in the Peptide Backbone**

Raymond Behrendt, Christian Renner, Michaela Schenk, Fengqi Wang, Josef Wachtveitl, Dieter Oesterhelt, and Luis Moroder*

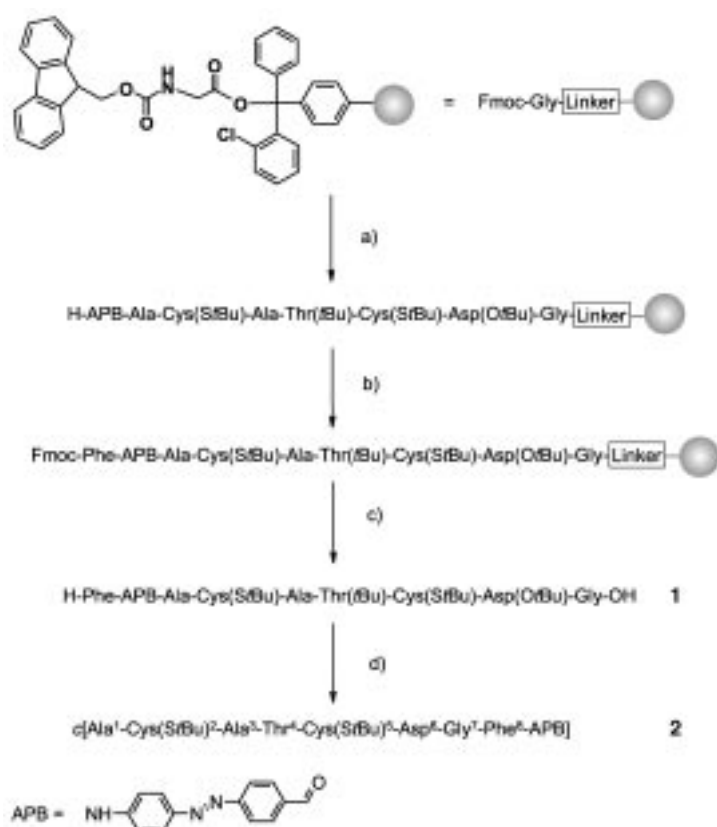
For photomodulation of conformational, physico-chemical, and biological properties of peptides, proteins, and phospholipids large use has been made of the *cis/trans* isomerization of azobenzene moieties grafted to specific sites of such biomaterials or related model systems.^[1, 2] Since the light-induced isomerization of azobenzene is accompanied by significant changes in geometry and polarity of the chromophore,^[3] this proved to be well suited for induction of local topochemical changes in conformationally more restricted small systems.^[4–10] Low-mass cyclic peptides are rigid structures that are extensively exploited for the design of libraries of conformers of defined bioactivities.^[11, 12] Thus, incorporation of the azobenzene moiety into the peptide backbone of such cyclic peptides is expected to represent an ideal system to probe the efficiency of this “light-switch” for induction of conformational transitions. With 4-(4-aminophenylazo)benzoyl (APB) as amino acid residue in the peptide backbone we succeeded in the present study to construct a very rigid, conformationally constrained cyclic peptide in the *trans* configuration which upon irradiation, relaxes into a largely free conformational space.

The distance between the two *para*-carbon atoms of the azobenzene unit in the *trans* configuration is 9 Å and in the *cis* configuration 5 Å. To transfer optimally these changes in geometry to the peptide backbone, H-APB-OH was synthesized according to known methods^[13] and fully characterized in its photochemical properties.^[14, 15] It was then incorporated into an octapeptide related to the active site of thioredoxine reductase (Scheme 1). Owing to the low nucleophilicity of the *para*-amino group of H-APB-OH, its protection in acylating the resin-bound peptide was not required, but difficulties were encountered in the subsequent acylation of this group. These were overcome by silylation and using the acid fluoride method for the peptide-chain extension step. Mild acidic cleavage from the resin produced the linear side chain protected pseudo-nonapeptide **1**, which was then cyclized by the PyBOP/HOBt/DIEA procedure. Final acidic deprotection generated the target compound **2** cyclo(Ala-Cys(SiBu)-Ala-Thr-Cys(SiBu)-Asp-Gly-Phe-APB).

Peptides **1** and **2** were characterized spectroscopically (Table 1). Compared to H-APB-OH [$\lambda_{\text{max}} = 420$ nm ($\pi - \pi^*$)

[*] Prof. Dr. L. Moroder, Dipl.-Chem. R. Behrendt, Dr. C. Renner, Dr. M. Schenk, Dr. F. Wang, Prof. Dr. D. Oesterhelt
Max-Planck-Institut für Biochemie
Am Klopferspitz 18A, D-82152 Martinsried (Germany)
Fax: (+49) 89-8578-2847
E-mail: moroder@biochem.mpg.de
Dr. J. Wachtveitl
Institut für Medizinische Optik der Universität
Oettingenstrasse 67, D-80538 München (Germany)

[**] The study was supported by the SFB 533 (grant A8 Moroder/Oesterhelt).



Scheme 1. Synthesis of **1** and **2**: a) Couplings with HBTU/HOBt/DIEA (1/1/2), except for Fmoc-Cys(SiBu)-OH where HBTU/HOBt/DIEA (1/1/1.2) was used; coupling of H-APB-OH without protection; Fmoc-removal with 20 % piperidine in NMP; b) DIEA, CH₃CON(SiMe₃)₂; Fmoc-Phe-F; c) 20 % piperidine in NMP; CH₂Cl₂/trifluoroethanol/AcOH/triethylsilane (8/1/1/0.15); d) PyBOP/HOBt/DIEA (1/1/2); trifluoroacetic acid/CH₂Cl₂/triethylsilane (95/3.5/1.5). HBTU = *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, HOBt = 1-hydroxybenzotriazole, DIEA = ethyldiisopropylamine, NMP = *N*-methylpyrrolidone, PyBOP = benzotriazolyl-1-oxyltris(pyrrrolidino)phosphonium hexafluorophosphate.

Table 1. Spectroscopic parameters of **1** and **2** in DMSO. The extinction coefficients (M⁻¹ dm³ cm⁻¹) were calculated from two isomeric mixtures; the different *cis/trans* isomer ratios were determined quantitatively from ¹H NMR spectra.

Compound	Configuration of the azobenzene unit	$\pi-\pi^*$		$n-\pi^*$	
		$\lambda_{\max}$ [nm]	$\epsilon \times 10^{-4}$	$\lambda_{\max}$ [nm]	$\epsilon \times 10^{-3}$
1	<i>trans</i>	370	2.0	450	4.7
1	<i>cis</i>	260	1.3	450	5.2
2	<i>trans</i>	370	3.4	450	2.8
2	<i>cis</i>	260	2.4	450	3.6

and 440 nm ($n-\pi^*$)^[14] the $\pi-\pi^*$ transition in both the linear and cyclic peptide is significantly blue-shifted, while the $n-\pi^*$ transition is located at similar wavelengths. The evolution of the *cis/trans* photoisomerization upon irradiation at 360 nm and 450 nm, respectively, shows for both the peptide **1** and **2** two isobestic points at 330 and 440 nm which indicate that the photoreaction follows a first-order kinetic, as exemplified for **2** in Figure 1. A comparison of the thermal isomerization rates of the cyclic peptide **2** with those of the linear peptide **1** indicates an enhanced hindrance of the *cis* $\rightarrow$ *trans* isomerization by the peptide backbone in the cyclized form

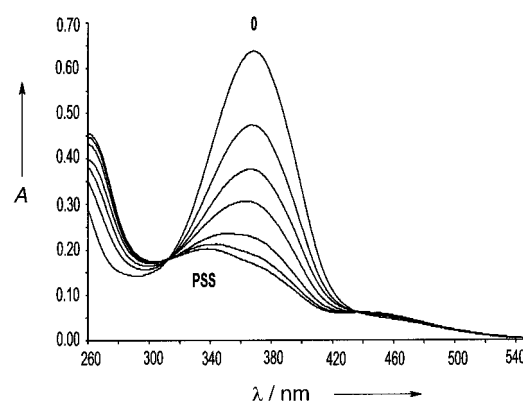


Figure 1. Absorption spectra of **2** in DMSO (concentration 10⁻⁵ M, *T* = 25 °C) before irradiation (0) and after irradiation (360 nm) with a light intensity of 0.5 mW cm⁻² for 0.1, 0.25, 0.5, 0.6, 1, and 4 min. Quantitative evaluation of the ¹H NMR spectra yielded for the ground state a practically 100 % *trans*-configured azobenzene and for the photostationary state (PSS) a *cis/trans* isomer ratio of 78:22; the limits of error are ± 2 to ± 3 %.

(Table 2). The difference in the activation energy of 24 kJ mol⁻¹ represents the increased energy barrier of the *cis* $\rightarrow$ *trans* transition resulting from the constrained conformational space of **2**. The thermal isomerization of both peptides

Table 2. Rate constants k_{ct} of the *cis* $\rightarrow$ *trans* thermal isomerization of **1** and **2** in DMSO determined by ¹H NMR spectroscopy at different temperatures (peptide concentration 3 $\times$ 10⁻³ M). The activation energy E_a was determined from Arrhenius plots; the limits of error are ± 10 kJ mol⁻¹.

Compound	k_{ct} [h ⁻¹]					E_a [kJ mol ⁻¹]
	22 °C	30 °C	40 °C	45 °C	50 °C	
1	0.057	0.16	0.57	0.91	1.6	96
2	0.011	0.042	0.20	0.38	0.72	120

at 22 °C is markedly slower than that of the free azobenzene derivative H-APB-OH, in which this process is completed in about 10 min. Thus, the slow thermal relaxation of compound **2** ($t_{1/2}$ = 62 h at 22 °C) allowed ¹H NMR experiments to be performed for the conformational analysis of the *cis* isomer.

The octapeptide fragment H-Ala-Cys-Ala-Thr-Cys-Asp-Gly-Phe-OH of the active site of thioredoxin reductase retains in the oxidized form the identical 3₁₀-helix turn structure as in the intact enzyme.^[16] This indicates an intrinsically high tendency of the sequence portion Ala-Thr-Cys-Asp for a turn conformation.^[17] The main goal of our work was to obtain a photoswitchable two-state system with a transition from a rigid to a flexible peptide conformation. Therefore this bis(cysteiny)-peptide was selected for our model studies to eventually allow for further conformational restriction through disulfide bridging to the bicyclic form, if required. As shown in Figure 2, already the monocyclic peptide with *trans*-configured azobenzene moiety is fully constrained in its conformational space. The azobenzene moiety is planar and the peptide backbone displays an overall extended rigid structure; only residue 5 exhibits dihedral angles of the α -helical type. While in the *trans* isomer primarily a 180° flip-flop of the azobenzene moiety is observed, in the *cis* isomer the free rotation of the two phenyl rings is restricted by mutual hindrance and by steric effects of the peptide moiety.

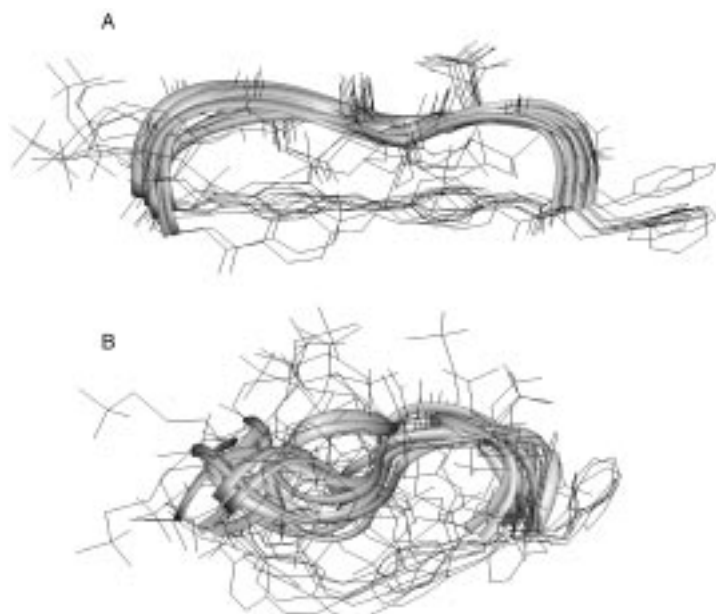


Figure 2. Ensembles of the ten structures of lowest energy for cyclo(Ala-Cys(SrBu)-Ala-Thr-Cys(SrBu)-Asp-Gly-Phe-APB) (**2**) in the *trans* (A) and *cis* configuration (B).

Even the peptide backbone is relaxed in the *cis* isomer into a significantly less constrained conformational space (Figure 2B). In its C-terminal peptide sequence a γ -turn centered on Gly-7 is largely populated, which fluctuates in an unconcerted mode with the rest of the peptide. The remaining part of the peptide chain bulges into a loose turnlike structure with a strongly 3_{10} -helical residue in position 4 and less helical Ala-3 and Cys-5 residues, which reflects the intrinsic tendency of this peptide portion to form an ordered fold. This makes the *cis* isomer a frustrated system consisting of an ensemble of energetically degenerate states. The N-terminus of the peptide part finally forms a short turn to the azobenzene moiety.

By using 4-(4-(aminomethyl)phenylazo)benzoic acid as building block in the cyclic octapeptide, as previously proposed by Ulysse et al.,^[9] the *cis* $\rightleftharpoons$ *trans* photoisomerization leads again to a conformational transition which, however, is less pronounced. In fact, under identical conditions the peptide moiety, already in the *trans*-configured azobenzene, exhibits two different conformations in a ratio of 3:1, as determined by NMR conformational analysis. Conversely, by using the chromophore APB that lacks the flexible methylene spacer we obtained a peptide template, whose photoisomerization proceeds in a two-state transition. It therefore represents a promising system for spectroscopic analysis of this conformational transition on different time scales, also because of the high quantum yields ($\Phi_{ic} \approx 20\%$ and $\Phi_{ci} \approx 50\%$ for the $n\text{-}\pi^*$ transition).^[18] Correspondingly, this template should also allow photomodulation of biological properties of peptidic receptor ligands.

Experimental Section

1: The linear peptide was synthesized by applying Fmoc/tBu chemistry on chlorotrityl resin (PepChem, Tübingen) and was cleaved from this with CH_2Cl_2 /trifluoroethanol/AcOH/triethylsilane. HPLC (Nucleosil 300/C18 (Machery & Nagel, Düren), linear gradient of acetonitrile/2 % H_3PO_4 from

5/95 to 80/20 in 30 min): $t_r = 28$ min; FAB-MS: m/z : 1320 [$M+\text{Na}^+$]; $M_r = 1297.4$ calcd for $\text{C}_{60}\text{H}_{57}\text{N}_{11}\text{O}_{13}\text{S}_4$; amino acid analysis (6 M HCl; 110°C ; 24 h): Asp 1.00 (1) Thr 0.75 (1) Gly 1.00 (1) Ala 1.94 (2) Cys 1.64 (2) Phe 0.94 (1); peptide content: 95 %

2: The linear peptide **1** was cyclized with PyBOP/HOBt/DIEA in DMF and the resulting compound was deprotected with trifluoroacetic acid/ CH_2Cl_2 /triethylsilane (95/3.5/1.5). The crude product was precipitated with diethyl ether and purified by extensive washings with MeOH; HPLC (Nucleosil 300/C18 (Machery & Nagel, Düren), linear gradient of acetonitrile/2 % H_3PO_4 from 5/95 to 80/20 in 30 min): $t_r = 24.35$ min; ESI-MS: m/z : 1168.4 [$M+\text{H}^+$]; $M_r = 1167.2$ calcd for $\text{C}_{52}\text{H}_{69}\text{N}_{11}\text{O}_{13}\text{S}_4$; amino acid analysis (6 M HCl; 110°C ; 24 h): Asp 1.01 (1) Thr 0.85 (1) Gly 1.00 (1) Ala 1.96 (2) Cys 1.65 (2) Phe 0.99 (1); peptide content: 93 %.

UV spectra were recorded at a peptide concentration of 10^{-5} M in DMSO on a Lambda 19 spectrometer (Perkin Elmer). A xenon lamp 450 XBO (Osram, München) was used for irradiation at 360 nm (filter from Itos, Mainz) with a light intensity of 0.5 mW cm^{-2} .

The ^1H NMR experiments (500.13 MHz, 295 K) were recorded on a Bruker AMX 500 spectrometer equipped with pulsed-field-gradient (PFG) accessories. The signals were assigned according to the method of Wüthrich.^[19] The 2D TOCSY spectra were recorded with a spin-lock period of 70 ms using the MLEV-17 sequence for isotropic mixing.^[20] Experimental distance constraints (*trans*-azo: 44; *cis*-azo: 41) were extracted from 2D NOESY experiments^[21] with mixing times of 50 ms and 200 ms and from 2D ROESY experiments with a mixing time of 100 ms. Angle constraints (*trans*-azo: 18; *cis*-azo: 12) were extracted from 2D DQF-COSY^[22] and simple ^1H -1D spectra. Structure calculations and evaluations were performed with the INSIGHTII (version 97.0) software package from MSI by simulating the solvent DMSO with a dielectric constant of 46.7. Structures were first generated by a distance geometry algorithm and subsequently refined with a short simulated annealing molecular dynamics protocol. The experimental constraints were applied at every stage of the calculation. To check for the stability of the resulting structures, molecular dynamics simulations over a period of 1 ns were performed for representative members of the structure ensembles. No significant violations of experimental constraints occurred for any of the calculated structures.

Received: February 25, 1999 [Z13081IE]
German version: *Angew. Chem.* **1999**, *111*, 2941–2943

Keywords: azo compounds • conformation analysis • isomerizations • peptides • solid-phase synthesis

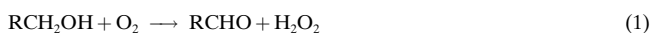
- [1] I. Willner, S. Rubin, *Angew. Chem.* **1996**, *108*, 419–439; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 367–385.
- [2] I. Willner, *Acc. Chem. Res.* **1997**, *30*, 347–356.
- [3] H. Rau in *Studies in Organic Chemistry: Photochromism, Molecules and Systems*, Vol. 40 (Eds.: H. Dürr, H. Bonas-Laurent), Elsevier, Amsterdam, **1990**, pp. 165–192.
- [4] H.-W. Losensky, H. Spelthann, A. Ehlen, F. Vögtle, J. Bargon, *Angew. Chem.* **1988**, *100*, 1225–1227; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1189–1191.
- [5] K. H. Neumann, F. Vögtle, *J. Chem. Soc. Chem. Commun.* **1988**, 520–522.
- [6] M. S. Voller, T. D. Clark, C. Steinem, M. Z. Ghadiri, *Angew. Chem.* **1999**, *111*, 1703–1706; *Angew. Chem. Int. Ed.* **1999**, *38*, 1598–1606.
- [7] T. Aoyagi, A. Ueno, M. Fukushima, T. Osa, *Macromol. Rapid Commun.* **1998**, *19*, 103–105.
- [8] T. Nagasaki, S. Tamagaki, K. Ogino, *Chem. Lett.* **1997**, 717–718.
- [9] L. Ulysse, J. Cubillos, J. Chmielewski, *J. Am. Chem. Soc.* **1995**, *117*, 8466–8467.
- [10] S. Rudolph-Böhner, M. Krüger, D. Oesterhelt, L. Moroder, T. Nägele, J. Wachtveitl, *J. Photochem. Photobiol. A* **1997**, *105*, 235–248.
- [11] G. Müller, M. Gurrath, H. Kessler, *J. Comput. Aided Mol. Des.* **1994**, *8*, 709–730.
- [12] H. R. Haubner, D. Finsinger, H. Kessler, *Angew. Chem.* **1997**, *109*, 1440–1456; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1375–1389.

- [13] K. H. Schündehütte in *Houben-Weyl, Methoden Org. Chem. (Houben-Weyl) 4th ed. 1965–, Vol. 10/3*, p. 240.
- [14] J. Wachtveitl, T. Nägele, B. Puell, W. Zinth, M. Krüger, S. Rudolph-Böhner, D. Oesterhelt, L. Moroder, *J. Photochem. Photobiol. A* **1997**, *105*, 283–288.
- [15] T. Nägele, R. Hoche, W. Zinth, J. Wachtveitl, *Chem. Phys. Lett.* **1997**, *272*, 489–495.
- [16] L. Moroder, D. Besse, H.-J. Musiol, S. Rudolph-Böhner, F. Siedler, *Biopolym. Pept. Sci.* **1996**, *40*, 207–234.
- [17] J. Kuriyan, T. S. R. Krishna, L. Wong, B. Guenther, A. Pahler, C. H. Williams, Jr., P. Moldel, *Nature* **1991**, *352*, 172–174.
- [18] J. Wachtveitl, T. Nägele, A. J. Wurzer, M. Schenk, L. Moroder in *Springer Series in Chemical Physics, Vol. 63* (Eds.: T. Elsaesser, J. G. Fujimoto, D. A. Wiersma, W. Zinth), Springer, Stuttgart, **1998**, pp. 609–611.
- [19] K. Wüthrich, *NMR of Proteins and Nucleic Acids*, Wiley, New York, **1986**.
- [20] A. Bax, D. G. Davis, *J. Magn. Reson.* **1985**, *65*, 355–360.
- [21] J. Jeener, B. H. Meier, P. Bachman, R. R. Ernst, *J. Chem. Phys.* **1979**, *71*, 4546–4553.
- [22] M. Rance, O. W. Sorensen, G. Bodenhausen, G. Wagner, R. R. Ernst, K. Wüthrich, *Biochem. Biophys. Res. Commun.* **1983**, *117*, 479–485.

Oxidation of Benzyl Alcohol with Cu^{II} and Zn^{II} Complexes of the Phenoxyl Radical as a Model of the Reaction of Galactose Oxidase**

Shinobu Itoh,* Masayasu Taki, Shigehisa Takayama, Shigenori Nagatomo, Teizo Kitagawa, Norio Sakurada, Ryuichi Arakawa, and Shunichi Fukuzumi*

Redox interactions between a transition metal ion and a redox-active amino acid side chain such as the phenol group of tyrosine have been recognized to play a crucial role in several biologically important processes.^[1] Recently, a tyrosyl radical directly coordinated to a Cu^{II} center has been discovered in the active site of galactose oxidase (GO, EC 1.1.3.9), which catalyzes the oxidation of D-galactose and primary alcohols to the corresponding aldehydes, coupled to the reduction of O₂ to H₂O₂ [Eq. (1)].^[1, 2] The crystal structure of GO at 1.7-Å resolution clearly shows that the tyrosine



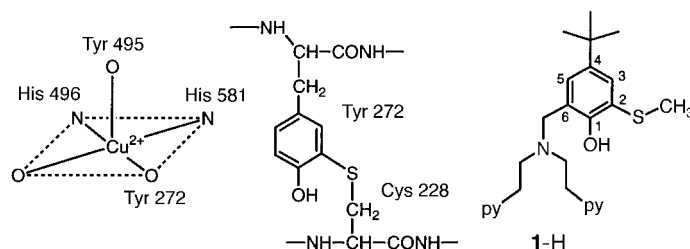
[*] Dr. S. Itoh, Prof. S. Fukuzumi, M. Taki, S. Takayama
Department of Material and Life Science
Graduate School of Engineering, Osaka University
2-1 Yamada-oka, Suita, Osaka 565-0871 (Japan)
Fax: (+81) 6-6879-7370
E-mail: fukuzumi@chem.eng.osaka-u.ac.jp

Dr. S. Nagatomo, Prof. T. Kitagawa
Institute for Molecular Science
Myodaiji, Okazaki 444-8585 (Japan)

N. Sakurada, Prof. R. Arakawa
Department of Applied Chemistry
Faculty of Engineering, Kansai University
3-3-35 Yamate-cho, Suita, Osaka 564-8680 (Japan)

[**] This study was financially supported in part by a Grant-in-Aid for Scientific Research on Priority Area (Molecular Biometallics: 10129218; Electrochemistry of Ordered Interface: 10131242) and a Grant-in-Aid for General Scientific Research (08458177) from the Ministry of Education, Science, Culture, and Sports of Japan.

residue (Tyr272), which is directly coordinated to a Cu²⁺ ion at the equatorial position, is covalently bound to the sulfur atom of the adjacent Cys228, constituting a new organic cofactor (Scheme 1).^[2] The active form of GO has recently been suggested to be the Cu^{II}–phenoxyl radical of this organic cofactor, which is converted into the two-electron reduced species [Cu^I(phenol)] in the oxidation of alcohols to aldehydes.^[3–6]



Scheme 1. Representation of the coordination at the Cu^{II} center of galactose oxidase (left; the unlabeled O atom is from an acetate ion or water), the organic cofactor (center), and the protonated form of the ligand used in the model complexes **1** (right; py = 2-pyridyl).

Extensive efforts have been made recently to develop synthetic model complexes that can mimic the catalytic function and the spectroscopic characteristics of the Cu^{II}–phenoxyl radical species of the native enzymes.^[7–10] Wieghardt et al. have succeeded in developing a very unique functional model of GO using 2,2'-thiobis(4,6-di-tert-butylphenol) (LH₂) as the ligand; this complex can oxidize alcohols under aerobic conditions.^[7b] In this system the active species has been shown to be the dimeric phenoxyl radical complex [Cu^{II}(L[•])₂]²⁺, in which only the radicals act as oxidation sites and no redox reaction occurs at the Cu^{II} site. Now the important question remains as to the essential role of the Cu^{II} site.

We report herein two synthetic model complexes whose structures and spectroscopic features are similar to those of the active form of GO. One is a Cu^{II}–phenoxyl radical complex that can accept two electrons, and the other is a Zn^{II}–phenoxyl radical complex that can accept only one electron. To our surprise, both model complexes can oxidize benzyl alcohol to yield the same product, benzaldehyde. The important difference between the two model complexes is found to lie in the different kinetic formulation for the oxidation of the alcohol. These features of our model complexes provide valuable insights into the catalytic mechanism of GO.

Addition of (NH₄)₂[Ce^{IV}(NO₃)₆] (ceric ammonium nitrate, CAN) to a solution of the dimeric copper(II)–phenolate complex [Cu^{II}(**1**)₂](PF₆)₂ (2.5 × 10^{−4} M in CH₃CN)^[11] caused an immediate decrease in the absorption band at 522 nm due to the dimeric copper(II)–phenolate complex (ligand-to-metal charge-transfer (LMCT) transition from the phenolate to the Cu²⁺ ion), accompanied by the concomitant increase in the new absorption bands at 415 nm (ε = 1790 M^{−1} cm^{−1}) and 867 nm (ε = 550 M^{−1} cm^{−1}) at 25 °C (Figure 1). A similar spectrum was obtained in the oxidation of [Zn^{II}(**1**)-(CH₃CN)]PF₆^[11] by CAN under the same experimental conditions (418 nm (ε = 1250 M^{−1} cm^{−1}) and 887 nm (ε = 510 M^{−1} cm^{−1}) in CH₃CN at 25 °C). The absorption bands in

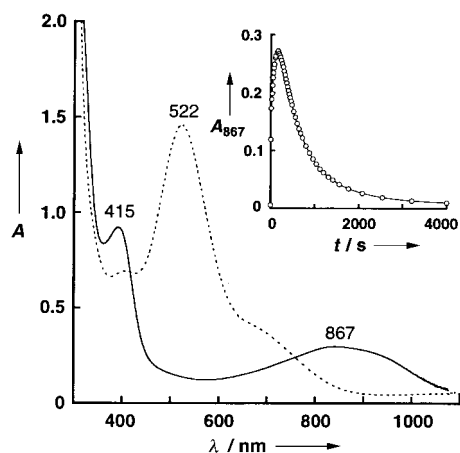


Figure 1. UV/Vis spectra of $[\text{Cu}^{\text{II}}(\text{1})_2](\text{PF}_6)_2$ ($2.5 \times 10^{-4} \text{ M}$ in CH_3CN , dotted line) and $[\text{Cu}^{\text{II}}(\text{1}^*)(\text{NO}_3)]^+$ (solid line) generated from the former by adding CAN ($5.0 \times 10^{-4} \text{ M}$) at 25°C . Inset: Time course of the absorption change at 867 nm due to the formation and decomposition of $[\text{Cu}^{\text{II}}(\text{1}^*)(\text{NO}_3)]^+$.

the resulting spectra are very similar to those of the phenoxyl radical species of 2-methylthio-*p*-cresol ($\lambda_{\text{max}} = 400$ and 830 nm)^[12, 13] and of the active form of GO (445 and ca. 800 nm).^[3] This indicates that the characteristic absorption bands obtained by the CAN oxidation are due to the phenoxyl radical species (1^*) of the ligand. Such an absorption band in the long-wavelength region (above 800 nm), a characteristic of the active form of GO, has never been observed for other synthetic Cu^{II} - and Zn^{II} -phenoxyl radical complexes reported so far except one recent example described by Halcrow et al.^[10]

Further evidence in support of the formation of $[\text{M}^{\text{II}}(\text{1}^*)(\text{NO}_3)]^+$ ($\text{M} = \text{Cu}$ or Zn) was obtained from the resonance Raman spectra ($\tilde{\nu} = 1512, 1589 \text{ cm}^{-1}$ for $\text{M} = \text{Cu}$; $\tilde{\nu} = 1517, 1595 \text{ cm}^{-1}$ for $\text{M} = \text{Zn}$), the electrospray ionization mass spectra (ESI-MS),^[14] and the ESR spectra of the solutions resulting from the CAN oxidation of the corresponding phenolate complexes (ESR-silent at -196°C in CH_3CN for $\text{M} = \text{Cu}$; phenoxyl radical at $g = 2.0052$ at -80°C in $\text{CH}_3\text{CH}_2\text{CN}$ for $\text{M} = \text{Zn}$). The isotropic hyperfine coupling constants ($a_{2\text{-SMe}} = 3.72 \text{ G}$, $a_{3\text{-H}} = 1.15 \text{ G}$, $a_{5\text{-H}} = 0.87 \text{ G}$, $a_{\text{CH}(\text{benzyl})} = 2.43 \text{ G}$) of $[\text{Zn}^{\text{II}}(\text{1}^*)(\text{NO}_3)]^+$ determined by computer simulation indicate that a significant amount of the spin density is delocalized into the methylthio group, as in the case of metal-free phenoxyl radicals.^[12] As a result, the structures and spectroscopic characteristics have been found to be almost the same for the Cu^{II} - and the Zn^{II} -phenoxyl radical complexes.

The Cu^{II} -phenoxyl radical complex is relatively stable at ambient temperature, but gradually decomposes to obey first-order kinetics ($k_{\text{dec}(\text{Cu})} = 1.62 \times 10^{-3} \text{ s}^{-1}$, see inset in Figure 1).^[15] Addition of a large excess of benzyl alcohol to a solution of $[\text{Cu}^{\text{II}}(\text{1}^*)(\text{NO}_3)]^+$ in CH_3CN accelerates the decay rate of the phenoxyl radical complex. Formation of $[\text{Cu}^{\text{I}}(\text{1-H})]^+$ as a final product was evident, since a) there were no characteristic absorption bands due to the LMCT and ligand field excitation (d-d) of the Cu^{II} complex in the final spectrum of the reaction, and b) the final product was ESR-

silent. Furthermore, ligand **1-H** was recovered almost quantitatively after workup with aqueous NH_3 , in contrast to the case of self-decomposition.^[15] Quantitative formation of benzaldehyde was confirmed by GC-MS.^[16] The rate of the oxidation of benzyl alcohol to benzaldehyde obeys pseudo-first-order kinetics, and the plot of the pseudo-first-order rate constant $k_{\text{obs}(\text{Cu})}$ versus the concentration of benzyl alcohol gives a straight line (Figure 2a). The second-order rate

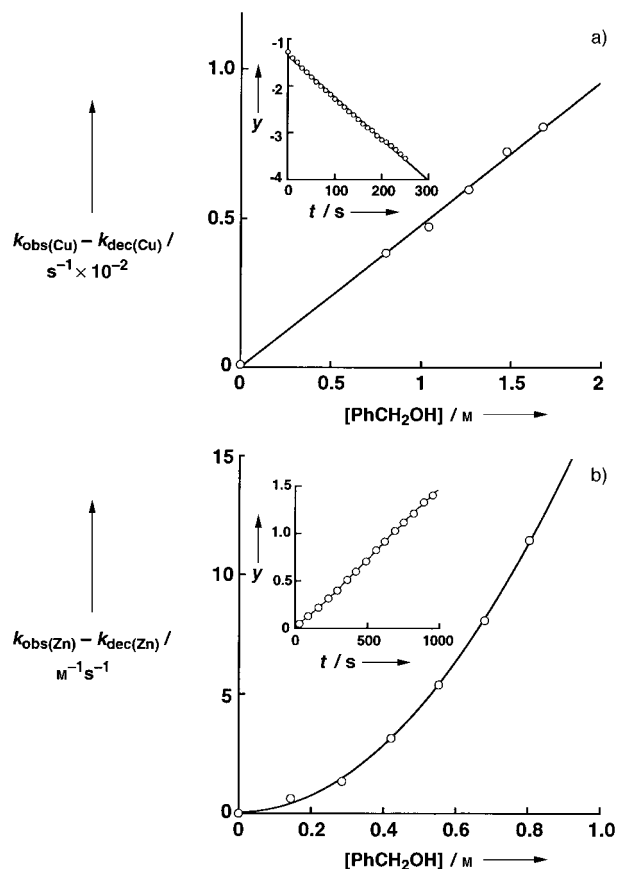
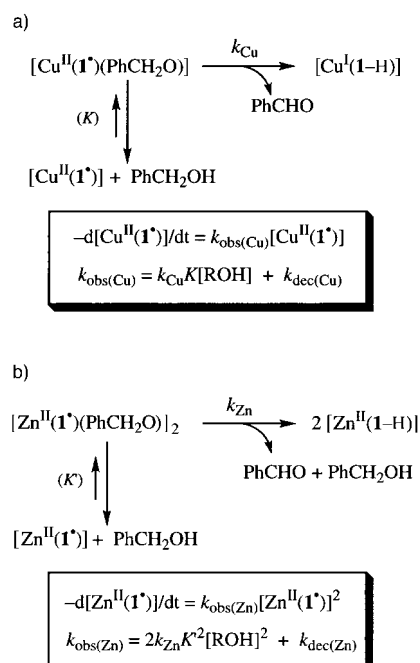


Figure 2. a) Plot of $(k_{\text{obs}(\text{Cu})} - k_{\text{dec}(\text{Cu})})$ versus the concentration of benzyl alcohol for the oxidation of benzyl alcohol by $[\text{Cu}^{\text{II}}(\text{1}^*)(\text{NO}_3)]^+$ in CH_3CN at 25°C . Inset: Pseudo-first-order plot for the oxidation; $y = \ln(A - A_\infty)$. b) Plot of $(k_{\text{obs}(\text{Zn})} - k_{\text{dec}(\text{Zn})})$ versus the concentration of benzyl alcohol for the oxidation of benzyl alcohol by $[\text{Zn}^{\text{II}}(\text{1}^*)(\text{NO}_3)]^+$ in CH_3CN at 25°C . Inset: Second-order plot for the oxidation; $y = (A_0 - A) / [\text{Zn}^{\text{II}}(\text{1}^*)(\text{NO}_3)]^+ (A - A_\infty) \times 10^{-4}$.

constant $k_{(\text{Cu})}$ was obtained from the slope as $4.79 \times 10^{-3} \text{ M}^{-1} \text{s}^{-1}$. A large kinetic deuterium isotope effect ($k_{(\text{Cu})}^{\text{H}} / k_{(\text{Cu})}^{\text{D}} = 6.8$) was obtained when PhCH_2OH was replaced by PhCD_2OH , indicating that the abstraction of the benzylic hydrogen atom is involved in the rate-determining step.

The same product, benzaldehyde, was also obtained in the reaction of benzyl alcohol and $[\text{Zn}^{\text{II}}(\text{1}^*)(\text{NO}_3)]^+$.^[16] In contrast to the case of $[\text{Cu}^{\text{II}}(\text{1}^*)(\text{NO}_3)]^+$, however, the reaction of the zinc-phenoxyl radical complex with benzyl alcohol obeys second-order kinetics with respect to the decay of the absorption at 887 nm , and the second-order rate constant $k_{\text{obs}(\text{Zn})}$ shows the second-order dependence on the alcohol concentration (Figure 2b).^[17] Furthermore, the yield of benzaldehyde was nearly half that of the copper case.

These results clearly show that the oxidation of benzyl alcohol by $[\text{Cu}^{\text{II}}(\mathbf{1}^*)(\text{NO}_3)]^+$ proceeds by means of coordination of benzyl alcohol in the monomeric form by formally a $2e^-/2\text{H}^+$ mechanism to give benzaldehyde and $[\text{Cu}^{\text{I}}(\mathbf{1}\text{-H})]$ quantitatively (Scheme 2a (type I)). On the other hand, no redox reaction is expected at the Zn site. In such a case, two



Scheme 2. Type I (a) and type II mechanisms (b) for the oxidation of benzyl alcohol by the copper and zinc model complexes, respectively. (The complexes are given without their charges.)

electrons can only be accepted by phenoxyl radical sites in a dimeric form (Scheme 2b (type II)). Thus, the reaction obeys second-order kinetics in the case of $[\text{Zn}^{\text{II}}(\mathbf{1}^*)(\text{NO}_3)]^+$. The latter mechanism of the zinc complex is very close to that of the system of Wieghardt et al. mentioned previously.^[7b] The enzymatic reaction has so far been considered to proceed by the type I mechanism. Thus, the different kinetic formulations of $[\text{Cu}^{\text{II}}(\mathbf{1}^*)(\text{NO}_3)]^+$ and $[\text{Zn}^{\text{II}}(\mathbf{1}^*)(\text{NO}_3)]^+$ disclosed in this study clearly demonstrate the importance of the redox cycle between Cu^{I} and Cu^{II} as well as the interconversion between the phenol and phenoxyl radical states for the efficient two-electron oxidation of alcohols at the mononuclear copper site of GO, which is fixed in the protein matrix.

Experimental Section

Kinetic studies and product analysis. The phenoxyl radical species of the Cu^{II} and Zn^{II} complexes were generated in situ by adding an equimolar amount of $(\text{NH}_4)_2[\text{Ce}^{\text{IV}}(\text{NO}_3)_6]$ (CAN, $5.0 \times 10^{-4} \text{ M}$) to a deaerated solution of $[\text{M}^{\text{II}}(\mathbf{1})_2](\text{PF}_6)_2$ ($\text{M} = \text{Cu}$ or Zn , $2.5 \times 10^{-4} \text{ M}$ in CH_3CN) ($\text{M} = \text{Cu}$ or Zn)^[11] in a UV cell (1-cm path length, sealed tightly with a silicon cap) at 25°C . The rate constants for the self-decomposition reaction (k_{dec}) of the phenoxyl radical complexes were determined by following the decrease in the absorption band due to the phenoxyl radical.

The oxidation of benzyl alcohol by the phenoxyl radical species was initiated by adding an excess amount of benzyl alcohol to the CH_3CN solution, after the absorption of the phenoxyl radical species had reached a maximum (a few minutes after the addition of CAN to the phenolate

complex solution) at 25°C . The rate constants (k_{obs}) for the redox reaction were also determined by following the decrease in the absorption due to the phenoxyl radical. The yield of benzaldehyde was determined by GC-MS with mesitylene as an internal standard.

Received: February 1, 1999

Revised version: April 13, 1999 [Z12979IE]

German version: *Angew. Chem.* **1999**, *111*, 2944–2946

Keywords: alcohols • copper • galactose oxidase • kinetics • phenoxyl complexes

- [1] J. Stubbe, W. A. van der Donk, *Chem. Rev.* **1998**, *98*, 705–762, and references therein.
- [2] a) N. Ito, S. E. V. Phillips, C. Stevens, Z. B. Ogel, M. J. McPherson, J. N. Keen, K. D. S. Yadav, P. F. Knowles, *Nature* **1991**, *350*, 87–90; b) N. Ito, S. E. V. Phillips, K. D. S. Yadav, P. F. Knowles, *J. Mol. Biol.* **1994**, *238*, 794–814.
- [3] M. M. Whittaker, D. P. Ballou, J. W. Whittaker, *Biochemistry*, **1998**, *37*, 8426–8436, and references therein.
- [4] R. M. Wachter, M. P. Montague-Smith, B. P. Branchaud, *J. Am. Chem. Soc.* **1997**, *119*, 7742–7749, and references therein.
- [5] a) K. Clark, J. E. Penner-Hahn, M. M. Whittaker, J. W. Whittaker, *J. Am. Chem. Soc.* **1990**, *112*, 6433–6434; b) K. Clark, J. E. Penner-Hahn, M. M. Whittaker, J. W. Whittaker, *Biochemistry* **1994**, *33*, 12553–12557.
- [6] Such a copper–phenoxyl radical motif has been also found as the catalytic form of glyoxal oxidase from *Phanerochaete chrysosporium* and in the prokaryotic FbfB protein: a) P. J. Kersten, *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 2936–2940; b) M. M. Whittaker, P. J. Kersten, N. Nakamura, J. Sanders-Loehr, E. S. Schweizer, J. W. Whittaker, *J. Biol. Chem.* **1996**, *271*, 681–687; c) P. Bork, R. F. Doolittle, *J. Mol. Biol.* **1994**, *236*, 1277–1282.
- [7] a) A. Sokolowski, J. Müller, T. Weyhermüller, R. Schnepf, P. Hildebrandt, K. Hildengrand, E. Bothe, K. Wieghardt, *J. Am. Chem. Soc.* **1997**, *119*, 8889–8900; b) P. Chaudhuri, M. Hess, U. Florke, K. Wieghardt, *Angew. Chem.* **1998**, *110*, 2340–2343; *Angew. Chem. Int. Ed.* **1998**, *37*, 2217–2220.
- [8] a) J. A. Halfen, V. G. Young, Jr., W. B. Tolman, *Angew. Chem.* **1996**, *108*, 1832–1835; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1687–1690; b) J. A. Halfen, B. A. Jazdzewski, S. Mahapatra, L. M. Berreau, E. C. Wilkinson, L. Que, Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1997**, *119*, 8217–8227.
- [9] a) Y. Wang, T. D. P. Stack, *J. Am. Chem. Soc.* **1996**, *118*, 13097–13098; b) Y. Wang, J. L. DuBois, B. Hedman, K. O. Hodgson, T. D. P. Stack, *Science* **1998**, *279*, 537–540.
- [10] M. A. Halcrow, L. M. L. Chia, X. Liu, E. J. L. McInnes, L. J. Yellowlees, F. E. Mabbs, J. E. Davies, *Chem. Commun.* **1998**, 2465–2466.
- [11] Details of the synthetic procedures for the ligand and the Cu^{II} and Zn^{II} complexes as well as the crystal structures and their physicochemical characteristics will be reported elsewhere. The structure and physicochemical data of a related Cu^{II} –phenolate complex have been reported in ref. [12].
- [12] S. Itoh, S. Takayama, R. Arakawa, F. Furuta, M. Komatsu, A. Ishida, S. Takamuku, S. Fukuzumi, *Inorg. Chem.* **1997**, *36*, 1407–1416.
- [13] M. M. Whittaker, Y.-Y. Chuang, J. W. Whittaker, *J. Am. Chem. Soc.* **1993**, *115*, 10029–10035.
- [14] Coordination of NO_3^- which comes from CAN was confirmed by ESI-MS.
- [15] Self-decomposition of the phenoxyl radical species gave a complicated mixture of products. An ESI mass spectrum of the resulting mixture indicated the formation of some S-oxygenated and N-dealkylated products of the ligand.
- [16] Benzaldehyde was the only product detected by GC-MS, and no C–C coupling products such as hydrobenzoin $[\text{PhCH}(\text{OH})\text{CH}(\text{OH})\text{Ph}]$ were observed.
- [17] Self-decomposition of $[\text{Zn}^{\text{II}}(\mathbf{1}^*)(\text{NO}_3)]^+$ also obeys second-order kinetics.

Transfer Catalysis Between Two Solids: Application to the Reduction of Nitroarenes**

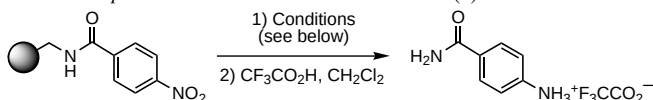
Anitha Hari and Benjamin L. Miller*

The need for new mild and selective methods for functional group transformations is a continuing driving force in synthetic organic chemistry. In addition, the rapidly growing field of combinatorial chemistry^[1] has triggered a surge in the development of methods which are amenable to solid-supported synthesis.

As part of a larger effort directed towards the design and synthesis of novel peptidomimetics, we required methods for the mild and selective reduction of nitroarenes. By analogy to the description by Ohta et al.^[2] of the ability of CrCl₂^[3] to reduce nitroarenes in refluxing acidic methanol, we recently reported that CrCl₂ in dimethylformamide (DMF) can effect this reaction on the solid phase at room temperature.^[4] However, the necessity of using a large excess of CrCl₂ (16 equiv) as a reducing agent is problematic with respect to preparative-scale reactions because of the cost and toxicity of the salt. The standard catalytic methods known for the solution-phase reduction of aromatic nitro compounds to anilines are hydrogenation reactions, which almost invariably employ a heterogeneous catalyst.^[5] Such heterogeneous catalysts, while generally useful for solution-phase chemistry, are clearly inapplicable to solid-supported synthesis.^[6] We sought a method that would be universally appropriate, and therefore began to explore methods under which our procedure could be rendered catalytic in chromium. Catalytic variants of the Nozaki–Hiyama–Kishi reaction involving the addition of organic halides to aldehydes^[7] and the Takai–Utimoto reaction of acrolein acetals with aldehydes^[8] have been reported.^[9] These reactions make use of a redox couple between Cr^{II} and Mn⁰, and employ trimethylsilyl chloride (TMSCl) as a proton surrogate. We now report the successful application and scope of the Cr^{II}/Mn⁰/TMSCl system for the reduction of nitroarenes. As described below, this method is particularly advantageous when applied to solid-phase synthesis, since it involves a *homogeneous* reductant. However, it is also quite amenable to solution-phase synthesis.

Our experiments started with the attachment of a nitrobenzoic acid onto Rink amide resin under standard coupling conditions as reported previously.^[4] As shown in Table 1, treatment of the resin-bound *p*-nitrobenzamide (**1**) with two equivalents of CrCl₂, 16 equivalents of Mn (up to 325 mesh powder), and 16 equivalents of TMSCl in DMF for 14 h at room temperature followed by trifluoroacetic acid mediated hydrolysis provided *p*-aminobenzamide as the trifluoro-

Table 1. Catalytic reduction of solid-supported *p*-nitrobenzamide (**1**) and isolation of *p*-ammonio benzamide trifluoroacetate (**2**).



1				2		
Entry	CrCl ₂ [equiv]	Mn ⁰ [equiv] ^[a]	TMSCl [equiv]	Solvent	Time [h]	Yield [%]
1	2	16	0	DMF	14	0
2	2	0	16	DMF/THF	14	0
3	2	16	16	DMF	14	70
4	2	16	16	CH ₂ Cl ₂	14	0
5	2	16	16	THF	14	0
6	1	16	16	DMF	14	77
7	0.5	16	16	DMF	14	74
8	0.25	16	16	DMF	14	75
9	0.1	16	16	DMF	24	60 ^[b]
10	0.05	16	16	DMF	192	33 ^[b]
11	0.25	16	16	NMP	14	78

[a] Mn powder (up to 325 mesh). [b] Indicates percent conversion as measured by ¹H NMR spectroscopy of the cleaved product, rather than the yield of isolated product.

acetate salt (**2**, isolated in 70% yield, entry 3). Both Mn⁰ and TMSCl are required for turnover of the chromium; leaving out either of these components prevents the reaction from occurring (entries 1 and 2). Substoichiometric quantities of CrCl₂ are equally successful, and we were able to run the reaction with as few as 0.25 equivalents of CrCl₂ without an increase in reaction time or diminishment of yield (entry 8). However, running the reaction with fewer than 0.25 equivalents of chromium results in lower conversion and longer reaction time (entries 9 and 10); since the solid-phase reactions were not run under anhydrous conditions, it is probable that turnover of the catalyst is reduced at longer reaction times because of hydrolysis of TMSCl. *N*-Methylpyrrolidone (NMP) is also a suitable solvent for this reaction (entry 11); however, the reduction does not proceed in THF or CH₂Cl₂.

As in the stoichiometric case, the catalytic reduction of solid-supported nitroarenes by Cr^{II} tolerates a wide range of substitution on the aromatic ring (Table 2). Halogens are unaffected by these conditions (entries 5 and 6). The moderate yields observed in each case are most likely the result of difficulties encountered in separating the product from Mn powder; we found that substitution of Mn chips (ca. 7 × 7 × 1 mm³) provided **2** from **1** in much higher purity and yield (88%). Likewise, other nitroarenes are uniformly reduced in higher yield and purity when Mn chips are employed. The use of Mn chips is particularly attractive since it suggests that reusable “catalytic converter”-type reaction chambers for a variety of Cr^{II}-catalyzed processes may be constructed; studies along such lines are in progress in our laboratory.

Similarly, we found that the Cr^{II}/Mn⁰ redox system readily reduced a variety of nitroarenes in solution (Table 3). As in the solid-supported case, the reaction is exquisitely selective for the nitro group, even in the presence of other readily reducible functionality. Unlike the solid-phase reaction, the

[*] Prof. B. L. Miller, A. Hari
Department of Chemistry
University of Rochester
Rochester, NY 14627 (USA)
Fax: (+1) 716-473-6889
E-mail: miller@miller1.chem.rochester.edu

[**] We thank Professor Robert Boeckman for helpful discussions. This research was supported by a generous grant from the Eastman Kodak Company.

Table 2. Catalytic reduction of nitrobenzoic and nitrocarboxylic acids to anilines on solid support.

Entry	Carboxylic acid	Product	Yield [%]	
			method a ^[a]	method b ^[b]
1			60	
2			58	
3			72	84
4			67	
5			64	76
6			63	
7			n.d. ^[c]	86
8			n.d. ^[c]	82 ^[d]

[a] Method a: Mn powder (up to 325 mesh, 16 equiv), TMSCl (16 equiv), CrCl₂ (0.25 equiv), DMF, 23 °C. [b] Method b: Mn chips (excess), TMSCl (16 equiv), CrCl₂ (0.25 equiv), DMF, 23 °C. [c] n.d. = not determined. [d] Wang resin (Advanced Chemtech).

reaction readily occurs in THF if Mn powder with up to 325 mesh is used.

In conclusion, a Cr^{II}/Mn⁰ redox couple has been successfully applied for the first time to the reduction of aromatic nitro compounds to anilines. The reaction proceeds cleanly at room temperature on the solid phase, and tolerates a wide range of additional substitution on the aromatic ring. We presume that the reaction proceeds by a catalytic cycle analogous to those proposed by Fürstner et al. and Boeckman et al.;^[9] efforts are underway to verify if this is indeed the case. As applied to the solid-phase reduction of nitroarenes, this methodology represents a rare example of the preparative use of transfer catalysis between two solid phases.^[10]

Experimental Section

General: All starting materials were purchased from commercial sources and used as received. Rink amide resin (100–200 mesh copoly(styrene-1% divinylbenzene)) was purchased from Novabiochem. TMSCl and solvents used for catalytic reaction were distilled over an appropriate drying agent prior to use. All solid-phase reactions were performed in a 2-mL Bio-Rad BioSpin polypropylene chromatography column equipped with a glass frit, and the mixtures were shaken on a Burrell wrist-action shaker.

Catalytic reduction of aryl nitro compounds on Rink amide resin: Resin **1**, obtained as reported^[2] from Rink amide resin (50 mg, 0.66 mmol g⁻¹), was

thoroughly washed and dried. To this resin in dry DMF were added CrCl₂ (1 mg, 0.25 equiv) and manganese (29 mg, 16 equiv). TMSCl (57.2 mg, 16 equiv) was then added, and the reaction mixture was shaken overnight. The resin (which settles at the top of the manganese) was then carefully transferred to another polypropylene tube and thoroughly washed with DMF, MeOH, and CH₂Cl₂. The amine was cleaved from the resin by treatment with trifluoroacetic acid/CH₂Cl₂ (95/5). After draining off the resin was washed with CH₂Cl₂. The combined organic layers were collected and evaporated to give the desired compound **2** (6.2 mg, 75 %).

Catalytic reduction of aryl nitro compounds in THF: To a mixture of 4-nitrobenzoic acid (42 mg, 0.25 mmol), manganese powder (220 mg, 4 mmol, 16 equiv), and CrCl₂ (1.5 mg, 0.0125 mmol, 0.05 equiv) stirring in THF at room temperature under N₂ was added TMSCl (0.25 mL, 2 mmol, 8 equiv). After 18 h the reaction mixture was filtered, and the solvent removed by rotary evaporation. Water (6 mL) was then added to the solid material remaining; after 3 h of stirring this mixture was filtered. The solid material remaining on the filter paper and the filtrate were extracted with ethyl acetate (5 × 10 mL). The combined extracts were dried over Na₂SO₄, filtered, and evaporated. The material remaining following evaporation of the solvent was purified by chromatography on silica (elution with hexane/ethyl acetate 1/3) to provide 4-aminobenzoic acid (29 mg, 85 %).

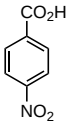
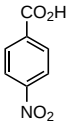
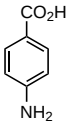
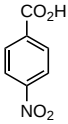
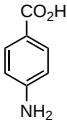
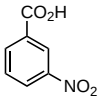
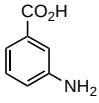
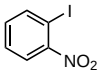
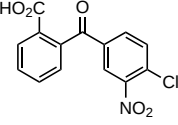
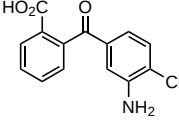
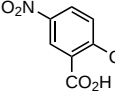
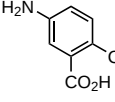
Received: February 16, 1999

Revised version: May 27, 1999 [Z13042IE]

German version: *Angew. Chem.* **1999**, *111*, 2938–2941

Keywords: chromium • manganese • reductions • solid-phase synthesis

Table 3. Catalytic solution-phase reduction of nitroarenes.^[a]

Entry	Nitroarene	CrCl ₂ [equiv]	Mn source (equiv) ^[b]	Product	Yield [%]
1		0.2	chips (excess)	n.r. ^[c]	0
2		0.2	powder (16)		83
3		0.05	powder (16)		85
4		0.2	powder (16)		80
5		0.2	powder (16)		55
6		0.2	powder (16)		70
7		0.2	powder (16)		73

[a] Entries 1–4 were conducted in THF, and employed eight equivalents of TMSCl. Entry 5 was carried out in DMF, and required treatment with tetrabutylammonium fluoride (TBAF) on workup. [b] Powder with up to 325 mesh. [c] n.r. = no reaction.

- [1] Reviews: a) J. S. Früchtel, G. Jung, *Angew. Chem.* **1996**, *108*, 19–46; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17–42; b) N. K. Terrett, M. Gardner, D. W. Gordon, R. J. Kobylecki, J. Steele, *Tetrahedron* **1995**, *51*, 8135–8173; c) A. Nefzi, J. M. Ostresh, R. A. Houghten, *Chem. Rev.* **1997**, *97*, 449–472.
- [2] Y. Akita, M. Inaba, H. Uchida, A. Ohta, *Synthesis* **1977**, 792–794.
- [3] Reviews on the applications of chromium(II) in organic synthesis: a) L. A. Wessjohann, G. Scheid, *Synthesis* **1999**, 1–36; b) T.-L. Ho, *Synthesis* **1979**, 1–20; c) J. R. Hanson, E. Premuzic, *Angew. Chem.* **1968**, *80*, 271–276, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 247–252.
- [4] A. Hari, B. L. Miller, *Tetrahedron Lett.* **1999**, *40*, 245–248.
- [5] a) R. A. W. Johnstone, A. H. Willby, I. D. Entistle, *Chem. Rev.* **1985**, *85*, 129–170; b) A. M. Tafesh, M. Beller *Tetrahedron Lett.* **1995**, *36*, 9305–9308; c) H. Weirer, J. Blum, Y. Sasson, *J. Org. Chem.* **1991**, *56*, 4481–4486.
- [6] An intriguing approach to multipolymer-supported catalysis using soluble polymers has been reported: K. D. Janda, H. Han, *Angew. Chem.* **1997**, *109*, 1835–1837, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1731–1733.
- [7] a) Y. Okude, S. Hirano, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1977**, *99*, 3179–3181; b) T. Hiyama, Y. Okude, K. Kimura, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561–568; c) K. Takai, K. Kimura, T. Kuroda, T. Hiyama, H. Nozaki, *Tetrahedron Lett.* **1983**, *24*, 5281–5284.
- [8] a) K. Takai, K. Nitta, K. Utimoto, *Tetrahedron Lett.* **1988**, *29*, 5263–5266; b) O. Fujimura, K. Takai, K. Utimoto, *J. Org. Chem.* **1990**, *55*, 1705–1706; c) K. Takai, Y. Kataoka, K. Utimoto, *Tetrahedron Lett.* **1989**, *30*, 4389–4392.

- [9] a) A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357; b) A. Fürstner, *Chem. Eur. J.* **1998**, *4*, 567–570; c) R. K. Boeckman, Jr., R. A. Hudack, *J. Org. Chem.* **1998**, *63*, 3524–3525.
- [10] The concept of transferring a stoichiometric amount of a reactive intermediate between two solid phases has been used by Rebek et al. as a mechanistic probe: J. Rebek, Jr., F. Gaviña, C. Navarro, *J. Am. Chem. Soc.* **1978**, *100*, 8113–8117.

STM Images of Individual Porphyrin Molecules on Cu(100) and Cu(111) Surfaces**

Nick Bampos, Charles N. Woodburn,
Mark E. Welland,* and Jeremy K. M. Sanders*

The pioneering work by Binnig and Rohrer on the development of scanning tunneling microscopy (STM)^[1] has led to a new way with which to “see” molecules at the atomic level. Much of the work reported in recent years has centered on the long-range ordering/reconstruction of metal surfaces and investigations of the properties of the conducting surface itself.^[2] Some of these images suffer from poor resolution due to thermally induced motion, poor adhesion of the substrate to the surface, poor instrumentation, or inferior tip preparation. Though many of these problems have been remedied by better surface preparation and molecular deposition or by improved instrumentation, sample preparation remains non-trivial. For organic molecules additional problems arise, mainly because interactions with the surface are often too weak to inhibit molecular motion. While STM images of organic systems, in particular, are notoriously difficult to interpret,^[3, 4] studies of individual molecules have been reported.^[5] In a seminal report of a highly symmetrical copper phthalocyanine molecule on Cu(100) image interpretation was achieved by using Elastic Scattering Quantum Chemistry (ESQC) calculations to successfully simulate the STM image.^[6] Such simulation techniques, while often very useful, are computationally demanding, which rather limits their appeal. However, we show here that more complicated molecules designed for genuine chemical applications can provide valuable additional information which may be used to understand the mechanism behind image contrast.

While recent advances have produced excellent images of molecules physisorbed onto surfaces, chemisorption generally results in superior images (particularly at room temperature), as the molecules are immobilized and not subject to thermal drift. For example, alkanethiols have proved useful on gold surfaces due to the covalent S–Au bond which pins the molecule to the surface, resulting in dense, highly ordered adlayers, in which the molecules stand perpendicular to the surface.^[7] In general, good images have been reported in air and in solution, but the images with the highest resolution have been obtained under ultrahigh vacuum (UHV) conditions. STM under UHV conditions has been used to image organic molecules such as coadsorbed benzene and CO on Rh(111),^[8] benzene^[9] and naphthalene^[10] on Pt(111), and

copper phthalocyanine on Cu(100).^[11] However, recent work on the imaging and manipulation of symmetrical porphyrin monomers, which will adsorb predominantly flat on the surface, is of greater relevance to our work.^[12, 13]

Although image contrast at the atomic level on idealized surfaces is feasible by STM, image contrast for molecules is the result of tip–molecule–surface interactions. Such contrast depends upon the symmetry and wavefunction mixing of the molecular orbitals with the substrate.^[14] This mixing can perturb the electronic structure of the molecule from that of its isolated state. Additionally, the contrast will also depend upon the direction of tunneling and magnitude of the tunneling voltage. In the case of a well-documented copper phthalocyanine molecule,^[11a] the fine structure of the image is in agreement with the calculated HOMO of the free molecule. High-resolution images have been obtained by Jung et al.^[13] by employing a tetrasubstituted copper porphyrin on Cu(100), Au(110), and Ag(110) surfaces under UHV conditions. In their study a) Cu is used to enhance chemisorption with the metal surface, b) the porphyrin used is highly symmetrical and image interpretation simplified as a result, and c) the porphyrin is relatively rigid, with large *tert*-butyl feet resting on the surface. The (four) lobes observed in these images were attributed, within instrumentation accuracy, to the (four) *meso* di-*tert*-butylphenyl substituents. Images of a tetrasubstituted porphyrin monomer on iodine-modified Au(111) in solution have also been used for conformational analysis and to determine the orientation of individual molecules.^[13a]

For a comprehensive understanding of the contrast observed whilst molecules are being imaged in the STM, significant modeling of the tip–molecule–surface interaction is required. Despite this, it is often possible to assign contrast in a qualitative way by directly comparing the known molecular structure with the STM images. In this case it is important to minimize the electronic contribution of the surface by choosing flat metallic surfaces with small corrugation amplitude. In this paper we describe the imaging of a porphyrin monomer, a linear porphyrin dimer, and cyclic oligomers which have not been chosen or engineered to maximize their interaction with the surface.

The Cu(111) and Cu(100) surfaces used in our studies were cleaned by cycles of sputtering by argon-ion bombardment and subsequent annealing at high temperature^[15] to give atomically flat regions free of impurities.^[16] This procedure must be repeated a number of times to give a workable surface, which can then be imaged by STM prior to sample deposition.

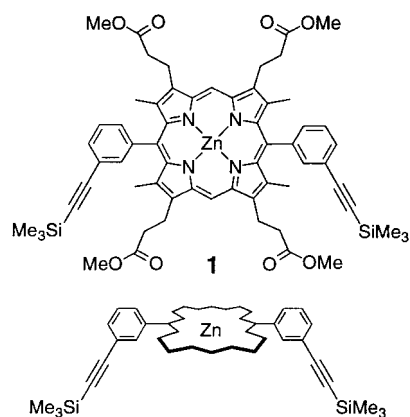
The lowest molecular weight molecule deposited (on Cu(111)) was the *meta*-substituted zinc porphyrin **1** ($M_w = 1119$), used previously as a building block in the preparation of cyclic oligomeric hosts.^[17] In the solution state (¹H NMR spectrum) **1** exhibits two-fold symmetry, as rapid rotation occurs about the porphyrin–phenyl bond. In the solid state the trimethylsilylalkynyl arms may be directed to the same or the opposite sides of a plane of symmetry.

Monomer **1** was deposited at close to the decomposition temperature (300–330 °C) under vacuum (5×10^{-8} mbar) over six hours. The ideal deposition conditions were a compromise between a low temperature, which minimizes

[*] Dr. M. E. Welland, Dr. C. N. Woodburn
Nanoscale Group, Department of Engineering
Trumpington Street, Cambridge CB2 1PZ (UK)
Fax: (+44) 1223-339263
E-mail: mew10@eng.cam.ac.uk

Prof. J. K. M. Sanders, Dr. N. Bampos
Cambridge Centre for Molecular Recognition
University Chemical Laboratory
Lensfield Road, Cambridge CB2 1EW (UK)
Fax: (+44) 1223-336017
E-mail: jkms@cam.ac.uk

[**] We thank the EPSRC (J.K.M.S. and N.B.) and ESPRIT project NANOWIRES (M.E.W. and C.N.W.) for financial support.



fragmentation of the molecule, and higher temperatures, which give greater deposition rates but increased likelihood of fragmentation. In all images presented here no significant fragmentation was observed. The best tunneling conditions for imaging were achieved at high gap impedances. To improve the contrast, tunneling currents below 0.2 nA were needed with approximately -3 V sample bias. The resulting images show the monomers preferentially populating the step edges. This may be due to the three-dimensional nature of the monomers, which would give the maximum interaction with the surface at the edges. In one region away from the step edge, two Zn monomers can be clearly identified (Figure 1). The spacing between the two bright peaks in the image was measured as approximately 12 Å, which corresponds to the distance between the phenyl groups in the individual monomers (for

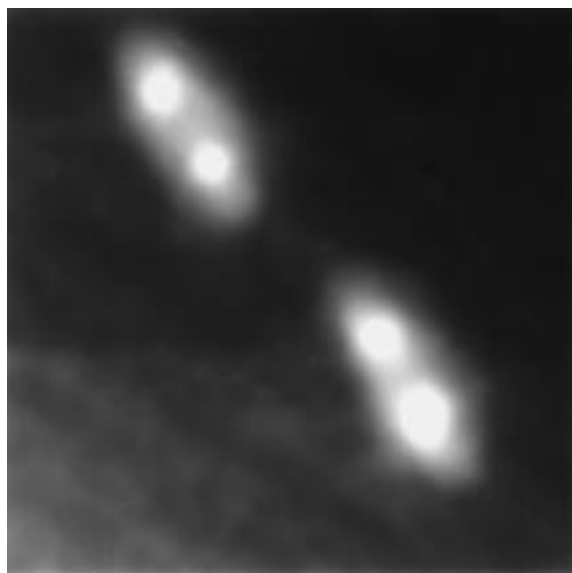
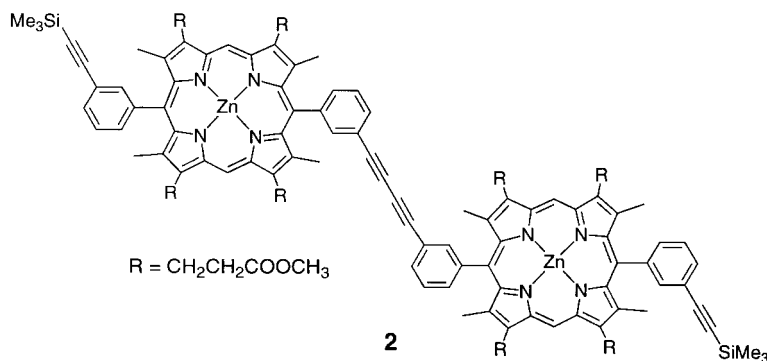


Figure 1. STM image of two molecules of zinc monomer **1** with common registration orientation to the surface; image size: 65×65 Å; $V_s = -2711$ mV, $I = 0.1$ nA. The distance between the two bright regions per porphyrin molecule approximately corresponds to the distance between the two *meso*-substituted phenyl groups. In this image the porphyrin plane is assumed to be perpendicular to the surface. Note that all the STM images have been filtered with a low-pass filter to remove high-frequency noise; the gray scale has been coded so that a high topographic feature appears white.

comparison, the smallest separation between trimethylsilyl (TMS) groups is approximately 19 Å) from molecular modeling (Cerius²)^[18] and single-crystal X-ray diffraction studies.^[19] Such a visualization of the molecule is not unlikely if we assume that the dominant contribution to the image is due to the *meso*-bound phenyl groups. The orientation of the two units suggests common registration with the surface, though on the whole, mobility at room temperature eventually results in significant aggregation at the step edges.

Linear dimer **2** ($M_w = 2090$) is one in a series of porphyrin oligomers investigated as a building block for large hosts.^[20] In



the solution state (¹H NMR spectrum) the molecule exhibits symmetry by virtue of the rotation about the butadiyne linker. In contrast to the other molecules imaged in this study linear dimer **2** is a long molecule with a defined shape and the possibility of two structurally distinct conformations, which should simplify the image interpretation. In order to overcome molecular diffusion (on Cu(100)) the STM was cooled to 98 K (liquid nitrogen) over a period of three days. While deposition rates were very low (0.3 Å h⁻¹ after 24 h), scanning the surface revealed isolated features on the surface terraces. The stability of the system permitted repeated scans at a variety of tip–substrate biases. Scanning at low temperature greatly improved resolution and allowed imaging at lower tip–substrate biases. The highest contrast was achieved with a sample bias of -1440 mV and a tunnel current of 0.08 nA. Lowering the impedance further (i.e. decreasing the distance between the tip and the conducting surface) resulted in the molecules being dragged by the tip.

Under the UHV conditions employed scanning of the plateaus at low coverage provided many high-quality images of single molecules adopting one of two orientations. The best interaction with the surface is achieved when the molecule rests on its side, allowing the ester chains and the TMS groups to come into contact with the surface. In this configuration the porphyrin plane sits perpendicular to the copper surface, and as they rest on the surface, the molecules may adopt a cisoid or transoid orientation; examples of each can be clearly distinguished in the images (Figure 2).

Molecular modeling indicates that the phenyl–phenyl distance across the butadiyne linker is 9 Å, while across the porphyrin it is 12 Å. From the STM image the spacing between the bright lobes was measured at $11(\pm 1)$ Å. In the images in Figure 2 the termini of the linear molecules exhibit features that can be attributed to the large TMS groups. It is, however, important to note that although the measured

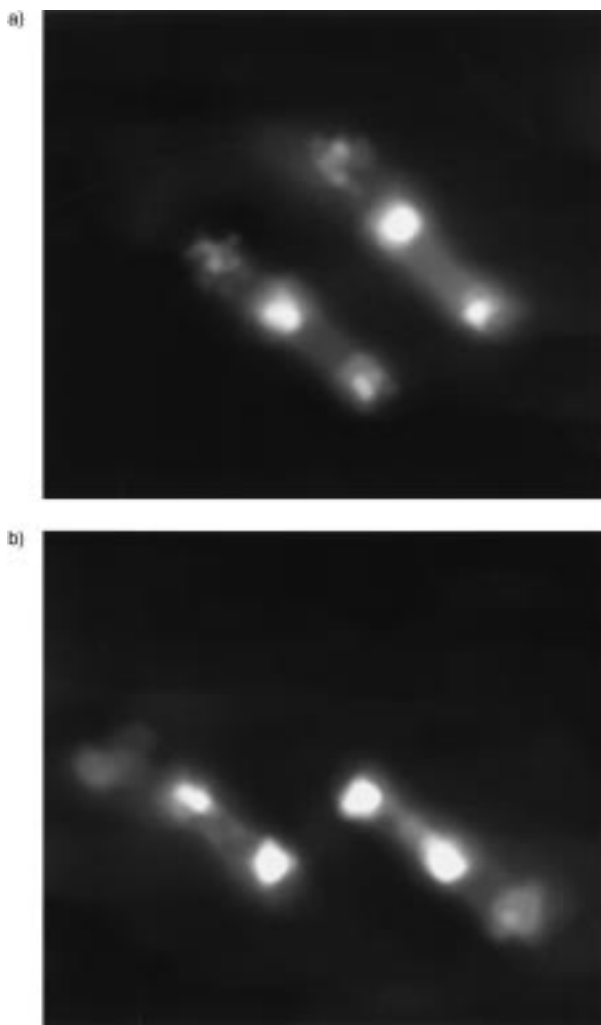
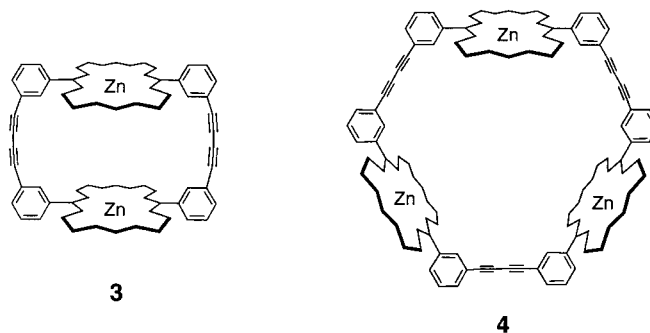


Figure 2. STM image of the linear dimer **2** in the cisoid (a) and transoid (b) conformations at 98 K; image size: $60 \times 40 \text{ \AA}$; $V_s = -1440 \text{ mV}$, $I = 0.08 \text{ nA}$. Conversion of one isomer to the other is achieved by rotation about the butadiyne linker prior to low-temperature imaging.

spacing of the groups within the molecules is consistent with molecular modeling, their positions are sometimes skewed relative to the rest of the molecule. This is probably due to a reorientation of the molecule as a result of the interaction with the surface. The bright features recorded may be attributed to the ester side chains pointing up and away from the surface, although their flexibility and distance from the conducting surface makes this very unlikely. We suggest that the image is the result of the interaction of the tip with the aromatic π system, and the distance between the bright lobes supports this. All the molecules we have investigated to date are *meta*-substituted on the phenyl groups and as a result are not flat.

The larger cyclic dimer **3** ($M_w = 1944$, on Cu(100)) and cyclic trimer **4** ($M_w = 2917$, on Cu(111)) give relatively simple ^1H NMR spectra by virtue of their C_n symmetry.^[20] In the solid state the high degree of symmetry was expected to aid the identification of these large hosts. Unfortunately, significant decomposition of these compounds occurred during deposition, resulting in extremely low deposition rates. Even when images were identified molecular diffusion made imaging



difficult. Images derived from these experiments were not very encouraging because long-range order or fine structure could not be detected. These results show the limits of sample deposition from the gas phase.

While these results have not in themselves led to a straightforward description of the mechanism of image contrast, they demonstrate the potential of STM to image molecular structure and conformation on a surface. This technique could act as an alternative to single-crystal X-ray diffraction for structure determination: crystals of this type of molecule are often difficult to obtain. For truly quantitative interpretation of the images, however, detailed modeling of the molecule–surface interaction is required. In addition, by using other molecules that differ in some controlled and predictable manner, the nature of image contrast can be studied in greater depth.

Received: June 4, 1998

Revised version: April 8, 1999 [Z11948IE]

German version: *Angew. Chem.* **1999**, *111*, 2949–2953

Keywords: porphyrinoids • scanning tunneling microscopy • ultrahigh vacuum

- [1] a) R. M. Feenstra, *Surf. Sci.* **1994**, *300*, 965; b) G. Binnig, H. Rohrer, C. Gerber, E. Weibel, *Phys. Rev. Lett.* **1982**, *49*, 57.
- [2] For example, see: a) J. Kuntze, J. Bomermann, T. Rauch, S. Speller, W. Heiland, *Surf. Sci.* **1997**, *394*, 150; b) S. Mizuno, H. Tochiwara, Y. Matsumoto, K. Tanaka, *Surf. Sci.* **1997**, *393*, L69; c) T. Kawamura, S. Kojima, T. Kanzawa, *J. Appl. Phys.* **1997**, *82*, 6031; d) A. A. Baski, S. C. Erwin, L. J. Whitman, *Surf. Sci.* **1997**, *392*, 69; e) A. A. Saranin, T. Numata, O. Kubo, M. Katayama, K. Oura, *Appl. Surf. Sci.* **1997**, *121*, 183; f) H. E. Hoster, M. A. Kulakov, B. Bullemer, *Surf. Sci.* **1997**, *382*, L658; g) F. Besenbacher, *Rep. Prog. Phys.* **1996**, *59*, 1732; h) M. A. Kulakov, G. Henn, B. Bullemier, *Surf. Sci.* **1996**, *396*, 49; i) M. Bode, R. Pascal, R. Wiesendanger, *Surf. Sci.* **1995**, *344*, 185; j) M. Hohage, T. Michely, G. Comsa, *Surf. Sci.* **1995**, *337*, 249; k) W. Arabczyk, S. Hinrich, H. J. Mussig, *Vacuum* **1995**, *46*, 473; l) X. S. Wang, W. H. Weinberg, *Surf. Sci.* **1994**, *314*, 71; m) H. Onishi, Y. Iwasawa, *Surf. Sci.* **1994**, *313*, L783; n) Y. Hasegawa, P. Avouris, *Science* **1992**, *258*, 1763; o) V. S. Iyer, K. Yoshimura, V. Enkelmann, R. Epsch, J. P. Rabe, K. Müllen, *Angew. Chem.* **1998**, *110*, 2843; *Angew. Chem. Int. Ed.* **1998**, *37*, 2696.
- [3] R. Wiesendanger, *Scanning Probe Microscopy, Methods and Applications*, Cambridge University Press, Cambridge, UK, **1994**.
- [4] S. Chiang, *Chem. Rev.* **1997**, *97*, 1083.
- [5] a) J. K. Gimzewski, E. Stoll, R. R. Schlittler, *Surf. Sci.* **1987**, *181*, 267; b) J. A. Venables, D. J. Smith, J. M. Cowley, *Surf. Sci.* **1987**, *181*, 235.
- [6] a) P. Sautet, C. Joachim, *Surf. Sci.* **1992**, *271*, 387; b) P. Sautet, *Chem. Rev.* **1997**, *97*, 1097.
- [7] a) C. A. Alves, E. L. Smith, M. D. Porter, *J. Am. Chem. Soc.* **1992**, *114*, 1222; b) S. J. Stranick, A. N. Parikh, Y. T. Tao, D. L. Allara, P. S. Weiss,

- J. Phys. Chem.* **1994**, *98*, 7636; c) G. E. Poirier, M. J. Tarlov, *Langmuir* **1994**, *10*, 2853; d) M. Sprik, E. Dalamarche, B. Michel, U. Rothlisbrger, M. L. Klein, H. Wolf, H. Ringsdorf, *Langmuir* **1994**, *10*, 4116; e) W. B. Caldwell, D. J. Cambell, K. Chen, B. R. Herr, C. A. Mirkin, A. Malik, M. K. Durbin, P. Dutta, K. G. Huang, *J. Am. Chem. Soc.* **1995**, *117*, 6071; f) G. E. Poirier, E. D. Pylant, *Science* **1996**, *272*, 1145.
- [8] H. Ohtani, R. J. Wilson, S. Chiang, C. M. Mate, *Phys. Rev. Lett.* **1988**, *60*, 2398.
- [9] P. S. Weiss, D. M. Eigler, *Phys. Rev. Lett.* **1993**, *71*, 3139.
- [10] V. M. Hallmark, S. Chiang, J. K. Brown, C. Woll, *Phys. Rev. Lett.* **1991**, *66*, 48.
- [11] a) P. H. Lippel, R. J. Wolson, M. D. Miller, C. Woll, S. Chiang, *Phys. Rev. Lett.* **1989**, *62*, 171; b) T. Fritz, M. Hara, W. Knoll, H. Sasabe, *Mol. Cryst. Liq. Cryst.* **1994**, *253*, 269.
- [12] a) M. Kunitake, U. Akiba, N. Batina, K. Itaya, *Langmuir* **1997**, *13*, 1607; b) N. J. Tao, G. Cardenas, F. Cunha, Z. Shi, *Langmuir* **1995**, *11*, 4445; c) M. Kunitake, U. Akiba, N. Batina, K. Itaya, *Langmuir* **1997**, *13*, 1607.
- [13] a) T. A. Jung, R. R. Schlitter, J. K. Gimzewski, H. Tang, C. Joachim, *Science* **1996**, *271*, 181; b) T. A. Jung, R. R. Schlitter, J. K. Gimzewski, *Nature* **1997**, *386*, 696; c) J. K. Gimzewski, C. Joachim, R. R. Schlitter, V. Langlais, H. Tang, I. Johannsen, *Science* **1998**, *281*, 531.
- [14] a) G. Binning, C. F. Quate, C. Gerber, *Phys. Rev. Lett.* **1986**, *56*, 930; b) M. M. D. Ramos, *J. Phys. Condens. Matter* **1993**, *5*, 2843.
- [15] D. P. Woodruff, T. A. Delchar, *Modern Techniques of Surface Science*, Cambridge University Press, Cambridge, UK, **1986**.
- [16] C. N. Woodburn, PhD Thesis, University of Cambridge, UK, **1996**.
- [17] H. L. Anderson, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 1* **1995**, *22*.
- [18] Cerius² Version 3, MSI Cambridge, Cambridge (England) running on an SGI R4000 computer.
- [19] N. Bampos, M. R. Prinsep, H. He, A. Vidal-Ferran, A. Bashall, M. McPartlin, H. Powell, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 2* **1998**, 715.
- [20] S. Anderson, H. L. Anderson, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2247.

The Intrinsic ³[dσ*→pσ] Emission of Binuclear Gold(I) Complexes with Two Bridging Diphosphane Ligands Lies in the Near UV; Emissions in the Visible Region Are Due to Exciplexes**

Wen-Fu Fu, Kwok-Chu Chan, Vincent M. Miskowski, and Chi-Ming Che*

Since the first report on the photoluminescence of [Au₂(dppm)₂]²⁺ (dppm = bis(diphenylphosphanyl)methane),^[1, 2] luminescent gold(I) compounds, particularly those involving Au–Au interactions, have received considerable attention.^[3] Polynuclear gold(I) phosphane complexes generally display long-lived emissions in the visible region, and this was usually attributed to excited states involving Au–Au bonding.^[1–11] The Au–Au interaction is expected to lower the energy of the

5dσ* → 6pσ transition, where 5dσ* and 6pσ refer to the antibonding combination of the 5d_{z²} and to the bonding combination of the 6s/6p_z orbitals, respectively, and the Au–Au axis is defined as the z axis. [Au₂(dppm)₂](ClO₄)₂ displays luminescence with λ_{max} at 575 nm in solution in acetonitrile.^[1, 2] Importantly, this emission, which was assigned to the ³[dσ*→pσ] excited state, is substantially red-shifted relative to the spin- and dipole-allowed ¹(dσ* → pσ) electronic absorption transition at 290 nm, an apparent Stokes shift of 17 100 cm^{−1} (2.1 eV). This is an extraordinarily large Stokes shift, particularly when compared to the Stokes shifts of 6000–8000 cm^{−1} reported for the phosphorescence of d⁸–d⁸ binuclear compounds from their ¹(dσ* → pσ) absorptions.^[12] The emissive state for these latter compounds is well established as ³[dσ*→pσ] and hence should be nominally analogous to the emissive state of the d¹⁰–d¹⁰ Au^I complexes. Our recent ab initio calculations on [Au₂(H₂PCH₂PH₂)₂]²⁺ predicted that its ³[dσ*→pσ] excited state emits at 331 nm, that is, much higher in energy than reported in the literature, but readily forms an exciplex with acetonitrile molecules that is predicted to emit at 557 nm at room temperature.^[13] Herein we describe experimental evidence for an intrinsic high-energy ³[dσ*→pσ] state and visible-region emissions of solvent or anion exciplexes for binuclear gold(I) phosphane complexes.

We synthesized complexes of the type [Au₂(dcpm)₂]Y₂ [dcpm = bis(dicyclohexylphosphanyl)methane, Y = ClO₄[−] (**1**), PF₆[−] (**2**), CF₃SO₃[−] (**3**), [Au(CN)₂][−] (**4**), Cl[−] (**5**), and I[−] (**6**); see Figure 1], and **1**, **4**, and **6** were characterized by single-crystal X-ray structure determination.^[14] The ligand conformations and Au–Au distances (2.9263(9), 2.9876(5), and 3.0132(6) Å for **1**, **4**, and **6**, respectively) are typical for bis(diphosphane)-bridged binuclear Au^I complexes.^[15, 16] The structure of **6** features short Au⋯I contacts (3.069(1) Å) that result in a T-shaped AuP₂I geometry at the Au atoms. This is also typical; Mason et al.^[15] reported a number of structures of halide (Cl[−], Br[−], I[−]) salts of [Au₂(diphosphane)₂]²⁺ cations [diphosphane = bis(dimethylphosphanyl)methane (dmpm) or bis(dimethylphosphanyl)ethane (dmpe)] that feature similar cation⋯anion interactions. Importantly for our present considerations, the closest Au⋯anion contacts in **1** (Au⋯OCIO₃ 3.36[2] Å) and **4** (Au⋯NCAuCN 3.33(1) Å) are significantly longer than those of **6**.

The UV/Vis spectroscopic data of the compounds are summarized in Table 1. For the compounds with weakly interacting counterions (ClO₄[−], PF₆[−], and CF₃SO₃[−]) the absorption spectra feature an intense absorption band at 277 nm (ε = 2.6–2.9 × 10⁴ mol^{−1} dm³ cm^{−1}) and a weak shoulder at about 315 nm (ε = 400 mol^{−1} dm³ cm^{−1}) (Figure 2), which are respectively assigned to the ¹(dσ* → pσ) and ³(dσ* → pσ) transitions. These assignments are based on previous studies of binuclear gold(I) complexes^[15] and are strongly supported by recent resonance Raman measurements that revealed

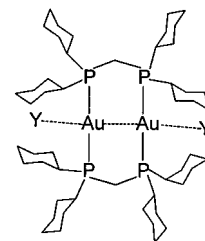


Figure 1. The structure of [Au₂(dcpm)₂]Y₂. Y = ClO₄[−], PF₆[−], CF₃SO₃[−], [Au(CN)₂][−], Cl[−], I[−].

[*] Prof. Dr. C.-M. Che, Dr. W.-F. Fu, K.-C. Chan, Dr. V. M. Miskowski
Department of Chemistry, The University of Hong Kong
Pokfulam Road, Hong Kong (China)
Fax: (+852) 2857-1586
E-mail: cmche@hkucc.hku.hk

[**] We are grateful for financial support from The University of Hong Kong and for a postdoctoral fellowship to W. F. F., as well as from the Research Council of the Hong Kong Special Administrative Region, China [HKU 7298/99P].

Table 1. Spectroscopic and photophysical properties of **1–6**.

Complex	Medium (<i>T</i> [K])	λ_{abs} [nm] (ϵ [dm ³ mol ⁻¹ cm ⁻¹])	λ_{em} [nm]/ τ [μ s] ^[c]	ϕ_{em}
[Au ₂ (dcpm) ₂](ClO ₄) ₂ (1)	CH ₃ CN (298) ^[a] glass (77) ^[b] solid (298)	243 (8846), 278 (28920), 317(sh) (389)	370(w)/0.74, 510(s)/4.96 362(s)/2.67, 410(w)/6.44 368(s)/4.88, 564(w)/4.73	0.048 ± 0.007
[Au ₂ (dcpm) ₂](PF ₆) ₂ (2)	CH ₃ CN (298) ^[a] glass (77) ^[b] solid (298)	243 (7676), 277 (25922), 315(sh) (414)	370(w)/0.85, 490(s)/5.12 360(s)/2.54, 405(w)/6.49 368(s)/1.71, 505(w)/6.39	0.025 ± 0.001
[Au ₂ (dcpm) ₂](SO ₃ CF ₃) ₂ (3)	CH ₃ CN (298) ^[a] glass (77) ^[b] solid (298)	243 (8679), 277 (29185), 320(sh) (386)	370(w)/0.83, 500(s)/5.54 360(s)/2.14, 411(w)/5.36 363(s)/1.17	0.027 ± 0.002
[Au ₂ (dcpm) ₂][Au(CN) ₂] ₂ (4)	CH ₃ CN (298) ^[a] glass (77) ^[b] solid (298)	240 (15110), 277 (24913), 314(sh) (376)	370(w)/0.33, 495(s)/3.57 360(s)/2.41, 417(s)/3.68 368(s)/3.78, 515(w)/5.43	0.013 ± 0.001
[Au ₂ (dcpm) ₂]Cl ₂ (5)	CH ₃ CN (298) ^[a] glass (77) ^[b] solid (298)	243 (6420), 277 (18379), 310 (1974)	513/5.74 370(s)/2.04, 481(m)/7.31 513/(6.68)	0.065 ± 0.004
[Au ₂ (dcpm) ₂]I ₂ (6)	CH ₃ CN (298) ^[a] glass (77) ^[b] solid (298) solid (77)	246 (37377), 275 (20783), 323 (6136), 365(sh)(1344)	530/1.61 460/8.02 473/1.87 475/2.74	0.085 ± 0.002

[a] Concentration: 6.0×10^{-5} M. [b] Solvent: EtOH/MeOH (1/4). [c] For emission spectra measurements, excitation wavelength: 280 nm. For luminescence lifetime measurements: excitation at 266 nm for high-energy emissions (360–417 nm); excitation at 355 nm for low-energy emissions (460–564 nm).

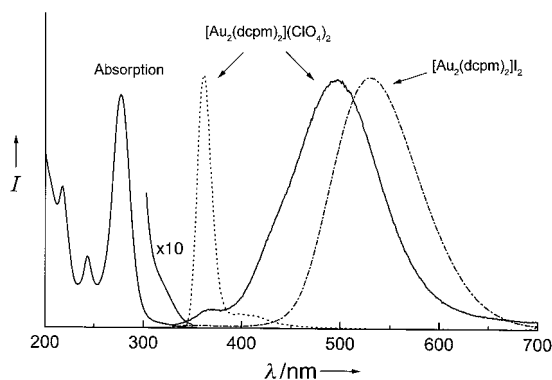


Figure 2. Electronic absorption (—) and emission spectra of [Au₂(dcpm)₂](ClO₄)₂ in degassed acetonitrile at room temperature (—) and in EtOH/MeOH (1/4) at 77 K (---), and emission spectrum of [Au₂(dcpm)₂]I₂ (•—•) in degassed acetonitrile at room temperature. *I* = intensity.

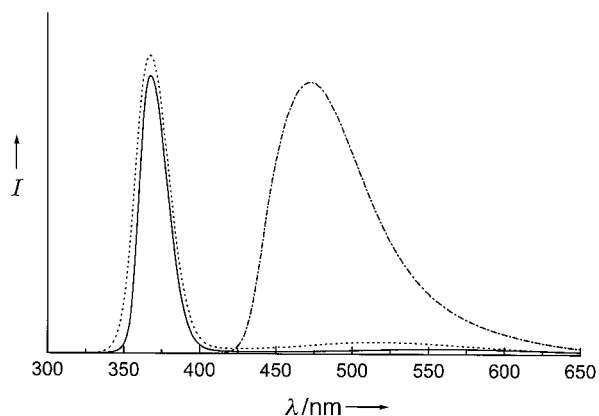


Figure 3. Room-temperature solid-state emission spectra of [Au₂(dcpm)₂](ClO₄)₂ (—), [Au₂(dcpm)₂][Au(CN)₂]₂ (---), and [Au₂(dcpm)₂]I₂ (•—•) with excitation at 280 nm. *I* = intensity.

major enhancement of the $\nu(\text{Au}_2)$ band for excitation resonant with the band at 277 nm.^[17] Compound **6** (6.0×10^{-5} M in acetonitrile) exhibits additional bands with λ_{max} at 323 nm ($\epsilon = 6136 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$) and 365 nm ($\epsilon = 1344 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$, sh); these features are presumably attributable to ground-state $\text{Au} \cdots \text{I}$ interactions. Indeed, **1–4** have similar ³¹P NMR chemical shifts ($\delta \approx 54.1$), but the ³¹P NMR signal of **6** (2.0×10^{-4} M) is at $\delta = 48.5$, and this indicates significant perturbation of [Au₂(dcpm)₂]²⁺ by complexation of I⁻. Halide (Cl⁻, Br⁻, I⁻) adducts of [Au₂(diphosphane)₂]²⁺ (diphosphane = dmpm or dmpe) were previously shown to exhibit similarly perturbed electronic absorption spectra, and the first association constants for complexation in solution in acetonitrile were on the order of 10^4 – 10^5 M^{-1} .^[15]

Upon excitation at 280 nm, **1–4**, both in the solid state at room temperature and as glassy solutions in MeOH/EtOH at 77 K, exhibit intense phosphorescence with λ_{max} at 360–368 nm (Figures 2 and 3). In contrast, crystalline **5** and **6** show only an intense low-energy emission with λ_{max} at 513 and 473 nm at room temperature, respectively (Table 1, Figure 3).

The near-UV emission is also observed for **5** ($\lambda_{\text{max}} = 370$ nm) in a MeOH/EtOH glassy solution at 77 K, but is not observable for **6** (2×10^{-5} M) under the same experimental conditions. Time-resolved emission measurements revealed that the emission of solid [Au₂(dcpm)₂](ClO₄)₂ at 368 nm follows a single-exponential decay (Figure 4). Lifetime measurements revealed that both the high- (360–370 nm) and low-energy (460–550 nm) emissions have lifetimes on the microsecond timescale (Table 1), consistent with assignment to triplet excited states. A high-energy (near-UV) emission has not been previously reported for binuclear Au^I complexes. It is, however, completely consistent with expectations for emission from the ³[dσ*po] state. The Stokes shifts of the room-temperature solid-state emission of **1** at 368 nm from the 278 nm ¹(dσ* → po) and 317 nm ³(dσ* → po) absorption bands are 8930 and 4570 cm⁻¹, respectively, in excellent agreement with values for the analogous transitions of d⁸–d⁸ complexes.^[12] We conclude that this near-UV emission is the “intrinsic” emission of the ³[dσ*po] excited state of

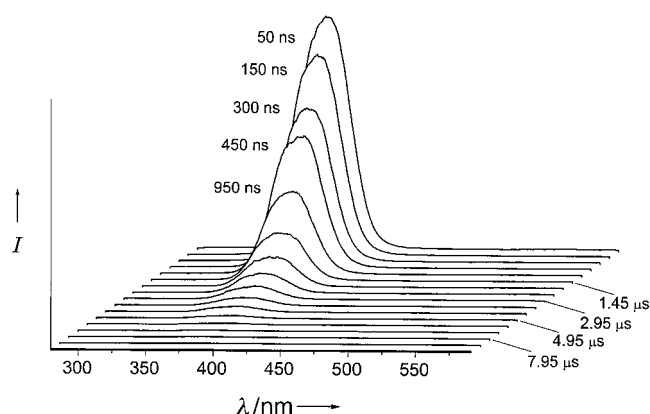


Figure 4. Room-temperature time-resolved emission spectra of solid $[\text{Au}_2(\text{dcpm})_2](\text{ClO}_4)_2$ (excitation at 266 nm). I = intensity.

$[\text{Au}_2(\text{dcpm})_2]^{2+}$, with an energy, width, and Stokes shift representative of the internal distortions that are characteristic for this excitation.

We assign the visible-region emissions to adducts of the excited state with solvent or counterions. In the case of halide as counterion, clear evidence exists for complexation of the ground state, and it seems reasonable to assign the absorption band observed for **6** at 365 nm (Table 1) to the spin- and dipole-allowed counterpart of the emission in solution at 530 nm; this assignment results in a reasonable Stokes shift of 8500 cm^{-1} . For **1–4**, emission from degassed acetonitrile solutions at room temperature is observed at about 500 nm. We attribute these emissions to an adduct of the excited state with the solvent, that is, an exciplex, since there is no evidence for complexation of the ground state. There is evidence for distortion of the excited state along coordinates other than Au–Au for the visible-emissive states, since the emission full widths at half height of $3200\text{--}3600\text{ cm}^{-1}$ are much larger than that of the near-UV emission ($1500\text{--}1850\text{ cm}^{-1}$).

We infer a large proclivity of the $\text{d}\sigma^* \rightarrow \text{p}\sigma$ excited states of these $\text{d}^{10}\text{--d}^{10}$ binuclear complexes towards an increased coordination number of the Au^{I} centers. A key difference between $\text{d}^{10}\text{--d}^{10}$ M_2L_4 and $\text{d}^8\text{--d}^8$ M_2L_8 complexes^[12] is that the z^2 and $x^2 - y^2$ $\text{d}\sigma^*$ orbitals of M_2L_4 can mix. A limiting case for the involvement of $x^2 - y^2$ is represented by the planar three-coordinate Au^{I} tris(phosphane) complex characterized by McCleskey and Gray,^[18] which, probably not coincidentally, displays emission at an energy very similar to that of the visible emissions of the binuclear Au^{I} compounds of this study. The distortion of the excited state in this case consists exclusively of shortening of the Au–L bonds, and we suggest that this type of excited-state distortion makes a significant contribution to the visible-emitting states of the binuclear complexes.

In view of the results presented here, we suggest that the interpretation of literature data on the luminescence of polynuclear d^{10} complexes may need revision in many cases.

Received: January 15, 1999 [Z12918IE]

German version: *Angew. Chem.* **1999**, *111*, 2953–2955

Keywords: binuclear complexes • exciplexes • gold • luminescence • UV/Vis spectroscopy

- [1] a) C. King, J. C. Wang, M. N. I. Khan, J. P. Fackler, Jr., *Inorg. Chem.* **1989**, *28*, 2145–2149; b) M. N. I. Khan, C. King, D. D. Heinrich, J. P. Fackler, Jr., L. C. Porter, *Inorg. Chem.* **1989**, *28*, 2150–2154.
- [2] a) C. M. Che, H. L. Kwong, V. W. W. Yam, K. C. Cho, *J. Chem. Soc. Chem. Commun.* **1989**, 885–886; b) D. Li, C. M. Che, H. L. Kwong, V. W. W. Yam, *J. Chem. Soc. Dalton Trans.* **1992**, 3325–3329.
- [3] L. H. Gade, *Angew. Chem.* **1997**, *109*, 1219–1221; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1171–1173.
- [4] a) S. J. Shieh, X. Hong, S. M. Peng, C. M. Che, *J. Chem. Soc. Dalton Trans.* **1994**, 3067–3068; b) B. C. Tzeng, C. M. Che, S. M. Peng, *J. Chem. Soc. Dalton Trans.* **1996**, 1769–1770; c) B. C. Tzeng, W. C. Lo, C. M. Che, S. M. Peng, *Chem. Commun.* **1996**, 181–182; d) H. Xiao, K. K. Cheung, C. M. Che, *J. Chem. Soc. Dalton Trans.* **1996**, 3699–3703; e) H. Xiao, Y. X. Weng, W. T. Wong, T. C. W. Mak, C. M. Che, *J. Chem. Soc. Dalton Trans.* **1997**, 221–226; f) B. C. Tzeng, C. K. Chan, K. K. Cheung, C. M. Che, S. M. Peng, *Chem. Commun.* **1997**, 135–136; g) B. C. Tzeng, C. M. Che, S. M. Peng, *Chem. Commun.* **1997**, 1171–1172.
- [5] a) J. C. Vickery, M. M. Olmstead, E. Y. Fung, A. L. Balch, *Angew. Chem.* **1997**, *109*, 1227–1229; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1179–1181; b) R. J. Lachicotte, M. A. Mansour, W. B. Connick, H. J. Gysling, R. Eisenberg, *J. Am. Chem. Soc.* **1998**, *120*, 1329–1330.
- [6] a) C. King, M. N. I. Khan, R. J. Staples, J. P. Fackler, Jr., *Inorg. Chem.* **1992**, *31*, 3236–3238; b) Z. Assefa, B. G. McBurnett, R. J. Staples, J. P. Fackler, Jr., *Inorg. Chem.* **1995**, *34*, 4965–4972.
- [7] a) N. Nagasundaram, G. Roper, J. Biscoe, J. W. Chai, H. H. Patterson, N. Blom, A. Ludi, *Inorg. Chem.* **1986**, *25*, 2947–2951; b) Z. Assefa, F. DeStefano, M. A. Garepapaghi, J. H. LaCasce, Jr., S. Ouellette, M. R. Corson, J. K. Nagle, H. H. Patterson, *Inorg. Chem.* **1991**, *30*, 2868–2876.
- [8] a) V. W. W. Yam, T. F. Lai, C. M. Che, *J. Chem. Soc. Dalton Trans.* **1990**, 3747–3752; b) V. W. W. Yam, S. W. K. Choi, *J. Chem. Soc. Dalton Trans.* **1996**, 4227–4232; c) V. W. W. Yam, C. K. Li, C. L. Chan, *Angew. Chem.* **1998**, *110*, 3041–3044; *Angew. Chem. Int. Ed.* **1998**, *37*, 2857–2859.
- [9] a) S. D. Hanna, J. I. Zink, *Inorg. Chem.* **1996**, *35*, 297–302; b) S. D. Hanna, S. I. Khan, J. I. Zink, *Inorg. Chem.* **1996**, *35*, 5813–5819.
- [10] a) A. Vogler, H. Kunkely, *Chem. Phys. Lett.* **1988**, *150*, 135–137; b) H. K. Yip, A. Schier, J. Riede, H. Schmidbaur, *J. Chem. Soc. Dalton Trans.* **1994**, 2333–2334.
- [11] D. F. Feng, S. S. Tang, C. W. Liu, I. J. B. Lin, Y. S. Wen, L. K. Liu, *Organometallics* **1997**, *16*, 901–909.
- [12] a) V. M. Miskowski, S. F. Rice, H. B. Gray, S. J. Milder, *J. Phys. Chem.* **1993**, *97*, 4277–4283; b) S. F. Rice, H. B. Gray, *Inorg. Chem.* **1988**, *27*, 4704–4708; c) S. F. Rice, H. B. Gray, *J. Am. Chem. Soc.* **1983**, *105*, 4571–4575; d) D. M. Roundhill, H. B. Gray, C. M. Che, *Acc. Chem. Res.* **1989**, *22*, 55–61; e) A. E. Stiegman, S. F. Rice, H. B. Gray, V. M. Miskowski, *Inorg. Chem.* **1987**, *26*, 1112–1116.
- [13] H. X. Zhang, C. M. Che, *Chem. Eur. J.*, in press.
- [14] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-116329–116331. 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).
- [15] H. R. C. Jaw, M. M. Savas, R. D. Rogers, W. R. Mason, *Inorg. Chem.* **1989**, *28*, 1028–1037.
- [16] a) P. Pykkö, Y. Zhao, *Angew. Chem.* **1991**, *103*, 622–623; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 604–605; b) J. Kozelka, H. R. Oswald, E. Dubler, *Acta Crystallogr. Sect. C* **1986**, *42*, 1007–1009; c) D. Perrault, M. Drouin, A. Michel, V. M. Miskowski, W. P. Schaefer, P. D. Harvey, *Inorg. Chem.* **1992**, *31*, 695–702.
- [17] K. H. Leung, D. L. Phillips, M. C. Tse, C. M. Che, V. M. Miskowski, *J. Am. Chem. Soc.* **1999**, *121*, 4799–4803.
- [18] T. M. McCleskey, H. B. Gray, *Inorg. Chem.* **1992**, *31*, 1733–1734.

The First Efficient Iodination of Unactivated Aliphatic Hydrocarbons**

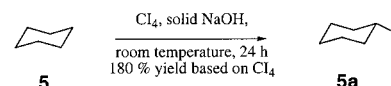
Peter R. Schreiner,* Oliver Lauenstein, Ekaterina D. Butova, and Andrey A. Fokin*

Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday

The selective and efficient manipulation of unreactive C–H bonds in aliphatic hydrocarbons is particularly difficult and is, despite extensive research efforts, one of the major challenges in chemistry.^[1–3] Activation per se is not so much of a problem, as carbenes,^[4] superacids,^[1, 5, 6] and highly reactive free radicals^[7] readily cleave alkane C–H and C–C bonds. However, many of these reactions show low selectivities and often lead to skeletal isomerizations as well as to oligomerizations.^[6] Considerable progress has been made in the selective activation and derivatization of aliphatic hydrocarbons by utilizing enzymatic processes^[7] and electronically unsaturated transition metal complexes.^[8–10] A major drawback of these reactions is their inability to lend themselves to large-scale production which limits their general applicability. We now report on an efficient and synthetically relevant method for the iodination of aliphatic hydrocarbons.^[11]

Radical halogenations probably are the simplest way to functionalize hydrocarbons because they only require a radical chain initiator, light, or higher temperatures.^[2] The direct free-radical halogenation of aliphatic hydrocarbons with iodine, in contrast to the other halogens, is about 20–30 kcal mol^{–1} endothermic and does not allow a chain reaction to occur.^[12–14] To date, there is no preparative method to produce iodoalkanes *directly* from aliphatic compounds.^[12, 13, 15, 16] In our efforts to develop new hydrocarbon activation methods, we recently reported on the bromination of alkanes with CBr₄ under phase-transfer (PT) catalytic conditions by employing alkanes over highly concentrated aqueous solutions of sodium hydroxide.^[17] The mechanistic evidence suggests that these reactions are initiated by reduction of CBr₄,^[18, 19] subsequently leading to the tribromomethyl radical, [•]CBr₃ (identified as a trapping product with a radical scavenger),^[18] which abstracts H[•] from RH to produce bromoform and alkyl radicals R[•]. These react with CBr₄ to afford the desired alkyl bromide and a new [•]CBr₃ radical.

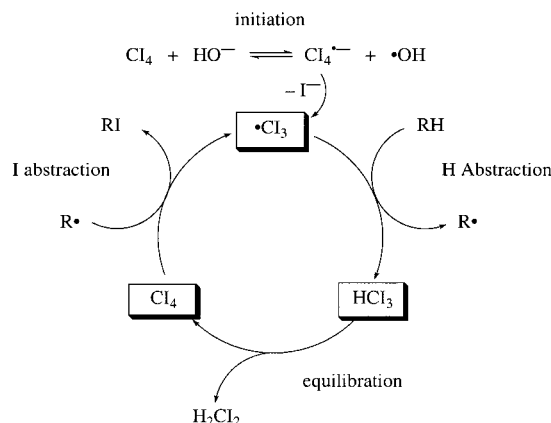
This method is not directly applicable to iodinations because water may hydrolyze Cl₄ and the desired iodoalkanes, which are generally more labile (though the solubilities in water are generally low) than the corresponding alkyl bromides. This also made the use of quaternary ammonium salts as phase-transfer catalysts, which are deactivated in the presence of iodide, unnecessary.^[20] With the resulting new experimental protocol involving a homogeneous liquid over a solid phase, we found that cyclohexane (**5**) could be iodinated cleanly (Scheme 1) in the presence of powdered NaOH in 180 % yield (based on Cl₄ since cyclohexane also serves as the solvent).



Scheme 1. Iodination of cyclohexane (**5**)

The fact that more than one iodine atom is transferred from the initial Cl₄ indicated that this species must be regenerated from iodoform during the reaction, unless the latter were to react directly in a similar fashion with hydrocarbons. Hence, we examined whether Cl₄ is formed by equilibration of iodoform dissolved in CH₂Cl₂ over solid NaOH; similar equilibria are known for other polyhalomethanes.^[21, 22] The identification of Cl₄ is difficult because its ¹³C NMR signal at $\delta = -292$ is strongly broadened.^[23] Both Raman and infrared intensities are very weak due to the high symmetry (*T_d*) and are not distinct from other polyhalomethane absorptions; UV spectroscopy is similarly unsuitable. We eventually succeeded in identifying Cl₄ in the {2 HCl₃ $\rightleftharpoons$ H₂Cl₂ + Cl₄} equilibration in either direction by low-energy electron-impact (EI) mass spectrometry. Diiodomethylene could be clearly identified by NMR spectroscopy in this specific equilibrium and in all iodinations described in the present work.

This finding suggested the use of the more stable and much cheaper iodoform instead of Cl₄ which would then be generated in situ (Scheme 2). In contrast to other haloforms, iodoform reluctantly gives diiodocarbene which may insert into C–H bonds under PT conditions; dihalocarbene side



Scheme 2. Mechanistic hypothesis for the iodination of aliphatic hydrocarbons under basic conditions. The R[•] radical produced in the initiation steps react with Cl₄ to give the desired iodoalkane and the more selective [•]Cl₃ radical which carries the chain further. Equilibration of iodoform regenerates Cl₄.

[*] Dr. P. R. Schreiner, Dipl.-Chem. O. Lauenstein
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: (+49) 551-399475
E-mail: pschrei@gwdg.de

Prof. Dr. A. A. Fokin, Dr. E. D. Butova
Department of Organic Chemistry, Kiev Polytechnic Institute
pr. Pobedy, 37, 252056 Kiev (Ukraine)
Fax: (+38) 044-2742004
E-mail: aaf@xtf.ntu-kpi.ua

[**] This work was supported by the Fonds der Chemische Industrie (Liebig-Fellowship for P.R.S.), the Deutsche Forschungsgemeinschaft (Schr 597/1–1 and Schr 597/3–1), the Volkswagenstiftung, and the Alexander von Humboldt Foundation (Fellowship for A.A.F.). P.R.S. thanks Prof. A. de Meijere for his continuing support.

reactions are negligible under our reaction conditions.^[24] As our working mechanism in Scheme 1 suggests,^[17, 18] the radical chain carrier is the triiodomethyl radical ($\cdot\text{CI}_3$) which is generated in the initial steps of the reaction in low concentrations, preventing polyiodination and other typical radical side reactions.

The iodination protocol is quite generally applicable (Table 1): when treated with iodoform in the presence of solid NaOH, straight chain (**1–3**), cyclic (**4–6**), acyclic branched (**7–9**), and cage (**10** and **11**) alkanes can be transformed into their corresponding alkyl monoiodides. Even the extremely unreactive *n*-alkanes **1–3** can be converted preparatively to their corresponding alkyl iodides; no *n*-alkane derived side products were detected by proton or carbon NMR spectroscopy. In some cases the yields can be improved either at higher temperatures or with longer reaction times if the resulting alkyl iodide is sufficiently stable. The yield increase of 1-iodocycloheptane **6a** to 73% at 105 °C is an illustrative example. Simple filtration of solid NaOH, removal of excess

hydrocarbon and distillation yields the monoiodide in pure form. Hence, the application of this method is quite practical and can be easily conducted on large scale.

Only secondary and tertiary positions are attacked in our halogenation processes. While secondary iodoalkanes are stable (no elimination or other side reactions were detected in preparative mass-balanced reactions; apart from the products only hydrocarbon starting materials were recovered with a mass loss of <5% for the overall reaction), some tertiary products are prone to elimination under the basic reaction conditions. For instance, the branched hydrocarbons **7–9** give no or little tertiary alkyl iodides and low yields of secondary products. Independent experiments show that **5a** is stable under our reaction conditions, while **7a** is not (elimination). Only mixtures of secondary iodides but no tertiary iodide could be detected (NMR spectroscopy) in the reactions of methylcyclohexane. Hence, 1-iodoadamantane could be isolated in high yield simply because it cannot eliminate.

Table 1. The reactions of some aliphatic hydrocarbons with HCl_3 in the presence of solid NaOH. Preparative yields^[a] and isomer ratio (NMR) in parentheses.

Substrate	Cond. ^[b]	<i>T</i> [°C]	<i>t</i> [h]	Products
 1	A ^[c]	25	24	 1a (32)
 2	A	25	24	 2a  2b (76, 4:1)
 3	A	25	24	 3a  3b (83, 1.5:1)
 4	A	25	16	 4a (92)
 5	A	25	24	 5a (75)
 6	A	25	96	 6a (39)
6	A ^[c]	105	36	6a (73)
 7	A ^[c]	25	72	 7a (traces)
 8	A	25	48	 8a (traces)  8b (27)
 9	A	25	48	 9a (traces)  9b (16)
 10	B	25	48	 10a  10b (42, 5:1)
 11	B	25	96	 11a (53) ^[d]  11b (5) ^[d]

[a] Yield relative to HCl_3 used. [b] Procedure A for liquid alkanes at room temperature; procedure B for solutions in CH_2Cl_2 .^[24] [c] Soluble in a pressure vessel. [d] Yield relative to the starting hydrocarbon after purification by column chromatography.

In summary, we have found the first *preparative* method for direct iodination of hydrocarbons. The procedure is simple yet efficient and even normally completely unreactive straight chain alkanes can be iodinated easily. Further developments of this method are likely to find application in the widely used biochemical radioiodination^[25] techniques and in the production of specialty chemicals for the pharmaceutical industry. Elaborate mechanistic studies are well underway in our laboratories.

Experimental Section

Representative preparative procedure for liquid and solid hydrocarbons: a) Iodocyclohexane (**5a**): Powdered NaOH (10.0 g) and iodoform (7.0 g, 17.8 mmol) were added to cyclohexane (100 mL). The solution was stirred for 24 h at room temperature. The organic phase was separated from the solid phase by filtration; vacuum distillation gave pure **5a** (2.8 g, 13.4 mmol, 75% relative to HCl₃). b) 1-Iodoadamantane (**11a**): Solid NaOH (2.4 g) was added to a solution of iodoform (0.79 g, 2.0 mmol), CH₂Cl₂ (20 mL), and substrate (0.27 g, 2.0 mmol). The solution was stirred for 96 h. The organic phase was separated from the solid phase by filtration, and the solid phase was washed with CH₂Cl₂ (3 × 20 mL); volatile components were removed by vacuum distillation. The products were purified by column chromatography (silica gel, petroleum ether, b.p. < 60 °C, *R_f* (**11a**) = 0.48; *R_f* (**11b**) = 0.25) to give 1-iodoadamantane (**11a**) (0.28 g, 1.1 mmol, 53%) and 1,3-diiodoadamantane (**11b**) (0.04 g, 0.1 mmol, 5%). All products were identified by GC, MS, and NMR analysis and were found to be identical to standard samples. Preparative yields are given in Table 1. Complete mass balances were determined for cyclohexane and adamantane.

Received: January 27, 1999 [Z12966IE]
German version: *Angew. Chem.* **1999**, *111*, 2956–2958

Keywords: C–H activation • heterogeneous systems • hydrocarbons • iodination • radicals

- [1] G. A. Olah, A. Molnár, *Hydrocarbon Chemistry*, Wiley, New York, **1995**.
- [2] C. L. Hill, *Activation and Functionalization of Alkanes*, Wiley, New York, **1989**.
- [3] J. A. Davies, P. L. Watson, J. F. Liebman, A. Greenberg, *Selective Hydrocarbon Activation, Principles and Progress*, VCH, Weinheim, **1990**.
- [4] M. Jones, R. A. Moss, *Carbenes*, Wiley, New York, **1973**.
- [5] G. A. Olah, O. Farooq, G. K. S. Prakash, *Activation and Functionalization of Alkanes*, Wiley, New York, **1989**.
- [6] J. Sommer, J. Bukala, *Acc. Chem. Res.* **1993**, *26*, 370–376.
- [7] P. A. Frey, *Chem. Rev.* **1990**, *90*, 1343–1357.
- [8] R. H. Crabtree, *Chem. Rev.* **1995**, *95*, 987–1007.
- [9] B. A. Arndtsen, R. G. Bergman, *Science* **1995**, *270*, 1970–1973.
- [10] S. E. Bromberg, W. Yang, M. C. Asplund, T. Lian, B. K. McNamara, K. T. Kotz, J. S. Yeston, M. Wilkens, H. Frei, R. G. Bergman, C. B. Harris, *Science* **1997**, *278*, 260–263.
- [11] P. R. Schreiner, A. A. Fokin, O. Lauenstein, E. D. Butova, patent pending.
- [12] L. Liguori, H.-R. Bjørsvik, A. Bravo, R. Fontana, F. Minisci, *Chem. Commun.* **1997**, 1501–1502.
- [13] D. D. Tanner, G. C. Gidley, *J. Am. Chem. Soc.* **1968**, *90*, 808–809.
- [14] D. D. Tanner, J. R. Rowe, A. Potter, *J. Org. Chem.* **1986**, *51*, 457–460.
- [15] G. A. Olah, Q. Wang, G. Sandford, G. K. S. Prakash, *J. Org. Chem.* **1993**, *58*, 3194–3195.
- [16] “Formation of carbon-halogen bonds (Cl, Br, I)”: Y. Sasson in *The Chemistry of functional groups, Supplement D2* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1995**, pp. 535–628.
- [17] P. R. Schreiner, O. Lauenstein, I. V. Kolomitsyn, S. Nadi, A. A. Fokin, *Angew. Chem.* **1998**, *110*, 1993–1995; *Angew. Chem. Int. Ed.* **1998**, *37*,

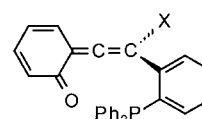
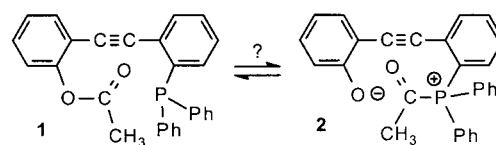
1895–1897; see also: *Nachr. Chem. Tech. Lab.* **1998**, *46*, 706; *Chem. Eng. News* **1998**, *76*(28), 55.

- [18] P. R. Schreiner, O. Lauenstein, A. A. Fokin, unpublished results.
- [19] D. T. Sawyer, J. L. Roberts, *Acc. Chem. Res.* **1988**, *21*, 469–476.
- [20] R. Mathias, P. Weyerstahl, *Angew. Chem.* **1974**, *86*, 42–44; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 132–133.
- [21] E. V. Dehmlow, M. Lissel, *Chem. Ber.* **1978**, *111*, 3873–3878.
- [22] J. A. Orvik, *J. Org. Chem.* **1996**, *61*, 4933–4936.
- [23] E. Breitmaier, W. Voelter, *Carbon-13 NMR Spectroscopy*, VCH, Weinheim, **1990**.
- [24] E. V. Dehmlow, S. S. Dehmlow, *Phase-Transfer Catalysis*, VCH, Weinheim, **1993**.
- [25] R. H. Seevers, R. E. Counsell, *Chem. Rev.* **1982**, *82*, 575–590.

Unusual Oxaphosphoranes by Acyl Transfer from *o*-Acetoxy-*o*'-diphenylphosphanyltolane**

Edwin Vedejs* and Peter L. Steck

As part of a study on phosphane-catalyzed acylations,^[1] we were interested in the chemistry of the *o*,*o*'-disubstituted tolane **1**. The linear acetylene linker provides for close proximity between the phosphorus atom and the carbonyl group,^[2] perhaps sufficient to promote bonding interactions



3a, X = C(O)CH₃

3b, X = H

that would lead to the P-acyl derivative **2** by intramolecular acyl transfer. In its zwitterionic resonance form, **2** is formally analogous to the *P*-acylphosphonium carboxylate ion pair that is the reactive intermediate in the acylation of phosphanes with anhydrides.^[1a] If **1** is capable of O to P acyl transfer, then **2** might function as an acyl donor towards external nucleophiles and could also serve as a geometrically restricted mechanistic analogue of *P*-acylphosphonium car-

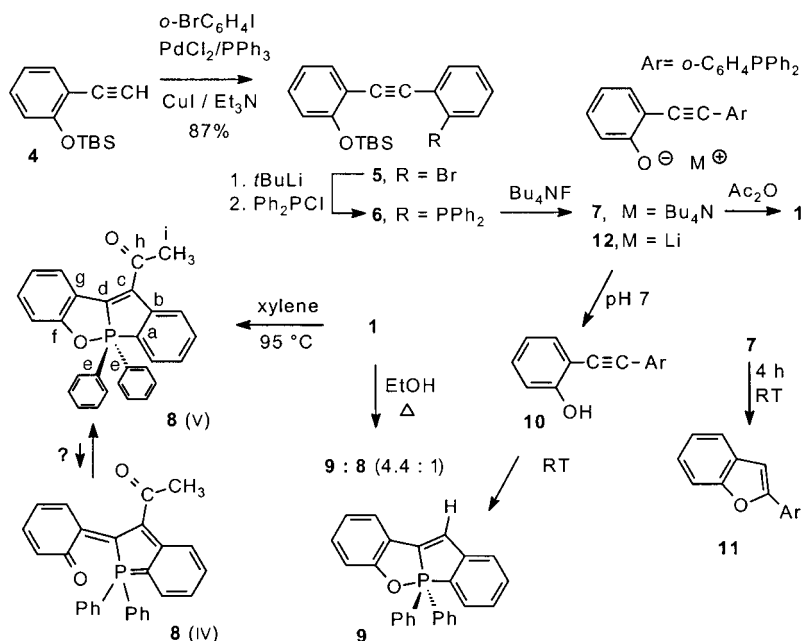
[*] Prof. E. Vedejs,^[+] P. L. Steck
Chemistry Department, University of Wisconsin
Madison, WI 53706

[+] Current address:
Department of Chemistry, University of Michigan
Ann Arbor, MI 48109
Fax: (+1) 734-615-1628
E-mail: edved@umich.edu

[**] This work was supported by the National Science Foundation and by the German-American Fulbright Commission, Bonn (fellowship to P.S.). The authors also thank Dr. D. R. Powell for determining the X-ray structures of **8**, **9**, and **11**.

boxylate intermediates. Alternatively, **2** might undergo internal acylation to generate the reactive intermediate **3a**. These possibilities stimulated the attempt to prepare **1** and to study its reactivity.

Conventional Sonogashira coupling^[3] of **4** with *o*-BrC₆H₄I gave **5**, and lithiation followed by treatment with Ph₂PCl afforded **6** in 70 % overall yield (Scheme 1). Initial attempts to deprotect **6** with Bu₄NF encountered unexpected complications, but using Bu₄NF in the presence of Ac₂O produced **1** in



Scheme 1. Synthesis and transformation of **1**. TBS = *t*BuMe₂Si.

94 % yield as a colorless, crystalline substance. However, **1** proved to have unusual properties. Upon storage in CDCl₃ or C₆D₆, **1** slowly developed a striking orange color. The color change was more dramatic at 95 °C in xylene, and conversion was complete after 4 h. The transformation was also observed on heating solid **1** above 100 °C in a melting-point apparatus. In all of these procedures, the same intensely colored product was formed, and isolation afforded red crystals. According to X-ray crystallography, the red substance is the phosphorane **8(V)** with an unusual bicyclic structure.^[4]

The exploration of acyl-transfer reactions was restricted by the thermal rearrangement of **1** to **8**, but there was a further complication. Heating **1** in absolute ethanol mainly led to deacylation, as anticipated if **2** were generated as an intermediate, and an orange-red color was observed. Formation of **8** as a by-product (ca. 20–25 %) was confirmed, but the ethanolysis experiment produced a second intensely colored product **9** that resembled **8** in several respects, including stability (both **8** and **9** are stable to air, water, and chromatography) and spectroscopic data.^[5] The appearance of a distinct new down-field signal for a vinylic hydrogen atom at $\delta = 7.92$ ($^3J_{\text{PH}} = 52.8$ Hz) suggested a deacylated benzo-phosphole subunit, and this was confirmed by X-ray crystallography. The P–O bonds of **9** (1.95 Å) and **8** (1.90 Å) are somewhat long compared to those of typical phosphoranes

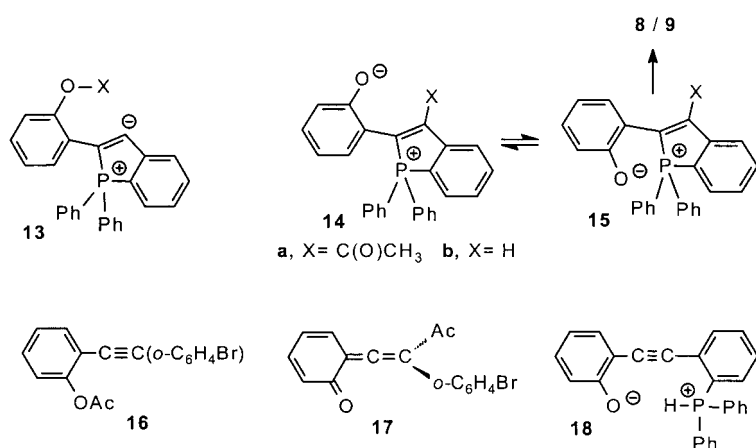
(1.75–1.85 Å),^[6] although shorter than in “bonding betaine”^[7] or analogous dipolar structures.^[4] Reported examples of the latter species have extensive delocalization and distinct visible chromophores, as do **8** and **9**. Therefore, the ¹³C NMR spectra were studied in detail to better define the solution structures.

Extensive heteronuclear multiple quantum coherence (HMQC) experiments allowed the assignment of the quaternary carbon atoms directly bound to phosphorus in **8** and **9**. If the structures in solution have substantial contributions from

tautomers containing tetravalent phosphorus, such as **8(IV)**, then all of the ¹J_{PC} values should be similar. On the other hand, pentacovalent **8(V)** should have characteristically large differences in ¹J_{PC} for the endocyclic aryl carbon atom C_a (apical) and the exocyclic aryl carbons C_e (equatorial). The latter situation was confirmed for both **8** and **9**: C_a of **8**: ¹J_{PC} = 29.2 Hz; C_a of **9**: ¹J_{PC} = 32.2 Hz; C_e of **8**: ¹J_{PC} = 141.1 Hz; C_e of **9**: ¹J_{PC} = 141.1 Hz. Furthermore, the endocyclic phosphole carbon atom C_d has a ¹J_{PC} value of 124 Hz in both **8** and **9**. This large coupling constant is expected for equatorial C–P bonds at trigonal-bipyramidal phosphorus atoms.^[8] The NMR data provide no clear evidence of tetravalent structures in solution, although a small contribution by **8(IV)** would help explain the red color.

Further investigations focused on the role of transient intermediates in the unusual rearrangements of **1**. The early experiments to deprotect **6** with Bu₄NF were repeated with greater care taken to intercept the phenol **10**. However, a variety of protic quenching agents gave only the red product **9** and/or a colorless isomer **11** (see Scheme 1; ³¹P NMR: $\delta = -9.32$; structure by X-ray crystallography).^[9] The latter was the sole product if the reaction mixture of **6** with Bu₄NF was allowed to stand for 4 h at room temperature before quenching, as expected from a literature precedent.^[2c] However, quenching with NH₄Cl after two minutes gave **9** as the only detectable product. The initially formed tetrabutylammonium phenoxide **7** was observed prior to quenching (³¹P NMR: $\delta = -8.02$, C₆D₆), but **10** could not be isolated without cyclization to **9**. A similar result was obtained after treatment of **1** with MeLi at –78 °C followed by workup with KH₂PO₄/Na₂HPO₄ buffer at pH 7. In this case a transient ³¹P NMR signal was observed ($\delta = -9.62$, THF) that may correspond to the elusive **10**, but removal of the solvent gave only **9**.

We found little precedent to explain the formation of **8** or **9**. However, there is a proposal that a phosphorus center may add to an adjacent triple bond to generate a dipolar intermediate.^[10] The analogous process for **1** might lead to **13a**, and subsequent acyl transfer to give **14a**, interconversion with the rotamer **15a**, and P–O bond formation would account for the thermal rearrangement of **1** to **8**. This could be a plausible mechanism in xylene, but we are skeptical that acyl transfer from **13a** to **14a** could compete with protonation of **13a** when the reaction is performed in absolute ethanol. The latter experiment gave **8** and **9** in a 1:4.4 ratio, a result that calls for a different explanation.



One possibility would be to invoke an unusual internal acyl transfer from **1** to directly give **3a**, followed by a precedented $[2n+4\pi]$ cyclization to give **8** (Scheme 1).^[11] The first step of this mechanism is suspect because it requires a linear sp²-hybridized carbon atom in a six-center transition state and produces a new C–C bond in **3a** that is orthogonal to the original π system, geometrical features that would disfavor a concerted process. Furthermore, control experiments with the model compound **16** revealed no sign of any reaction at 95 °C in xylene. If **17** had been generated, surely the highly reactive *ortho*-quinone methide subunit would have encountered opportunities for self-destruction. This experiment indicates that phosphorus plays a key role in the rate-determining step. One possibility is acyl transfer concerted with C–P bond formation in **1** to directly give **14**, but we prefer the alternative path via *P*-acylphosphonium salt **2**. Subsequent P-to-C acyl transfer should provide a low-energy pathway to **3a** and internal $[2+4]$ addition would then give **8(V)**.^[11]

Similar mechanistic possibilities can be considered for the rapid conversion of phenol **10** to **9** at room temperature via the quinone methide intermediate **3b**. However, concerted cyclization of **10** to give **14b** becomes increasingly plausible, because a similar concerted proton transfer/nucleophilic attack mechanism has been established by Letsinger et al. for the transformation of diphenylacetylene-*o,o'*-dicarboxylic acid into a substituted pyrone.^[2b] The phenolic proton in **10** is clearly important for the exceptional reactivity, and so is the phosphorus atom.^[12] In the corresponding acetate **1**, the carbonyl group is the best available electrophile, and the rearrangement is much slower. We cannot formally distinguish between mechanistic options that proceed directly from **10** to **14** versus the alternatives based on **3b** or **18**, nor can we rule out eight-membered ring phosphorane intermediates derived from **18** by P–O bond formation.^[13]

Received: January 4,

Revised version: June 10, 1999 [Z12862IE]

German version: *Angew. Chem.* **1999**, *111*, 2958–2961

Keywords: acylations • alkynes • phosphorus heterocycles • rearrangements • zwitterionic states

- [1] a) E. Vedejs, S. T. Diver, *J. Am. Chem. Soc.* **1993**, *115*, 3358–3359; b) E. Vedejs, O. Daugulis, S. T. Diver, *J. Org. Chem.* **1996**, *61*, 430–431.
- [2] a) R. L. Letsinger, J. R. Nazy, *J. Am. Chem. Soc.* **1959**, *81*, 3013–3017; b) R. L. Letsinger, E. N. Oftedahl, J. R. Nazy, *J. Am. Chem. Soc.* **1965**, *87*, 742–749; c) F. Vögtle, H. Schaefer, C. Ohm, *Chem. Ber.* **1984**, *117*, 955–958; d) K. L. Evans, P. Prince, E. T. Huang, K. R. Boss, R. D. Gandour, *Tetrahedron Lett.* **1990**, *31*, 6753–6756; e) D. S. Kemp, Z. Q. Li, *Tetrahedron Lett.* **1995**, *36*, 4175–4178; f) O. Saied, M. Simard, J. D. Wuest, *Organometallics* **1996**, *15*, 2345–2349.
- [3] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470; b) R. D. Stephens, E. C. Castro, *J. Org. Chem.* **1963**, *28*, 3313–3320.
- [4] a) We could find no prior example containing the 1-phospha-2-oxabicyclo[3.3.0]octa-3,5,7-triene subunit; for a dihydro analogue, see J. Silberzahn, H. Pritzkow, H. P. Latscha, *Z. Naturforsch. B* **1991**, *46*, 197–201; b) for related dipolar structures, see B. Merk, M. Fath, H. Pritzkow, H. P. Latscha, *Z. Naturforsch. B* **1997**, *52*, 1–8.
- [5] **8**: Red prisms from methanol, m.p. 247 °C; UV/Vis: λ_{max} = 430 nm, ϵ = 7500; HR-MS calcd for C₂₆H₂₁O₂P [M⁺]: 420.12790; found: 420.1271; elemental analysis calcd for C₂₆H₂₁O₂P: C 79.98, H 5.04; found: C 79.77, H 5.20; ¹H NMR (250 MHz, CDCl₃): δ = 7.75–7.65 (4H, m), 7.41–6.96 (12H, m), 6.73–6.64 (2H, m), 2.75 (3H, s); partial ¹³C NMR (75 MHz, CDCl₃): δ = 205.0 (²J_{PC} = 22.9 Hz, C₆), 159.5 (²J_{PC} = 1.9 Hz, C₇), 146.6 (²J_{PC} = 16.5 Hz, C₈), 146.0 (¹J_{PC} = 29.2 Hz, C₉), 136.4 (²J_{PC} = 24.8 Hz, C₆), 133.7 (¹J_{PC} = 141.8 Hz, C₉), 125.3 (¹J_{PC} = 124.0 Hz, C₄), 117.8 (²J_{PC} = 23.5 Hz, C₈), 31.0 (C₁); ³¹P NMR (121 MHz, CDCl₃): δ = –41.4. **9**: Red prisms from methanol, m.p. 239 °C; UV/Vis: λ_{max} = 422.0 nm, ϵ = 9670; HR-MS calcd for C₂₆H₁₉OP [M⁺]: 378.11740; found: 378.1184; elemental analysis calcd for C₂₆H₁₉OP: C 82.52, H 5.07, P 8.18; found: C 82.22, H 5.30, P 8.02; ¹H NMR (300 MHz, CDCl₃): δ = 7.92 (1H, dd, ³J_{PH} = 52.8, *J* = 0.7 Hz), 7.74–7.66 (5H, m), 7.40–7.27 (7H, m), 7.22 (1H, tt, *J* = 7.5, 1.1 Hz), 7.16–7.11 (1H, m), 7.09–7.02 (1H, m), 7.00–6.98 (1H, m), 6.71 (1H, tt, *J* = 7.5, 1.5 Hz), 6.63 (1H, d, *J* = 7.9 Hz); partial ¹³C NMR (75 MHz, CDCl₃): δ = 159.4 (²J_{PC} = 1.9 Hz, C₇), 146.5 (²J_{PC} = 31.2 Hz, C₈), 139.3 (¹J_{PC} = 26.1 Hz, C₉), 134.3 (²J_{PC} = 17.2 Hz, C₈), 133.3 (¹J_{PC} = 141.1 Hz, C₉), 129.2 (¹J_{PC} = 124.0 Hz, C₄), 119.6 (²J_{PC} = 23.5 Hz, C₈); ³¹P NMR (121 MHz, CDCl₃): δ = –39.8. Oxaphosphorane **9** was stable under neutral conditions in aqueous solution, but exposure to HCl/H₂O resulted in rapid formation of a yellow phosphonium salt corresponding to O-protonation of **14** (UV/Vis: λ_{max} = 393 nm, ϵ = 4870; ³¹P NMR (121 MHz, CD₃OD): δ = 33.7). Treating the salt with Et₃N/CDCl₃ regenerated red **9**.
- [6] a) W. C. Hamilton, S. J. LaPlaca, F. Ramirez, C. P. Smith, *J. Am. Chem. Soc.* **1967**, *89*, 2268–2272; b) R. D. Spratley, W. C. Hamilton, J. Ladell, *J. Am. Chem. Soc.* **1967**, *89*, 2272–2278; c) R. Francke, W. S. Sheldrick, G. V. Roeschenthaler, *Chem. Ber.* **1989**, *122*, 301–306; d) H. J. Bestmann, C. Riemer, R. Doetzer, *Chem. Ber.* **1992**, *125*, 225–229.
- [7] I. Kawamoto, T. Hata, Y. Kishida, C. Tamura, *Tetrahedron Lett.* **1972**, *13*, 1611–1614.
- [8] a) H. Schmidbaur, P. Holl, *Chem. Ber.* **1979**, *112*, 501–509; G. Buono, J. R. Llinas, *J. Am. Chem. Soc.* **1981**, *103*, 4532–4540; b) S. Kay, S. Trippett, *J. Chem. Res. S* **1986**, 62–63; c) E. Vedejs, C. F. Marth, *J. Am. Chem. Soc.* **1989**, *111*, 1519–1520; d) F. Bangerter, M. Karpf, L. A. Meier, P. Rys, P. Skrabal, *J. Am. Chem. Soc.* **1998**, *120*, 10653–10659.
- [9] 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-112758 (**8**), -112759 (**9**), and -112760 (**11**). 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).
- [10] T. Butters, I. Haller-Pauls, W. Winter, *Chem. Ber.* **1982**, *115*, 578–592.
- [11] a) F. Ramirez, *Acc. Chem. Res.* **1968**, *1*, 168–174; N. K. DeVries, H. M. Buck, *Phosphorus Sulfur* **1987**, *31*, 267–279; b) A. A. El-Kateb, L. S. Boulos, H. A. Abdel-Malek, *Phosphorus Sulfur Relat. Elem.* **1993**, *83*, 105–110.

- [12] The C protonation and C–P bond formation in **10** is complete within 2 min in the presence of NH_4Cl . If the phenol is protected, as in **6**, then no reaction occurs upon treatment with $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$ at room temperature (30 min). An *o,o'*-dihydroxy analogue of **10** is quite stable.^[2c] Hence, the nucleophilicity of the phosphanyl group and the proton-donor capability of the phenol are important for the high reactivity of **10**.
- [13] Rearrangement of an alkyloxyphosphorane to a benzophosphole is structurally related to the title reaction: H. J. Bestmann, K. Roth, R. W. Saalfrank, *Angew. Chem.* **1977**, 89, 915; *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 877; we thank a referee for this reference.

Detection of Reaction Selectivity on Catalyst Libraries by Spatially Resolved Mass Spectrometry**

Matthias Orschel, Jens Klein, Hans-Werner Schmidt, and Wilhelm F. Maier*

While combinatorial chemistry has established its importance for drug development,^[1–3] combinatorial methods are just starting to be applied increasingly in the field of materials research and catalyst development.^[4–6, 16] In analogy to the development of new drugs, the major problems are not centered on the synthesis of new libraries—25 000 different components on a few square centimeters have already been realized^[4]—but on the reliable, fast, and spatially resolved detection of the desired properties of the library components.^[7, 8]

For the combinatorial development of new catalyst materials, the catalytic activity and selectivity of the library components have to be determined quickly and reliably. Very few examples for the determination of reactivity behavior of the components of combinatorial libraries have been reported. A very sensitive and fast method for investigating catalytic activity is emissivity-corrected IR thermography,^[9] which allows the reliable and spatially resolved detection of the heat change on heterogeneous catalysts in gas-phase reactions^[9] as well as the heat change of homogeneously catalyzed reactions in the liquid phase.^[10] Although the relative activity of catalysts is easily determined by such thermographic methods, no information on catalytic selectivity is obtained. A mass spectrometer specially developed for high-throughput screening in combinatorial catalyst development has been applied by Weinberg et al. to catalyst libraries generated in situ by evaporation techniques.^[11, 12] Disadvantages of such a solution are its high cost and that it is not accessible to general synthetic or academic laboratories. Although mass spectrometry should be able to identify reaction selectivities, only catalytic activities have been reported. The identification of

selectivity differences of heterogeneous catalysts on libraries by spatially resolved mass spectrometry has not yet been demonstrated.

The aim of our study was the detection of selectivity changes on the different components of a catalyst library in the product distribution of a gas-phase reaction by spatially resolved mass spectrometry. The components used for this task were a commercially available gas analyzer and a synthesis robot. The basic idea was to exchange the pipetting unit of the robot for the capillary of the inlet system of a conventional gas analyzer. This combination allows use of the spatial library information of the synthesis robot for the product analysis. To allow the investigation of general gas-phase reactions the MS capillary had to be combined with another capillary providing the feed gas (capillary bundle).

In Figure 1 the experimental setup is shown schematically. The pipetting unit of the commercial robot (spatial resolution in *x,y,z* direction 0.1 mm) was exchanged for the capillary

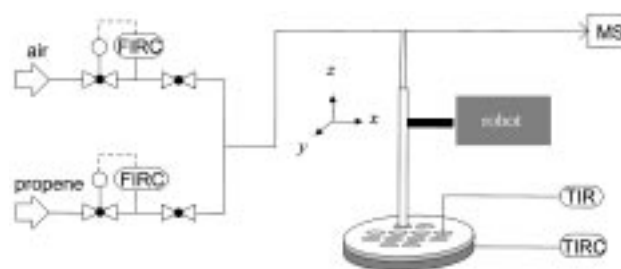


Figure 1. Schematic representation of the setup for spatially resolved mass spectrometry on a catalyst library with control of the capillary bundle with a pipetting robot. FIRC = mass-flow controller, TIR = temperature indicator, TIRC = temperature controller.

bundle (Figure 2). The capillary bundle (length 15 cm) consists of an outer steel capillary (outer diameter 2.0 mm, inner diameter 1.5), two inner steel capillaries (outer diameter

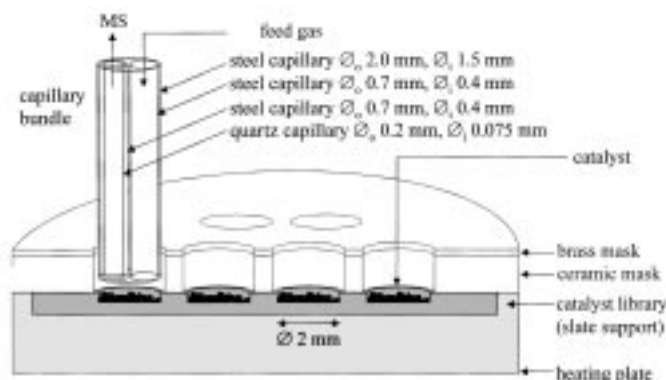


Figure 2. Schematic representation of the positioning of the capillary bundle in the library compartments. Ø_o = outer diameter, Ø_i = inner diameter.

0.7 mm, inner diameter 0.4 mm), and the MS capillary (quartz capillary, outer diameter 0.2 mm). One of the inner capillaries is used for feed gas supply, and the other one is principally available for other uses, depending on the reaction conditions. In the present case the second inner steel capillary simply

[*] Prof. Dr. W. F. Maier, M. Orschel, J. Klein, H.-W. Schmidt
Max-Planck-Institut für Kohlenforschung
45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2987
E-mail: maier@mpi-muelheim.mpd.de

[**] W.F.M. thanks the Fonds der Chemischen Industrie for continuous support.

hosts the MS capillary. A simple gas analyzer (Pfeiffer/Balzars) controlled by the Quadstar software was used as mass spectrometer; it continuously analyzes product gas sampled through the 2 m long quartz capillary (inner diameter 75 μm).

Figure 2 shows the schematic setup of the detection system in connection with the catalyst library. Unusual is the open construction, where the feed gas flow is directed onto the surface of the library component and the mass spectrometer thus samples and analyzes a mixture of feed gas and products. The excess of this mixture, which effectively displaces the air above the library component, leaves through the space between the capillary bundle and the drill hole wall of the ceramic mask. The library is heated directly from below with an electric heating plate. The temperature is controlled through thermocouples in the heating plate and a hole directly in the library. Radiative losses above the library are reduced by an additional ceramic mask placed on top of the library. Its hole pattern (hole diameter 2.4 mm) matches that of the library, thus enlarging the "reactor volume" above the catalyst components. This allows the capillary bundle to sink more deeply into each library compartment, thus shielding the reactants more effectively from the laboratory air. On top of the ceramic mask an additional brass plate mask is positioned. Its conical holes, which match that of the ceramic mask, help to guide the capillary bundle into the library compartments. The capillary bundle is positioned in the compartment so that it touches the outer surface of the library, which ensures a uniform distance of 2 mm from the end of the capillary bundle to the compartment bottom. With this setup the library has been transformed into an array of extremely simple microreactors. It should be emphasized that the present activities in the field of microreactors are not only of general interest as a new reactor technology,^[13] but may very well become relevant for future aspects of combinatorial catalyst research.

The precise dosage of the reactants is achieved by an electronic mass flow controller, allowing precise feed flow adjustments ($> 100 \mu\text{L min}^{-1}$). The feed gases can be mixed before entering the capillary bundle or, by feeding through separate capillaries, directly above the component in the library compartment. With this construction the feed gas only reaches the component investigated and is isolated from the rest of the library. The feed gases are supplied to the capillary bundle through a flexible polymer tube (inner diameter 2 mm) that does not hinder the movement of the robot. Product compositions can be monitored continuously through the MS capillary. The library can be investigated sequentially or by following well-defined components of interest. In this investigation product composition was monitored by mass spectrometry for 15 to 180 s following a sequential pattern under isothermal conditions as well as with a change in temperature for selected library components. Data acquisition and storage was achieved by the controlling computer with commercial software.

To demonstrate the performance of this setup, the selective oxidation of propene with air was selected as a model reaction of technical interest. Besides CO_2 , the undesired product of total oxidation, the following oxidation products are selectively formed: acrolein, 1,5-hexadiene, benzene, allyl alcohol, and propylene oxide. The selectivities for propene oxidation of several AMM-type catalysts (AMM = amorphous microporous mixed oxide), observed by Orzesek et al. in the gas phase at normal pressure in a conventional gas-phase flow reactor, were used as a reference.^[14] For the screening study a sol-gel catalyst library was prepared on a slate substrate, as summarized in Table 1. The slate plate contained component

Table 1. AMM catalyst library.

	1	2	3	4	5	6
1	Sc_2Si	Y_2Si	V_2Si	Ta_2Si	Cr_2Si	Fe_2Si
2	Co_2Si	Rh_2Si	Ni_2Si	Cu_6Si	Ag_2Si	Au_2Si
3	In_2Si	Si	Sn_2Si	Bi_{10}Si	Te_2Si	W_2Si
4	W_2Zr	Mo_2Ti	Mo_2Zr	Sb_2Ti	Sb_2Zr	Cu_2Ti
5	Cu_2Zr	In_2Ti	In_2Zr	Re_2Ti	Re_2Zr	Cr_2Ti
6	Cr_2Zr	Fe_2Ti	Fe_2Zr			

holes of 2 mm diameter and 2 mm depth, similar to the library described earlier.^[5] The holes were filled with 2 mg each of the AMM catalysts. A matrix of 33 catalysts was selected for the experiment. The molar catalyst compositions are given in Table 1. At a total feed flow of 7 mL min^{-1} a propene/air composition of 0.4 was continuously dosed through the capillary bundle. Because of the low flow rate of the feed gases and the low total feed gas volume, there was no special safety concern, and the experiments could be conducted in the laboratory air.

In Figure 3 the mass spectra (after correction by subtraction of the mass spectrum of the feed gas) obtained for the Cu-containing catalyst AMM- Cu_6Si are shown as a function of the reaction temperature. The temperature axis is not linear

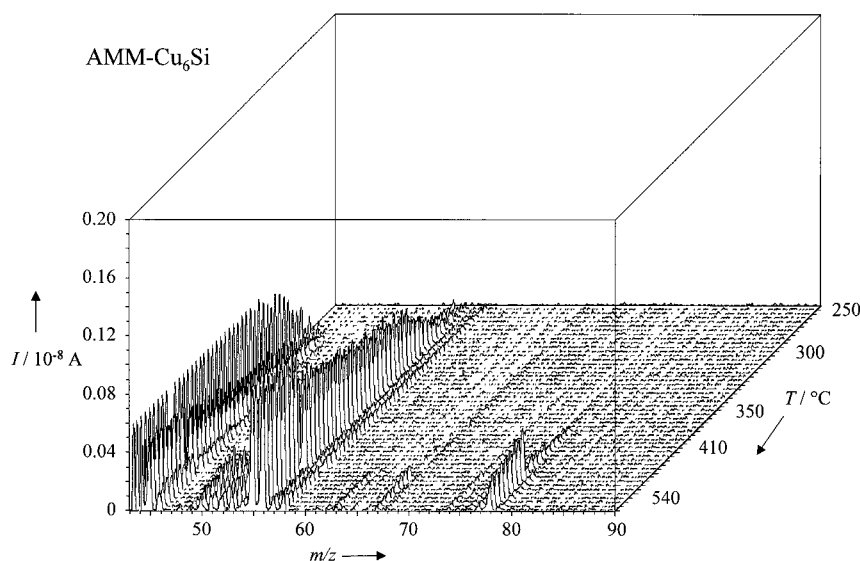


Figure 3. Change in the mass spectra with increasing temperature for a library compartment containing the AMM- Cu_6Si catalyst. Clearly visible is the increase in intensity I for mass peaks $m/z = 55$ and 56 , typical for acrolein.

since a constant heating rate was not chosen. The reaction was carried out by decreasing the temperature from 550 to 250 °C in 15 min. Selective oxidation of propene starts around 255 °C.

At low conversion below 300 °C exclusive formation of acrolein ($m/z = 55, 56$) is observed. Total oxidation, identified by production of CO_2 ($m/z = 44$), starts at 300 °C and remains a minor side reaction. Around 400 °C the beginning of benzene formation ($m/z = 78$) can be recognized. At 550 °C, in addition to the products observed at lower temperatures, 1,5-hexadiene ($m/z = 67$) appears. In further experiments the catalytic response of the catalyst with time was studied at 500 °C. It was found that the relatively high initial activity for the formation of acrolein dropped within 4 min to about 40 % and remained constant for another 4 min. Re-activation of the catalyst with air resulted in an increase to about 80 % of the initial activity, which again dropped to about 40 % after 4 min. Apparently the observation of activity changes with time or regeneration phenomena can be studied readily on selected components.

The spectra obtained for the In-containing catalyst AMM-In₃Si under identical conditions, but with an increase in temperature from 380 to 550 °C (the library was heated at the maximum rate, total time 8 min), shows a significantly different reaction behavior (Figure 4). Product formation starts only at 380 °C with total oxidation (CO_2) as the dominant reaction accompanied by production of acrolein. At 420 °C traces of 1,5-hexadiene and benzene appear (the peaks at $m/z = 50-55$ are fragmentation peaks of these two products). Relative to the Cu-containing catalyst, 1,5-hexadiene formation is significantly increased. These results confirm the data obtained previously with the same catalysts in a conventional gas-phase flow reactor.^[14, 15] The unusual selective formation of 1,5-hexadiene on the In-containing catalyst under conventional reaction conditions has also been described in more detail.^[15]

These studies of individual component behavior in a catalytic reaction also demonstrate that component performance can readily be studied over an increased time interval or a wider temperature range, an option of potential importance for the investigation of induction, regeneration, or deactivation phenomena. Nevertheless, such time-consuming experiments should be carried out under conventional reaction conditions, since more detailed studies are required to judge the feasibility of combinatorial screening studies aimed at such phenomena.

In the third experiment shown here the catalytic performance of the library components was studied sequentially at 500 °C in one-minute intervals. The total time required for all catalysts studied was therefore only 33 minutes. Although due to the high reaction temperature the spectra are dominated by the peak at $m/z = 44$ for the product of total oxidation (CO_2), the selectivities observed at the higher mass range perfectly

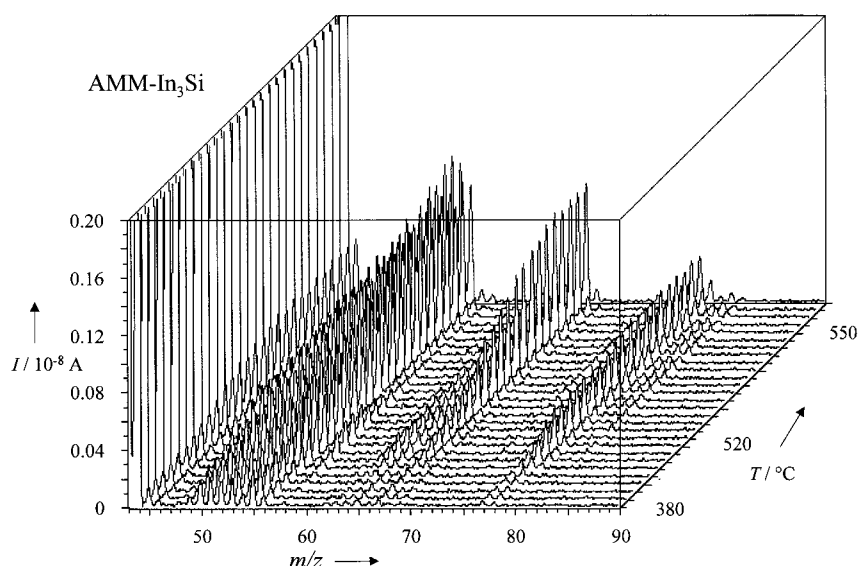


Figure 4. Change in the mass spectra with increasing temperature for a library compartment containing the AMM-In₃Si catalyst. Clearly visible is the increase in intensity I for mass peak $m/z = 67$, typical for 1,5-hexadiene.

reproduce those identified earlier under conventional reaction conditions.^[14] The spectra displayed in Figure 5 document the different catalytic selectivities. For comparison the product composition of the propene oxidation on pure microporous silicon dioxide is also shown. Besides AMM-Cu₆Si (Figure 3) and AMM-Cr₂Si, the AMM-Te₂Si catalyst shows the highest selectivity for acrolein formation. While such a selectivity is well known for Cu- and Cr-containing catalysts, it had not been observed for Te-containing silica. In

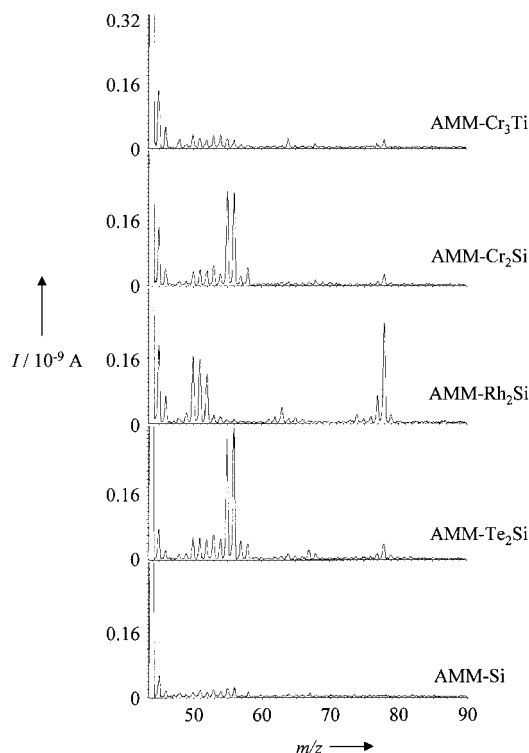


Figure 5. Mass spectra for the reaction of propene with air obtained automatically on selected library components at 500 °C. The different catalytic selectivity is documented.

contrast to the silica-based AMM-Cr₂Si, the titania-based AMM-Cr₂Ti shows no significant selectivity for formation of acrolein or another product at this temperature, indicating a strong matrix effect on the catalyst activity and selectivity of the active site element Cr. In contrast to the other catalysts, the Rh-containing AMM-Rh₂Si shows a high selectivity for benzene formation from propene, indicative of an oxidative dehydrocyclization.

It has been shown here for the first time that significantly different selectivities of the components on catalyst libraries can be automatically detected by spatially resolved mass spectrometry. Advantages of the setup shown are the relatively low cost owing to the use of a commercial quadrupole-based gas analyzer, a commercial pipetting robot to control spatial resolution and analysis time, and the direct analysis of catalytic performance on the library without the need for a special reactor. This combination also allows reuse of the spatial information of the synthesis program as an integral part the screening procedure. Prerequisite for the use of such high-throughput screening procedures are the absence of induction periods of the catalysis studied. New catalysts requiring time-consuming activations cannot be discovered by such fast methods. However, this may not necessarily be a disadvantage since catalysts without an induction period are also of interest.

A disadvantage of the protocol presented here is its limitation to normal pressure. The fact that the complete library can be heated to the reaction temperature may be an advantage in oxidation reactions (regeneration of all components not under investigation), but a disadvantage for reduction reactions, where catalysts may have to be reduced to be active for hydrogenation reactions. Simple hydrogenation reactions, however, have already been conducted in our setup without problem. Presumably the small total amount of catalyst is reduced rapidly with the hydrogen-containing feed gas.

This investigation also opens the door for further developments of combinatorial methods in catalyst development. Especially the direct combination of IR thermography with spatially resolved mass spectrometry seems attractive, since on large libraries with several hundred or thousand components only active components can be selected for mass spectrometric identification of selectivity. Furthermore, the setup used can be readily modified, and by variation of the capillaries attached to the capillary bundle in the robot a large number of analytical techniques such as GC, GC-MS, IR, UV/VIS, and Raman spectroscopy, and capillary electrophoresis can be applied to libraries in a spatially resolved manner.

Received: April 26, 1999

Revised version: July 5, 1999 [Z.13311 IE]

German version: *Angew. Chem.* **1999**, *111*, 2961–2965

Keywords: combinatorial chemistry • heterogeneous catalysis • mass spectrometry • microreactors • oxidations

[1] Special issue "Combinatorial Chemistry": *Acc. Chem. Res.* **1996**, *29*.

[2] G. Lowe, *Chem. Soc. Rev.* **1995**, *24*, 309.

[3] S. R. Wilson, A. W. Czarnik, *Combinatorial Chemistry – Synthesis and Application*, Wiley, **1997**.

- [4] D. R. Liu, P. G. Schultz, *Angew. Chem.* **1999**, *111*, 36; *Angew. Chem. Int. Ed.* **1999**, *38*, 37.
- [5] J. Klein, C. W. Lehmann, H.-W. Schmidt, W. F. Maier, *Angew. Chem.* **1998**, *110*, 3557; *Angew. Chem. Int. Ed.* **1998**, *37*, 3369.
- [6] P. G. Schultz, X.-D. Xiang, *Curr. Opin. Solid State Mater. Sci.* **1998**, *3*, 153.
- [7] T. Bein, *Angew. Chem.* **1999**, *111*, 335; *Angew. Chem. Int. Ed.* **1999**, *38*, 323.
- [8] W. H. Weinberg, B. Jandeleit, K. Self, H. Turner, *Curr. Opin. Solid State Mater. Sci.* **1998**, *3*, 104.
- [9] A. Holzwarth, H.-W. Schmidt, W. F. Maier, *Angew. Chem.* **1998**, *110*, 2788; *Angew. Chem. Int. Ed.* **1998**, *37*, 2647.
- [10] M. T. Reetz, M. H. Becker, K. M. Kühling, A. Holzwarth, *Angew. Chem.* **1998**, *110*, 2792; *Angew. Chem. Int. Ed.* **1998**, *37*, 2647.
- [11] P. Cong, R. D. Doolen, Q. Fan, D. M. Giaquinta, S. Guan, E. W. McFarland, D. M. Poojary, K. Self, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *111*, 508; *Angew. Chem. Int. Ed.* **1999**, *38*, 484.
- [12] W. H. Weinberg, E. W. McFarland, P. Cong, S. Guan (Symyx Technologies), WO-A 98/15969 A2, **1998** [*Chem. Abstr.* **1998**, *128*, 289491].
- [13] T. Zech, D. Hoenicke, *Erdoel Erdgas Kohle* **1998**, *114*, 578.
- [14] H. Orzesek, R. P. Schulz, U. Dingerdissen, W. F. Maier, *Chem. Eng. Technol.* **1999**, *22*, 691.
- [15] S. Bukeikhanova, H. Orzesek, U. Kolb, K. Kühlein, W. F. Maier, *Catal. Lett.* **1998**, *50*, 93.
- [16] Current review: B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *111*, 2648; *Angew. Chem. Int. Ed.* **1999**, *38*, 2494.

High-Throughput Testing of Heterogeneous Catalyst Libraries Using Array Microreactors and Mass Spectrometry**

Selim Senkan,* Kevin Krantz, Sukru Ozturk, Veysel Zengin and Isik Onal

Combinatorial chemistry holds the promise to significantly accelerate the pace of research for the discovery and optimization of heterogeneous catalysts and to contribute to our understanding of catalytic function. However, to realize this potential advances must be made in two complementary areas: 1) the rapid generation and processing of a large diversity of structurally and compositionally different solid-state materials, and 2) high-throughput testing of these libraries for desired catalytic properties.^[1]

Solid-state libraries can be prepared using techniques that can basically be categorized into two major groups: 1) thin film deposition based methods of synthesis,^[2–4] and 2) solution-based methods for preparation of combinatorial libraries.^[5–7] These techniques recently were used for the discovery

[*] Prof. Dr. S. Senkan, K. Krantz, S. Ozturk, V. Zengin, I. Onal
Department of Chemical Engineering
University of California
Los Angeles, CA 90095 (USA)
Fax: (+1) 310-267-0177
E-mail: senkan@seas.ucla.edu

[**] We would like to thank LCS Inc. and ATG Inc. for support and use of their facilities.

and optimization of superconducting,^[2a] magnetoresistive,^[2b] and luminescent materials^[3–5, 8] as well as electrochemical^[6] and heterogeneous catalysts.^[7, 9]

Once solid-state catalyst libraries are prepared, they have to be tested for activity, selectivity, resistance to poisoning, and operational lifetimes to identify leads that are of practical significance. To date several methods have been proposed to screen heterogeneous catalyst libraries: 1) in situ optical methods based on IR thermography,^[10, 11] the use of fluorescent indicators,^[6] and resonance enhanced multiphoton ionization (REMPI) spectroscopy;^[7, 12] and 2) probe sampling followed by mass spectrometry.^[9]

Optical methods allow the high-speed acquisition of data on the activities of catalysts in libraries without the need to take samples. However, their applications present some challenges. For example, in the case of IR thermography, no information on selectivity or specific reaction products is generated. Fluorescence screening requires that either the products are fluorescent or that product-specific fluorescent indicators are available or can be developed for each product. Among the optical methods, REMPI spectroscopy represents the most broadly applicable catalyst screening technique. However, in this case the development and availability of suitable REMPI strategies for the desired reaction products are necessary.^[7]

On the other hand, mass spectrometry is a mature and universal detection technology and can readily be used to analyze complex gaseous mixtures. However, its application to combinatorial catalysis requires the development and implementation of new strategies. Recently, Cong et al.^[9] reported a mass spectrometer based system to screen heterogeneous catalyst libraries in a sequential fashion. The total time to heat and screen one catalyst site was reported to be about one minute. It is important to recognize that the sequential screening system developed by Cong et al.^[9] is slow and is only useful to determine the initial activities and selectivities of catalysts. Consequently, it will be of limited utility to identify leads for practical applications. The limitation arises from the fact that the activities and selectivities of heterogeneous catalysts significantly change (decrease and sometimes increase) with time on stream, which renders short-time data practically useless to assess the long-time performance of catalysts.

Array microreactors developed earlier in our laboratories are well suited to monitor the activities and selectivities of heterogeneous catalyst libraries over extended periods of time in a parallel fashion.^[7] Recently we also coupled our array microreactors with capillary microprobe sampling and on-line mass spectrometry for the high-throughput testing of heterogeneous catalyst libraries. Here we report the results of time-on-stream testing of a Pt/Pd/In library with 66 combinations for the catalytic dehydrogenation of cyclohexane to benzene, a system that was previously studied using REMPI screening as well.^[7]

The catalyst library consisted of 66 ternary combinations of Pt, Pd, and In prepared in 0.1 wt % increments of each metal with a total metal loading of 1 wt % on alumina using the conventional coimpregnation method. Pellets were prepared by compacting high surface area γ -Al₂O₃ powder (30 mg,

150 m² g^{−1}) into a cylindrical shape (0.4 cm diameter, 0.1 cm height) using a die. These pellet dimensions were chosen to allow for easy characterization and scale-up of newly discovered and/or optimized catalysts for commercial applications. Stock solutions of the metal precursors were prepared from high-purity H₂[PtCl₆], PdCl₂, InCl₃, and aqueous HCl. The solution library was prepared automatically by mixing predetermined volumes of different catalyst precursor solutions into individually addressable test tubes in an array using a computer-controlled x,y,z translation table and a high-accuracy liquid-delivery system. Alumina pellets were then added into each test tube and allowed to impregnate under competition with HCl. Subsequently, the solutions were slowly evaporated, and the pellets dried and then calcined at 500 °C for 2 h.

Catalyst reduction and testing were accomplished in a modified version of the array microreactors described previously.^[7] In the present design, each reactor array consisted of 20 rectangular channels that were micromachined on a flat nonporous silica ceramic slab (7.5 cm × 3.75 cm × 0.63 cm). Channels were 0.1 cm wide, 0.1 cm deep, and 2 cm long, and possessed a cylindrical well (0.4 cm diameter, 0.2 cm deep) to hold the cylindrical catalyst pellets (0.4 cm diameter, 0.1 cm high). In this configuration, the flat top surface of the catalyst pellet, when placed into the well would be flush with the bottom of the reactor channel. A similar flat ceramic slab was used to cover the microreactor array slab and to form isolated channels. The flat and rigid nature of the ceramic slabs also result in the formation of a good gas seal, thereby isolating each channel from one another under a broad range of temperatures. This design results in unobstructed gas flow through the channels, with only “wall skin friction” providing flow resistance. Consequently, nearly identical flow rates in each channel, and therefore identical contact times between the reactant gases and the catalyst pellets in each microreactor, were feasible. Gas flow rates in the channels were determined to be within 5 % of one another using hot-wire anemometry measurements.

In the current arrangement four microreactor arrays, each having 20 channels, were stacked and placed inside an aluminum heating block (Figure 1). Thus it was possible to test 80 different catalysts in parallel. Clearly, a larger number of catalysts can easily be tested by stacking more arrays or by increasing the number of channels in each array. In Figure 1, one of the arrays has been pulled out to show internal details. The heating block was precision machined from a single piece of aluminum.

As can be seen in Figure 1, each array was surrounded with 1.25 cm thick aluminum walls to ensure temperature uniformity and compact design. Individual microreactor arrays were also fitted with dedicated quartz feed lines to separately adjust their flow rates. However, in the present set of experiments feed gas flow was maintained at the same rate for each array. Feed lines pass through a preheater system that was also machined from a solid aluminum block. The reactor and preheat blocks were thermally insulated using a porous ceramic board (Figure 1). During the actual catalyst testing process, a ceramic panel is also attached to the front of the reactor to further minimize heat loss and to maintain temper-

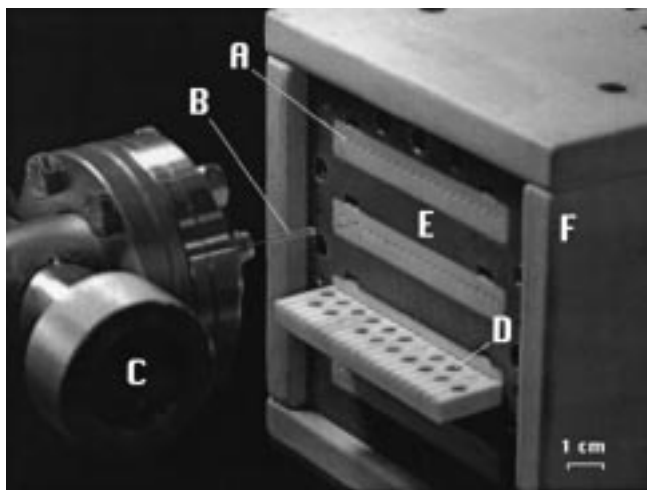


Figure 1. Microreactor system for catalyst screening. A: Array microreactor; B: capillary sampling probe; C: mass spectrometer; D: catalyst pellets; E: aluminum heating block; F: insulation.

ature uniformity within the array. This panel has been removed in Figure 1 to better illustrate the details of the reactor system. The temperatures of the array microreactors were regulated with electrical heating cartridges and thermocouples inserted into the aluminum blocks and by using PID controllers. Gas temperatures in the vicinity of the catalyst sites were separately monitored by small thermocouples inserted from the reactor exit to assess uniformity across the array, and to determine the time periods for heat-up and cool-down. These studies revealed the presence of a nearly uniform temperature, within 1 °C, across each array and between the arrays.

The entire reactor system was mounted on a stand that was part of a high-precision, computer-controlled *x,y,z* movement mechanism. Catalyst testing proceeded in the following manner: First, all 66 calcined pellets, together with selected duplicates and blanks (pure aluminum oxide), were placed into the wells of the microreactors, and the library was heated to 350 °C under argon as carrier gas. Upon reaching the set point temperature, the gas flow was switched to pure hydrogen and the pellets were reduced for 2 h. After reduction, the gas flow was changed back to argon and the temperature was lowered to the desired test temperature. Once the test temperature was reached, the gas stream was switched to the feed stream (about 10% cyclohexane in argon). Under the experimental conditions, the nominal contact time between the feed gas and the pellets was about 0.004 s.

The levels of the reactants, products, and the inert carrier gas were determined by withdrawing a small stream (about 1 cm³ min⁻¹) from each microreactor channel using a capillary sampling probe (50 μm diameter). The probe was inserted 2 mm into the channels to ensure the acquisition of representative samples. The gas was analyzed by quadrupole mass spectrometry (QMS). The sampling probe and the analysis

system are also indicated in Figure 1. Each microreactor effluent was sequentially analyzed by moving the heated reactor block relative to the stationary sampling probe with the aid of the *x,y,z* positioning system. Gas samples entering the QM spectrometer were immediately subjected to 70 eV energy electrons and analyzed. To accelerate the data acquisition and to minimize the volume of data acquired, only selected mass ions, determined earlier in the scoping experiments, were monitored during the testing process. These were: cyclohexane (C₆H₁₂, 84 Da), cyclohexene (C₆H₁₀, 82 Da), C₆H₈ (80 Da), benzene (C₆H₆, 78 Da), and argon (40 Da). It is particularly interesting that although different levels of benzene production were observed from different catalysts, partially dehydrogenated cyclohexane products were not detected in any of the reactor effluents under the conditions investigated.

The data were acquired by rapidly inserting the capillary probe into each microreactor channel and sampling for about five seconds. This time period was adequate to acquire 2–5 sets of data, which was deemed sufficient for the present work. The probe subsequently was withdrawn from the channel and positioned into the next channel. By repeating this approach for each microreactor, we were able to screen the entire 80-channel library in about 10 min. Further acceleration of the data acquisition process is clearly possible. However, this was not necessary for the library size considered here. Even the conservative screening rate of 80 microreactors per 10 min achieved with the present system represents an improvement by a factor of 8 over the scanning mass spectrometer system of Cong et al.^[9]

In Figure 2 the benzene ion current signals determined by QMS during the screening process are presented as a function of nominal channel number (reaction at 300 °C). The peaks correspond to benzene levels measured in each microreactor effluent, while the sharp drops correspond to the movement of the capillary probe from one site to the next. As evident from Figure 2, the measurement technique developed allows for easy discrimination of the individual sites. The relative activities of the different catalyst sites are readily discernible, illustrating the potential utility of the system as a high-throughput screening tool. Particularly significant are the stark differences that exist between catalytic and blank sites.

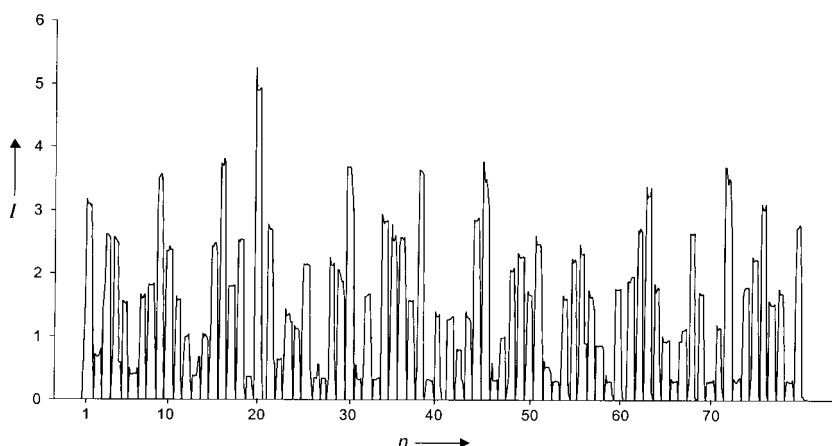


Figure 2. Intensities *I* of the benzene signals as a function of microreactor channel number *n*. The total time to acquire this information was less than 10 min.

The data presented in Figure 2 were also transformed into a triangular bar chart indicating the catalyst composition (Figure 3). It is seen that both Pt and Pd individually exhibited catalytic activities, with Pt being more active than Pd. On the

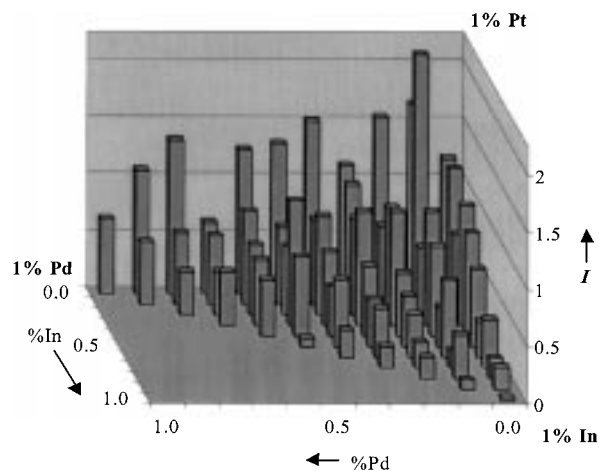


Figure 3. Initial activity I for benzene formation of the 66-combination Pt/Pd/In catalyst library.

other hand In was not catalytic towards benzene production from cyclohexane, and the ternary mixture of 0.8% of Pt, 0.1% of Pd, and 0.1% of In exhibited superior benzene productivity when compared to all other metal combinations investigated. These results are in complete agreement with those obtained using REMPI screening and the same catalyst and operating conditions.^[7]

As noted earlier, an important concern in the development of practical catalysts is time-on-stream performance. For example, although catalysts can exhibit high initial activities, this may degrade with time as a consequence of a number of events that can include coking, sintering, or poisoning. Alternately, selectivities to desired products can also change with time. The array microreactors coupled with QMS can readily address these concerns. To demonstrate this capability, we evaluated the performance of our ternary Pt/Pd/In catalyst library over 24 h. In Figure 4, the levels of benzene in the reactor effluents are presented as a function of time for the higher activity catalysts. Data for other catalysts were omitted to avoid congestion. The legend on the right side of Figure 4 indicates the catalyst compositions. It should be noted that the time-on-stream

data points shown in Figure 4 represent only a subset of the data acquired by QMS to avoid clutter and to clearly illustrate a number of issues. First, as evident from Figure 4, all the catalysts, without any exception, experienced deactivation over the 24 h period investigated; deactivation was most significant early on in the experiments. Surface analysis of the used catalysts indicated that the mechanism of deactivation was coke formation. This was supported by the fact that most of the initial activity was regained after calcination in air. Second, it is significant that different catalysts deactivated at different rates, with the activity profiles of some catalysts crossing each other over time. These issues clearly demonstrate the inadequacy of the initial activity/selectivity data as a screening criterion for catalyst development.^[9]

The trends presented in Figure 4 also provide useful practical and fundamental insights on catalyst formulation. For example, consider the comparative deactivation behavior of catalysts with 0.9% of Pt/0.1% of Pd and 0.9% of Pt/0.1% of In (solid lines). As evident from Figure 4, both catalysts exhibited virtually the same initial activity. However, the catalyst with 0.9% of Pt/0.1% of Pd deactivated significantly faster than the catalyst with 0.9% of Pt/0.1% of In, suggesting the positive impact of In in slowing the rate of coke formation.

In Figure 5 the bar diagrams for benzene levels in the exhausts of all the microreactor channels are presented at the beginning of the reaction and after 2, 4, and 24 h of operation. The ternary mixture of 0.8% of Pt, 0.1% of Pd, and 0.1% of In, which exhibited the highest initial activity, maintained its relative superiority over the entire testing period. However, the activities of all the catalysts decreased significantly during the testing period.

The array microreactor and QMS system developed also was used for the acquisition of information on reaction kinetics, from which reactor design parameters can be determined. To illustrate this we studied the effects of reaction temperature on benzene formation. This was accom-

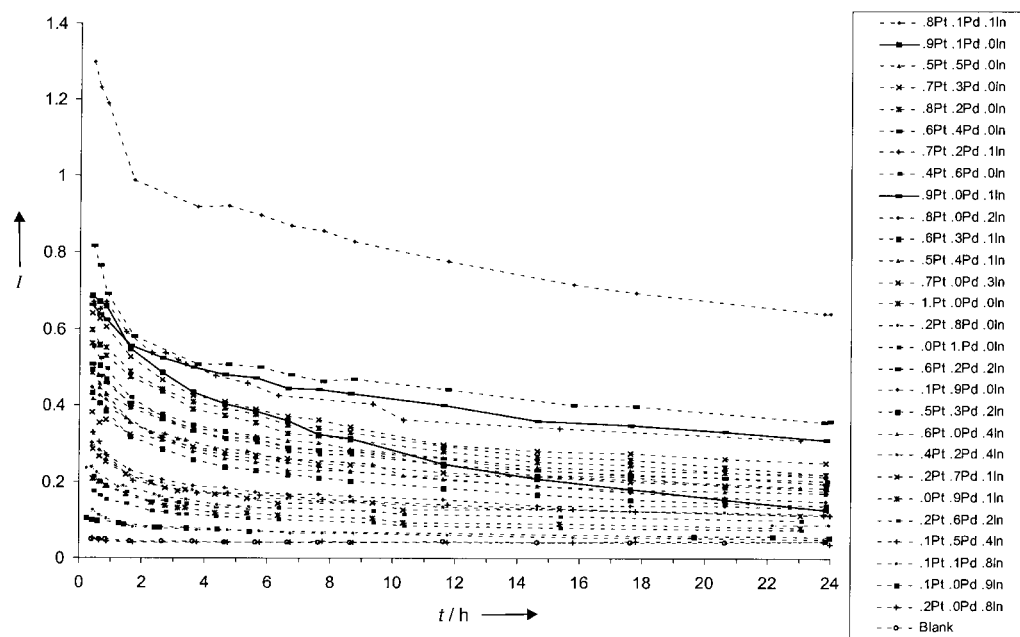


Figure 4. Activity I of selected catalysts as a function of time on stream.

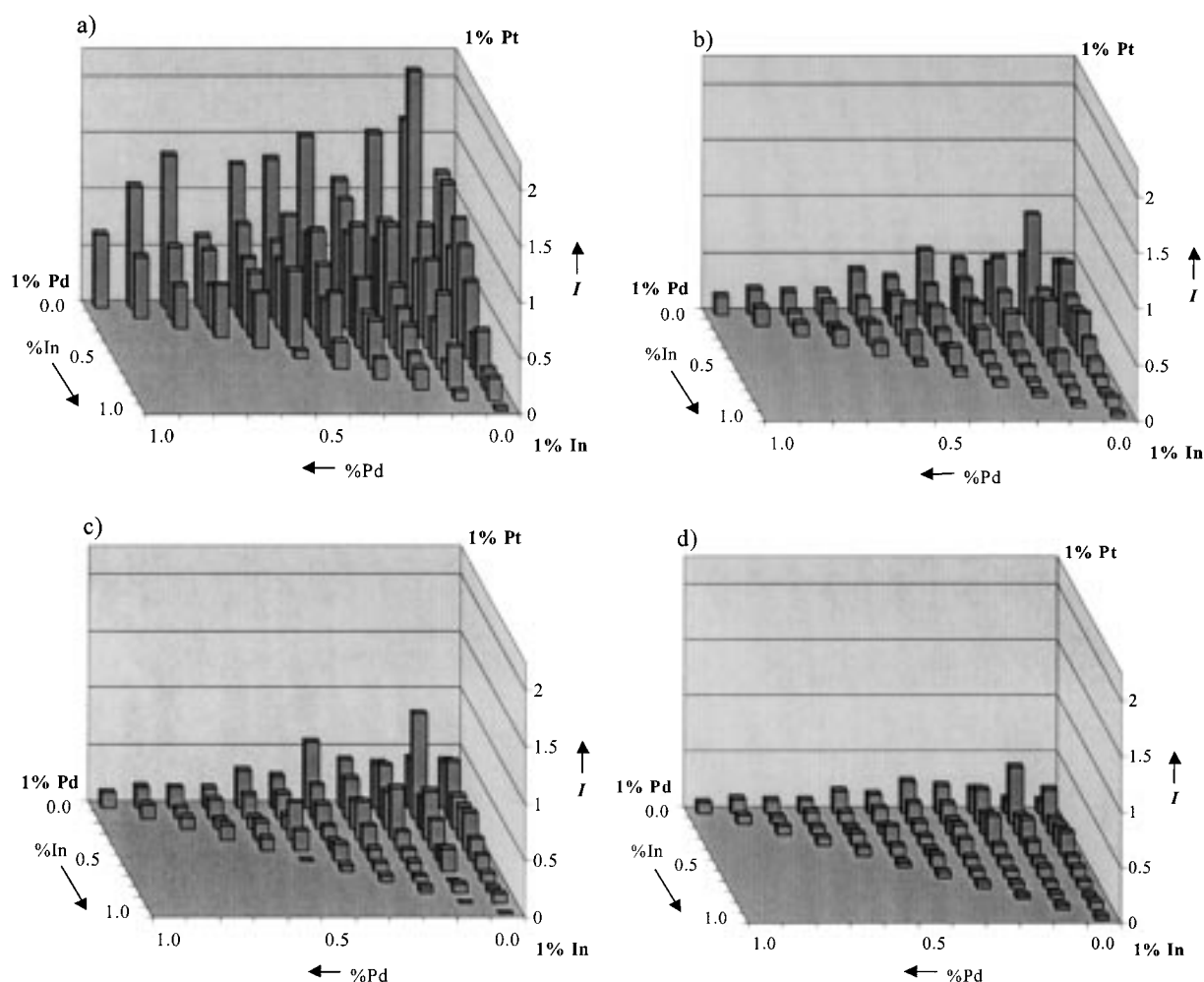


Figure 5. Benzene formation activity for the 66-combination Pt/Pd/In catalyst library: a) initial activity; b) after 2 h; c) after 4 h; d) after 24 h.

plished by starting with a freshly calcined—that is, coke-free—catalyst library. The array microreactor system was first heated to 150 °C and then screened for activity and selectivity. At 150 °C both benzene formation and catalyst deactivation rates were low. After data acquisition, the temperature of the reactor was increased to 200 °C, again under an inert gas flow. Following the establishment of the steady reaction temperature, the catalyst library was again screened for activity and selectivity. This procedure was repeated at 250 °C and then 300 °C. The total time to screen 80 microreactor channels at four different temperatures was about 3 h.

Heterogeneous reactions in porous catalyst particles proceed through a number of sequential events. These events include the transport of reactants to the external surface of the particle followed by internal (pore) diffusion, adsorption, and surface reactions.^[13] Products then desorb from the surface and are transported back through the pores into the bulk gas stream. The temperature influences each of these steps differently. Generally surface reaction kinetics and desorption rates dominate product formation rates at lower temperatures due to their higher activation energies. However, increasing temperatures increase intrinsic reaction and desorption rates significantly more than diffusion rates, and thus the latter begin to influence the overall rate of conversion. These

changes typically manifest themselves by decreases in observed (apparent) activation energies with increasing temperature.^[13] In other words, Arrhenius diagrams (plots of $\ln(\text{rate})$ versus $1/T$) exhibit nonlinear behavior.

To explore the above issues with the current catalyst system, the benzene signals measured at different temperatures have been analyzed using Equation (1). Here $I_{\text{C}_6\text{H}_6}$ is

$$d[I_{\text{C}_6\text{H}_6}]/dt = k_0 e^{(-E/RT)} f(C) \quad (1)$$

the intensity of the benzene signal, which is proportional to the concentration, t the time, k_0 the preexponential factor, E the apparent (overall) activation energy, and $f(C)$ the concentration-dependent part of the rate expression, which can be in any functional form. Assuming differential conversion of cyclohexane, the Equation (1) can be integrated along the pellet and, under isothermal conditions, arranged to yield Equation (2). Here τ is the total contact time for the pellet, which is a constant for each microchannel reactor.

$$\ln(I_{\text{C}_6\text{H}_6}) = \ln(k_0) - E/RT + \ln(f(C)) + \ln(\tau) \quad (2)$$

In Figure 6 the benzene data are presented in accordance with the above relationship, again for the higher activity

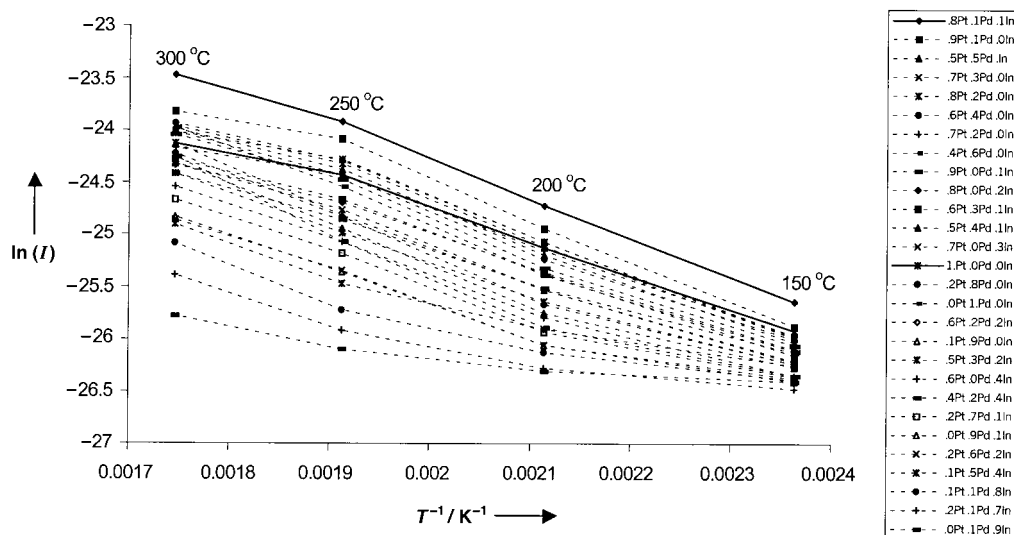


Figure 6. Arrhenius diagrams for selected catalysts.

catalysts. All the catalysts exhibited nonlinear Arrhenius behavior, suggesting changes in rate-controlling mechanisms with increasing temperature. In particular, the rate of formation of benzene exhibited higher apparent activation energies at lower temperatures than at higher temperatures for the higher activity catalysts, suggestive of the increasing importance of diffusion limitations with increasing temperature. Clearly, it is also possible that catalyst deactivation could have contributed to this behavior. However, due to the shortness of the test period (15 min at each temperature) and the fact that experiments at lower temperatures were conducted first, coke formation should not be a significant factor even at 300 °C. For the highest activity catalyst (0.8 % of Pt/0.1 % of Pd/0.1 % of In), the apparent activation energy was about 7 kcal mol⁻¹ in the temperature interval 150–250 °C, but decreased to 5 kcal mol⁻¹ in the temperature range 250–300 °C (see the upper solid line in Figure 6).

For the pure Pt catalyst (1.0 % of Pt), the apparent activation energy was about 6 kcal mol⁻¹ over the 150–200 °C range (lower solid line in Figure 6). This value is smaller than that reported earlier from packed bed experiments (9.6 kcal mol⁻¹) where 40–65 mesh pellets of Pt catalysts were used.^[14] However, these results are consistent with the fact that, owing to the larger pellets used in our experiments, the reactions would be more prone to diffusion limitations and thus exhibit smaller activation energies.^[13]

It is also interesting that the activation energies of lower activity catalysts increased with increasing temperature over the temperature range considered (Figure 6). In addition, all of these catalysts were rich in indium, a fundamentally significant result that could be useful for the development practical catalysts.

Received: May 22, 1999

Revised version: July 5, 1999 [Z134571E]

German version: *Angew. Chem.* **1999**, *111*, 2965–2971

Keywords: combinatorial chemistry • heterogeneous catalysis • high-throughput screening • mass spectrometry • microreactors

- [1] Current review on combinatorial materials science and catalysis: B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *111*, 2648; *Angew. Chem. Int. Ed.* **1999**, *38*, 2476.
- [2] a) X.-D. Xiang, X. Sun, G. Briceno, Y. Lou, K.-A. Wang, H. Chang, W. G. Wallace-Freedman, S.-W. Chen, P. G. Schultz, *Science* **1995**, *268*, 1738; b) G. Briceno, H. Chang, X.-D. Sun, P. G. Schultz, X.-D. Xiang, *Science* **1995**, *270*, 273.
- [3] X.-D. Sun, C. Gao, J. Wang, X.-D. Xiang, *Appl. Phys. Lett.* **1997**, *70*, 3353.
- [4] E. Danielson, J. H. Golden, E. W. McFarland, C. M. Reaves, W. H. Weinberg, X. D. Wu, *Nature* **1997**, *389*, 944.
- [5] X.-D. Sun, K.-A. Wang, Y. Yoo, W. G. Wallace-Freedman, C. Gao, X.-D. Xiang, P. G. Schultz, *Adv. Mater.* **1997**, *9*, 1046.
- [6] E. Reddington, A. Sapienza, E. Guraou, R. Viswanathan, S. Sarangapani, E. S. Smotkin, T. E. Mallouk, *Science* **1998**, *280*, 1735.
- [7] S. Senkan, S. Ozturk, *Angew. Chem.* **1999**, *111*, 867; *Angew. Chem. Int. Ed.* **1999**, *38*, 791.
- [8] J. Wang, Y. Yoo, C. Gao, I. Takeuchi, X.-D. Sun, H. Chang, X.-D. Xiang, P. G. Schultz, *Science* **1998**, *279*, 1712.
- [9] P. Cong, R. Doolen, Q. Fan, D. M. Giaquinta, S. Guan, E. McFarland, D. M. Poojary, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *111*, 508; *Angew. Chem. Int. Ed.* **1999**, *38*, 483.
- [10] F. C. Moates, M. Somani, J. Annamalai, J. T. Richardson, D. Luss, R. C. Willson, *Ind. Eng. Chem. Res.* **1996**, *35*, 4801.
- [11] S. J. Taylor, J. P. Morken, *Science* **1998**, *280*, 267.
- [12] S. M. Senkan, *Nature* **1998**, *394*, 350.
- [13] C. N. Satterfield, *Mass Transfer in Heterogeneous Catalysis*, MIT Press, Boston, **1970**.
- [14] K. Ahmed, H. M. Chowdhury, *Chem. Eng. J.* **1992**, *50*, 165.

Parallel Synthesis and Testing of Catalysts under Nearly Conventional Testing Conditions**

Christian Hoffmann, Anke Wolf, and Ferdi Schüth*

*Dedicated to Professor Ewald Wicke
on the occasion of his 85th birthday*

High-throughput techniques are well established in the pharmaceutical industry and have also received considerable interest in recent years in the fields of materials science and catalysis.^[1] Several publications have appeared dealing with the preparation and testing of catalysts under high-throughput conditions. The first work in this field used IR thermography to analyze an array of 16 conventionally prepared catalyst pellets in the H_2/O_2 reaction.^[2] This methodology was then substantially refined by the background correction technique introduced by Maier and co-workers^[3] and later proved to be suitable for liquid-phase reactions, if it can be ensured that catalyst particles float on the liquid surface to prevent screening of the thermal effects by the liquid.^[4, 5] Common to these approaches is the fact that no selectivity information can be obtained, which is crucial for most catalytic reactions of industrial interest.

The resonance enhanced multiphoton ionization (REMPI) technique introduced by Senkan et al.^[6] is in principle suitable for analyzing selectivity as well; however, only benzene was detected and no information on selectivity was obtained. Quantification is not straightforward, and the analysis of complex product mixtures will be very difficult with REMPI spectroscopy.

Weinberg and his co-workers at Symyx used a scanning mass spectrometric technique to analyze libraries of catalysts.^[7] This procedure is in principle able to detect activity of catalysts as well as selectivity; however, the technique is used under conditions which are very different from those for conventional catalyst testing.

The techniques mentioned are certainly very valuable in an early development stage (stage I screening), but promising candidates have to be analyzed in more detail in a next step that is closer to real operation conditions (stage II screening). Such a stepwise approach in the parallelized development is also used in the pharmaceutical industry. In addition to the concentration of previous studies on stage I testing, there is an additional problem with most of these investigations: Usually no validation of the data—for example a check of the reliability by repeated library synthesis and control of the catalytic data in conventional reactors—was given. Such information, however, is absolutely crucial for a high-throughput approach to be successful.

We therefore report studies on parallelized catalyst synthesis and testing a) which are close to conventional catalysis research, but parallelized, and b) for which reproducibility and precision of all steps have been checked carefully. The data presented show that catalyst synthesis and testing can be accelerated by between one and two orders of magnitude without much loss of information compared to conventional testing.

The identification and optimization of gold-based catalysts for the room-temperature oxidation of CO was chosen as a test case. These catalysts were discovered by Haruta,^[8] but the synthesis is not completely documented and extremely ill reproducible. Therefore a large number of preparation and test experiments are necessary to establish proper synthesis conditions for highly active catalysts. The system described here is meanwhile used in routine operation in our laboratory for this purpose.

The synthesis system is based on a Gilson XL 232 automated dispenser. We prepared different Au/Co_3O_4 catalysts by coprecipitation and Au/TiO_2 catalysts by precipitation of gold onto the support with different concentrations, pH values during precipitation, temperatures of calcination, and support materials. The precipitation and coprecipitation reactions are carried out in 50-mL test tubes placed on a shaker tray to avoid settling of the precipitate. The suspensions of the precipitates are transferred by means of a stainless steel tube of 1 mm inner diameter, attached to the dispenser, to a filtration unit with 4×4 wells which has the same format as the catalytic test reactor. In this unit the suspensions are filtered and the collected solids rinsed with water. The whole filtration unit can then be placed in an oven with controlled atmosphere to prepare the final catalyst. After the thermal treatment, the catalysts are loosened with a spatula, transferred manually, and then weighed separately into the sinter plate. The weighing step is important to guarantee the identical space velocity over all 16 catalysts. Several sets of four identical catalyst batches were prepared, manually as well as in the automated system, in order to check the reproducibility of the synthesis. The synthesis of the gold-based catalysts is known to be difficult to reproduce. Seemingly identical preparations resulted in catalysts which differed in activity by 50 % or more. Such high deviations were never observed for catalysts prepared automatically, although also in this case some scatter of up to 35 % in activity occurred. This shows that automatic preparation, if carried out properly, is at least as reliable as manual catalyst synthesis. This advantage will become even more pronounced if, as in industrial laboratories, catalysts are frequently synthesized by different operators, which introduces an additional degree of uncertainty.

A schematic drawing of the test reactor is shown in Figure 1a, and a photograph in Figure 1b. It consists of a brass block with 16 wells of 1 cm diameter each, equipped with nine heating cartridges which ensure a homogeneous temperature over the whole reactor. Temperature differences between the wells, measured with thermocouples in the wells filled with catalyst under flowing air, are less than 1 K. The gas is admitted from the top to all 16 wells simultaneously. Catalysts are placed on a plate with 16 wells (inner diameter

[*] Prof. Dr. F. Schüth, C. Hoffmann, A. Wolf
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2395
E-mail: schueth@mpi-muelheim.mpg.de

[**] This project was supported by the BMBF under contract number FKZ.03 D 0068 A2. We would also like to thank B. Spliethoff for the TEM analysis and Dr. B. Matthiasch for the elemental analysis.

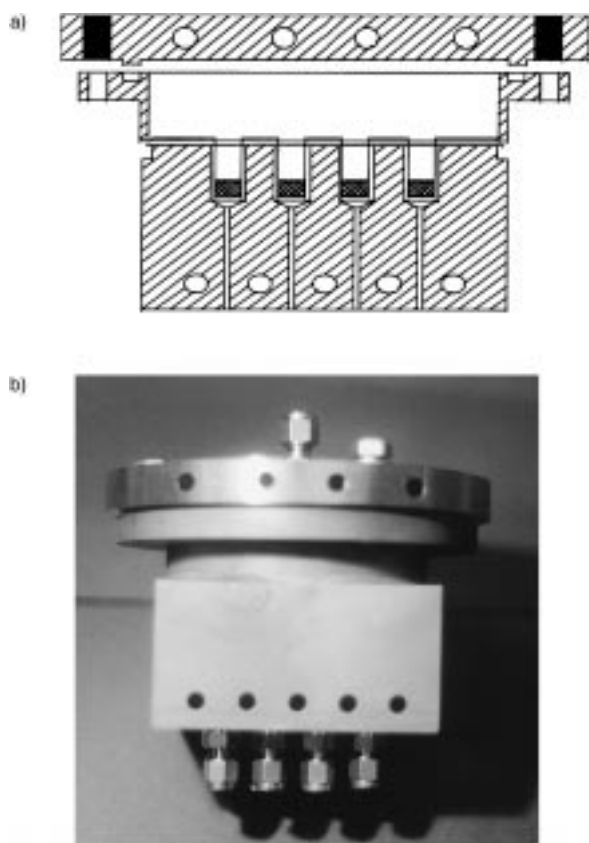


Figure 1. a) Schematic drawing of the 16-pass reactor and b) photograph of the reactor.

6 mm) which is sealed against the brass body. This plate can also be used to store the libraries. The gases are then passed through individual capillaries, each equipped with a three-way valve to switch the offstream of one catalyst to an analytical instrument. The remaining 15 streams of gas are passed to the reactor outlet. This means that during the entire test all catalysts are exposed to the reaction gas, so that the catalysts are equilibrated. If deactivation is a problem, the library can be scanned several times in order to monitor changes in catalyst activity.

Initial experiments with 16 identical catalysts in all wells proved that severe flow inhomogeneities can occur in the test module if no precautions are taken. An additional problem can be created by strong backmixing. The reactor was modified accordingly to solve these problems. Capillaries are placed in the offstream to present the major flow resistance, so that the highest pressure drop is not over the catalyst bed, but through the capillaries. Differences in the catalyst packing therefore do not substantially influence the flow through the individual wells. In addition, the line to the analytical instrument is equipped with a flow controller so that during analysis all catalysts are operated under identical flow conditions. The homogeneous distribution of the inlet gas and the prevention of backmixing is achieved through a diffusor plate which consists of 16 1-mm holes over the wells. The linear flow in these bores is so high that no backmixing is detectable. With all these precautions, conversion over the different wells with identical catalysts do not differ by more than $\pm 5\%$. The result of such a run can be seen in Figure 2.

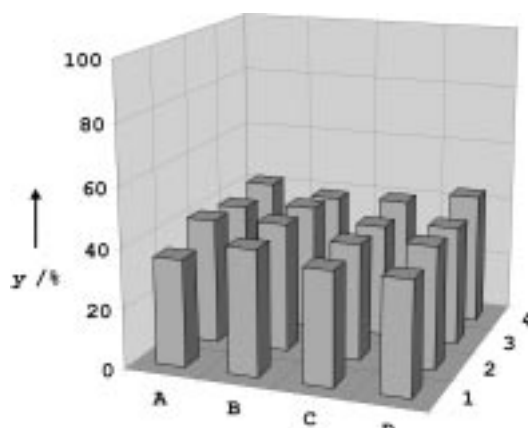


Figure 2. Parallel testing of 16 identical Pt/TiO₂ catalysts. y = yield of CO₂, space velocity over each catalyst = 20000 mL h⁻¹ g_{cat}⁻¹.

Reproducibility of the catalytic test was also better than 5% in different runs. These checks were all carried out under conditions where conversions were substantially lower than 100%, since at 100% conversion no activity differences could be detected.

There is in principle no limitation with respect to the analytical technique used to determine the activity of the catalysts. In this case nondispersive IR is used to determine CO and CO₂ concentrations, but GC or mass spectrometry are suitable as well. Catalytic testing of the gold catalysts was carried out at four different temperatures to identify not only the room-temperature active catalysts, but to also determine ignition temperatures of the less active materials.

Figure 3 shows the activity of one sample library of catalysts for the oxidation of CO. The library consists of Au/Co₃O₄ catalysts with different contents of Au (0.4–26.0 wt %). For half of the catalysts a second washing step was carried out after calcination, whereas the others were tested directly. The results show the eight catalysts that were washed after calcination already catalyze CO conversion at room temperature. The catalysts which were used without a second washing step only start to catalyze CO oxidation at or above 125 °C. The second washing step after calcination is therefore crucial for the removal of catalyst poisons deposited during preparation. X-ray fluorescence measurements show that the activity in CO oxidation increases with increasing Au content of the catalysts. According to high-resolution transmission electron microscopy (TEM), Au particles with a broad particle size distribution ranging from 2 to 200 nm are present. The catalyst with the highest activity had extremely large Au particles of 60–200 nm, although some particles that are smaller than the detection limit of TEM could be present.

To check another preparation technique the Au/TiO₂ catalysts, prepared by deposition–precipitation, were investigated. Various supports were used, including several commercial samples as well as anatase, mesoporous TiO₂, and microporous TiO₂, which were synthesized in our laboratory. The most suitable catalyst was based on anatase with a surface area of 180 m² g⁻¹ and a Au particle size of 5 nm. This catalyst showed 100% conversion already at room temperature, which confirms Harutas results that highly dispersed Au particles are necessary for a high catalytic activity.

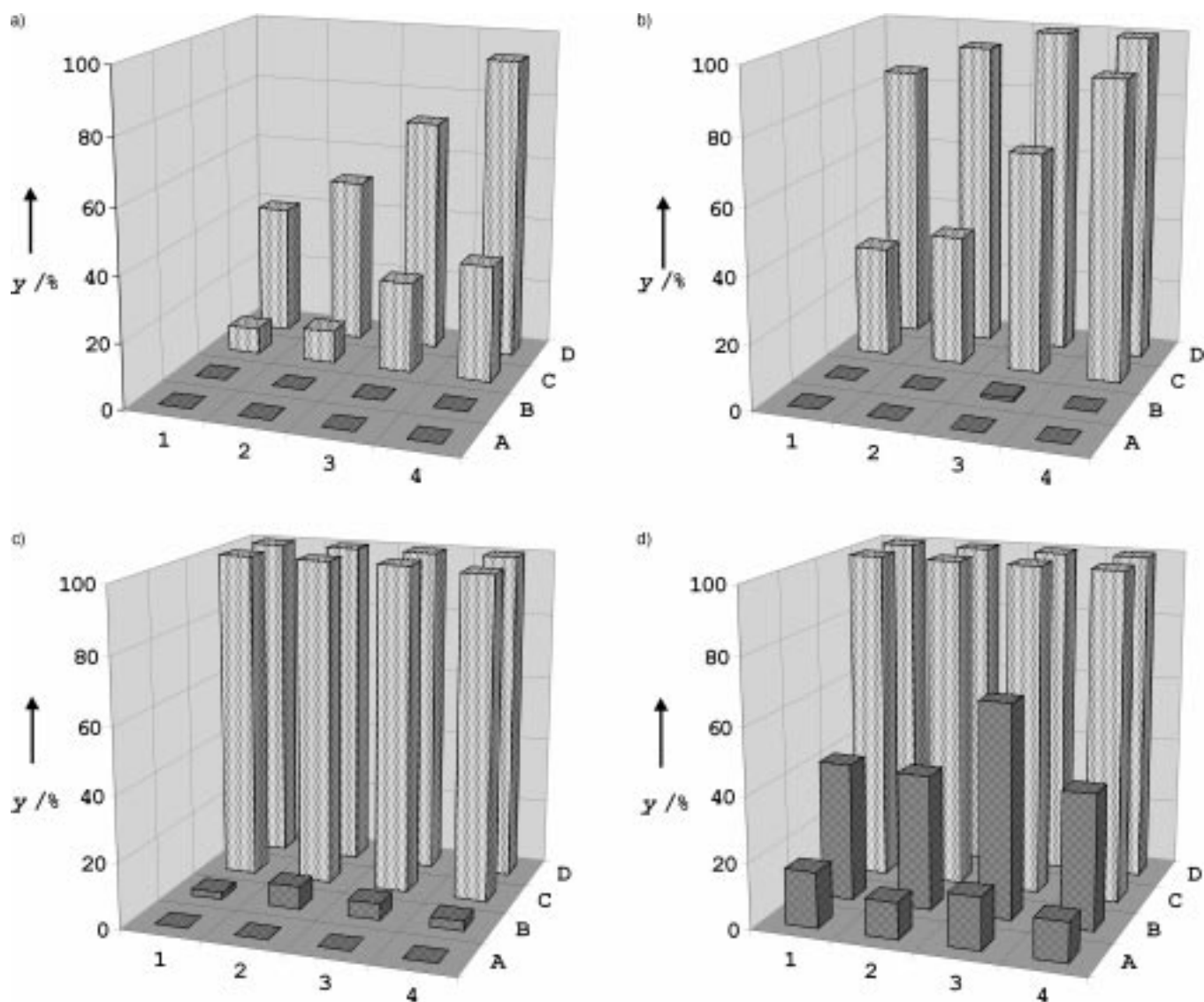


Figure 3. Parallel testing of Au/Co₃O₄ catalysts. y = yield of CO₂. Catalysts in the two front rows were not washed after calcination, those in the back rows were washed. Au content (wt %) from left to right and from front to back for the two sets of catalyst: 0.4, 1.0, 1.6, 3.4, 6.4, 9.8, 12.3, 26.0. $T_{\text{reactor}} = 25^{\circ}\text{C}$ (a), 70°C (b), 125°C (c), 180°C (d).

Three of the catalysts for which the activity is low at room temperature, but increases at elevated temperatures, were also tested in the conventional flow system. Such materials with moderate activity allow the most meaningful comparison between the parallelized system and the conventional tests, since whole temperature/conversion curves can be compared. As can be seen in Figure 4, the activity curve measured in the parallel flow reactor and the conventional flow system differ by 10 K at most, which shows that reliable catalytic data can be obtained in the parallel flow system.

With this setup an acceleration of the development process by a factor of 15 was achieved. Higher integration is possible to a certain extent with similar reactor setups. However, one has to keep in mind that the probability of failures, for instance in valves, increases with the number of components present. Therefore, there is a limit to higher integration. Currently a 48-pass parallel flow reactor, which uses a multiport valve to simplify the setup, is in initial testing. This reactor is coupled to a GC instrument and will be used in the

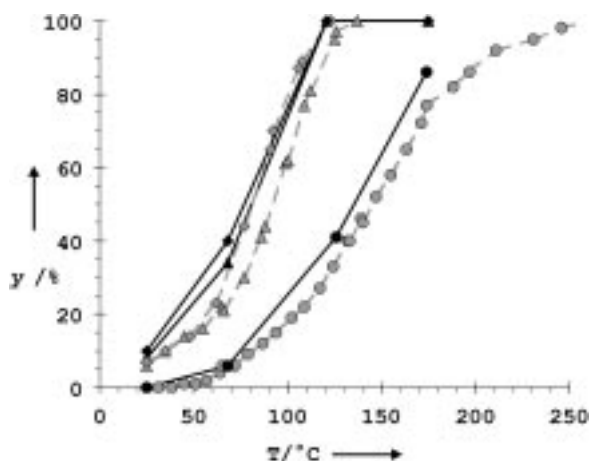


Figure 4. Comparison of parallel testing and testing in a conventional flow system for three different catalysts. Yield (y) of CO₂ as a function of catalyst temperature. Space velocity in all cases: $20000\text{ mL h}^{-1}\text{ g}_{\text{cat}}^{-1}$, (Δ) 0.4 wt % Au/Co₃O₄, ($\blacklozenge$) 1.0 wt % Au/Co₃O₄, ($\bullet$) 15.6 wt % Au/TiO₂. Parallel test: solid line, conventional test: dashed line.

near future for investigations of the partial oxidation of methane. The system will increase the throughput by another factor of 3, which will mean that 10 000 catalysts per year can be tested using this technique.

Experimental Section

Synthesis: The synthesis system is based on a Gilson automated dispenser (model XL 232) which has been modified to suit our needs. The modifications are an integrated shaker (Heidolph, DSG-304), a bigger steel tube, and a filtration unit. Especially the precipitation step is somewhat difficult, since it normally involves relatively large amounts of liquids. Precipitation reactions are therefore carried out in relatively large vessels (50 mL) which are continuously shaken to prevent settling of the precipitate. The suspension is then pipetted onto a 16-well filtering unit which has the same dimensions as the catalytic reactor. The filtering unit is made of high-grade steel, with an outer diameter of 94 mm and a height of 40 mm. The bottom is formed from a sinter metal frit plate to allow filtration. The preparation steps described below were carried out in identical fashion in the automated module as well as manually.

Au/Co₃O₄ catalysts were prepared by coprecipitation. A solution of H[AuCl₄] and Co(NO₃)₂ was added to a solution of 1 M Na₂CO₃. The mixture was agitated for 1 h. The resulting precipitate was isolated by filtration, washed several times, dried at 90 °C, and calcined in air at a temperature of 400 °C for 4 h. For several catalysts a second washing step was carried out after calcination.

Au/TiO₂ catalysts were prepared by deposition–precipitation. As support materials anatase, mesoporous TiO₂, and microporous TiO₂ were used. The support materials were prepared as described in the literature.^[9, 10]

The support materials were suspended in H₂O. Aqueous solutions of H[AuCl₄] and Na₂CO₃ were added in turn in three portions to the suspension. The mixture was then agitated for 10 h. The precipitates isolated by filtration were treated as above; the materials were calcined at 300 °C.

Catalysis: All catalysts were pretreated in air at 150 °C for 1 h in the catalytic test unit. Conventional catalytic measurements were carried out in a fixed bed flow reactor with 200 mg of catalyst sieved to 125–250 µm. For high-throughput experimentation 46 mg of powdered catalyst were inserted in each well without further preparation. A standard reaction gas of 1 % CO in air was passed through the catalyst bed with 67 mL min⁻¹ for conventional tests and 250 mL min⁻¹ (15.6 mL min⁻¹ per well) for high-throughput experimentation to obtain the same space velocity of

20 000 mL h⁻¹ g_{cat}⁻¹ for both systems. The concentrations of CO and CO₂ were determined by a nondispersive IR analyzer (URAS 3E, Hartmann and Braun).

Characterization: The gold contents were determined by X-ray fluorescence spectroscopy using a Philips PW-1400 apparatus. X-ray powder diffraction patterns were obtained on a STOE STADIP transmission diffractometer for Au/TiO₂ and on a STOE STADIP reflection diffractometer for Au/Co₃O₄. High-resolution electron micrographs were recorded using a Hitachi HF-200 microscope. The surface areas were determined with a Micrometrics ASAP-2010 analyzer.

Received: July 5, 1999 [Z13674IE]

German version: *Angew. Chem.* **1999**, *111*, 2971–2975

Keywords: combinatorial chemistry • heterogeneous catalysis • high-throughput screening • high-throughput synthesis

- [1] Current review on combinatorial materials science and catalysis: B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *111*, 2648–2689; *Angew. Chem. Int. Ed.* **1999**, *38*, 2494–2532.
- [2] F. C. Moates, M. Somani, J. Annamalai, J. T. Richardson, D. Luss, R. C. Willson, *Ind. Eng. Chem. Res.* **1996**, *35*, 4801–4803.
- [3] A. Holzwarth, H.-W. Schmidt, W. F. Maier, *Angew. Chem.* **1998**, *110*, 2788–2792; *Angew. Chem. Int. Ed.* **1998**, *37*, 2644–2647.
- [4] M. T. Reetz, M. H. Becker, K. M. Kühling, A. Holzwarth, *Angew. Chem.* **1998**, *110*, 2692–2695; *Angew. Chem. Int. Ed.* **1998**, *37*, 2647–2650.
- [5] S. J. Taylor, P. J. Morken, *Science* **1998**, *280*, 267–270.
- [6] a) S. S. Senkan, *Nature* **1998**, *394*, 350–353; b) S. S. Senkan, S. Ozturk, *Angew. Chem.* **1999**, *111*, 867–871; *Angew. Chem. Int. Ed.* **1999**, *38*, 791–795; see also the preceding paper: S. Senkan, K. Krantz, S. Ozturk, V. Zengin, I. Onal, *Angew. Chem.* **1999**, *111*, 2965–2971; *Angew. Chem. Int. Ed.* **1999**, *38*, 2794–2799.
- [7] P. Cong, R. D. Doolen, Q. Fan, D. M. Giaquinta, S. Guan, E. W. McFarland, D. M. Poojary, K. Self, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *111*, 508–512; *Angew. Chem. Int. Ed.* **1999**, *38*, 483–488.
- [8] M. Haruta, *Catal. Today* **1997**, *36*, 153–166.
- [9] S. Schunk, Dissertation, Universität Frankfurt, **1998**.
- [10] M. Thieme, F. Schüth, *Micropor. Mater.* **1999**, *27*, 193–200.

ScAl₂

TiAl TiAl₃

VAl CrAl₄ MnAl

FeAl₂ FeAl₃ CoAl NiAl

NiAl₃ CuAl₂ YAl₂ ZrAl ZrAl₂

ZrAl₃ Zr₂Al₃ MoAl₂ MoAl₃ RuAl RuAl₂

RhAl PdAl Pd₂Al₃ PdAl₃ LaAl₂ HfAl₂ HfAl₃

TaAl₃ WAl₄ ReAl₂ OsAl₂ IrAl Pt₂Al₃ PtAl₂ PtAl₃

AuAl CeAl₂ CeAl₃ SmAl₂ SmAl₃ ThAl₂ YbAl₂

YbAl₃ Sc₅Ga₃ TiGa₂ TiGa₃ V₂Ga₅ CrGa

MnGa₃ FeGa₃ CoGa CoGa₃ NiGa

Ni₂Ga₃ CuGa₂ YGa₂ ZrGa

Mo₃Ga RuGa₃ RhGa₂

RhGa₃ PdGa

LaGa LaGa₂ HfGa

HfGa₂ HfGa₃ TaGa₃ OsG

IrGa₂ IrGa₃ PtGa PtGa₂ Pt₂Ga₃

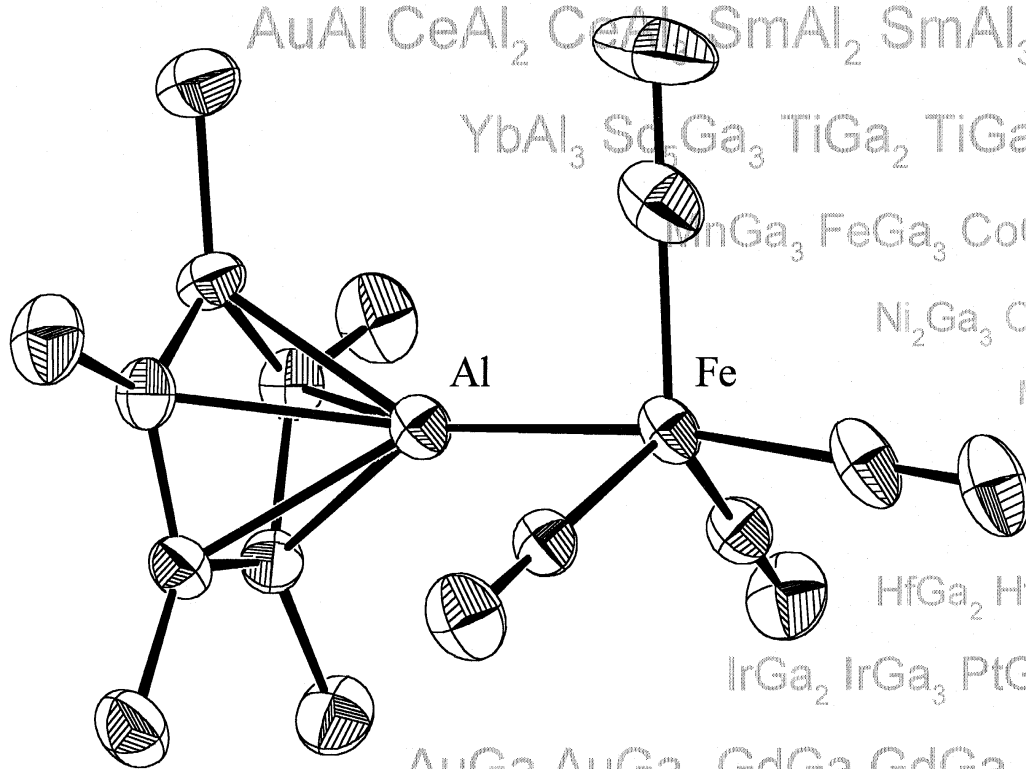
AuGa AuGa₂ GdGa GdGa₂ HoGa₂ PrGa₂

SmGa₂ TbGa₂ ThGa₂ CeGa₂ Sc₃In Ti₃In₄ CrIn₃

Mn₃In CoIn CoIn₂ NiIn Ni₂In₃ Cu₂In YIn₃ ZrIn₃

RuIn₃ RhIn RhIn₃ PdIn Pd₂In₃ PdIn₃ LaIn₃ Hf₃In₄

IrIn₃ PtIn₂ AuIn AuIn₂ CeIn₃ NdIn₃ TbIn₃ Th₂In



Coordination Chemistry of Aluminum, Gallium, and Indium at Transition Metals

Roland A. Fischer* and Jurij Weiß

The surge in the interest in the coordination chemistry of aluminum, gallium, and indium at transition metals is attributed to impulses that have only recently become effective and which originate from two different motivations. One stems from the understanding that organometallic compounds are potential precursors for applications in the field of new materials, and the other from the resurgence of the chemistry of low-valent Group 13 metals (earth metals), which is currently being extended to the coordination chemistry at d-block metals. A special highlight is the compound

$[\text{Ni}(\text{InR})_4]$ ($\text{R} = \text{C}(\text{SiMe}_3)_3$), a first example for the existence of complexes that are homoleptic with respect to the earth metal as ligator. This compound and the complexes $[\text{CpNi-AlCp}^*]_2$, $[\text{Cp}^*\text{Al-Fe}(\text{CO})_4]$, and $[(\text{CO})_4\text{Fe-GaAr}^*]$ ($\text{Ar}^* = 2,6\text{-bis}(2,4,6\text{-triisopropylphenyl})\text{phenyl}$) illustrate the lively development and the current trends in this field. A series of reports on the quantum chemical description of the bonding have originated not least in connection with the debate on the postulated Fe–Ga triple bond in the complex $[(\text{CO})_4\text{Fe-GaAr}^*]$. According to these theoretical papers the very

polar M–E bonds of the different types of complexes fit well into the Lewis donor/acceptor concept for metal–ligand bonds. Multiple bonds in the traditional sense play only a minor role. Remarkably little is known about the reactivity of the M–E complexes if one disregards the chemistry relevant for metal-organic chemical vapor deposition (MOCVD).

Keywords: aluminum • chemical vapor deposition • density functional calculations • gallium • indium • metal–metal interactions

1. Introduction

Complexes with M–E bonds between d-block metals (M) and the earth metals aluminum, gallium, indium, and thallium (E) have a long tradition. Hieber, pioneer of systematic metal carbonyl chemistry, reported in 1942 the high-pressure carbonylation of a mixture of finely dispersed indium and cobalt to form $[\text{In}\{\text{Co}(\text{CO})_4\}_3]$.^[1] The existence of two-center, two-electron bonds, $\sigma(\text{In-Co})$, was later confirmed crystallographically by Robinson and Schussler.^[2] Since then this chemistry has been stimulated time and again with new goals. Complexes of d-block metals and aluminum initially became important in the context of olefin polymerization by Ziegler–Natta catalysts. In 1960 Natta et al. reported a red, diamagnetic compound, which they obtained by treating AlEt_3 with $[\text{Cp}_2\text{TiCl}_2]$.^[3] They originally considered the product to be a complex with a covalent Ti–Al bond comparable to the above-mentioned In–Co complex.^[4] As we know today, typical M/Al complexes, though, involve bridging structures

M–X–Al ($\text{X} = \text{Cl}, \text{H}, \text{CO}, \text{CR}_n$) and covalent M–Al bonds are absent.^[5–7] The first complex with an $\sigma(\text{M-Al})$ bond, the Lewis acid/base adduct $[\text{Cp}(\text{CO})_2\text{Fe-AlPh}_3]$ ^[11] originates from the chemistry of metal bases, in which compounds of the type ER_3 ($\text{R} = \text{alkyl, aryl}$) serve as probes for Lewis base centers.^[8–10]

Since the discovery of the Fischer-carbene and -carbyne complexes^[12] the coordination chemistry and the bonding of carbene analogues or, more accurately, “isoelectronic” fragments of the higher homologues of carbon as well as neighboring main group elements have received unbroken attention. Two more recent examples are the Fe–Ge and Fe–Ga complexes $[\{\text{Cp}^*(\text{CO})_2\text{Fe-GeMe}_2(\text{dmap})^+\}]$ ($\text{dmap} = 4\text{-dimethylaminopyridine}$)^[13] and $[(\text{CO})_4\text{Fe-GaAr}^*]$ ($\text{Ar}^* = 2,6\text{-bis}(2,4,6\text{-triisopropylphenyl})\text{phenyl}$).^[14] Ogino et al. discuss a Fe–Ge double bond, Robinson et al. refer to a Fe–Ga triple bond. The cationic Fe–Ge system prepared by Ogino et al. is isoelectronic to the neutral gallium complex $[\text{Cp}(\text{CO})_2\text{Fe-GaR}_2(\text{py})]$ ($\text{R} = \eta^1\text{-C}_5\text{H}_4\text{Me}$).^[15] the neutral Fe–Ga complex of Robinson et al. formally corresponds to a cationic Fischer-carbyne.^[16–21] Since the mid-1980s the study of unusual multiple bond relations has shaped the chemistry of complexes from main group elements and d-block metals. This field was established by work by, among others, Huttner

[*] Prof. Dr. R. A. Fischer, Dr. J. Weiß
Lehrstuhl für Anorganische Chemie II der Universität
D-44780 Bochum (Germany)
Fax: (+49) 234-7094-174
E-mail: rfischer@aci.ruhr-uni-bochum.de

et al. on inidene complexes^[22] and by Herrmann et al. on complexes and metal cumulenes with substituent-free main group elements,^[23] and has been covered in a series of review articles and monographies.^[24–29] In comparison to the elements of Groups 14, 15, and 16 the respective chemistry of Group 13 (earth metals) has not attracted the same attention.^[30] Important general summaries of synthetic and structural chemical conclusions have been compiled by M. J. Taylor (1975), A. T. T. Hsieh (1975), N. C. Norman et al. (1990), and P. P. Power et al. (1996).^[31–34]

The recent surge in the interest in the coordination chemistry of aluminum, gallium, and indium at d-block metal fragments since the beginning of the 1990s stems from the finding that organometallic compounds are potential precursors for a whole host of applications in material science. Prototypical of this trend is the development of alternative precursors for the generation of III/V semiconductor layers (GaAs, InP) by chemical vapor deposition (CVD).^[35–39] One basic idea that was taken up by many groups is the concept of single-source precursors. For compound semiconductors such as GaAs, precursors were developed which contain the atoms relevant for the material, Ga and As, covalently linked in one *single* molecule, and which indeed allow the deposition of the crystalline material in thin layers,^[40–42] for example, GaAs or currently especially important: GaN. Accordingly single-source precursors were synthesized for other material systems like II/IV semiconductors, oxides, hard materials like carbides, borides, or nitrides, and analyzed in view of their suitability for MOCVD.^[41–42] The concept of the single-source precursor also proved to be effective for intermetallic phases, as was shown among others by Kaesz et al., who described the deposition of the β -CoGa phase of the complex $[(\text{CO})_4\text{-}$

$\text{Co-GaCl}_2(\text{thf})]$ by a MOCVD method.^[43, 44] The interest in this intermetallic phase in form of a thin layer comes from the fact that certain binary intermetallic phases of earth metals and d-block metals, for example Co/Ga, are suitable as interface-stable, epitaxial contact metals for (ideal) Schottky barriers and Ohmic contacts on III/V semiconductor surfaces (see the frontispiece of this article). The β -CoGa phase can be grown onto GaAs(100) epitaxially. The heteroepitaxial system forms an atomically abrupt interface, which is stable to diffusion of As up to 800°C. We performed a series of experiments along these lines with the aim of preparing optimized precursors for the deposition of β -CoGa and related intermetallic phases on III/V semiconductor surfaces.^[38, 41, 46–50] Thus, initially the coordination chemistry of aluminum, gallium, and indium at selected d-block metals had to be re-examined from the new perspective of using these complexes as precursors for MOCVD. Of special importance was the chemistry of organo-element fragments ER_a and their donor-stabilized derivatives $\text{ER}_a(\text{L})_b$ ($a, b = 1, 2$; $\text{R} = \text{H}$, alkyl, aryl, Cp^* , etc.). The required properties of MOCVD precursors are: volatility and long-term stability of the compounds under evaporation conditions, low heteroatom content in the ligand sphere around both metal centers (ideally mainly hydrocarbon ligands), and a bond as strong as possible between the atoms that constitute the layer. This had to be achieved for the combinations M/E.^[51–64]

In parallel the chemistry of low-valent earth metal compounds also received significant attention. Examples are the cluster $[(\text{Cp}^*\text{Al})_4]$,^[65, 66] its alkyl analogues $[(\text{ER}')_4]$ and $[\text{R}'_2\text{E-ER}'_2]$ ($\text{R}' = \text{C}(\text{SiMe}_3)_3$, $\text{R}' = \text{CH}(\text{SiMe}_3)_3$, $\text{E} = \text{Al}$, Ga , In)^[67–73] and the anions $(\text{R}'_2\text{Al-AlR}'_2)^-$ ^[74, 75] or $(\text{Ar}^*\text{Ga-GaAr}^*)^{2-}$.^[76] Thus regardless of the aims mentioned

Roland A. Fischer, born in Rosenheim, Germany, in 1961 studied chemistry at the Technische Universität München (1981–1986). In 1989 he received his doctorate for work on alkyne complexes of rhenium under the guidance of W. A. Herrmann. After a postdoctoral fellowship at the University of California at Los Angeles with H. D. Kaesz (1989–1990), he returned to the Technische Universität München and completed his habilitation in 1995 on the coordination chemistry of aluminum, gallium, and indium at transition metals and on the use of these complexes as MOCVD sources for intermetallic phases. From 1996 to 1997 he was Professor for Inorganic Chemistry at the Ruprecht-Karls-Universität Heidelberg, and in 1998 he moved to the Ruhr-Universität Bochum. His scientific work has been honored among others with the Heinz-Meier-Leibnitz award from the Bundesministerium für Bildung und Forschung (Federal Ministry for Education and Science) (1993), a Karl-Winnacker scholarship (1995), and the award of the Alfred-Krupp-von-Bohlen-und-Halbach Foundation (1996). His research interests include the coordination chemistry of main group elements at transition metals, MOCVD of metals and semiconductors (especially gallium nitride) as well as the organometallic precursor chemistry for nanoscale materials (surfaces, colloids, ceramic compounds).



R. A. Fischer



J. Weiß

Jurij Weiß, born 1969 in Dachau, Germany, studied chemistry at the Technische Universität München (1989–1995). He completed his PhD thesis on the synthesis, structure and bonding of new aluminum and indium complexes, and the CVD functionalization of self-assembled organic monolayers at the Ruprecht-Karls-Universität Heidelberg in 1997. Since 1998 he is a member of the scientific staff at the Lehrstuhl II für Anorganische Chemie der Ruhr-Universität Bochum.

above the interests in this latter field were more and more directed towards the coordination chemistry of organo-element fragments to d-block metals. Especially fragments of the RE type played an important role, in which E exhibits the low formal oxidation state +1 and the substituents R are sterically demanding. Isolable RE compounds of this type were used as starting materials for complex syntheses. Noteworthy is the compound $[\text{Ni}(\text{InR})_4]$ ($\text{R} = \text{C}(\text{SiMe}_3)_3$),^[77] which represents a first example of the existence of complexes that are homoleptic with regard to an earth metal as ligator. This example and the complexes $[\text{CpNiAlCp}^*]_2$,^[78] $[\text{Cp}^*\text{Al-Fe}(\text{CO})_4]$,^[79] and $[(\text{CO})_4\text{Fe-GaAr}^*]$ ($\text{Ar}^* = 2,6\text{-bis}(2,4,6\text{-triisopropylphenyl})\text{phenyl}$)^[14] indicate the lively development and the current trends in this field.

2. Constitutions and Structure Types

The main new development during the last few years has centered on the establishment of the chemistry of organo R_aE fragments ($\text{E} = \text{Al}, \text{Ga}, \text{and In}; a = 1 \text{ and } 2$) in the coordination sphere of d-block metals. The steric shielding of the low-valent centers E as well as the intramolecular adduct stabilization proved to be successful guidelines. Both concepts have long-been known in different contexts but have only recently been increasingly used in the coordination chemistry of earth metals. The summary of representative results and the discussion of the ensuing perspectives is the main topic of this review.

For a better classification of the new results first of all a concise but comprehensive survey of the known constitutions and structures of M–E complexes ($\text{M} = \text{d-block metal}, \text{E} = \text{Al}, \text{Ga}, \text{In}, \text{or Tl}$) is given (Figure 1). Excluded are all those complexes which either do not contain a covalent or donor–acceptor bond between M–E or do have a heteroatom bridge between M and E in addition to the M–E bonds (here, heteroatoms are all those atoms except M and E). The types M_2E , M_3E , and M_4E (**A–C**) correspond to compounds containing substituent-free centers E, which are only di-, tri-, or tetra-coordinated by d-block metal fragments M (homoleptic substitution with regard to E as center). Among these the monomeric, symmetrically substituted complexes of type **B**, being derivatives of the element trihalides EX_3 , naturally form the biggest group. Their chemistry, especially for In and Tl, has been studied mainly by Norman et al. and is reviewed elsewhere.^[33, 106–108] In comparison there is apparently only one representative with linear dicoordinate E, namely $[(\text{CO})_5\text{Cr-Tl-Cr}(\text{CO})_5]^-$ (Figure 1, type **A**).^[109] For structure type **C** there are only few examples which have to be regarded as “ate” complexes or Lewis base adducts to the M_3E type **B**. Recently complexes have been found in which monoalkyl units RE ($\text{R} = \text{Cp}^*, \text{C}(\text{SiMe}_3)_3, \text{Ar}^*$) appear as formal CO analogues, and in terminal position (type **D**), or $\mu^{2,3}$ -bridged (types **E** and **F**, Figure 1 and Scheme 5). Compounds displaying these structural elements are the subject of lively debate.^[110] Noteworthy contributions in this area have been made by H. J. Haupt et al. In the sense of an isolobal relation between the alkyl group R and the 18e fragment $[(\text{CO})_5\text{M}]^-$ ($\text{M} = \text{Mn}, \text{Re}$), the fragments RE and $[(\text{CO})_5\text{M}]^-$ corre-

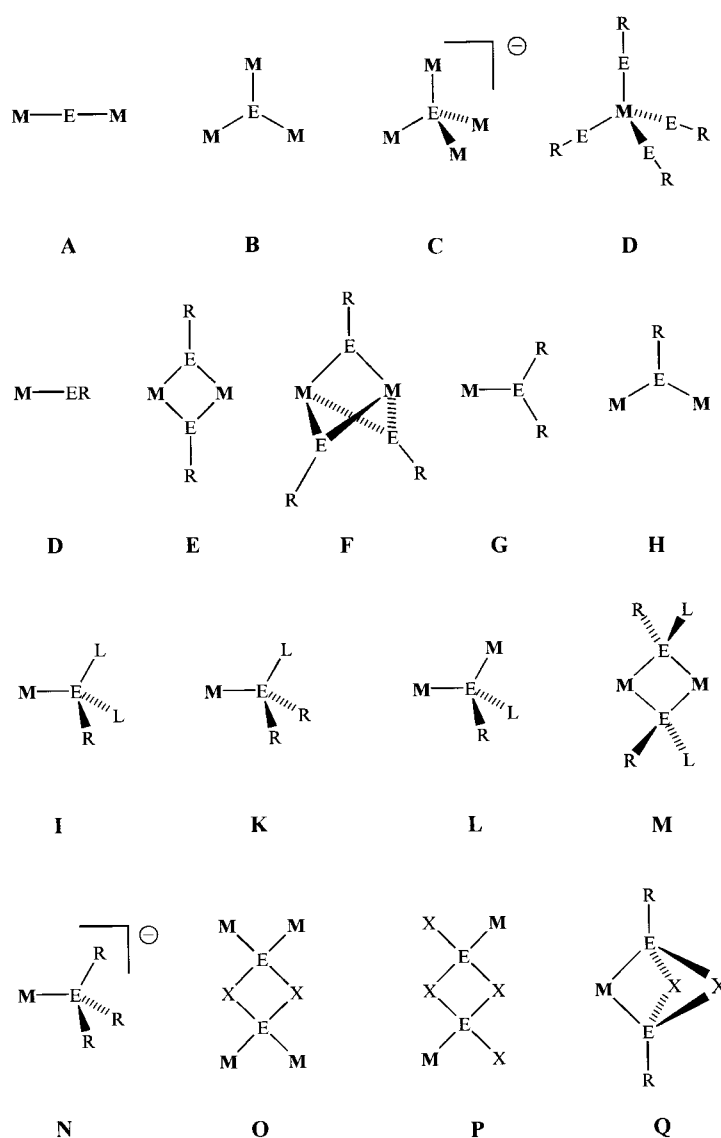


Figure 1. Structure types of M–E complexes ($\text{L} = \text{neutral } 2e\text{-}\sigma$ donor ligand).

spond to each other. Metal carbonyl clusters in which the units $[\text{M}(\text{CO})_5\text{E}]$ with E as ligator adopt CO-analogous, M–M bridging positions (type **E**), are also known from work by Haupt et al. (Figure 1).^[111–114] As deduced from the alkyls ER_3 , the donor-free complexes of types MER_2 (**G**) and M_2ER (**H**) with a tri-coordinate center E with sterically less demanding alkyl groups ($\text{R} = \text{CH}_3, \text{Et}$) for thermodynamic reasons often tend to decompose into the homoleptic products M_3E (**B**) and R_3E . Steric shielding (bulky alkyl groups and/or metal fragments M) stabilizes the structures **G** and **H** kinetically. A lot of complexes with tetra-coordinate centers E of the general formula $[\text{M}_a\text{E}(\text{R}, \text{X})_b(\text{L})_c]$ ($a + b + c = 4$, types **I–N**) also do exist. In the case of simple groups R such as methyl or halide the complexes of type **D** are unknown, but these and the very rare representatives of type **G** and **H** have been isolated in the form of adducts ($\text{L} = \text{py}, \text{C}_4\text{H}_8\text{O}, \text{NR}_3, \text{tmeda}, \text{dmf}, \text{etc.}$): types **I–M** (Figure 1).

Complexes containing the d-block metal fragment as Lewis base complete the family: type **N** ($\text{R} = \text{alkyl or halide}$).

Halide-containing complexes with EX, EX₂, or ERX fragments in general form dimeric halide-bridged structures [M₂EX₂]₂ (type **O**) or [MEX₂]₂ (type **P**; (Figure 1). Starting from here with Lewis bases L (e.g. coordinating solvent molecule) the tetra-coordinate monomers of the types **K** and **L** are accessible. To our knowledge there is only one single example of form **Q**. It is a special case with intramolecular halide bridges. A consequence of the fact that most of the constitutions and structures are derived from the basic trihalides or trialkyl compounds EX₃ and ER₃, respectively, and their coordination chemistry is that the ratio of the metal atoms M and E in complexes typically is M/E ≥ 1. Complexes that contain more than one earth metal per d-block metal are remarkably rare. In total only eight of these compounds have been described, which are listed in Table 1.

The type **D** complex [Ni(InR)₄] (R = C(SiMe₃)₃, Figure 1) is quite interesting, as it can be viewed as an inverted type **C**, now homoleptic with regard to the substitution at the d-block metal. Moreover, it is notable from this overview that the examples from indium chemistry are dominant, followed by thallium and gallium, whereas the aluminum chemistry takes a special position. Even the corresponding chemistry of boron at metal centers, recently summarized in this journal, shows more examples.^[115] The few crystallographically verified complexes with nonbridged M–Al structural elements are shown in Table 1. It is also remarkable that the majority of the described M–E compounds (including E = B) contain metal carbonyl fragments [L(CO)_nM] (L = CO, PR₃, Cp). Complexes without CO ligands, for example those carrying only hydrocarbon-ligands or those stabilized by phosphane ligands, are extremely rare. Therefore the Ir–In complex [(Me₃P)₃Ir–(H)(Et)(InEt₂)], the Pt–Ga and Pt–In complexes [L₂Pt(R)–(ER₂)] (E = Ga, In; Figure 2), which do correspond to type **G** [see also Eqs. (6) and (7)], and the Au–In cluster [(dppe)₂–Au₃In₃Cl₆(thf)₆], which belongs to type **K** (Figure 3) have to be emphasized.^[105]

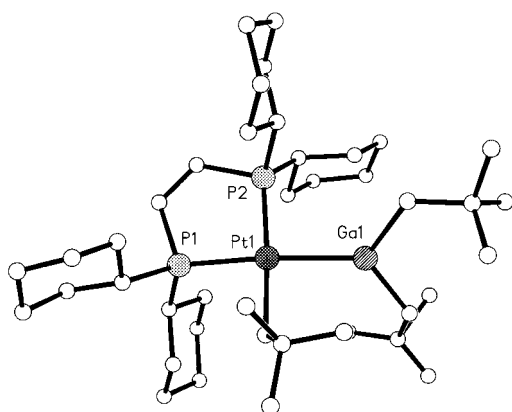


Figure 2. Molecular structure of [cis-(Cy₂PCH₂CH₂PCy₂)(Np)Pt–GaNP₂] in the crystal. Np = neopentyl.^[51]

A survey of CO-free complexes is given in Table 1. Aluminum centers that are not shielded by sterically demanding groups or by base-adduct formation in the case of metal carbonyl fragments tend to form isocarbonyl structures M–CO–Al. A classic example for this is the compound [Cp(CO)₃W]₃Al(thf)₃, which is obtained by transmetalation

Table 1. Selected examples for structurally characterized M/E complexes.

Compound	Structure	M/E	Ref.
<i>aluminum complexes</i>			
[(CO) ₅ W–Al(R)(L ₂)]	I	1	[80]
(R = Cl, Et, <i>t</i> Bu; L ₂ = tmeda, tmpda)			
[(CO) ₄ Fe–AlCp*]	D	1	[79]
[(CO) ₅ CrAlCp*]	D	1	[172]
[Cp(CO) ₂ Fe–Al(<i>i</i> Bu)(R ^N)]	K	1	[60]
[Cp(CO) ₂ Fe–AlPh ₃] [–]	N	1	[11]
[Cp(CO) ₂ Fe] ₂ AlAr]	H	2	[81]
[Cp(CO) ₂ Fe–Al(tmp) ₂]	G	1	[82]
[Co ₂ (CO) ₆ (μ-AlCp*) ₂]	E	1	[83]
<i>gallium complexes</i>			
[(CO) ₅ Cr–GaCp*]	D	1	[84]
[(CO) ₅ Cr–Ga(R)(tmeda)]	I	1	[80, 85]
(R = Cl, Me)			
[(CO) ₄ Fe–Ga(C ₂ H ₅)(thf) ₂]	M	1	[86]
[(CO) ₄ Fe–GaCp*]	D	1	[84]
[(CO) ₄ Fe–GaAr*]	D	1	[14]
[(CO) ₄ Fe–GaCl(tmeda)]	I	1	[87]
[Fe ₂ (CO) ₆ (μ-GaCp*) ₃]	F	2/3	[84]
[Fe ₂ (CO) ₆ (μ-GaSi(SiMe ₃) ₃) ₂ (μ-CO)]	F	1	[88]
[Fe ₂ (CO) ₆ (μ-GaSi(SiMe ₃) ₃) ₃]	F	2/3	[88]
[Cp(CO) ₂ Fe] ₄ Ga ₄ S ₄	P	1	[89]
[(CO) ₄ Fe–Ga(Me)Fe(CO) ₄] ^{2–}	H	2	[90]
[Ru(CO) ₃ {GaCl(thf) ₂ }{GaCl ₂ (thf) ₂ }]	I/K	1/3	[91]
[Co ₂ (CO) ₆ (μ-GaCp*) ₂]	E	1	[84]
<i>indium complexes</i>			
[(CO) ₅ CrInCp*]	D	1	[173]
[(CO) ₅ Cr–In(Br)Cr(CO) ₅] ^{2–}	H	2	[92]
[(CO) ₅ Cr–InBr(thf) _∞]	I	1	[93]
[(CO) ₅ W–In{HB(3,5-Me ₂ pz) ₃ }]	D	1	[94]
[Mn ₂ (CO) ₈ (μ-InC(SiMe ₃) ₃) ₂]	E	1	[95]
[Cp(CO) ₂ Mn–InAr*]	D	1	[96]
[Cp(CO) ₂ Fe–In(R ^N) ₂]	K	1	[59]
[(CO) ₄ Fe–In{HB(3,5-Me ₂ pz) ₃ }]	D	1	[94]
[Fe ₂ (CO) ₆ (μ-InC(SiMe ₃) ₃) ₃]	F	2/3	[97]
[(Me ₃ Si) ₃ C–In(μ-Cl)] ₂ {Fe(CO) ₄ }	Q	1/2	[98]
[Co ₂ (CO) ₆ (μ-InC(SiMe ₃) ₃) ₂]	E	1	[99]
<i>carbonyl-group-free d-block metal/earth metal complexes</i>			
[(Cp) ₂ Ti–AlEt ₂] ₂	G	1	[4]
[Cp*(η ² -C ₂ H ₄)Co–Al(C ₂ H ₅) ₂]	E	1	[100]
[Cp(PMe ₃) ₂ Rh–AlMe(Cl)(μ-Cl)AlMe ₂ (Cl)]	K	1/2	[101]
[Cp(PMe ₃) ₂ Rh–AlMe ₂ (μ-Cl)AlMe ₂ (Cl)]	K	1/2	[101]
[CpNiAlCp*] ₂	E	1	[78]
[Ni{GaC(SiMe ₃) ₃ }] ₄	K	1/4	[73b]
[cis-(Cy ₂ PCH ₂ CH ₂ PCy ₂)(Np)PtGaNP ₂]	G	1	[51]
[IrH(Et)(InEt ₂)(PMe ₃) ₃]	G	1	[102]
[[Cp(PEt ₃)Ni] ₂ InCl] ₂	O	2	[15b]
[[Cp(PEt ₃)Ni] ₃ In]	B	3	[15b]
[Cp(PPh ₃)Ni–InBr ₂ (OPPh ₃)]	K	1	[103]
[Cp ^N (PMe ₃)Ni–InI ₂]	K	1	[104]
[Ni{InC(SiMe ₃) ₃ }] ₄	D	1/4	[77]
[cis-(Cy ₂ PCH ₂ CH ₂ PCy ₂)(Np ^{Si})Pt–GaNP ₂ ^{Si}]	G	1	[54]
[(dppe) ₂ Au ₃ In ₃ Cl ₆ (thf) ₆]	K	1	[105]

Ar = 2-(dimethylaminomethyl)phenyl; Ar* = 2,6-bis(2,4,6-triisopropylphenyl)-phenyl; Cp = η⁵-C₅H₅; Cp* = η⁵-C₅Me₅; Cp^N = [2-(dimethylamino)ethyl]cyclopentadienyl; Cy = cyclohexyl; dppe = 1,2-bis(diphenylphosphanyl)ethane; Np = neopentyl; Np^{Si} = trimethylsilylmethyl; pz = pyrazolyl; R^N = 3-(dimethylamino)propyl; tmeda = *N,N,N',N'*-tetramethylethylenediamine; tmp = 2,2,6,6-tetramethylpiperidine; tmpda = *N,N,N',N'*-tetramethylpropylendiamine.

from Al and [Cp(CO)₃W]₂Hg] in THF, the structure of which does not correspond to type **B** (or a THF adduct) that is well known for Ga and In chemistry but contains the structural element W–CO–Al [Eq. (1)].^[116] Suitable steric and coordinative shielding allows M–Al bond formation (Table 1). The

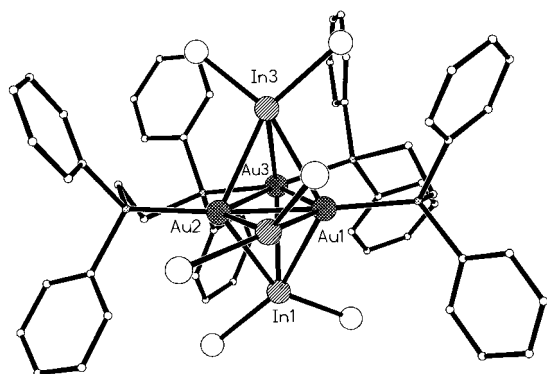
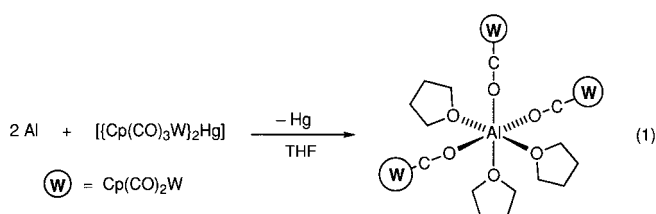


Figure 3. Molecular structure of $[(\text{dppe})_2\text{Au}_3\text{In}_3\text{Cl}_6(\text{thf})_6]$ in the crystal. The thf ligands are omitted for clarity.^[105]

diamidoaluminum complex $[\text{Cp}(\text{CO})_2\text{Fe}-\text{Al}(\text{NR}_2)_2]$ belongs to type **G**.^[82] So far the only indication of an analogue dialkyl complex of aluminum is the correspondence of NMR-spectroscopic characteristics of $[(\text{L})_2\text{Pt}(\text{R})(\text{AlR}_2)]$ with the homologous gallium and indium complexes [Figure 2, see Eq. (7)], which are secured by single-crystal X-ray diffraction. Against this background the synthesis of the complexes $[(\text{CO})_4\text{FeAlCp}^*]$ (see Scheme 4), $[\{\text{CpNiAlCp}^*\}_2]$ and $[(\text{CO})_3\text{CoAlCp}^*]_2$ [Figure 4 and Eqs. (2) and (3)] marks important progress.

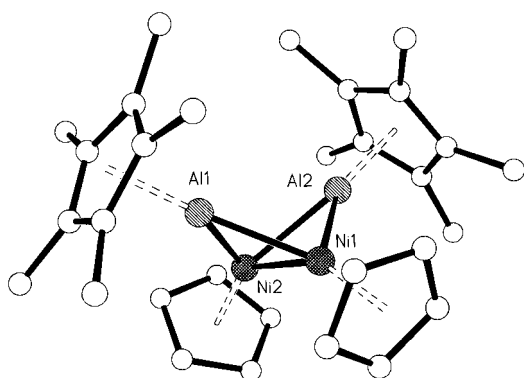
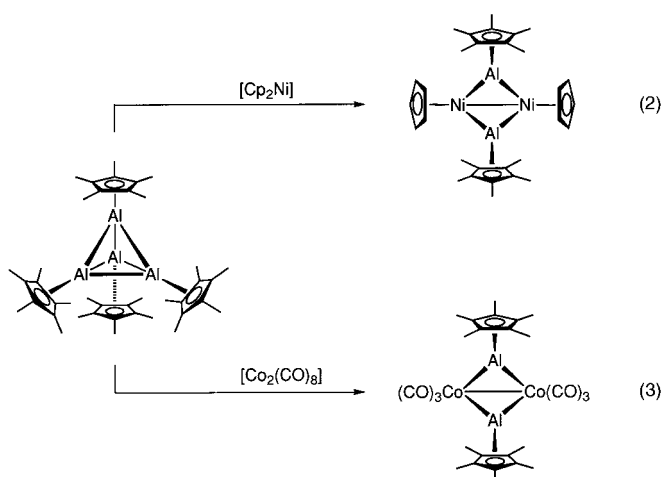


Figure 4. Molecular structure of $[\{\text{CpNiAlCp}^*\}_2]$ in the crystal.^[78]

As will be discussed in the following section the dominance of metal carbonyl fragments in the coordination chemistry of earth metals at d-block metal fragments stems from synthetic limitations which have only been overcome recently mainly by the preparative availability of low-valent organo earth metal compounds RE .^[72, 73]

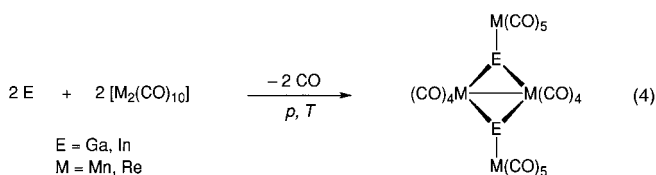


3. Synthesis

A whole series of methods has proved to be worthwhile for the synthesis of $\text{M}-\text{E}$ complexes; for details we refer to former surveys.^[31–34] The applicability and the preparative success strongly depends on the selected metal combination as well as on the type of d-block metal mainly stabilized with CO ligands.

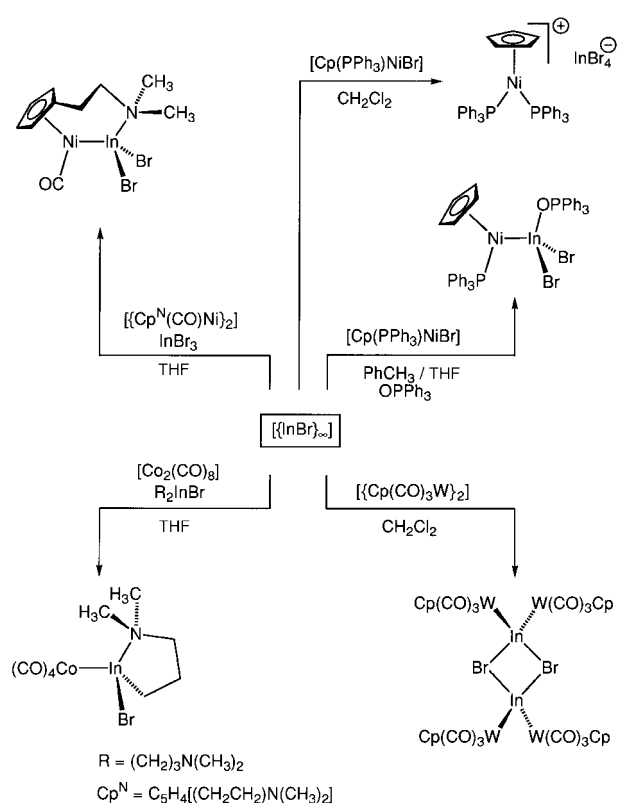
3.1 Pressure Carbonylation

The heavy homologues Ga, In, and Tl react as elements with finely dispersed d-block metals, typically Co, Mn, Re, or their respective metal carbonyls under CO pressure (200 atm) at increased temperature (100–200 °C) to give the corresponding carbonyl derivatives $[(\text{CO})_n\text{M}]_3\text{E}$ or metal clusters such as $[\{\text{M}_2(\text{CO})_8(\mu\text{-EM}(\text{CO})_5)_2\}]$ ($\text{M} = \text{Mn, Re; E} = \text{Ga, In}$)^[111, 113] and $[\text{Re}_4(\text{CO})_{12}(\mu^3\text{-InRe}(\text{CO})_5)_4]$.^[112, 114] The use of the halides EX_3 , E_2X_4 ($\text{E} = \text{Ga, In}$) in respective reactions also leads to carbonyl clusters in which fragments of the type $[\{\text{L}(\text{CO})_n\text{M}\}\text{E}]$ (isolobal to RE) appear in a bridging, CO-analogous position [Eq. (4)]. Aluminum complexes $\text{M}-\text{Al}$ have not yet been obtained in this way.



3.2. Insertion Reactions

Insertion reactions of low-valent halides E_2X_4 and EX ($\text{E} = \text{Ga, In}$) in metal–metal bonds and metal–halide bonds also belong to the established repertoire. For metal carbonyl complexes this access is very reliable and has been well documented.^[15, 32, 117–123] The insertion of InX into the $\text{M}-\text{M}$ bonds of $[\text{Cp}(\text{CO})_3\text{M}]_2$, leading to the dimer complexes $[\{\text{InBr}\{\text{Cp}(\text{CO})_3\text{M}\}_2\}]$ ($\text{M} = \text{Cr, Mo, W}$) (Scheme 1)^[124] is typical. The synthesis of the RuGa_3 complex $[(\text{CO})_3\text{Re}-$



Scheme 1. Synthesis of M–In complexes by the insertion route.

$\{\text{GaCl}(\text{thf})_2\}\{\text{GaCl}_2(\text{thf})_2\}$ from Ga_2Cl_4 and $[\text{Ru}_3(\text{CO})_{12}]$ is derived from the insertion concept as well.^[91] Green et al. give an example for analogous reactions with “GaI”.^[15]

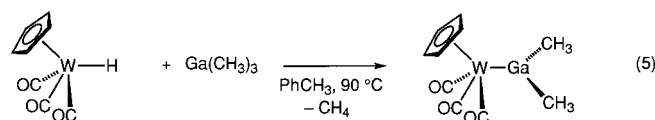
Nothing is known about insertions with low-valent AIX derivatives in M–M or M–X bonds. Insertions in “CO-free” d-block metal complexes are less well documented. Earlier work by Hsieh et al. contains references on reactions of $[\text{Ph}_3\text{PAuCl}]$, $[(\text{Et}_3\text{P})_2\text{PtCl}_2]$, or *trans*- $[\text{Pt}(\text{Cl})(\text{SiPh}_3)(\text{PMe}_2\text{-Ph})_2]$ with InCl , in which the formation of complexes with a unit “M–InCl₂” were assumed on the basis of elemental analysis and IR-spectroscopic data.^[122] Recent investigations of these reactions showed that this simple conception is not correct and that rather complex processes accompanied by redox processes take place. Thus in the system $\text{Ph}_3\text{PAuCl}/\text{InCl}$ mainly the salt $[(\text{Ph}_3\text{P})_2\text{Au}][\text{InCl}_4]$ is formed and also in the case of the combination $[(\text{CO})_5\text{Mn}-\text{AuPPh}_3]/\text{InBr}$, $[(\text{CO})_5\text{-Mn-InBr}_3][(\text{Ph}_3\text{P})_2\text{Au}]$ is obtained.^[125] Only through addition of chelating phosphane ligands such as 1,2-bisdiphenylphosphinoethane (Diphos) was it possible to isolate various Au–In clusters from the reaction mixture of $[(\text{PPh}_3)\text{AuCl}]/\text{InCl}$ (Figure 3).^[105] There are no indications of a monomer or dimer species of the type $[\text{Ph}_3\text{PAu-InCl}_2]$ (type **G** or **P**).

As with the chemistry of gold the product spectrum of the reaction of $[\text{Cp}(\text{Ph}_3\text{P})\text{NiBr}]$ with InBr strongly depends on the reaction conditions. The preferred redox product $[\text{Cp}(\text{Ph}_3\text{-P})_2\text{Ni}][\text{InBr}_4]$ can only be avoided by using suitable reactant ligands such as $\text{O}=\text{PPh}_3$ or quinuclidine (NC_7H_{13}) as well as special reaction conditions (Scheme 1).^[103] Because of the availability of low-valent organo-element compounds insertion proves to be very interesting for forming M–E bonds especially for CO-free systems. The reaction of $[(\text{Cp}^*\text{Al})_4]$

with $[\text{Cp}_2\text{Ni}]$ to form the butterfly cluster $[(\text{CpNiAlCp}^*)_2]$, which formally can be regarded as insertion of AlCp^* into a Ni–C(Cp) bond [Eq. (2)] is currently the only example for this concept (Figure 4).^[78]

3.3. Alkane Elimination

The first complex containing a GaR_2 unit (type **G**) was obtained by reacting $[\text{Cp}(\text{CO})_3\text{WH}]$ with $\text{Ga}(\text{CH}_3)_3$ with elimination of one equivalent of CH_4 [Eq. (5)]. Corresponding reactions are known for the chemistry of indium and

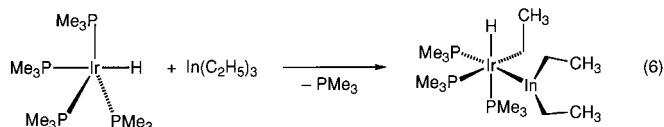


thallium.^[126, 127] This elimination of alkane, often formally classified as protolysis, presumably proceeds according to a radical mechanism.^[127] In the past a few complexes were isolated and characterized according to this method. In principle this alkane elimination offers an elegant strategy for forming M–E bonds. A series of hydrides and polyhydrides with different substituent patterns, also CO-free systems, are known. Nevertheless selective reactions of this kind are rare and restricted to comparatively reactive M–H functions and apparently to simple sterically less hindered homoleptic organo compounds of the earth metals. In addition, raised reaction temperature and photoactivation are necessary in most cases. Both factors favor the redistribution of the substituents at the center E leading to release of ER_3 . Thus complexes of the types **G** or **K** are only available with difficulty by this route.

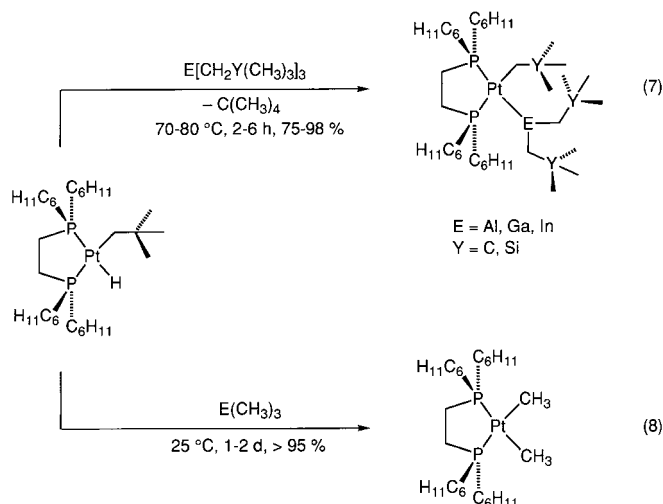
3.4. Bimolecular Addition Reactions of Alkyl Earth Metal Compounds at d-Block Metal Fragments

For this type of reaction only d-block metal complexes that do not carry any halide, alkoxide, or amide function or reactive M–H groups could be used. Otherwise unwanted alkylation or alkane elimination takes place (see above). In this context Thorn et al. have investigated the interaction of R_3E compounds ($\text{E} = \text{Al}, \text{Ga}, \text{In}; \text{R} = \text{Me}, \text{Et}$) with various CO-free and reactive d-block metal complexes of iridium, rhodium, and platinum.^[102] Typically complex product mixtures were obtained from which pure substances could be isolated only in a few cases.^[102] The characterization of the products was often achieved by in situ NMR spectroscopy of the reaction solution. Thus AlMe_3 reacts with $[\text{IrMe}(\text{PMe}_3)]$ under excessive ligand exchange to give a mixture, which, on the basis of NMR spectroscopic data, probably consists of the complexes $[\text{Me}_3\text{AlPMe}_3]$, $[\text{MeIr}(\text{PMe}_3)_x\text{AlMe}_3]$, and $[\text{MeIr}(\text{AlMe}_2)(\text{PMe}_3)_3]$. Structurally characterized examples for M–Al chemistry which have been obtained similarly are listed in Table 1. InEt_3 exchanges with $[\text{Me}_2\text{Pt}(\text{cod})]$ to form $[\text{Et}_2\text{Pt}(\text{cod})]$ ($\text{cod} = \text{cyclooctadiene}$); $[\text{Me}_2\text{Pt}(\text{bpy})]$ ($\text{bpy} = 2,2'$ -bipyridine) reacts reversibly with InMe_3 , probably form-

ing $[\text{Me}_2\text{Pt}(\text{bpy})(\text{InMe}_2)]$, and $[(\eta^2\text{-C}_2\text{H}_4)\text{Pt}(\text{PPh}_3)_2]$ forms unstable $[(\text{Me}_2\text{In})(\text{Me})\text{Pt}(\text{PPh}_3)_2]$ with InMe_3 . Only the complex $[\text{fac}-(\text{Me}_3\text{P})_3(\text{H})(\text{Et})\text{Ir}-\text{InEt}_2]$, obtained in 20% yield according to Equation (6), could be characterized structurally.



A selective and quantitative synthesis of stable complexes of the type $[\text{L}_n\text{M}-\text{ER}_2]$ (**G**) by formal oxidative addition of a E-C bond to a coordinated unsaturated d-block metal fragment is only known for the reaction of the alkylplatinum hydride $[(\text{L})_2\text{Pt}(\text{H})(\text{CH}_2t\text{Bu})]$ ^[128, 129] with R_3E ($\text{R} = \text{CH}_2t\text{Bu}$, CH_2SiMe_3 ; $\text{E} = \text{Al}$, Ga , In ; $\text{L} = (\text{C}_6\text{H}_{11})\text{PCH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_{11})$) as reaction partner and at the same time as solvent [Eq. (7)].^[51, 54] Upon heating, the Pt complex slowly releases



neopentane in a controlled manner in a first-order reaction. The reactive fragment thus formed, $[\text{cis}-(\text{L})_2\text{Pt}]$, then is available for a series of subsequent reactions.^[128, 129] It has to be emphasized that the course of the reaction is strongly influenced by small variations of the groups R. According to Equation (8) quantitative alkylation or alkyl exchange and the formation of $[(\text{L})_2\text{PtR}_2]$ is observed for $\text{R} = \text{CH}_3$, C_2H_5 , isobutyl. The work of Schneider et al. on the interaction of alkylaluminum compounds with transition metal fragments should be noted in this context. Among complexes of this kind structurally characterized were those with the rare Co-Al bonds (see Table 1).^[100]

3.5. Salt Elimination

Salt metathesis of earth metal halides $\text{X}_{3-a}\text{ER}_a$ ($a = 1, 2$; $\text{R} = \text{H}$, alkyl, aryl, Cp^*) with carbonylmetalates $[\text{L}(\text{CO})_n\text{M}]^{m-}$ ($\text{L} = \text{CO}$, Cp , Cp^* , PR_3 ; $\text{M} = \text{Cr}$, Mo , W , Mn , Re , Fe , Ru , Co , Ni) is the method of choice for the synthesis of the organyl derivatives of the types **I-N** (Figure 1, Figure 5; Schemes 2–5).

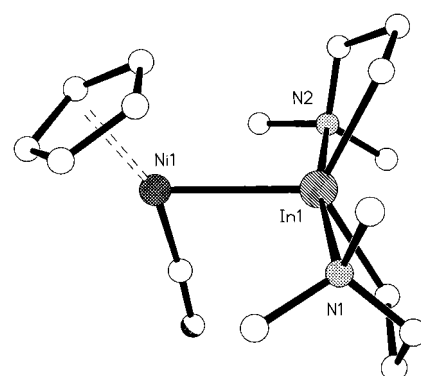
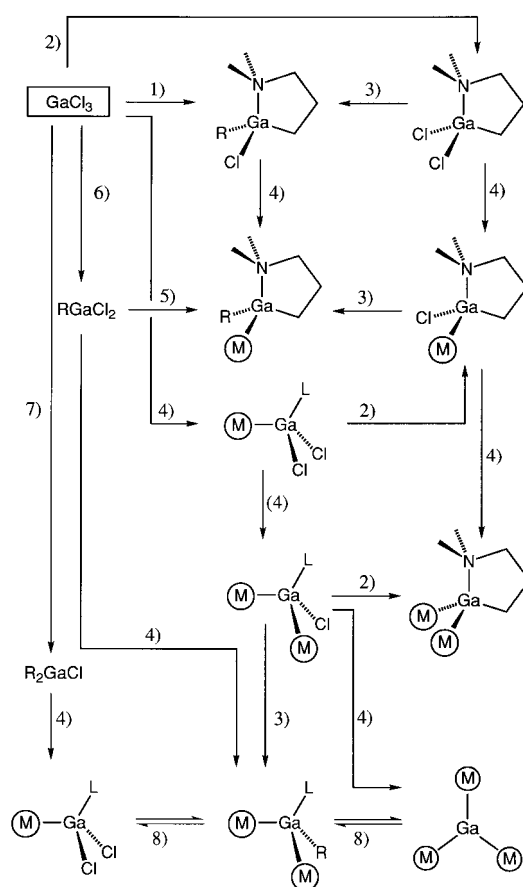
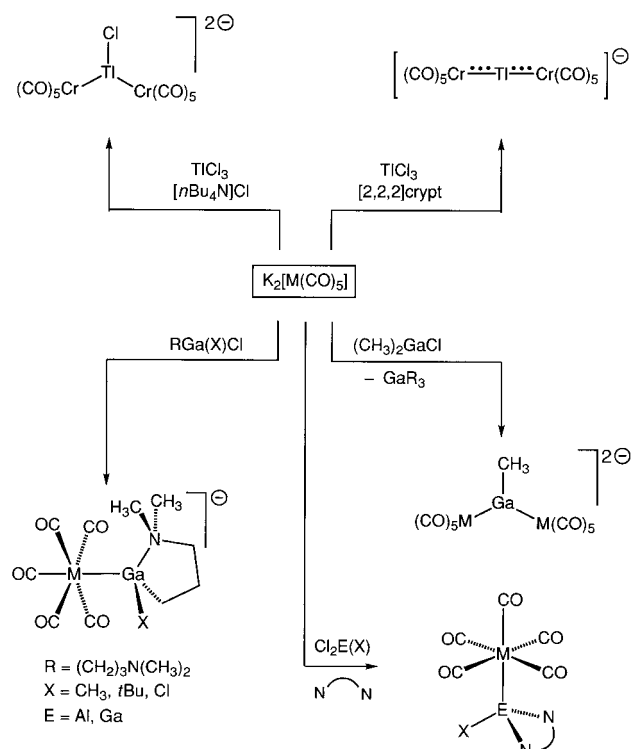


Figure 5. Molecular structure of $[\text{Cp}(\text{CO})\text{Ni}-\text{In}(\text{R}^{\text{N}})_2]$ in the crystal $[\text{R}^{\text{N}} = 3-(N,N\text{-dimethylamino})\text{propyl}]$.^[53]

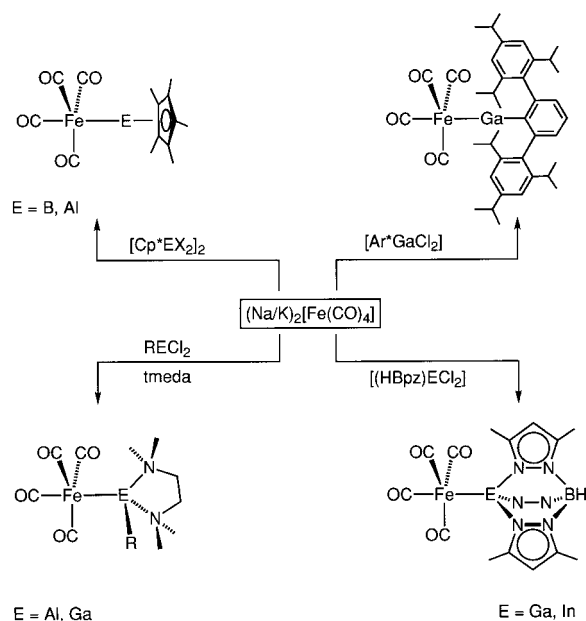


Scheme 2. Synthesis and modification of the transition metal-substituted gallanes of the general type $[\text{L}'(\text{CO})_n\text{M}]_a[\text{GaR}_{3-a}(\text{L})]$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}, \text{Mn}, \text{Re}, \text{Fe}, \text{Ru}, \text{Co}, \text{Ni}$; $\text{L}' = \text{Cp}, \text{Cp}^*, \text{CO}, \text{PR}_3$; $n = 1-4$; $a = 1, 2, 3$; $\text{R} = \text{H}$, alkyl, aryl; $\text{L} = \text{O}^-, \text{N}^-, \text{P-Lewis donor}$). 1) R_4Si ; 2) $\text{Li}[(\text{CH}_2)_3\text{NMe}_2]$, Et_2O ; 3) $\text{R} = \text{alkyl, aryl}$: RLi , toluene; $\text{R} = \text{H}$: $\text{Li}[\text{BEt}_3\text{H}]$, THF; $\text{R} = \text{BH}_4$: $\text{Li}[\text{BH}_4]$, Et_2O ; 4) $[\text{L}(\text{CO})_n\text{M}](\text{Na/K})$; 5) $\text{R} = \text{H}$, alkyl: 1. $\text{Li}[(\text{CH}_2)_3\text{NMe}_2]$, pentane; 2. $[\text{L}(\text{CO})_n\text{M}](\text{Na/K})$; 6) Me_3SiH ; 7) 1. 3 equiv RLi ; 2. 0.5 equiv GaCl_3 ; 8) $T > 0\text{ }^\circ\text{C}$, $\text{Do} = \text{THF}$, $\text{R} = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5$.

Functionalization (e.g. alkylation) of halide derivatives (**O, P**) is possible, but the yields are not always good. Typical complications are the formation of “ate” complexes and the redistribution of substituents in the case of sterically unhindered, coordinatively unsaturated centers E. The nucleophil-

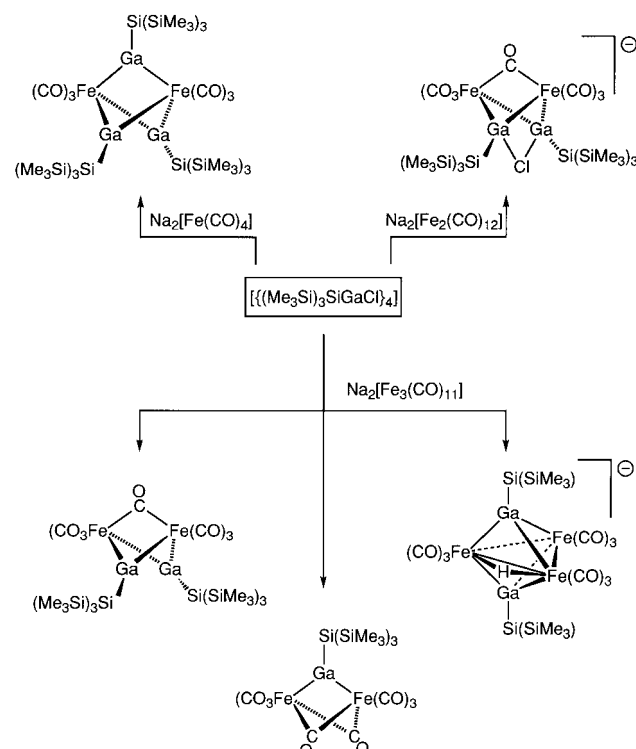


Scheme 3. Synthesis of M–E complexes of the types **A**, **H**, **I**, and **K** by salt metathesis with divalent carbonylmetalates ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$).



Scheme 4. Synthesis of Fe–E complexes of the types **D** and **I** by salt metathesis.

icity of the carbonylmetalate compared to the solvent and the leaving group X as well as the Lewis acidity and the steric conditions at the center E are decisive for a successful synthesis. The weak nucleophiles $[(\text{CO})_n\text{M}]^-$ ($\text{M} = \text{Co}, \text{Mn}; n = 4, 5$) do not react in polar, coordinating solvents (THF, CH_3CN , HMPT, etc.). In these solvents complexes of the type $[(\text{CO})_n\text{M}-\text{ER}_2(\text{L})]$ (type **K**) are subject to a heterolytic dissociation of the M–E bond according to the polarities



Scheme 5. Synthesis of Fe–Ga clusters of the types **E** and **F** by salt metathesis.

$\text{M}(\delta^-)$ and $\text{E}(\delta^+)$. In the presence of dissolved halide ions as competing nucleophiles the organo-element halides reform. Syntheses with weak nucleophilic carbonylmetalates are ideally carried out in nonpolar, noncoordinating solvents, in which the insoluble carbonylmetalate is suspended. The alkali metal halide is also insoluble in this medium; however, the product complex is well soluble. The presence of equimolar amounts of a Lewis base for a coordinative saturation of the center E is often necessary, though. M–Al bonds can only be realized in this way with strong nucleophiles, otherwise isocarbonyl-bridged polynuclear complexes are formed [see Eq. (1)]. The latter is the case for reactions of AlCl_3 with $\text{Na}[\text{Co}(\text{CO})_4]$ in toluene.^[130] For $[\text{Me}_3\text{P}(\text{CO})_3\text{Co}]^-$ as a stronger nucleophile in THF as medium, Co–Al-bonded complexes were obtained.^[53]

Whereas for the majority of the syntheses monovalent carbonylmetalates were used, recently there has been a rising interest in the reactivity of divalent carbonylmetalates, for example $[(\text{CO})_n\text{M}]^{2-}$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}; \text{Fe}, \text{Ru}$), toward earth metal halides (Figure 6). Thus according to Scheme 3 complexes of the metal cumulene type **A** or indenyl type **H** have been obtained for $\text{E} = \text{Ga}, \text{In}$, and Ti .^[90, 92, 109] Again, redox processes are possible and can be elegantly used. A nice series of Fe/Ga clusters, the structures of which all obey the Wade–Mingos rules, has been synthesized and characterized by G. Linti et al. (Scheme 5; Figure 7).^[88]

The reaction of a suspension of $[(\text{CO})_4\text{Fe}]_2\text{K}_2$ in THF with $\text{ClGa}(\text{R})(\text{R}^N)$ ($\text{R}^N = \text{CH}_2\text{CH}_2\text{CH}_2\text{NMe}_2$) primarily leads to the soluble and isolable anion $[(\text{CO})_4\text{Fe}-\text{Ga}(\text{R})(\text{R}^N)]^-$. The digallium complex $[(\text{CO})_4\text{Fe}\{\text{Ga}(\text{R})(\text{R}^N)\}_2]$ (see Scheme 11) is only formed after an exchange of solvent (toluene for THF),

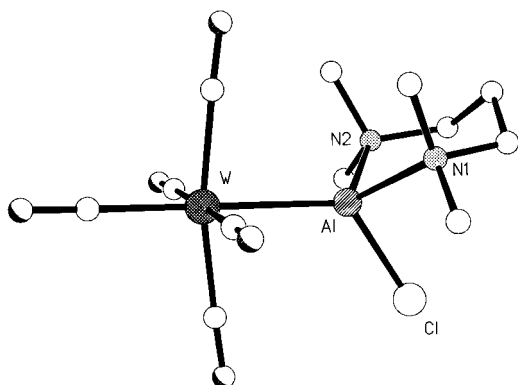


Figure 6. Molecular structure of $[(\text{CO})_5\text{W}-\text{Al}(\text{Cl})(\text{tmpda})]$ (tmpda = N,N,N',N' -tetra-methylpropylendiamine) in the crystal.^[80]

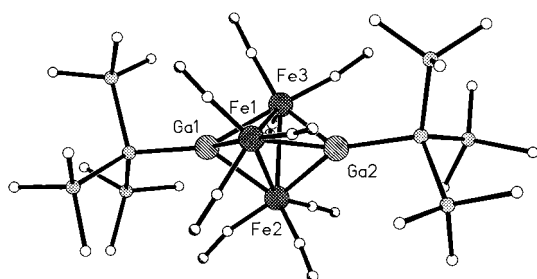


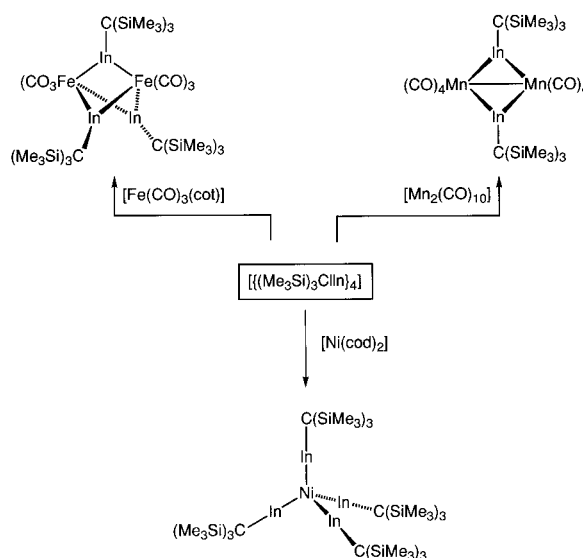
Figure 7. Molecular structure of the cluster ion $[((\text{CO})_3\text{Fe})_3\{\text{GaSi}(\text{SiMe}_3)_2\text{H}\}]^-$ in the crystal.^[88]

in accord with the lower nucleophilicity of the intermediate. The pentacarbonyl derivatives $[(\text{CO})_5\text{M}-\text{Ga}(\text{R})(\text{R}^N)]^-$, though, do not react further because of the higher steric demand and at the same time lower nucleophilicity (Scheme 3). The same is valid for $[(\text{NO})(\text{CO})_3\text{Mn}-\text{Ga}(\text{R})(\text{R}^N)]^-$. The reaction of $\text{K}_2[\text{Fe}(\text{CO})_4]$ with $\text{Cl}_2\text{Ga}(\text{R}^N)$ provides the dimeric complex $[[\mu-\text{Ga}(\text{R}^N)][(\text{CO})_4\text{Fe}]_2]$. Steric hindrance at the α -C atom in the case of $\text{Cl}_2\text{Ga}\{\text{C}(\text{TMS})_2\text{CH}_2\text{CH}_2\text{NMe}_2\}$ as gallium compound prevents dimerization and the reaction stops at the level of the monoanion.^[63, 131, 132] The importance of sterically demanding groups R or intramolecular adduct stabilization is proved by the differing reaction behavior of ClGaR_2 ($\text{R} = \text{CH}_3$, C_2H_5) under otherwise identical reaction conditions. In these cases after elimination of GaR_3 , the dianionic GaR-bridged complexes of the indenyl type **H** (Scheme 3) are obtained. The complexes of types **D** and **I** can also be obtained by salt elimination starting from X_2ER . By adding strong Lewis bases (tmeda, NR_3) or by using special sterically very demanding groups R [$\text{R} = \text{Cp}^*$, Ar^* , $\{\text{HB}(3,5\text{-Me}_2\text{pz})_3\}$] the formation of trinuclear complexes of type **H** is suppressed (Scheme 4). So far there are no results on the reactivity of tetravalent carbonylmetalates $[(\text{CO})_n\text{M}^{4-}]$.

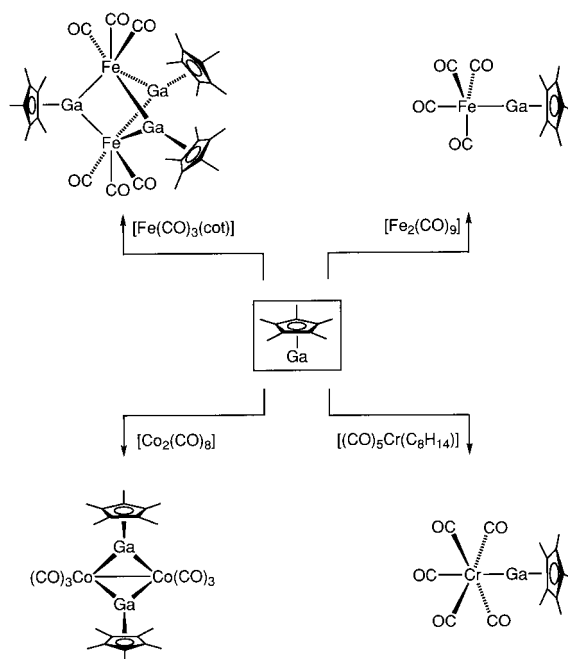
3.6. Ligand Substitution

The availability of monovalent organo derivatives RE or clusters $(\text{RE})_4$ ($\text{R} = \text{Cp}^*$, $\text{C}(\text{SiMe}_3)_3$, $\text{Si}(\text{SiMe}_3)_3$) as starting materials for syntheses recently has allowed coordination of

RE as a potent $2e$ -donor ligand to the d-block metal fragment by displacement of *weaker* bonded ligands (CO, alkenes). This route opens up truly new perspectives. The most striking example is the possibility to achieve complexes with “inverted” ratio $\text{E}/\text{M} > 1$. This is exemplified by the synthesis of the homoleptic NiIn_4 complex from $[\text{Ni}(\text{cod})_2]$ and $[[(\text{SiMe}_3)_3\text{C}]\text{In}]_4$ ^[77] or the $[\text{Fe}_2(\text{CO})_9]$ analogues $[(\text{CO}_3\text{Fe}(\mu\text{-ER}))_3\text{Fe}(\text{CO})_3]$ ($\text{E} = \text{Ga}$, In ; $\text{R} = \text{Cp}^*$, $\text{C}(\text{SiMe}_3)_3$)^[84, 97] [Scheme 6, Scheme 7; Eq. (3)]. Clusters such as $[\text{Ni}_4(\mu\text{-Cp}^*\text{Ga})_4(\text{CO})_6]$ (Figure 8) with μ^2 - and μ^3 -bridging Cp^*Ga units^[84] or $[(\mu\text{-Cp}^*\text{Al})_2\text{Co}_2(\text{CO})_6]$,^[83] which were derived from $[\text{Ni}(\text{CO})_4]$ or $[\text{Co}_2(\text{CO})_8]$, respectively, by CO substitution impressively prove this method. Interesting results can be expected from this promising new field.^[172, 173]



Scheme 6. Synthesis of M-In complexes and clusters of the types **D**, **E**, and **F** by ligand substitution. cot = cyclooctatetraene; cod = cyclooctadiene.



Scheme 7. Synthesis of M-Ga complexes and clusters of the types **D**, **E**, and **F** by ligand substitution.

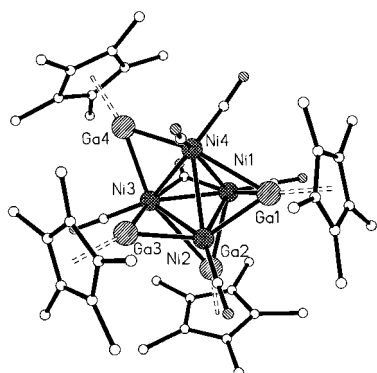
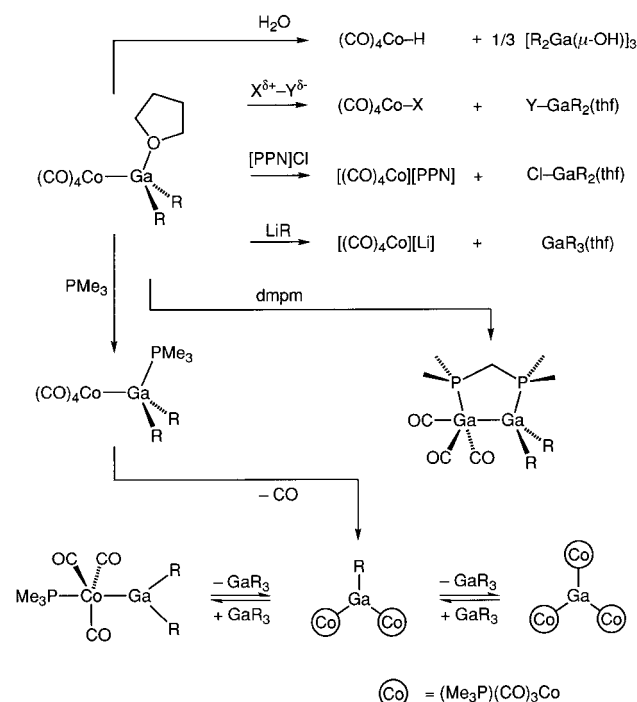


Figure 8. Molecular structure of $[\text{Ni}_4(\mu\text{-GaCp}^*)_4(\text{CO})_6]$ in the crystal.^[84]

4. Reactivity

Remarkably few investigations have considered the chemical reactivity of M–E complexes, if one does not count the chemistry relevant for MOCVD applications (see Chapter 6). The typical Lewis acidity at the earth metal and the use of substituent exchange or transfer reactions for preparative purposes for halogeno complexes of the types **O** and **P** in combination with their homoleptic congeners **B** and **C** has already been discussed in previous surveys.^[32, 33] Here, though, some conditions characteristic for the organo derivatives shall be stressed, for which the chemistry of the Co–Ga and Fe–Ga series are representative examples. The chemical properties of these M–Ga complexes (types **B**, **K**, and **L**) are characterized a) by the polar character of the M–Ga bond which can easily be split by electrophilic or nucleophilic reaction partners, b) by the competition of both metal centers for donor ligands, and c) by the selective conversion of Ga–X functions (X = halide).

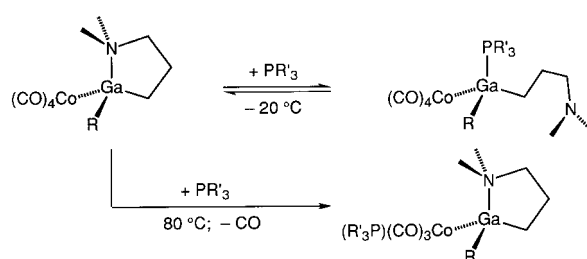
According to Scheme 8 the reaction of Co–Ga complexes with one equivalent of water leads to the direct formation of $[(\text{CO})_4\text{CoH}]$ and the trimeric (volatile) alkylgallium hydroxide. A selective hydrolysis to form transition metal substituted gallium oxide cage molecules (Fe–Ga) has recently been described.^[174] Electrophilic reaction partners like trimethyl- and triphenylstannyl chloride (also mercury halides, bromine, iodine, etc.) instantly split the metal–metal bonds. This is also true for the complexes of types **D** and **I**. The instability of the Co–Ga bond of complexes of the general formula $[(\text{L}')(\text{CO})_3\text{CoGaR}_2(\text{L})]$ (type **K**) in solution is also apparent in their tendency to heterolytic dissociation depending on the substitution pattern at both metal centers as well as on the solvent. According to the IR solution spectra the complexes are undissociated in pentane, cyclohexane, or benzene. Only the four $\tilde{\nu}(\text{CO})$ absorptions that can be expected for C_s -symmetrical complexes $[\text{LCo}(\text{CO})_4]$ (here, L stands for the earth metal fragment) appear. In THF the Co–Ga complexes start to dissociate, in acetonitrile, DMSO, and HMTP dissociation is completed. Dissociation is suppressed in the case of strong nucleophilic carbonylmetalates. Fast and quantitative nucleophilic cleavage of M–E bonds in $[(\text{CO})_4\text{Co–GaR}_2(\text{thf})]$ occurs if chloride ions are added to polar media (dichloromethane, THF, acetonitrile, DMSO) (Scheme 8). This also explains why salt elimination according to Scheme 2 in these solvents causes problems. Basic ligands



Scheme 8. Selected examples for the reactivity of $\sigma(\text{Co–Ga})$ bonds. dmpm = bis(dimethylphosphanyl)methane.

such as THF coordinated to the Ga center can be displaced by phosphanes from -20°C onwards. In solution the isolable adducts are unstable above 0°C . For monodentate phosphanes, after thermal CO substitution the complexes are subject to substituent redistribution at the Ga center, and an equilibrium mixture is formed (Scheme 8). However, reactions with diphosphane chelate ligands to give Co–Ga-bridged systems proceed in a uniform manner. This again proves the instability of tricoordinate units $\text{R}_2\text{Ga–M}$.

In this context Scheme 9 shows how an effective suppression of the substituent redistribution can be achieved by intramolecular adduct stabilization if one wants to avoid the



Scheme 9. Effect of the intramolecular adduct formation on the stability of organogalliocobalt complexes compared to alkyl group substitution.

alternative, that is the introduction of sterically very demanding ligands of high-molar mass. This is of special importance with regard to the necessary volatility for MOCVD applications. A compromise has to be found between molar mass and stabilizing effects for adequately volatile as well as long-term stable M/E precursors. Sterically very demanding ligands or groups R thus are a problem. Intramolecular adduct formation is the preferred method. The reaction of intramolecularly adduct-stabilized Co–Ga model compounds of Scheme 2 with

alkylphosphanes of the type PR_3 ($\text{R} = \text{CH}_3, \text{C}_2\text{H}_5$) in pentane at -78°C yields isolable phosphane adducts at low temperatures through opening of the chelate ring (Scheme 9). In a closed system (vacuum-sealed NMR tube; toluene solution) between -80°C and room temperature an equilibrium can be observed by ^{31}P NMR spectroscopy in which the Ga-coordinated phosphane exists with the open chelate, and free phosphane exists with the closed chelate ring. On heating to about $+80^\circ\text{C}$, thermal decarbonylation takes place at the cobalt atom, while at the same time phosphane is coordinated *trans* to the gallium center. This process proved to be reversible. As the sample was cooled down to room temperature, the signal of Co-coordinated phosphane decreased ($\delta = 49.1$ to 50) and the signals of Ga-coordinated and free phosphane increased in intensity (-11.3 to -12.8 and $\delta = -17.2$). Also in the related In compound $[(\text{C}_6\text{H}_5)_3\text{P}(\text{CO})_3\text{Co-InCl}_2]$, the metal centers compete for the phosphane ligand; phosphane coordination at the In center is preferred for the Co-In complex.^[139] In the open system (removal of the released CO by inert gas stream or by evacuation in vacuo) the *trans*-phosphane-substituted complexes were isolated in substance. For sterically more demanding phosphanes (PCy_3 , PPh_3 ; $\text{Cy} = \text{cyclohexyl}$) the Ga-phosphane intermediates could not be identified spectroscopically. Alkyl exchange reactions took place in none of these cases. Selective derivatization of GaCl_n functions ($n = 1, 2$) is possible in many cases (Scheme 2).

Reactions with carbonylmetalates lead to the corresponding M_nGa complexes ($n = 2, 3$). The introduction of alkyl groups or other nucleophilic groups is also possible for dissociation-stable M-Ga bonds, which is the case for strongly nucleophilic d-block metal fragments. One example of this is the selective insertion of hydrido and tetrahydridoborate groups into Fe-Ga complexes to give $[\text{Cp}(\text{CO})_2\text{Fe-Ga}(\text{R}^n)(\text{Y})]$ ($\text{Y} = \text{H}, \text{BH}_4$) by means of superhydride, $\text{Li}[\text{BEt}_3\text{H}]$, or $\text{Li}[\text{BH}_4]$ in diethyl ether without splitting the Fe-Ga bond or attacking the Fe-CO ligands. The borane-derivative in Scheme 10 has to be regarded as the first example of a borane complex of gallium structurally characterized in the solid state. It was used as MOCVD precursor for FeGa films (Chapter 6).

Unlike the chemistry of d-block metal borylenes, which has been studied with regard to applications in organic synthesis up to the point where a d-block metal catalyzed borylation reaction has been developed,^[115] the chemistry of the higher homologues of Group 13 has not really been investigated in any great detail.^[174] Up to now the synthesis and the investigation of the structure and bonding conditions of the complexes have been in the foreground. A suggestion for future investigations is as follows: The M-E complexes can be regarded as potential carriers of negatively polarized d-block metal fragments $\text{L}_n\text{M}^{(\delta-)}$. This is above all important in the case of d-block metal fragments which, in contrast to carbonylmetalates, are not easily available as a nucleophilic synthetic building block. Thus the insertion or the bimolecular addition for the synthesis of M-E complexes, for example starting from $\text{M}^{(\delta+)}\text{-Y}^{(\delta-)}$ functions ($\text{Y} = \text{H}, \text{halide}, \text{alkyl}$), can also be regarded as a reversion of the polarity of the d-block metal fragments (i.e. reduction). A lot can be expected in this direction.

5. Bonding Conditions

The neutral d-block metal complexes of the terminal coordinated donor-free fragments EX , EX_2 , RE , and R_2E (types **D** and **G**) are isoelectronic to cationic carbyne or carbene complexes or the corresponding complexes of the higher homologues of Group 14. This fact and the observation that M-E bond lengths vary systematically over a wide range, depending on the substituents at both metal centers and on the coordination number at the center E, might be responsible for the recently increased discussion on the degree of backbonding of the type $\text{M}(\text{d}_\pi) - \text{E}(\text{p}_\pi)$. Power et al. have considered this problem for M-E complexes with tricoordinate centers E mainly on the basis of structural data and arrive at the conclusion that π multiple bonds are hardly of any importance.^[34] The concept proposed by Robinson et al.^[14] of a Fe-Ga triple bond in the complex $[(\text{CO})_4\text{Fe-GaAr}^*]$ based on a very short Fe-Ga distance was criticized.^[140] In the light of a fast developing chemistry of low-coordinate centers E, some remarks on the M-E bonding conditions and the substituent effects seem to be warranted. Quantum chemical DFT calculations have meanwhile been carried out by several groups on the model complexes $[(\text{CO})_4\text{Fe-AlCp}]$,^[79, 83] $[(\text{CO})_5\text{CrAlCp}]$,^[172] $[(\text{CO})_4\text{Fe-Ga}(\eta^1\text{-C}_6\text{H}_5)]$,^[136, 140] $[(\text{CO})_5\text{M-EX}]$, $[(\text{CO})_5\text{M-EXL}_2]$ ($\text{E} = \text{B}, \text{Al}, \text{Ga}, \text{In}, \text{Tl}$; $\text{X} = \text{H}, \text{Cl}$; $\text{L} = \text{NH}_3$)^[80] and $[\text{L}'(\text{CO})_3\text{Co-GaX}_2\text{L}]$ ($\text{X} = \text{H}, \text{Cl}$; $\text{L}' = \text{PH}_3$).^[141] All model complexes were compared to closely related examples, the molecular structures of which were known. This is also true for the Fe/Ga clusters mentioned in Section 3.5 (Scheme 5).^[88] Thus the characteristic environments for terminally coordinated earth metal fragments of types **D**, **I**, and **K** have been recorded, namely linearly dicoordinate as well as the tetracoordinate adduct-stabilized variations. Thus the discussion of the structures and bonding conditions shall be limited to these examples. For complexes of the types **B**, **G**, and **P** see the references.^[34]

5.1. M-E Bond Lengths and Calculated Dissociation Energies

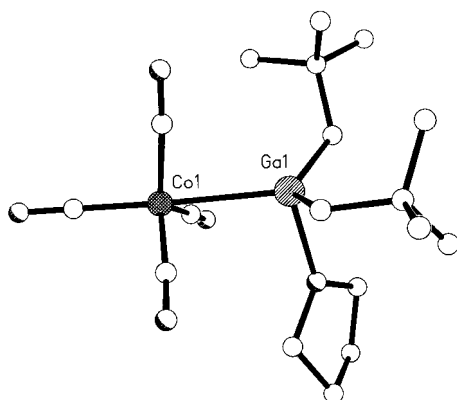
The most comprehensive data material is available for the series of the earth metal complexes at $(\text{CO})_5\text{M}$ fragments ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$).^[80] Let us first turn to the donor-stabilized species (type **I**). The optimized C_s -symmetrical structures of the model complexes agree very well with the X-ray crystallographic data. The tendency to a certain shortening of the bond in the series $\text{X} = \text{alkyl}, \text{H}, \text{halide}$ (model examples: $[(\text{CO})_5\text{W-Al}(\text{H})(\text{NH}_3)_2]$ 260.5 pm and $[(\text{CO})_5\text{W-Al}(\text{Cl})(\text{NH}_3)_2]$ 257.5 pm) corresponds to the experimental conditions: $[(\text{CO})_5\text{Cr-Ga}(\text{Et})(\text{tmeda})]$ 251.71(4) pm and $[(\text{CO})_5\text{Cr-Ga}(\text{Cl})(\text{tmeda})]$ 245.55(11) pm. This variation in bond lengths becomes more significant if also the structurally characterized complexes **K** or the solvent-free systems **D** are included in the comparison. In the series $[(\text{L}')(\text{CO})_3\text{Co-GaX}_2(\text{L})]$ the extreme values vary in a range of 25 pm: $[\text{Me}_3\text{P}(\text{CO})_3\text{Co-GaCl}_2(\text{NMe}_3)]$ 234.2(1) pm and $[(\text{CO})_4\text{Co-Ga}(\text{CH}_2\text{tBu})_2(\text{thf})]$ 257.83(4) pm (Table 2, Figure 9).

Table 2. Structurally characterized cobalt–gallium complexes: $\sigma(\text{Co–Ga})$ bond lengths and IR data.

Compound	$d(\text{Co–Ga})$ [pm]	$\tilde{\nu}(\text{CO})$ [cm^{-1}]	Ref.
$[(\text{PMe}_3)(\text{CO})_3\text{Co–GaCl}_2(\text{NMe}_3)]$	234.2(1)	1992 (m), 1953 (vs), 1940 (vs) ^[a]	[133]
$[(\text{PPh}_3)(\text{CO})_3\text{Co–Ga}\{(\text{CH}_2)_3\text{NEt}_2\}(\text{Cl})]$	237.78(4)	2010 (w), 1946 (vs), 1925 (vs) ^[a]	[64]
$[\text{Co}_2(\text{CO})_6(\mu\text{–GaCp}^*)_2]$	237.84(5)–239.59(5)	2023 (s), 1989 (s), 1953 (vs), 1948 (vs, sh) ^[b]	[84]
$\{[(\text{CO})_4\text{Co}]_2\text{Ga}\{2,4,6\text{–}i\text{Bu}_3\text{C}_6\text{H}_2\}\}$	248.1(2)	2092 (s), 2076 (s), 2017 (m), 2002 (s), 1993 (s), 1982 (s), 1964 (m) ^[b]	[134]
$[(\text{PPh}_3)(\text{CO})_3\text{Co–Ga}\{(\text{CH}_2)_3\text{NEt}_2\}(\text{CH}_3)]$	249.5(1)	1929 (vs), 1941 (vs) ^[c]	[64]
$\{[(\text{CO})_4\text{Co}]_2\text{Ga}\{2,6\text{–}(\text{Me}_2\text{NCH}_2)_2\text{C}_6\text{H}_3\}\}$	253.6(19), 260.2(16)	2080 (s), 2059 (s), 2013 (m), 1986 (s), 1973 (s), 1878 (m) ^[b]	[135]
$\{[(\text{CO})_4\text{Co}]_2\text{Ga}\{(\text{CH}_2)_3\text{NEt}_2\}\}$	254.02(9), 254.60(9)	2083 (s), 2066 (s), 2019 (s), 2009 (s), 1997 (vs), 1975 (vs), 1962 (s) ^[c]	[57]
$[(\text{CO})_4\text{Co–GaNP}_2(\text{thf})]$	257.83(4)	2066 (s), 1997 (s), 1968 (vs), 1955 (vs) ^[d]	[56]
$[(\text{CO})_4\text{Co–GaEt}_2(\text{NC}_7\text{H}_{13})]$	258.67(10)	2065 (s), 2010 (m), 1980 (sh), 1957 (vs) ^[a]	[133]

[a] Toluene. [b] KBr pellet. [c] *n*-Pentane. [d] *n*-Hexane.Table 3. Structurally characterized iron–gallium complexes: $\sigma(\text{Fe–Ga})$ bond lengths and IR data.

Compound	$d(\text{Fe–Ga})$ [pm]	$\tilde{\nu}(\text{CO})$ [cm^{-1}]	Ref.
$[(\text{CO})_4\text{Fe–GaAr}^*]$	222.48(7)	2032 (s), 1959 (s), 1941 (vs), 1929 (vs) ^[a]	[14]
$[(\text{CO})_4\text{Fe–GaPh}]^{\text{[#]}}$	225.6	2038, 1985, 1959	[136]
$[(\text{CO})_4\text{Fe–GaCp}^*]$	227.31(4)	2037 (s), 1966 (s), 1942 (vs) ^[b]	[84]
$[(\text{CO})_4\text{Fe–GaCp}]^{\text{[#]}}$	232.7	2040, 1983, 1959	[136]
$\{[(\text{CO})_3\text{Fe}]_3[\text{GaSi}(\text{SiMe}_3)_2]\text{GaFe}(\text{CO})_4\}^-$	228.9(1)–254.7(1)	–	[88]
$[\text{Cp}(\text{CO})_2\text{Fe–GaS}]_4$	233.7(1)	2001 (s), 1993 (vs), 1976 (vs), 1923 (vs), 1896 (vs)	[89]
$[(\text{CO})_4\text{Fe–GaCl}(\text{tmeda})]$	233.78(15)	2011 (vs), 1928 (vs), 1881 (vs) ^[c]	[87]
$[\text{Cp}(\text{CO})_2\text{Fe–GaSe}]_4$	234.7(1)	2001 (s), 1991 (vs), 1975 (vs), 1922 (vs), 1895 (sh)	[89]
$[\text{Fe}_2(\text{CO})_6(\mu\text{–GaCp}^*)_3]$	235.4(4)–245.4(3)	1951 (vs, sh), 1923 (vs) ^[d]	[84]
$[\text{Cp}(\text{CO})_2\text{Fe–GaTe}]_4$	235.7(2)	2001 (s), 1998 (vs), 1984 (vs), 1927 (s)	[89]
$[\text{Cp}(\text{CO})_2\text{Fe–GaCl}_2(\text{NMe}_3)]$	236.18(3)	1989 (vs), 1934 (vs) ^[c]	[64]
$[\text{Cp}(\text{CO})_2\text{Fe–Ga}(\text{R}^N)(\text{BH}_4)]$	237.5(1)	1975 (vs), 1920 (vs) ^[c]	[58]
$[\mu\text{–GaSi}(\text{SiMe}_3)_2(\mu\text{–CO})\text{Fe}_2(\text{CO})_6]$	238.15(8)–239.38(6)	2026 (s), 1999 (s), 1971 (s), 1962 (s), 1948 (s), 1920 (s), 1784 (s) ^[c]	[88]
$\{[\text{Fe}_2(\text{CO})_6[\mu\text{–GaSi}(\text{SiMe}_3)_2]]_3\}$	238.18(7)	1964 (s), 1921 (s) ^[d]	[88]
$[\text{Cp}(\text{CO})_2\text{Fe–Ga}(\text{tBu})]$	240.6(1), 241.6(1)	1978 (vw, sh), 1967 (vs), 1927 (vs), 1915 (vw)	[137]
$[(\text{CO})_4\text{Fe–Ga}(\text{Me})\text{Fe}(\text{CO})_4]^{2-}$	241.58(6)	1952 (vs), 1874 (vs, sh), 1851 (vs), 1827 (vs, sh) ^[f]	[90]
$[\text{Cp}(\text{CO})_2\text{Fe–Ga}(\text{tBu})_2]$	241.7(1)	1980 (vs), 1928 (vs)	[137]
$\{[(\text{CO})_3\text{Fe}]_3[\text{GaSi}(\text{SiMe}_3)_2\text{H}]^-\}$	242.3(2)–251.0(2)	2009 (w), 1971 (s), 1956 (m), 1943 (s), 1920 (m), 1914 (s), 1903 (m), 1888 (m), 1873 (m) ^[d]	[88]
$[\text{Cp}(\text{CO})_2\text{FeGa}(\eta^1\text{–C}_5\text{H}_4\text{Me})_2(\text{NC}_5\text{H}_5)]$	242.72(9)	–	[15]
$[\text{Cp}(\text{CO})_2\text{Fe}]_3\text{Ga}$	243.6(1)–245.6(1)	1987 (m), 1965 (s), 1929 (s) ^[f]	[138]
$[\text{Cp}(\text{CO})_2\text{Fe–Ga}(\text{tBu})_2[\text{Cp}(\text{CO})_2\text{Fe}]_2]$	244.1(1)	1982 (ssh), 1963 (vs), 1930 (vs), 1915 (ssh), 1788 (s), 1758 (s)	[137]
$[\text{Fe}_2(\text{CO})_6[\mu\text{–GaSi}(\text{SiMe}_3)_2(\mu\text{–CO})] \cdot \text{Na}(\text{thf})(\text{OEt}_2)_2\text{Cl}]$	244.1(2)–245.5(2)	2013 (s), 2005 (s), 1995 (s), 1984 (s), 1977 (sh), 1939 (s), 1818 (w) ^[d]	[88]
$[\text{Cp}(\text{CO})_2\text{Fe–Ga}(\text{R}^N)(\text{Et})]$	245.65(4)	1968 (s), 1960 (vs), 1911 (s), 1904 (vs) ^[d]	[58]
$[(\text{CO})_4\text{FeGa}_3[\text{Si}(\text{SiMe}_3)_3(\text{OH})_4]]$	248.36(12)–248.98(12)	–	[88]
$\{[(\text{CO})_4\text{Fe–Ga}(\eta^1\text{–C}_2\text{H}_5)(\text{thf})_2]\}$	251.0(1)	–	[86]

[#] Data for bond lengths and IR frequencies determined on the basis of DFT calculations. [a] Nujol pulverization. [b] *n*-Hexane. [c] CH_2Cl_2 . [d] KBr pellet. [e] Toluene. [f] THF. [g] *n*-Pentane. Abbreviations see Table 1.Figure 9. Molecular structure of $[(\text{CO})_4\text{Co–GaNp}_2(\text{thf})]$ in the crystal. Np = neopentyl.^[56]

The same is true for the series $[\text{Cp}(\text{CO})_2\text{Fe–GaX}_2(\text{NR}_3)]$, the Fe–Ga distances of which vary between 236.18(3) pm for $\text{X} = \text{Cl}$ and 245.65(4) pm for $\text{X} = \text{alkyl}$ (Table 3). An unusually short Fe–Ga bond length of 222.48(7) pm is found for $[(\text{CO})_4\text{Fe–GaAr}^*]$ with a linearly dicoordinate Ga atom (Table 3). The complex $[\text{Cp}(\text{CO})_2\text{Fe–Al}(\text{iBu})(\text{R}^N)]$ with a tetracoordinate Al center has a Fe–Al distance of 245.6(1) pm. A parallel to this for the $(\text{CO})_5\text{M}$ series can be found in the comparison of $[(\text{CO})_5\text{Cr–GaCp}^*]$ (240.46(7) pm) with $[(\text{CO})_5\text{Cr–Ga}(\text{Et})(\text{tmeda})]$ (251.71(4) pm).

The relative ordering of the calculated bond dissociation energies (MP2/II level) of the model complexes $[(\text{CO})_5\text{W–L}]$ ($\text{L} = \text{earth metal fragment}$) in $\{(\text{CO})_5\text{W}\}$ and L are very interesting (Table 4). For W–Al bonds the energies of around 90–100 kcal mol^{−1} are found for the tetracoordinate deriva-

Table 4. Results of the NBO analysis at the MP2/II-level.^[80] Partial charges q ; hybridization of the lone-pair donor orbital at the atom E^[a] (s contribution); calculated dissociation energies D_e of the W–E bond.^[a]

Molecule	$q(\text{W})$	$q(\text{W}(\text{CO})_5)$	$q(\text{E})^{[a]}$	s Contribution [%]	D_e [kcal mol ⁻¹]
[(CO) ₅ WAlH(NH ₃) ₂]	–0.67	–0.93	1.09	23.0	100.9
[(CO) ₅ WAlCl(NH ₃) ₂]	–0.72	–0.90	1.24	23.9	93.1
[(CO) ₅ WAlH]	–0.93	–0.64	1.07	62.5	70.0
[(CO) ₅ WAlCl]	–0.94	–0.58	1.13	64.1	58.4
[AlH(NH ₃) ₂]	–	–	0.32	77.5	33.1 ^[b]
[AlCl(NH ₃) ₂]	–	–	0.54	84.0	30.5 ^[b]
AlH	–	–	0.60	91.5	–
AlCl	–	–	0.68	93.8	–
[(CO) ₅ WGaCl(NH ₃) ₂]	–0.73	–0.72	1.07	18.3	70.9
[(CO) ₅ WBCl(NH ₃) ₂]	–0.53	–0.63	0.19	35.2	119.6
[(CO) ₅ WInCl(NH ₃) ₂]	–0.71	–0.77	1.18	19.8	70.5
[(CO) ₅ WTiCl(NH ₃) ₂]	–0.70	–0.61	1.08	36.2	47.8

[a] E = B, Al, Ga, In, Tl. [b] Dissociation energies for two NH₃ ligands.

tives. As expected the tendency to dissociate decreases from Al to Tl. The high bonding energy of the hypothetical W–B complexes is remarkable. Quite recently the first d-block metal complexes with terminal borylene units, [(CO)₄Fe–BCp*] and [(CO)₅W–BN(SiMe₃)₂] as homologues to the above-mentioned Al and Ga complexes, have been described.^[142] The dissociation energy of [W(CO)₆] into {W(CO)₅} and CO (calculated at the same level) is 54.9 kcal mol⁻¹, whereas the experimental value is 46.0 ± 2 kcal.^[143] Thus the W–B bonds are very strong compared to the W–CO bonds, which explains the substitution of CO for the fragments RE. The calculated dissociation energy of about 53 kcal mol⁻¹ for [(CO)₄Fe–AlCp] corresponds to the general tendency towards weaker metal–metal bonds for the 3d series than for the 4d and 5d series. That the donor-stabilized fragments EXL₂ show significantly higher dissociation energies than the donor-free variants EX is most remarkable (Table 4). This is in a way opposed to the drastically shortened bond lengths described above for the donor-free, dicoordinate complexes of the type MEX and MER, if the shorter bonds are taken as an indication for stronger bonds and correspondingly significant π interactions are inferred which should be possible for MEX but not for MEXL₂.^[14, 88] The term “multiple bond” in the classical sense often implies a higher bond strength and shorter bonds; however, this view is quite problematic.^[34, 144] The opinion underlying the interpretation of the Fe–Ga bond in [(CO)₄Fe–GaAr*] that significantly short bonds are diagnostic for an increased bonding order, for π -multiple bonds thus “strong” bonds, has repeatedly been critically discussed in literature, especially when metal–metal bonds and heavy elements are concerned.^[144] The longer W–Al bond of the donor-stabilized model complexes is explained within the framework of fragment formalism from the increased coordination number at Al and the thus different hybridization of the 2e- σ donor orbital on the Al side relevant for the W–Al bond. The lone pair of electrons of a (hypothetical) fragment AlH has 91.5% s character, while the corresponding donor orbital of a fragment AlH(NH₃)₂ has an s proportion of 77.5%. Also the weaker substituent effects follow this line: 85% s character for AlCl(NH₃)₂ and a correspondingly shorter bond than in AlH(NH₃)₂, but lower dissociation energy (Table 4). The closest relatives of the complexes of

CpE and EXL₂ fragments discussed here are pyrazolylborato derivatives such as [(CO)_nM–E{HB(3,5Me₂pz)₃H}].^[94, 145]

5.2. Bonding Polarity

The shortening of the bond lengths Al–Cl and Al–N in the complexes compared to those of the “free” ligand fragments is also informative (Table 4), which is connected to the electron donation Al $\Rightarrow$ W. The calculated partial increase of the positive nature of the Al center is clearly greater than in the hypothetically “free” ligands (Table 4). The effect of the donor ligands on the calculated charge distribution is also informative. While the conditions at the earth metal center change only slightly on going from EX to EXL₂ (from +1.08 to 1.24, Table 4), the amine ligands transfer the charge density to the {(CO)₅W} fragment (from –0.58 to –0.93, Table 4). The Cp* and the pyrazolylborato ligands also fit into these considerations, as they, being strong η^5 - and η^3 -bonded π and σ donors, respectively, have a similar effect on the charge distribution between the metal centers as the presence of amine ligands in EXL₂ fragments. Being a soft donor, the Cp* ligand is rather flexible and the distance E–Cp* is a sensitive measure of the positive polarization of the centre E in the M–E complexes.^[83, 84, 172] Already the very different electronegativities of the metal atoms M and E suggest strong polar M–E bonds, and the more so if the group electronegativity of the carbonyl metal fragments, which are similar to O and F atoms, is taken into account.^[146] Thus the description of the fragments Cp*E in the carbonyl metal complexes in the sense of a formally lower oxidation state of +1 for E has also been criticized.

Thus, the model complex [(CO)₄Fe–AlCp] was compared with a series of relevant molecules, including the hypothetical particle [CpAl=O] and the structurally valid cation [Cp₂*Al]⁺, and the charge distributions (Mulliken population analysis) were calculated. The comparison showed that the increase of the positive nature of the Al center of [CpAl=O] and [Cp₂*Al]⁺ is quite similar (+0.42 and +0.36, respectively), whereas a stronger increase of the positive nature of the Al atom of +0.7 was calculated for [(CO)₄Fe–AlCp]. This trend is also apparent from the Al–C distances, which for [Cp₂*Al]⁺

are 213.7(8)–218.4(8) pm and for $[(\text{CO})_4\text{Fe}-\text{AlCp}^*]$ are 214.0(5)–215.3(5) pm. The Al–C distances in $[\text{Cp}^*\text{Al}]_4$ are 229.2(13)–237.8(11) pm and thus significantly longer. The calculated positive partial charge at the Al center in the model fragment $\{\text{CpAl}\}$ is correspondingly low: +0.16. Thus for $[(\text{CO})_4\text{Fe}-\text{AlCp}^*]$ a polar description as contact ion pair $[(\text{CO})_4\text{Fe}^{2-}][\text{AlCp}^{*2+}]$ was preferred over a covalent view in the sense of complex stabilization of the Cp^*Al fragment. Consequently, the carbenoid character of the $\{\text{Cp}^*\text{Al}\}$ unit does not exist in the complex, it is rather an Al^{III} center.^[83]

Within the SEN formalism (shared electron number), which is used as means to get a standard number for the covalent bond strength, the SEN for the complex $[(\text{CO})_4\text{Fe}-\text{AlCp}]$ is 1.48 and for the Co–Al bonds in the Co/Al cluster ($[\text{Eq. (3)}]$) the SEN is 1.12. For the series of Fe/Ga clusters (Table 3, Scheme 5) the SENs for the various Fe–Ga bonds are between 1.14 and 1.89, the latter result applying to the hypothetical model complex $[(\text{CO})_4\text{Fe}-\text{GaH}]$.^[88] For comparison: C–C bonds have a SEN of around 1.4, C=C of around 2.2, and the NaF molecule of around 0.3. Thus, we favor the description of M–E bonds as strong polar but covalent donor–acceptor bonds over the extreme formulation as contact ion pairs. The fragments RE (R = Cp^* , $\{\text{HB}(3,5\text{-Me}_2\text{pz})_3\}$; E = Al, Ga, In) and EXL_2 (X = H, halide, alkyl; E = Al, Ga) should be seen as potent 2e-donor ligands, similar to the ligands of the amine or phosphane type. The pyrazolylborato derivatives and the Cp and Cp^* complexes smoothly fit into this picture. This relationship is also evident from the electron spectra (absorption and luminescence) of representatives of this family of compounds such as $[(\text{CO})_5\text{W}-\text{Al}(\text{X})(\text{tmpda})]$ (X = Cl, *i*Bu; tmpda = *N,N,N',N'*-tetramethylpropylenediamine), which in their characteristics, also in terms of the substituent effects at the “ligand” EXL_2 , totally correspond to the well-known pyridine complexes $[(\text{CO})_5\text{W}(\text{py})]$.^[147] This connection could also be of interest for the photochemistry of M–E complexes. In the lowest electronically excited state an efficient dissociation of the W–N bond of $[(\text{CO})_5\text{W}(\text{py})]$ takes place.^[148] In accordance with the calculated dissociation energies and correcting an earlier note^[80] it must be emphasized that the W–Al bonds do not dissociate thermally. A displacement by other ligands (CO, isocyanides, phosphanes) and a splitting of the fragments EXL_2 can probably only be achieved by using photochemistry.

5.3. π -Backbonding

Is it justified to discuss significant π -bond components in complexes like $[(\text{CO})_4\text{Fe}-\text{GaAr}^*]$ starting out from the structural and spectroscopic facts and based on different quantum chemical methods? On the basis of semiempirical EHMO calculations on M–In complexes of the type M_3E (type **B**) the extent of possible M–In π -backbonding was rated to be very small and the favorable relative orientation of the M fragments in the solid for such bonds was attributed to the minimization of steric interactions.^[106] The lack of a rotation barrier around the Fe–Ga bond in $[\text{Cp}(\text{CO})_2\text{Fe}-\text{Ga}(\text{iBu})_2]$ and the $\tilde{\nu}(\text{CO})$ absorptions which are very clearly

shifted by around 32 cm^{-1} to lower wave numbers compared to the boryl analogue $[\text{Cp}(\text{CO})_2\text{Fe}-\text{B}(\text{C}_6\text{H}_5)_2]$ were also taken as an indication for insignificant Fe–Ga π interactions.^[137] Backbonding into energetically matching $\sigma^*(\text{E}-\text{X})$ bonds (X = Cl, NR_2 , CR_3) corresponding to the interpretation of acceptor properties of PR_3 ligands in phosphane complexes ($\sigma^*\text{-P-X}$)^[149] were also taken into account but later discarded because of the results of Fenske–Hall calculations.^[94] The typical apical position of the E fragment in complexes of the $[(\text{CO})_4\text{M}]$ type has also been taken as an indication against classic π -bonds.^[34]

Recent DFT calculations on $[(\text{CO})_4\text{Fe}-\text{Ga}(\eta^5\text{-Cp})]$ (**M1**) and $[(\text{CO})_4\text{Fe}-\text{Ga}(\eta^1\text{-Ph})]$ (**M2**) as models for the Robinson compound with a linearly dicoordinated Ga center now show that within the charge decomposition analysis (CDA) formalism^[136] apparently increased π -backbonding components $\text{Ga} \leftarrow \text{Fe}$ can be calculated for **M2** in comparison to **M1**. For **M2** a donor/acceptor relation of 1.51 was determined, for **M1**, however, the value of 2.94 was obtained. Values around 0.35 e were found for the population of the $4p(\pi)$ orbital in **M2**. Interestingly, a calculation of the CO-stretching vibration frequencies at the BP86/I level for **M1** and **M2** revealed that they hardly differ from each other. The experimental values for the complexes $[(\text{CO})_4\text{Fe}-\text{GaR}]$ (R = Cp^* and Ar^*) are quite similar to each other but clearly shifted to higher wave numbers compared to $[(\text{CO})_4\text{Fe}-\text{GaCl}(\text{tmpda})]$ and $[(\text{CO})_4\text{Fe}-\text{Ga}\{\text{HB}(3,5\text{-Me}_2\text{pz})_3\}]$ (Table 3). The position of the $\tilde{\nu}(\text{CO})$ frequencies, however, depends on purely electrostatic polarization effects as well as on the extent of the assumed, covalent π -backbonding $\text{M} \Rightarrow \text{CO}$. Thus especially in the case of polar bonds M–E the importance of π backbonds $\text{M} \Rightarrow \text{E}$ can hardly be inferred from the $\tilde{\nu}(\text{CO})$ frequencies!^[150]

On balance this reasoning stresses that none of the discussed observable quantities, namely bond lengths, rotation barriers, and the position of the $\tilde{\nu}(\text{CO})$ frequencies require the concept of a Fe–Ga multiple bond and considerable $\text{Fe} \Rightarrow \text{Ga}$ backbonding for $[(\text{CO})_4\text{Fe}-\text{GaAr}^*]$ and related compounds. Depending on the level of the quantum chemical calculations and the chosen description model (especially the method and concepts used for calculating the charge distributions) more or less detailed pictures of the bonding conditions are obtained, the common and dominating factor of which is the bond polarity. This can be determined according to the series $\text{E}(\text{R})\text{L}_2 > \text{E}(\text{X})\text{L}_2 > \text{ER}$ and $\text{Al} > \text{Ga}$, In depending on the coordination number of E and the substituents R, X, and L bonded to E. Especially the coordinatively saturated fragments $\text{EX}(\text{L})_2$ here widely correspond to the amine or phosphane ligands (py, NR_3 , PR_3) but because of the more electropositive character of the center E allow clearly increased negative charge densities at the d-block metal. The preference of Cr–Ga versus Cr–P coordination in η^5 -phospholylgallium complexes of the $(\text{CO})_5$ fragment nicely shows this situation.^[175] The M–E bonds in the discussed complexes thus should best be viewed as strong polar Lewis acid/base adducts. There is certainly an analogy of the RE ligands to the CO ligand in a structural or coordination chemical view. The answer to the question of whether a distinctive π -acceptor capacity of the fragments RE does or

does not exist or whether it is limited to Ar^*Ga or $(\text{SiMe}_3)_2\text{SiGa}$ or $(\text{SiMe}_3)_3\text{CIn}$, very much depends on the standard of the theoretical way of looking at things, however, there still is no experimental evidence.

6. Precursor for MOCVD of Intermetallic Phases

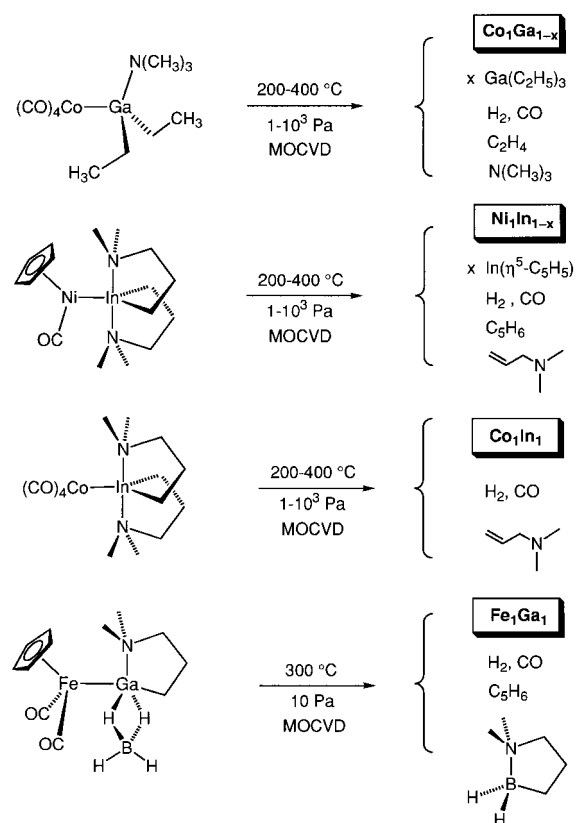
The general interest in organometallic precursors for new materials and especially for MOCVD as an alternative to physical coating methods was, as mentioned in the introduction, an important impulse for the renaissance of the coordination chemistry of $\text{M}-\text{E}$ complexes. While the precursor chemistry for MOCVD for pure elemental metals (e.g. Cu, Al, Pt, Pd, Au) and a whole host of metal oxides, carbides, and nitrides as well as for semiconductors of the III/V and II/VI types continues to be intensively investigated, there are hardly any surveys on precursors for the deposition of intermetallic phases.^[36, 151–153]

As was set out in the introduction, certain intermetallic phases from combinations of Al, Ga, and In with d-block metals are especially suitable as epitaxial metallizations being inert against unwanted interface reactions and useful for Schottky barriers for III/V semiconductor techniques; thus MOCVD processes are of interest for these materials.^[154–157] Thin films from CoGa or similar phases have been discussed for the fabrication of hetero bipolar transistors (HEMT), resonant tunnel diodes or transistors (DBRT, RTBTs), and quantum dot hetero structures. Examples for these “thermodynamically stable metal contacts” are Ni/Al (GaAs),^[158–160] Mn/Al (AlAs),^[161] Pt/Ga (GaAs),^[162] Co/Ga (GaAs)^[163] and Rh/Ga (GaAs)^[164] systems prepared by molecular-beam orientation crystallization according to UHV techniques (MBE, molecular beam epitaxy). The system Co/Ga on GaAs is prototypical for this: The ternary Co-Ga-As phase diagram contains two intermetallic phases CoGa_3 and $\text{Co}_{1-\delta}\text{Ga}_\delta$ ($0.36 > \delta > 0.64$) which are coexistent with GaAs. Because the arsenide phases Co_3As_x , equally thermodynamically stable towards GaAs, are semiconductors, they are less interesting as metallizations than the metallic cobalt gallides. The β -CoGa phase (CsCl-type) exhibits a defect structure, the lattice constant of which is very close to half of the characteristic lattice constant of GaAs (ZnS-type). Stoichiometric β - $\text{Co}_{1-\delta}\text{Ga}_\delta$ ($\delta = 0.50$) with a lattice misfit of about 2% is stable up to about 600 °C, perfectly epitaxial β - $\text{Co}_{1-\delta}\text{Ga}_\delta$ with $\delta = 0.62$ is stable up to about 800 °C against GaAs. The Schottky barrier height of 0.76 eV remains unchanged even after tempering at 500 to 600 °C.

Starting from two independent precursors $[\text{CpCo}(\text{CO})_2]$ and GaEt_3 Kaesz et al. proved the organometallic chemical vapor-phase epitaxy (OMVPE) of β -CoGa on GaAs(100).^[168] Control of the composition of such multinary CVD films in technical applications is effected from a precise adjustment of the mole fractions of the different precursors for the film constituting components in the gas phase. The molecular source components, however, show individual homogenous and heterogenous fragmentation chemistry and kinetics, physi- and chemisorption as well as different surface mobilities of the molecular fragments. A difficult optimization

problem can result from that for a binary or multinary CVD process.

One approach to widely reduce control engineering and to make such binary metal films easily available by process engineering is the inclusion of all kinds of film-constituting atoms into one single precursor molecule. This is called a single-source precursor. Process control in this case is shifted to the constitutional and structural optimization of the precursor. The property profile comprises: properly selected metal combination, acceptable vapor pressure (>1 Pa at 25 °C), low proportion of heteroatoms in the ligand sphere, weakly bonded ligands, mild pyrolysis ($T > 400$ °C), and sufficient long-term stability under evaporation conditions. The alkyl derivatives of the types **L** and **M** (Figure 1) agree with this profile. An example for this group of substances is the vapor pressure of the CoIn system (Scheme 10), which at



Scheme 10. Ligand control of the film composition for the MOCVD of M/E films using precursors of the type **K**.

20 °C is approximately 0.0250(5) mbar and which allows film growth rates around $1 \mu\text{m h}^{-1}$ ($10 \text{ \AA s}^{-1}$).^[171] In comparison to this halide-containing complexes of the types **K**, **O**, or **P** are less volatile and, furthermore, as a source of impurities of the films the halide group is unwelcome. The analysis of the deposited films and exhaust gases revealed that the metal composition of the precursors in the deposited films is not necessarily reproduced. The loss of earth metal was a frequent effect which under given conditions is controlled by the ligands at both metal centers (Scheme 10).

In principle, also films rich in earth metals $\text{M}_1\text{E}_{1+\delta}$ are obtained from precursors with $\text{E/M} > 1$. According to mass spectrometric investigations the liberation of the donor ligand

L at the center E together with the liberation of CO are the favored first steps of molecular degradation. The composition of the film is determined by the competition between (alkyl) ligand fragmentation and ligand reorganization combined with the cleavage of the M–E bonds. This was investigated with a series of CoGa precursors.^[169] Cobalt-rich films are obtained at a substrate temperature of 200 °C from $[(\text{CO})_4\text{-Co-GaEt}_2(\text{NMe}_3)]$ and a corresponding proportion of GaEt_3 gets into the waste gas; at higher substrate temperatures of around 350 °C stoichiometric films $\text{Co}_{0.50}\text{Ga}_{0.50}$ are formed (Figure 10). The fragmentation of the Ga–C bond then takes

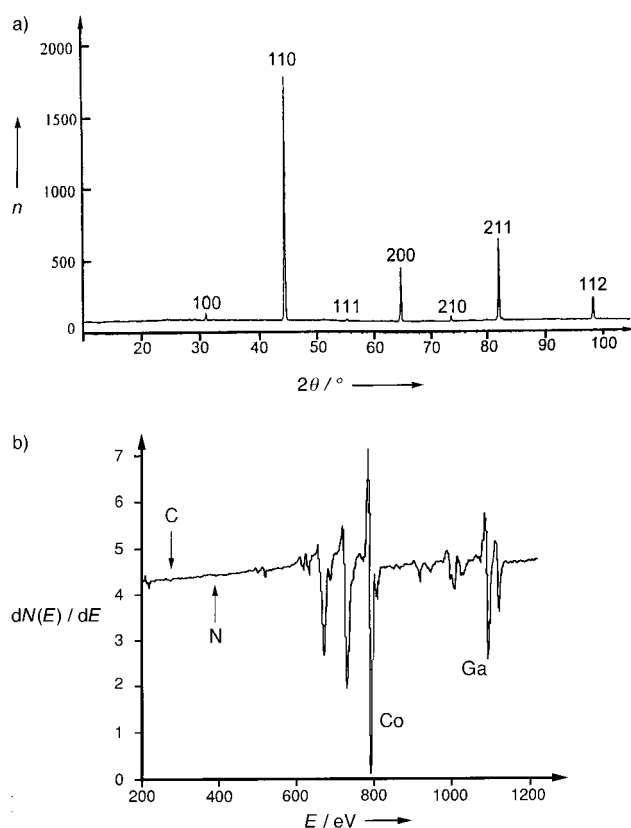


Figure 10. a) X-ray diffractogram of a CoGa film obtained from the precursor $[(\text{CO})_4\text{Co-GaEt}_2(\text{NMe}_3)]$ at a substrate temperature of 350 °C and a pressure of 10^{-2} Torr by MOCVD; n = count rate. b) Auger electron spectrum (AES) of the film after short-time purification of the surface by sputtering with Ar ions.

place fast enough. Similarly, the deposition of CoGa from a 1:1 mixture of $\text{Ga}(\text{C}_2\text{H}_5)_3$ and $[\text{Cp}(\text{CO})_2\text{Co}]$ at 250–300 °C and 1010 mbar (flow reactor) provides cobalt-rich, metastable $\alpha\text{-Co}_1\text{Ga}_{1-\xi}$ films ($\xi \geq 0.41$). Only a tenfold excess of the gallium precursor compensates the inefficient pyrolysis of these films and—in a mass transport limited regime—leads to $\beta\text{-CoGa}$ films. The degradation of the single-component sources to the film is, however, kinetically controlled, as Co and Ga fragments are transported to the surface in the same proportion independent of pressure and temperature.

The complexes are mostly less stable than the homoleptic alkylgallium compounds. Thus it is possible to define the composition of the film by temperature control and structure optimization of the precursor. If the formation of thermally stable metal-containing degradation products during film

growth is insignificant the limiting value $M/E_{(\text{precursor})} = M/E_{(\text{film})}$ will already be reached at low temperatures. The deposition of mixed-metal CrGa films from the precursor $[(\text{CO})_5\text{Cr-Ga}(\text{Et})(\text{tmeda})]$ already leading to CrGa films at low temperatures of 250 °C onwards without the loss of Ga^[85] corresponds to this concept. Formation of GaEt_3 was not observed. In this context the fragmentation behavior of the complexes after ionization in the mass spectrometer is of interest. Complexes of the type **K** show a complicated fragmentation pattern in which breakage of the M–E bond often dominates.^[170] In contrast, complexes of the type **I** decompose more clearly, and fragments with intact M–E bond are frequent. For $[(\text{CO})_5\text{Cr-ECp}^*]$ the ion $[\text{CrECp}^*]^+$ is found as base peak ($E = \text{Al, Ga}$).^[84, 172]

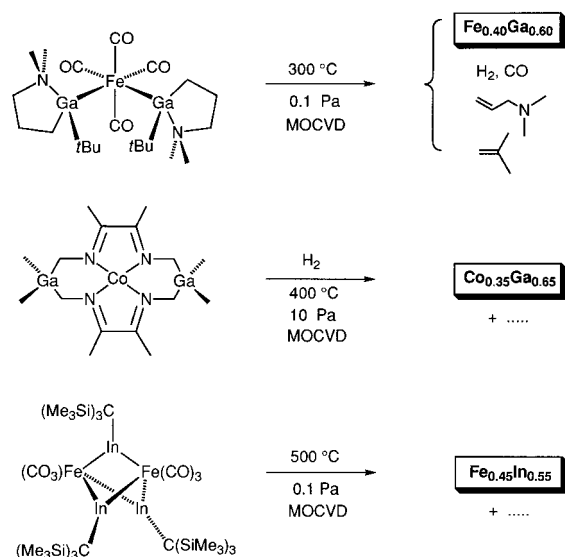
The fragmentation behavior of a potential MOCVD precursor under the conditions prevailing in a mass spectrometer cannot automatically be compared to the conditions of a thermal MOCVD experiment. In the cases we examined, however, a correlation was observed. Precursors whose mass spectra are rich in mixed-metal fragments provide films, the metal concentration of which corresponds to the structure of the precursor.

Not only the substituents at the earth metal control the degradation process, but also the ligands at the d-block metal are important (Scheme 10). While $[(\text{CO})_4\text{Co-In}(\text{R}^N)_2]$ ($\text{R}^N = \text{CH}_2\text{CH}_2\text{CH}_2\text{NMe}_2$) only provides Co_1In_1 films, the closely related NiIn source $[\text{Cp}(\text{CO})\text{Ni-In}(\text{R}^N)_2]$ yields films with $\text{Ni/In} = 3.0$ to 1.0 depending on the substrate temperature. This is an example of an unexpected Cp transfer to the In atom, leading to stable $[\text{CpIn}]$, which desorbs and gets into the exhaust gas.^[61] Also transportation of the d-block metal is possible, as shown by the release of ferrocenes in the MOCVD of Fe/In films from $[\text{Cp}(\text{CO})_2\text{Fe-In}(\text{R}^N)_2]$. Such a ligand control of the film composition is an important aspect of the MOCVD chemistry. This is especially true if during pyrolysis part of the ligand sphere takes part in rearrangements or redistributions and is bonded without fragmentation in the form of stable and volatile by-products.

An example for the use of such a reaction process is the selective formation of Fe/Ga films from the tetrahydrido-borate-substituted system $[\text{Cp}(\text{CO})_2\text{Fe-Ga}(\text{R}^N)(\text{BH}_4)]$ (Scheme 10).^[62] This result is the more remarkable if one considers that the formation of iron boride would thermodynamically be preferred here. The majority of the obtained M/E films was remarkably low in impurities. Typical values are 1–4 atom % C and ≥ 1 atom % O (N, P not detectable; XPS and AES analyses). The best conductivities are close to literature values, for example, for CoGa around $120 \mu\Omega \text{ cm}^{-1}$. It turned out that the residual content of carbon is due to the hydrocarbon groups and not to the CO ligands. Oxygen contaminations are determined by the leakage rate of the reactor and the sample manipulation or the purity of the precursors which are partly very sensitive to hydrolysis. The films are composed according to the binary phase diagram of the metal combination in question (thermodynamic control). All CoGa films obtained from the CoGa precursors of type **K** proved to be, for example, single-phase, polycrystalline $\beta\text{-CoGa}$ with a dominant $[110]$ reflection or with strong preferred orientation in 100 direction on GaAs substrates.^[169]

In the Co/In system only CoIn_2 and CoIn_3 are stable. Co_1In_1 films deposited from $[(\text{CO})_4\text{Co}-\text{In}(\text{R}^N)_2]$ display reflections which have to be assigned to these phases.^[171] The phase diagrams of other interesting alloys such as Mn/Al, Mn/Ga, Co/Al, Fe/Ga, Ni/Ga, and Ni/In are more complex, the homogeneity area is more narrow. Thus it is very difficult to get single-phase films. This was successfully demonstrated for NiIn films deposited from $[\text{Cp}(\text{CO})\text{Ni}-\text{In}(\text{R}^N)_2]$ at 350 °C. The fully indexed X-ray diffractogram only contains reflections of the hexagonal ε -NiIn phase.^[61]

The suitability of the M/E complexes as single-source precursors for MOCVD thus has been comprehensively documented. However, technical relevance in the field of microelectronics has not yet become apparent. For that it would be necessary to produce a currently important material in a uniquely simple way compared to other processes. This would mean in the case discussed here to epitaxially deposit the Ga-rich phase $\beta\text{-Co}_{1-\delta}\text{Ga}_\delta$ with $\delta=0.62$ from a volatile precursor in pure form at $T < 400^\circ\text{C}$ on GaAs (100). The single-source precursor for this process needs the composition CoGa_2 . The Co–Ga complex shown in Scheme 11 fulfils this criterion and has indeed been used as a MOCVD precursor



Scheme 11. Single-source precursor for MOCVD of M/E films rich in earth metals.

for Ga-rich CoGa films.^[43] But the vapor pressure of the compound is too low and the obtained film purity remained unsatisfactory due to the structure bridged by heteroatoms. The outlined coordination chemistry of $\{\text{Cp}^*\text{Ga}\}$ fragments at d-block metals could be a step further if it were possible to derive compounds such as $[\text{CpCo}(\text{GaCp}^*)_2]$ or $[(\text{NO})(\text{CO})\text{-Co}(\text{GaCp}^*)_2]$. These hypothetical complexes should to exist and should be characterized by strong enough Co–Ga bonds; however, the stability of the fragment $\{\text{Cp}^*\text{Ga}\}$ could be a problem. In chemical beam epitaxy (CBE) experiments it survives substrate temperatures up to 600 °C without problems.^[84] A loss of earth metal during deposition seems to be predetermined. It remains to be seen if an elegant solution will be found for these contrary effects, that is stability and volatility of the precursors on the one hand and the kinetic

conditions of the decomposition chemistry under MOCVD requirements on the other.

7. Summary and Outlook

This review summarizes a selection of results and current trends of the past decade in the field of the coordination chemistry of the earth metals Al, Ga, and In at d-block metals. Important progress has been made with the expansion of the coordination chemistry of (intramolecular) donor-stabilized fragments ER_2L and ERL_2 to the coordinatively unsaturated, “donor-free” analogues RE ($\text{R} = \text{Cp}^*$, Ar^* and $\text{C}(\text{SiMe}_3)_3$). The synthetic potential of low-valent earth metal compounds in coordination chemistry is impressively documented and holds promise for some more surprises in the future. Thus for the first time mixed M–E clusters and complexes with a relation $\text{E}/\text{M} > 1$ are available. The latter compounds also offer new perspectives as novel MOCVD precursors for intermetallic phases and alloys, which could be interesting for III/V semiconductors in form of epitaxial films as special metal contacts. The discussion on the existence of a Fe–Ga triple bond in the complex $[(\text{CO})_4\text{Fe}-\text{GaAr}^*]$ has led to a series of reports on the quantum chemical description of the bonding conditions in M–E complexes at the DFT level. The M–E bonds in the different types of complexes agree well with the usual donor/acceptor concept. The dominating factor is the bonding polarity (i.e. ionic contributions). Multiple bonds in the traditional sense only play a minor role. These findings are only strictly valid if one considers carbonyl-metalates to be the bonding partners. The variation of the ligands as well as the coordination at the center, E, is now quite well understood.^[136] However, experimental and theoretical studies regarding ligands surrounding the transition metal center M are lacking, and the synthesis of M–E complexes without strong π -acceptors (e.g. CO, Cp) is therefore encouraged. These complexes may provide interesting insight into how a reduction of the ionic contribution in the M–E bond influences the stability and reactivity of the compounds. Remarkably little is still known about the reactivity of the M–E complexes. The question remains open as to what extent the many new compounds can be used as building blocks for further synthesis.

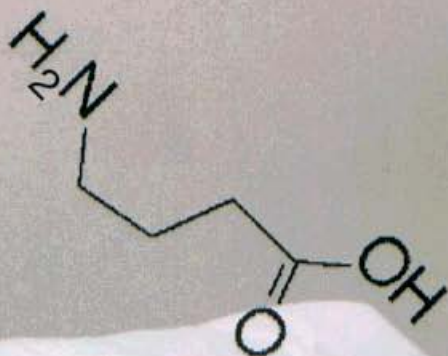
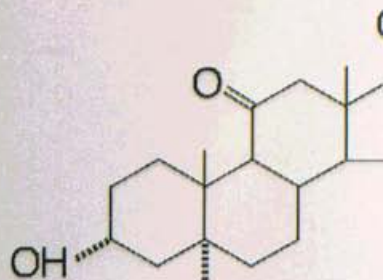
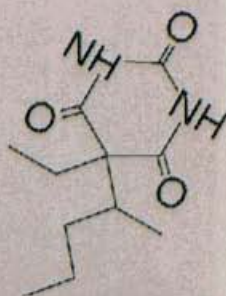
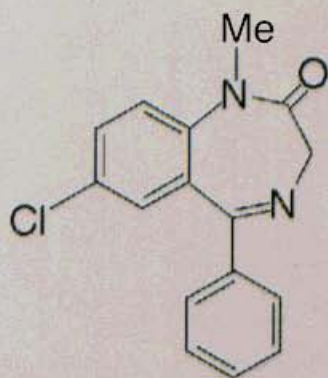
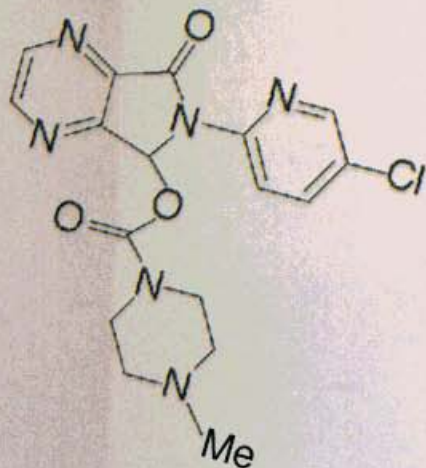
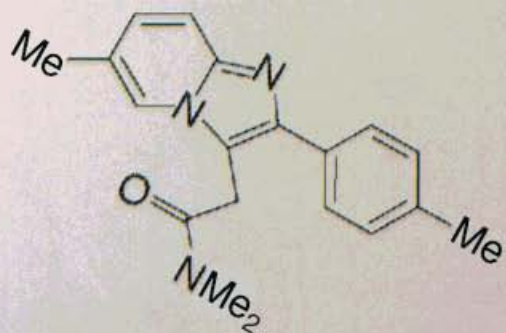
We are indebted to the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, and the Alfred-Krupp-von-Bohlen-und-Halbach Foundation for their long-term generous support. R. A. F. would like to thank his co-workers H. Fölsing, H. Hoffmann, A. Miehr, T. Priermeier, W. Rogge, M. Schulte, O. Segnitz, D. Weiß, and J. Weiß for their perseverance and creativity without which many of the results set down in this article would not have been produced. He would also like to thank G. Frenking (Marburg) for the fruitful cooperation over the past years. Special thanks go to all colleagues who have contributed to this work by means of data material, critical comments, and good advice.

Received: September 18, 1998 [A301 IE]
German version: *Angew. Chem.* **1999**, *111*, 3002–3022

- [1] W. Hieber, U. Teller, *Z. Anorg. Allg. Chem.* **1942**, 249, 43–57.
- [2] W. R. Robinson, D. P. Schussler, *Inorg. Chem.* **1973**, 12, 848–854.
- [3] G. Natta, G. Mazzanti, *Tetrahedron* **1960**, 8, 86–100.
- [4] P. Corradini, A. Sirigu, *Inorg. Chem.* **1967**, 6, 601–605.
- [5] F. N. Tebbe, L. J. Guggenberger, *J. Chem. Soc. Chem. Commun.* **1973**, 227–228.
- [6] G. Erker, R. Zwettler, C. Krüger, R. Noe, S. Werner, *J. Am. Chem. Soc.* **1990**, 112, 9620–9621.
- [7] G. Erker, M. Albrecht, C. Krüger, S. Werner, P. Binger, F. Langhauser, *Organometallics* **1992**, 11, 3517–3525.
- [8] H. Brunner, P. C. Wailes, H. D. Kaesz, *Inorg. Nucl. Chem. Lett.* **1965**, 1, 125–129.
- [9] R. Kumar, H. Rahbarnoohi, M. J. Heeg, D. G. Dick, J. P. Oliver, *Inorg. Chem.* **1994**, 33, 1103–1108.
- [10] A. Alich, N. J. Nelson, D. Strobe, D. F. Shriver, *Inorg. Chem.* **1972**, 11, 2976–2983.
- [11] J. M. Burlitch, M. E. Leonowicz, R. B. Petersen, R. E. Hughes, *Inorg. Chem.* **1979**, 18, 1097–1105.
- [12] E. O. Fischer, *Angew. Chem.* **1974**, 86, 651–663.
- [13] H. Tobita, K. Ishiyama, Y. Kawano, S. Inomata, H. Ogino, *Organometallics* **1998**, 17, 789–794.
- [14] J. Su, X.-W. Li, R. C. Crittendon, C. F. Campana, G. H. Robinson, *Organometallics* **1997**, 16, 4511–4513.
- [15] a) M. L. H. Green, P. Mountford, G. J. Smout, S. R. Speel, *Polyhedron* **1990**, 9, 2763–2765; b) J. J. Schneider, U. Denninger, J. Hagen, C. Krüger, D. Bläser, R. Boese, *Chem. Ber.* **1997**, 130, 1433–1440.
- [16] E. O. Fischer, D. Wittmann, D. Himmelreich, U. Schubert, K. Ackermann, *Chem. Ber.* **1982**, 115, 3141–3151.
- [17] H. Fischer, A. Motsch, U. Schubert, D. Neugebauer, *Angew. Chem.* **1981**, 93, 483–487; *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 463–465.
- [18] U. Schubert, E. O. Fischer, D. Wittmann, *Angew. Chem.* **1980**, 92, 662–663; *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 643–644.
- [19] M. R. Terry, C. Kelley, N. Lugan, G. L. Geoffroy, B. S. Haggerty, A. L. Rheingold, *Organometallics* **1993**, 12, 3607–3617.
- [20] M. Bottrill, M. Green, A. G. Orpen, D. R. Saunders, I. D. Williams, *J. Chem. Soc. Dalton Trans.* **1989**, 511–518.
- [21] M. Green, A. G. Orpen, I. D. Williams, *J. Chem. Soc. Chem. Commun.* **1982**, 493–495.
- [22] G. Huttner, *Acc. Chem. Res.* **1986**, 19, 406–413.
- [23] W. A. Herrmann, *Angew. Chem.* **1986**, 98, 57–77; *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 56–76.
- [24] T. P. Fehlner, *Comments Inorg. Chem.* **1988**, 7, 307–332.
- [25] O. J. Scherer, *Angew. Chem.* **1985**, 97, 905–924; *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 924–943.
- [26] O. J. Scherer, *Comments Inorg. Chem.* **1987**, 6, 1–22.
- [27] M. D. Vaira, P. Stoppioni, M. Peruzzini, *Polyhedron* **1987**, 6, 351–382.
- [28] K. H. Whitmire, *J. Coord. Chem.* **1988**, 17, 95–204.
- [29] W. A. Nugent, *Metal-Ligand Multiple Bonds*, Wiley, New York, **1988**.
- [30] S. K. Boocock, S. G. Shore, *Comprehensive Organometallic Chemistry*, Pergamon, Oxford, **1982**.
- [31] M. J. Taylor, *Metal to Metal Bonding*, Academic Press, London, **1975**.
- [32] A. T. T. Hsieh, *Inorg. Chim. Acta* **1975**, 14, 87–104.
- [33] N. A. Compton, R. J. Errington, N. C. Norman, *Adv. Organomet. Chem.* **1990**, 31, 91–182.
- [34] P. J. Brothers, P. P. Power, *Adv. Organomet. Chem.* **1996**, 39, 1–69.
- [35] G. B. Stringfellow, *Organometallic Vapor-Phase Epitaxy, Theory and Practice*, Academic Press, San Diego, **1989**.
- [36] M. L. Hitchman, K. F. Jensen, *Chemical Vapor Deposition*, Academic Press, London, **1993**.
- [37] C. J. Carmalt, S. R. Whaley, P. S. Lall, A. H. Cowley, R. A. Jones, B. G. McBurnett, J. G. Ekerdt, *J. Chem. Soc. Dalton Trans.* **1998**, 553–557.
- [38] A. H. Cowley, R. A. Jones, *Angew. Chem.* **1989**, 101, 1235–1243; *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 1208–1216.
- [39] a) M. Bochmann, *Chem. Vap. Deposition* **1996**, 2, 85–96; b) D. G. Colombo, D. C. Gilmer, V. G. Young, S. A. Campbell, W. L. Gladfelter, *Chem. Vap. Deposition* **1998**, 4, 220–222.
- [40] A. H. Cowley, B. L. Benac, J. G. Ekerdt, R. A. Jones, K. B. Kidd, J. Y. Lee, J. E. Miller, *J. Am. Chem. Soc.* **1988**, 110, 6248–6249.
- [41] J. E. Miller, J. G. Ekerdt, *Chem. Mater.* **1992**, 4, 7–9.
- [42] a) V. Lakhotia, D. A. Neumayer, A. H. Cowley, R. A. Jones, J. G. Ekerdt, *Chem. Mater.* **1995**, 7, 546–552; b) H. S. Park, S. D. Waezsada, A. H. Cowley, H. W. Roesky, *Chem. Mater.* **1998**, 10, 2251–2257.
- [43] F. Maury, L. Brandt, H. D. Kaesz, *J. Organomet. Chem.* **1993**, 449, 159–165.
- [44] Y.-J. Chen, H. D. Kaesz, Y. K. Kim, H.-J. Müller, R. S. Williams, Z. Xue, *Appl. Phys. Lett.* **1989**, 55, 2760–2762.
- [45] R. S. Williams, *Appl. Surf. Sci.* **1992**, 60/61, 613–618.
- [46] H. M. Manasevit, W. I. Simpson, *J. Electrochem. Soc.* **1969**, 116, 1725–1732.
- [47] H. M. Manasevit, *Appl. Phys. Lett.* **1968**, 12, 156–159.
- [48] H. M. Manasevit, *J. Cryst. Growth* **1972**, 13/14, 306–314.
- [49] E. Yablonovith, *Science* **1989**, 246, 347–351.
- [50] D. Bradley, *New Sci.* **1988**, 14, 38–41.
- [51] R. A. Fischer, H. D. Kaesz, S. I. Khan, H.-J. Müller, *Inorg. Chem.* **1990**, 29, 1601–1602.
- [52] R. A. Fischer, W. Scherer, M. Kleine, *Angew. Chem.* **1993**, 105, 778–780; *Angew. Chem. Int. Ed. Engl.* **1993**, 105, 774–776.
- [53] R. A. Fischer, J. Behm, T. Priermeier, W. Scherer, *Angew. Chem.* **1993**, 105, 776–778; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 772–774.
- [54] R. A. Fischer, J. Behm, *J. Organomet. Chem.* **1991**, 413, C10–C14.
- [55] R. A. Fischer, J. Behm, E. Herdtweck, C. Kronseder, *J. Organomet. Chem.* **1992**, 437, C29–C34.
- [56] R. A. Fischer, J. Behm, *Chem. Ber.* **1992**, 125, 37–42.
- [57] R. A. Fischer, J. Behm, T. Priermeier, *J. Organomet. Chem.* **1992**, 429, 275–286.
- [58] R. A. Fischer, T. Priermeier, W. Scherer, *J. Organomet. Chem.* **1993**, 459, 65–71.
- [59] R. A. Fischer, E. Herdtweck, T. Priermeier, *Inorg. Chem.* **1994**, 33, 934–943.
- [60] R. A. Fischer, T. Priermeier, *Organometallics* **1994**, 13, 4306–4314.
- [61] R. A. Fischer, M. Kleine, O. Lehmann, M. Stuke, *Chem. Mater.* **1995**, 7, 1863–1872.
- [62] R. A. Fischer, A. Miehr, M. M. Schulte, *Adv. Mater.* **1995**, 7, 58–61.
- [63] R. A. Fischer, M. M. Schulte, T. Priermeier, *J. Organomet. Chem.* **1995**, 493, 139–142.
- [64] R. A. Fischer, A. Miehr, T. Priermeier, *Chem. Ber.* **1995**, 128, 831–843.
- [65] C. Dohmeier, C. Robl, M. Tacke, H. Schnöckel, *Angew. Chem.* **1991**, 103, 594–595; *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 564–565.
- [66] S. Schulz, H. W. Roesky, H. J. Koch, G. M. Sheldrick, D. Stalke, A. Kuhn, *Angew. Chem.* **1993**, 105, 1828–1830; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1729–1732.
- [67] C. Schnitter, H. W. Roesky, C. Röpken, R. Herbst-Irmer, H.-G. Schmidt, M. Noltemeyer, *Angew. Chem.* **1998**, 110, 2059–2062; *Angew. Chem. Int. Ed.* **1998**, 37, 1952–1955.
- [68] W. Uhl, A. Jantschak, *J. Organomet. Chem.* **1998**, 555, 263–269.
- [69] W. Uhl, W. Hiller, M. Layh, W. Schwarz, *Angew. Chem.* **1992**, 104, 1378–1380; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 1364–1366.
- [70] W. Uhl, R. Graupner, M. Layh, U. Schütz, *J. Organomet. Chem.* **1995**, 493, C1–C5.
- [71] W. Uhl, S. U. Keimling, K. W. Klinkhammer, W. Schwarz, *Angew. Chem.* **1997**, 109, 64–66; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 64–66.
- [72] C. Dohmeier, D. Loos, H. Schnöckel, *Angew. Chem.* **1996**, 108, 141–161; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 129–149.
- [73] a) W. Uhl, *Angew. Chem.* **1993**, 105, 1449–1461; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1386–1397; b) W. Uhl, *Rev. Inorg. Chem.* **1998**, 18, 239–282.
- [74] R. J. Wehmschulte, K. Ruhlandt-Senge, M. M. Olmstead, H. Hope, B. E. Sturgeon, P. P. Power, *Inorg. Chem.* **1993**, 32, 2983–2984.
- [75] W. Uhl, A. Vester, W. Kaim, J. Poppe, *J. Organomet. Chem.* **1993**, 454, 9–13.
- [76] J. Su, X.-W. Li, C. Crittendon, G. H. Robinson, *J. Am. Chem. Soc.* **1997**, 119, 5471–5472.
- [77] W. Uhl, M. Pohlmann, R. Wartchow, *Angew. Chem.* **1998**, 110, 1007–1009; *Angew. Chem. Int. Ed.* **1998**, 37, 961–963.
- [78] C. Dohmeier, H. Krautscheid, H. Schnöckel, *Angew. Chem.* **1994**, 106, 2570–2571; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 2482–2483.
- [79] J. Weiß, D. Stetzkamp, B. Nuber, R. A. Fischer, C. Boehme, G. Frenking, *Angew. Chem.* **1997**, 109, 95–97; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 70–72.

- [80] R. A. Fischer, M. M. Schulte, J. Weiß, L. Zsolnai, A. Jacobi, G. Huttner, G. Frenking, C. Boehme, S. F. Vyboishchikov, *J. Am. Chem. Soc.* **1998**, *120*, 1237–1248.
- [81] H. Braunschweig, J. Müller, B. Ganter, *Inorg. Chem.* **1996**, *35*, 7443–7444.
- [82] B. N. Anand, I. Krossing, H. Nöth, *Inorg. Chem.* **1997**, *36*, 1979–1981.
- [83] C. Üffing, A. Ecker, R. Köppe, H. Schnöckel, *Organometallics* **1998**, *17*, 2373–2375.
- [84] P. Jutzi, B. Neumann, G. Reumann, H.-G. Stämmler, *Organometallics* **1998**, *17*, 1305–1314.
- [85] M. M. Schulte, E. Herdtweck, G. Raudaschl-Sieber, R. A. Fischer, *Angew. Chem.* **1996**, *108*, 489–491; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 424–426.
- [86] J. C. Vanderhooft, R. D. Ernst, F. W. Cagle, R. J. Neustadt, T. H. Cymbaluk, *Inorg. Chem.* **1982**, *21*, 1876–1880.
- [87] M. M. Schulte, Dissertation, Technische Universität München, **1996**.
- [88] G. Linti, W. Köstler, *Chem. Eur. J.* **1998**, *4*, 942–949.
- [89] U. App, K. Merzweiler, *Z. Anorg. Allg. Chem.* **1997**, *623*, 478–482.
- [90] R. A. Fischer, M. M. Schulte, E. Herdtweck, M. R. Mattner, *Inorg. Chem.* **1997**, *36*, 2010–2017.
- [91] G. N. Harakas, B. R. Whittlesey, *Inorg. Chem.* **1997**, *36*, 2704–2707.
- [92] O. J. Curnow, B. Schiemenz, G. Huttner, L. Zsolnai, *J. Organomet. Chem.* **1993**, *459*, 17–20.
- [93] H. Behrens, M. Moll, E. Sixtus, G. Thiele, *Z. Naturforsch. B* **1977**, *32*, 1109–1113.
- [94] D. L. Reger, S. S. Mason, A. L. Rheingold, B. S. Haggerty, F. P. Arnold, *Organometallics* **1994**, *13*, 5049–5053.
- [95] W. Uhl, S. U. Keimling, W. Hiller, M. Neumayer, *Chem. Ber.* **1995**, *128*, 1137–1139.
- [96] S. T. Haubrich, P. P. Power, *J. Am. Chem. Soc.* **1998**, *120*, 2202–2203.
- [97] W. Uhl, M. Pohlmann, *Organometallics* **1997**, *16*, 2478–2480.
- [98] J. L. Atwood, S. G. Bott, P. B. Hitchcock, C. Eaborn, R. S. Shariffudin, J. D. Smith, A. C. Sullivan, *J. Chem. Soc. Dalton Trans.* **1987**, 747–755.
- [99] W. Uhl, S. U. Keimling, W. Hiller, M. Neumayer, *Chem. Ber.* **1996**, *129*, 397–400.
- [100] J. J. Schneider, C. Krüger, M. Nolte, I. Abraham, T. S. Ertel, H. Bertagnolli, *Angew. Chem.* **1994**, *106*, 2537–2540; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2435–2438.
- [101] J. M. Mayer, J. C. Calabrese, *Organometallics* **1984**, *3*, 1292–1298.
- [102] D. L. Thorn, R. L. Harlow, *J. Am. Chem. Soc.* **1989**, *111*, 2575–2580.
- [103] J. Weiß, T. Priermeier, R. A. Fischer, *Inorg. Chem.* **1996**, *35*, 71–75.
- [104] R. A. Fischer, S. Nlate, H. Hoffmann, E. Herdtweck, J. Blümel, *Organometallics* **1996**, *15*, 5746–5752.
- [105] a) F. P. Gabbaï, A. Schier, J. Riede, H. Schmidbaur, *Inorg. Chem.* **1995**, *34*, 3855–3856; b) F. P. Gabbaï, S.-C. Chung, A. Schier, S. Krüger, N. Rösch, H. Schmidbaur, *Inorg. Chem.* **1997**, *36*, 5699–5705.
- [106] M. L. Clarkson, W. Clegg, D. C. R. Hockless, N. C. Norman, T. B. Marder, *J. Chem. Soc. Dalton Trans.* **1991**, 2229–2239.
- [107] W. Schatz, H.-P. Neumann, B. Nuber, B. Kanellakopulos, M. L. Ziegler, *Chem. Ber.* **1991**, *124*, 453–463.
- [108] J. C. Calabrese, L. M. Clarkson, T. B. Marder, N. C. Norman, N. J. Taylor, *J. Chem. Soc. Dalton Trans.* **1992**, 3525–3529.
- [109] B. Schiemenz, G. Huttner, *Angew. Chem.* **1993**, *105*, 1840–1841; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1772–1773.
- [110] R. Dagani, *Chem. Eng. News* **1998**, *76*, 31–35.
- [111] H. Preut, H.-J. Haupt, *Chem. Ber.* **1974**, *107*, 2860–2869.
- [112] H. Preut, H.-J. Haupt, *Acta Crystallogr. Sect. B* **1979**, *35*, 1205–1207.
- [113] H.-J. Haupt, F. Neumann, *J. Organomet. Chem.* **1974**, *74*, 185–195.
- [114] U. Flörke, P. Balsaa, H.-J. Haupt, *Acta Crystallogr. Sect. C* **1986**, *42*, 275–277.
- [115] a) H. Braunschweig, *Angew. Chem.* **1998**, *110*, 1882–1898; *Angew. Chem. Int. Ed.* **1998**, *37*, 1786–1801; b) G. J. Irvine, M. J. G. Lesley, T. B. Marder, N. C. Norman, C. R. Rice, E. G. Robins, W. R. Roper, G. R. Whittell, L. J. Wright, *Chem. Rev.* **1998**, *98*, 2685–2722.
- [116] R. B. Petersen, J. J. Stezowski, C. Wan, J. Burlith, R. E. Hughes, *J. Am. Chem. Soc.* **1971**, *93*, 3532–3533.
- [117] A. T. T. Hsieh, M. J. Mays, *J. Organomet. Chem.* **1972**, *37*, 9–14.
- [118] D. J. Patmore, W. A. G. Graham, *J. Chem. Soc. Chem. Commun.* **1965**, 591.
- [119] D. J. Patmore, W. A. G. Graham, *Inorg. Chem.* **1966**, *5*, 1586–1590.
- [120] J. Chatt, C. Eaborn, P. N. Kapoor, *J. Organomet. Chem.* **1970**, *23*, 109–115.
- [121] J. Hoyano, D. J. Patmore, W. A. G. Graham, *Inorg. Nucl. Chem. Lett.* **1968**, *4*, 201–203.
- [122] A. T. T. Hsieh, M. J. Mays, *Inorg. Nucl. Chem. Lett.* **1971**, *7*, 223–225.
- [123] A. T. T. Hsieh, M. J. Mays, *J. Chem. Soc. Chem. Commun.* **1971**, 1234–1235.
- [124] L. M. Clarkson, W. Clegg, D. C. R. Hockless, N. C. Norman, L. J. Farrugia, S. G. Bott, J. L. Atwood, *J. Chem. Soc. Dalton Trans.* **1991**, 2241–2252.
- [125] J. Weiß, Dissertation, Ruprecht-Karls-Universität Heidelberg, **1997**.
- [126] a) B. Walther, C. Rockstroh, *J. Organomet. Chem.* **1972**, *44*, C4–C6; b) J. N. StDenis, W. Butler, M. D. Glick, J. P. Oliver, *J. Organomet. Chem.* **1977**, *129*, 1–16.
- [127] D. L. Thorn, *J. Organomet. Chem.* **1991**, *405*, 161–171.
- [128] M. Hackett, J. A. Ibers, G. M. Whitesides, *J. Am. Chem. Soc.* **1988**, *110*, 1436–1448.
- [129] M. Hackett, G. M. Whitesides, *J. Am. Chem. Soc.* **1988**, *110*, 1449–1462.
- [130] a) K. E. Schwarzans, H. Steiger, *Angew. Chem.* **1972**, *84*, 587–588; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 535–536; b) J. J. Schneider, U. Denninger, C. Krüger, *Z. Naturforsch. B* **1994**, *49*, 1549–1553.
- [131] M. M. Schulte, R. A. Fischer, *J. Chem. Soc. Chem. Commun.* **1994**, 2609–2610.
- [132] R. A. Fischer, A. Miehr, M. M. Schulte, E. Herdtweck, *J. Chem. Soc. Chem. Commun.* **1995**, 337–338.
- [133] A. Miehr, Dissertation, Technische Universität München, **1996**.
- [134] A. H. Cowley, A. Decken, C. A. Olazabal, N. C. Norman, *Inorg. Chem.* **1994**, *33*, 3435–3437.
- [135] C. A. Olazabal, F. P. Gabbaï, A. H. Cowley, C. J. Carrano, L. M. Mokry, M. R. Bond, *Organometallics* **1994**, *13*, 421–423.
- [136] a) C. Boehme, Dissertation, Universität Marburg, **1998**; b) C. Boehme, G. Frenking, *Chem. Eur. J.* **1999**, *5*, 2814–2190.
- [137] X. He, R. A. Bartlett, P. P. Power, *Organometallics* **1994**, *13*, 548–552.
- [138] R. M. Campbell, L. M. Clarkson, W. Clegg, D. C. R. Hockless, N. L. Pickett, N. C. Norman, *Chem. Ber.* **1992**, *125*, 55–59.
- [139] L. M. Clarkson, K. McCrudden, N. C. Norman, *Polyhedron* **1990**, *9*, 2533–2547.
- [140] F. A. Cotton, X. Feng, *Organometallics* **1998**, *17*, 128–130.
- [141] G. Frenking, personal communication, **1997**, **1998**.
- [142] a) A. H. Cowley, V. Lomeli, A. Voigt, *J. Am. Chem. Soc.* **1998**, *120*, 6401–6402; b) H. Braunschweig, C. Kollann, U. Englert, *Angew. Chem.* **1998**, *110*, 3355–3356; *Angew. Chem. Int. Ed.* **1998**, *37*, 3177–3178.
- [143] K. E. Lewis, D. M. Golden, G. P. Smith, *J. Am. Chem. Soc.* **1984**, *106*, 3905–3913.
- [144] K. W. Klinkammer, *Angew. Chem.* **1997**, *109*, 2414–2416; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2320–2322.
- [145] D. L. Reger, D. G. Garza, A. L. Rheingold, G. P. A. Yap, *Organometallics* **1998**, *17*, 3624–3626.
- [146] K. D. Sen, M. C. Böhm, P. C. Schmidt, *Structure and Bonding*, Springer, Berlin, **1987**.
- [147] J. Weiß, R. A. Fischer, Y. Pelletier, C. Reber, *Inorg. Chem.* **1998**, *37*, 3316–3320.
- [148] C. H. Langford, C. Moralejo, E. Lindsay, D. K. Sharma, *Coord. Chem. Rev.* **1991**, *111*, 337–343.
- [149] A. G. Orpen, N. G. Connelly, *Organometallics* **1990**, *9*, 1206–1210.
- [150] a) S. Dapprich, G. Frenking, *J. Phys. Chem.* **1995**, *99*, 9352–9362; b) A. J. Lupinetti, S. Fau, G. Frenking, S. H. Strauss, *J. Phys. Chem. A* **1997**, *101*, 9551–9559.
- [151] T. T. Kodas, M. J. Hampden-Smith, *The Chemistry of Metal CVD*, VCH, Weinheim, **1994**.
- [152] W. S. Rees, *CVD of Nonmetals*, VCH, Weinheim, **1996**.
- [153] A. C. Jones, P. O'Brien, *CVD of Compound Semiconductors*, VCH, Weinheim, **1996**.
- [154] H. D. Kaesz, R. S. Williams, R. F. Hicks, J. I. Zink, Y.-J. Chen, H.-J. Müller, Z. Xue, D. Xu, D. K. Shuh, Y. K. Kim, *New J. Chem.* **1990**, *14*, 527–534.
- [155] F. Y. Shiau, Y. A. Chang, L. J. Chen, *J. Electron. Mater.* **1988**, *17*, 433–441.
- [156] J. S. Solomon, S. R. Smith, *J. Vac. Sci. Technol.* **1987**, *A5*, 1809–1815.

- [157] K. M. You, W. Walukiewicz, L. M. Jaklevic, H. H. Heller, *Appl. Phys. Lett.* **1987**, *51*, 189–191.
- [158] J. P. Harbison, T. Sands, N. Tabatabaie, W. K. Chan, L. T. Florez, G. Karamidas, *Appl. Phys. Lett.* **1988**, *53*, 1717–1719.
- [159] N. Tabatabaie, T. Sands, J. P. Harbison, L. H. Gilchrist, V. G. Karamidas, *Appl. Phys. Lett.* **1988**, *53*, 2528–2530.
- [160] T. Sands, J. P. Harbison, W. K. Chan, A. Schwarz, C. C. Chang, J. Palmstrom, V. G. Karamidas, *Appl. Phys. Lett.* **1988**, *52*, 1216–1218.
- [161] J. P. Harbison, T. Sands, R. Ramesh, L. T. Florez, B. J. Wilkens, V. G. Karamidas, *J. Cryst. Growth* **1991**, *111*, 978–983.
- [162] Y. K. Kim, D. A. Baugh, D. K. Shuh, R. S. Williams, L. P. Sadwick, K. L. Wang, *J. Mater. Res.* **1990**, *5*, 2139–2151.
- [163] D. A. Baugh, A. A. Talin, R. S. Williams, T.-C. Kuo, K. L. Wang, *J. Vac. Sci. Technol.* **1991**, *B9*, 2154–2157.
- [164] A. Guivarc'h, M. Secoue, B. Guenais, *Appl. Phys. Lett.* **1988**, *52*, 948–950.
- [165] F.-Y. Shiao, Y. Zuo, J.-C. Lin, X.-Y. Zheng, Y. A. Chang, *Z. Metallkd.* **1989**, *80*, 544–548.
- [166] F.-Y. Shiao, S.-L. Chen, M. Loomans, Y. A. Chang, *Mater. Res. Soc. Symp. Proc.* **1992**, *230*, 40–45.
- [167] F.-Y. Shiao, Y. A. Chang, *Mater. Res. Soc. Symp. Proc.* **1992**, *230*, 47–52.
- [168] F. Maury, A. A. Talin, H. D. Kaesz, R. S. Williams, *Chem. Mater.* **1993**, *5*, 84–89.
- [169] R. A. Fischer, A. Miehr, *Chem. Mater.* **1996**, *8*, 497–508.
- [170] C. Kronseder, T. Schindler, C. Berg, R. A. Fischer, G. Niederschattburg, V. E. Bondybey, *J. Organomet. Chem.* **1994**, *475*, 247–256.
- [171] R. A. Fischer, J. Weiß, W. Rogge, *Polyhedron* **1998**, *17*, 1203–1210.
- [172] Q. Yu, A. Purat, A. Douchev, H. Schnöckel, *J. Organomet. Chem.* **1999**, *584*, 94–97.
- [173] P. Jutzi, B. Neumann, G. Revmann, L. O. Schebaum, H.-G. Stämmler, *Organometallics* **1999**, *18*, 2550–2552.
- [174] A. S. Borovik, S. G. Bott, A. R. Barron, *Organometallics* **1999**, *18*, 2668–2676.
- [175] A. Schnepf, G. Stöber, D. Carmichael, F. Mathey, M. G. Schnöckel, *Angew. Chem.* **1999**, *111*, 1757–1759; *Angew. Chem. Int. Ed.* **1999**, *38*, 1646–1649.



Sleep and Its Modulation by Drugs That Affect GABA_A Receptor Function

Marike Lancel* and Axel Steiger

Insomnia, which can be defined as a discrepancy between the need for sleep and the perceived quantity and/or quality of sleep, constitutes a major medical problem. The most frequently prescribed sleeping pills are agonistic modulators of GABA_A receptors. To examine the changes in sleep that can be induced by a stimulation of GABA_A receptor function, this article reviews the hypnotic properties of the different classes of agonistic modulators of GABA_A receptors—barbiturates, benzodiazepines, zolpidem, zopiclone, and neuro(active) steroids—and of selective GABA_A agonists assessed in various mammalian species, including noninsomniac subjects. Although quantitative differences clearly exist,

the agonistic modulators appear to have many actions in common. They are very effective in inducing and maintaining sleep, but, with the possible exception of the neurosteroids, inhibit the dream-associated rapid eye movement (REM) stage of sleep. With regard to the signals in the electroencephalogram during non-REM sleep, all these drugs promote the occurrence of spindles, which are characteristic for shallow sleep, and, with the exception of barbiturates, have been shown to depress slow waves, which usually identify deep sleep. Upon chronic usage, all these drugs may produce tolerance and dependence. This occurs to the greatest extent with the barbiturates, and to the least

extent with the newer hypnotics zolpidem and zopiclone. The small number of studies on the GABA analogues and the selective GABA_A agonists muscimol and 4,5,6,7-tetrahydroisoxazolo-pyridin-3-ol (THIP) indicate that these compounds have little effect on sleep initiation, but may increase sleep maintenance and promote deep sleep, without disrupting REM sleep. The hypnotic properties of these GABA_A agonists seem to differ considerably from those of agonistic modulators, and may have beneficial effects in the treatment of disturbances in maintaining sleep and of nonrefreshing sleep.

Keywords: electroencephalograms • GABA agonists • receptors • sleep

1. Introduction

Sleep is one of the most time-consuming behaviors. Humans, for instance, spend up to 30 % of their lives sleeping. Although the precise function of sleep is still debatable, it is a general experience that sleep loss leads to fatigue. Furthermore, numerous studies demonstrated that prolonged wakefulness may have manifold consequences, ranging from an impairment of cognitive and psychomotor performance^[1] and a lowering of immune competence^[2] to the production of transient emotional lability and psychotic symptomatology.^[3] Thus, sleep seems essential to physiological and psychological integrity.

Sleep disturbances are very common, with estimates varying between 4 and 45 % of the adult population.^[4] In addition to specific sleep disorders—such as sleep apnea (cessation of respiration), nocturnal myoclonus (involuntary contraction of a muscle), and narcolepsy (excessive daytime sleepiness)—a lot of people have complaints concerning the quantity or quality of their sleep. These complaints include difficulty in going to sleep, multiple or long-lasting nocturnal awakenings, early morning awakening, and superficial, nonrefreshing sleep. In view of the nightly distress associated with insomnia and its impact on well-being, it is not astonishing that many people suffering from poor sleep use hypnotics.^[5] In the early 1900s the first generation of powerful sleeping pills, the barbiturates, was introduced. They are disfavored now because of their toxicity and the rapid development of tolerance and of physical as well as psychological drug-dependency. Barbiturate withdrawal produces a rebound insomnia, a transient worsening of insomnia beyond pretreatment levels. From the 1960s the barbiturates were replaced by the benzodiazepines. Benzodiazepines are much safer than barbiturates. However, chronic use has serious disadvantages: They readily cause tolerance and dependency and rebound

[*] Dr. M. Lancel

Max-Planck-Institut für Psychiatrie
Kraepelinstrasse 2, D-80804 München (Germany)

Fax: (+49) 89-30622-200

E-mail: lancel@mpipsykl.mpg.de

Prof. Dr. A. Steiger

Max-Planck-Institut für Psychiatrie
Kraepelinstrasse 10, D-80804 München (Germany)

Fax: (+49) 89-30622-548

E-mail: steiger@mpipsykl.mpg.de

insomnia can occur upon abrupt discontinuation, particularly of the shorter acting benzodiazepines. A few years ago a third generation of hypnotics, the compounds zolpidem and zopiclone, came on the market. Both compounds seem to have a lower habituation and dependency potential than barbiturates and benzodiazepines.^[6] Although these three generations of hypnotics differ with respect to their tolerability profile and dependence potential, they have a striking feature in common: All of these compounds are ligands for one of the multiple allosteric binding sites at the γ -amino-butyric acid (GABA)_A receptor complex and enhance GABA_A receptor function upon binding.

To examine the hypnotic properties of ligands for different binding sites associated with the GABA_A receptor, this article reviews the effects on sleep of drugs that either potentiate or activate GABA_A receptor mediated transmission. Given the vast literature, which precludes a complete review, we restricted ourselves to reports on the acute or short-term effects of peripherally administered substances on polysomnographically recorded sleep in healthy humans without sleep complaints and in the most extensively studied animals, namely, cats and rats. The review begins with a brief description of the structure and regulation of sleep and with an overview of the configuration and function of GABA_A receptors.

2. Sleep Structure and Regulation

In mammals sleep consists of two different stages, rapid eye movement (REM) sleep and non-REM sleep. These states of

sleep are usually distinguished from each other by measuring the electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG). The predominant state of sleep, non-REM sleep, is characterized by salient signals in the EEG, particularly spindles and slow waves (Figure 1). Spin-

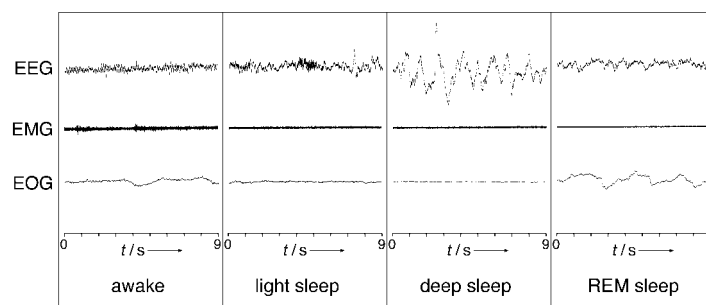


Figure 1. Electroencephalographic (EEG), electromyographic (EMG), and electrooculographic (EOG) recordings in an adult subject during wakefulness, light sleep, deep sleep, and REM sleep. The EEG for the awake state contains alpha waves (8–12 Hz), which typically occur during relaxed wakefulness with closed eyes. The EEG of the light sleep sample contains sleep spindles, and that of deep sleep slow waves.

dles, which constitute the landmark of sleep onset, last 0.5 to 2 s and are composed of sigma frequencies (11–16 Hz) with a waxing and waning amplitude. Slow waves are high-amplitude waves in the delta frequency range (1–4 Hz). As awakening thresholds rise with the increased occurrence of slow waves,^[7] spectral power in the slow wave frequencies (slow wave activity, SWA) is commonly used as an index for non-REM sleep intensity. In general, eye movements are absent and,

Marika Lancel, born in 1959 in Leiden, The Netherlands, studied physiological psychology at the University of Leiden. In 1991 she completed her PhD in psychology at the University of Basel, Switzerland, based on experiments performed in the CNS department of Ciba Geigy, Basel, on sleep regulation in mammalian species. Thereafter, she was at the Max Planck Institute of Psychiatry in Munich as the head of the animal sleep laboratory and since 1998 also as the head of the research group Pharmacology of Sleep. From 1997 on, she has received a grant from the Deutsche Forschungsgemeinschaft to complete a habilitation. She is a member of the scientific board of the "Deutsche Gesellschaft für Schlaforschung und Schlafmedizin" and of the "European Sleep Research Society". Her main fields of interest are sleep regulatory processes, the influence of hormones on sleep, and the interaction between immune system function and sleep–wake behavior.



M. Lancel



A. Steiger

Axel Steiger, born in 1953 in Kaiserslautern, Germany, studied medicine in Heidelberg and Vienna. In 1979 he finished his MD with a thesis on the mechanism of REM sleep induction by γ -hydroxybutyric acid. After one year of work in experimental neurophysiology at the University of Munich he started training in psychiatry at the University of Essen. From 1981 to 1987 he worked as a physician in the Departments of Psychiatry and Neurology of the University of Mainz and was there head of the sleep laboratory. He then moved as senior psychiatrist and director of the sleep laboratory to the University of Freiburg, where he completed a habilitation on sleep-endocrine activity in depressed patients and normal controls. Since 1990 he is senior psychiatrist, member of the executive board, and head of the sleep and hormone group at the Max Planck Institute of Psychiatry in Munich. His main fields of interest are pharmacopsychiatry and sleep-endocrinology in psychiatric patients and normal humans.

except for occasional postural adjustments, the muscles are relaxed during non-REM sleep. In humans, non-REM sleep is subdivided into four stages:^[8] Stages 1 and 2 represent shallow sleep, and stages 3 and 4 reflect deep, slow wave sleep (SWS). In contrast to non-REM sleep, REM sleep is an activated brain state and associated with dreams. It is accompanied by typical rapid eye movements, a very low muscle tonus, and EEG signals that are reminiscent of those observed during wakefulness (low-voltage, fast activity in primates and regular theta activity (4–9 Hz) in rodents). In animals such as cats and rats, the transition from non-REM to REM sleep, called pre-REM sleep here, can easily be recognized by the occurrence of long-lasting, high-amplitude spindlelike EEG signals on a background of theta activity.^[9] In most studies pre-REM sleep was considered as part of non-REM sleep, but in some investigations it was treated as a separate stage. Non-REM and REM sleep alternate, giving rise to non-REM/REM cycles of about 90 min in adult humans (Figure 2) and of a much shorter duration in smaller species.^[10]

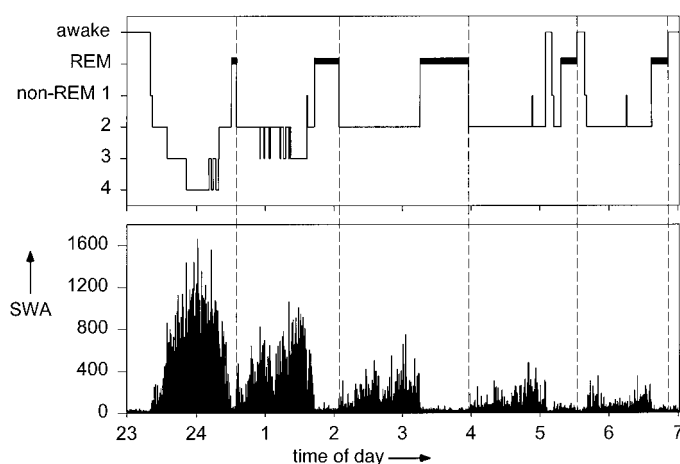


Figure 2. Typical time course of vigilance stages and EEG slow wave activity (μV^2 ; 0.78–4.29 Hz) from 11 p.m. to 7 a.m. the following day in a young adult. The end of five completed non-REM/REM cycles is indicated by dashed vertical lines.

A vast number of studies showed that sleep is regulated by an interaction between circadian and homeostatic components. Circadian regulatory processes determine the timing of sleep. For instance, humans usually sleep during the night, and rats during the day; cats do not exhibit one predominant sleep phase, but are highly active during dusk and dawn. Furthermore, circadian processes have a major impact on the structure of sleep, including sleep maintenance and the duration of the REM episodes, which tends to increase across the main sleep period (Figure 2).^[11] Lesion studies demonstrated that, along with many other diurnally fluctuating parameters, the sleep–wake rhythm is triggered in the suprachiasmatic nuclei of the hypothalamus.^[12] In contrast, the intensity of non-REM sleep is primarily a function of prior sleep and wakefulness. This is shown by the monotonic decline of SWS and SWA in the course of sleep^[13] (Figure 2) and by the fact that naps decrease^[14] whereas extended wakefulness increases SWS and SWA during subsequent sleep.^[13b–g, 15] The duration of prior wakefulness also affects sleep propensity, duration, and

continuity. These sleep–wake-dependent processes are generally assumed to be mediated by endogenous sleep-promoting substances that accumulate during wakefulness and are eliminated during sleep.^[16] In addition to the factors of the time of day and the need for sleep, sleep is markedly affected by age. Polysomnographic studies revealed consistent age-related changes in sleep. In general, the ability to fall asleep is barely affected, but the ability to stay asleep decreases with age, as reflected by an increase in nocturnal awakenings. Furthermore, both SWS and SWA progressively decline during aging, which indicates a decrease in sleep intensity.^[17] In view of the fact that sleep quality deteriorates with age, it is not surprising that the regular usage of hypnotics is particularly heavy in the elderly.^[5b]

3. Structure of GABA_A Receptors

GABA is one of the most prevalent neurotransmitters in the mammalian central nervous system.^[18] As 20–50 % of all central synapses use GABA as their neurotransmitter,^[19] it controls the activity of a large percentage of the neurons. GABA interacts with two types of membrane-bound receptors, GABA_A and GABA_B receptors, which differ in function as well as in pharmacology.^[20] In most brain regions, GABA_A receptors outnumber GABA_B receptors.^[21] GABA_A receptors constitute fast-acting ligand-gated anion channels (Figure 3).

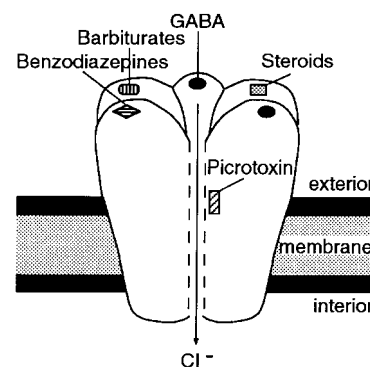
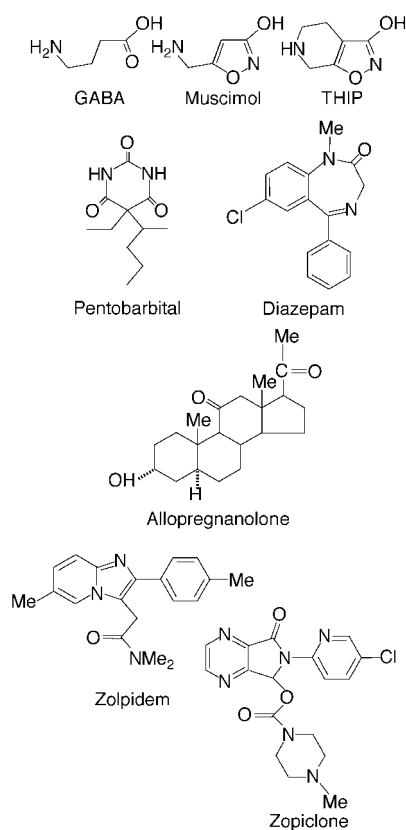


Figure 3. Schematic illustration of the GABA_A receptor complex.

Upon activation by GABA or an appropriate analogue (GABA_A agonist, see Scheme 1 for some examples), the membrane conductance for anions, mainly chloride ions, increases. Owing to the fact that the chloride ion concentration within the neurons is generally low, GABAergic transmission usually produces a slight, short-lasting hyperpolarization and thus reduced excitability of the recipient neuron. In addition to GABA recognition sites, GABA_A receptors are endowed with several other binding sites, including those for barbiturates, benzodiazepines, and anesthetic steroids (see Scheme 1 for examples). The binding of an appropriate ligand induces a conformational change and thereby enhances (agonistic modulators) or attenuates (inverse agonistic modulators) GABA-evoked chloride ion flux



Scheme 1. Chemical structures of various agonists and agonistic modulators of GABA_A receptors.

or inhibits the action of agonistic modulators (antagonistic modulators).

The GABA_A receptor complex is a pentameric glycoprotein composed of combinations of multiple polypeptide subunits. To date, five structurally related families of subunits have been identified (α , β , γ , δ , and ρ), each with its own isoforms; there is 70–80% sequence identity within each family.^[20b] The precise combination of protein subunits determines the physiological and pharmacological properties of a GABA_A receptor.^[22] Coexpression studies demonstrated that a channel with the properties of native receptors requires the combination of at least one α , one β , and one γ subunit.^[23] While most native GABA_A receptors are susceptible to modulation by barbiturates and neurosteroids, many are insensitive to benzodiazepines. Sensitivity to benzodiazepines requires the presence of the $\gamma 2$ subunit.^[23a] Furthermore, the pharmacological influence of benzodiazepines depends on the type of α subunit. The benzodiazepine type I receptor, which contains an $\alpha 1$ subunit, displays high-affinity binding for certain benzodiazepine receptor ligands, including the benzodiazepines quazepam and cinolazepam and the imidazopyridines zolpidem and alpidem. In contrast, the benzodiazepine type II receptor, which contains $\alpha 2$ - or $\alpha 3$ -subunits, has a low affinity for these drugs.^[20a,b, 22a] Both receptor types are present throughout the brain, but are distributed unevenly: Type I receptors are selectively enriched in the cerebellum and type II receptors predominate in limbic structures, such as the hippocampus, and also occur in spinal motor neurons.^[20b, 22a]

4. Effects of Agonistic Modulators of GABA_A Receptors on Sleep

4.1. Barbiturates

The influence of depressant barbiturates on GABA_A receptor function seems to depend on the dose. At high, anaesthetic concentrations they are able to open GABA_A-associated chloride channels directly.^[24] At lower concentrations, barbiturates increase the affinity for and enhance the response to GABA, primarily by increasing the average open duration of the chloride channels.^[25]

In the rat, acute administration of various doses of pentobarbital has been found to shorten the latency to non-REM sleep, to increase pre-REM sleep, and to decrease REM sleep as a function of dose in comparison to placebo. The latter effect is caused by a prolongation of REM sleep latency and by a decrease in the number of REM sleep episodes.^[26a]

In the cat, acute administration of phenobarbital appeared to increase non-REM sleep and to decrease wakefulness as well as REM sleep in a dose-related manner compared with the placebo.^[26b] Another study assessed the sleep changes during chronic sodium barbital treatment, which was administered in slowly increasing doses to counteract the effects of drug tolerance. Compared with control recordings, sodium barbital persistently increased non-REM sleep and suppressed REM sleep.^[26c] Analysis of REM architecture showed that the barbiturate-induced suppression of REM sleep is entirely due to a decrease in the number of REM episodes.^[26c,d] Studies in which pre-REM and non-REM sleep were distinguished revealed that pentobarbital particularly promotes pre-REM sleep.^[26e] Experiments focussed on cortical EEG signals showed that moderate doses of barbiturates evoke bursts of rhythmic waves in the frequency range 6–13 Hz, with a waxing and waning amplitude, in cats as well as in other mammalian species.^[26f] These signals closely resemble naturally occurring sleep spindles and appear simultaneously in the thalamus^[26f], where spindle oscillations originate.^[26g] An *in vivo* electrophysiological study in cat thalamocortical neurons revealed that pentobarbital-induced anesthesia elicits spindle-related firing, but prevents delta oscillations.^[26h]

Various reports on the effects of barbiturates on nocturnal sleep in young, noninsomniac subjects exist. Phenobarbital as well as thiopental, given to a relatively small number of subjects, appeared to decrease the percentage of wakefulness, while slightly increasing SWS, and to prolong REM sleep latency in comparison to placebos or with respect to control recordings.^[27a,b] Pentobarbital has been shown to reduce the number of awakenings, to shorten sleep onset latency, and to increase total sleep time and non-REM sleep, without significantly affecting any of its substages. In addition, it decreases the percentage of REM sleep, which is related to a delay of REM latency and to a decrease in both the number and duration of REM episodes.^[27c,d] Amobarbital reportedly reduces sleep onset latency, decreases the percentage of stage 1, increases the percentage of stage 2, prolongs REM latency, and decreases the percentage of REM sleep. Furthermore, it reduces intra-sleep restlessness, as reflected by a

decrease in the number of switches to wakefulness, movement time, or to stage 1.^[27e] Qualitatively similar effects are produced by heptobarbital^[27f] and secobarbital,^[27g-i] whereby the secobarbital-induced suppression of REM sleep was found to be caused by a shortening of the REM sleep episodes.

Taken together, depressant barbiturates generally increase the ability to fall and to stay asleep, promote non-REM and/or pre-REM sleep, facilitate the occurrence of sleep spindles, and decrease REM sleep owing to a suppression of REM initiation and, at least in humans, to a shortening of the REM episodes.

4.2. Benzodiazepines

Electrophysiological experiments showed that sedative benzodiazepines are inactive at the GABA_A receptor complex in the absence of GABA, but enhance the frequency of GABA-induced chloride channel openings.^[25a, 28] Possibly, benzodiazepines strengthen the coupling between the GABA_A receptor and the chloride ion channels and thereby augment the efficiency of GABA to open the chloride channel.^[20b]

Figure 4 presents the typical dose-dependent alterations in sleep structure and EEG power densities within non-REM sleep induced by the benzodiazepine midazolam in the rat. Placebo-controlled studies in the rat showed that acute, systemic administration of the benzodiazepines flurazepam, diazepam, triazolam, and midazolam produces a dose-dependent shortening of sleep onset latency and an increase in non-REM sleep. The promotion of non-REM sleep is most pronounced during the dark period, which is probably due to the small amount of spontaneously occurring sleep. Additionally, these drugs consistently delay the latency to REM

sleep and decrease REM sleep time.^[29a-i] Reports on the influence of benzodiazepines on REM sleep architecture are contradictory: While diazepam, triazolam, and midazolam have been shown to shorten the duration of the REM sleep episodes in one study,^[26a] midazolam was found to mainly decrease the number of REM sleep episodes in another.^[29h] Experiments in which pre-REM sleep was distinguished revealed that benzodiazepines markedly increase this stage.^[26a] Spectral analysis of the EEG signals following midazolam administration yielded a depression of slow EEG components and an elevation in the spindle and higher frequencies within non-REM sleep in a dose-related manner (Figure 4B).^[29f,h] A more detailed analysis showed that midazolam produces a general attenuation of SWA and enhancement of spindle activity during non-REM sleep, without affecting their time course within the non-REM sleep episodes.^[29h]

In contrast to the soporiferous effects in rats, benzodiazepines induce vigilance in cats. Administration of nitrazepam has been shown to produce restlessness and to increase wakefulness, at the expense of non-REM and REM sleep, in a dose-dependent fashion.^[26b, 29j] The suppression of sleep is generated both by a decrease in the number and duration of the non-REM and REM episodes.^[29j] Qualitatively similar effects have been observed after administration of flunitrazepam,^[26b, 29k,l] diazepam,^[29j,m] triazolam, and midazolam^[29l] to cats. It has not been readily explained why cats, similar to rats and humans, respond to barbiturates with sleep, while benzodiazepines lack a hypnotic action in this species. Electrophysiological experiments indicate that barbiturates selectively depress neurons of the brainstem reticular formation, which constitute a major arousal system, whereas benzodiazepines seem primarily to inhibit parts of the limbic

system and may thereby enhance both activating and deactivating systems.^[26f] Thus, differences in the physiology of species may contribute to their differential response—restlessness versus sedation—to benzodiazepines. Spectral analysis of the EEG signals in the cat revealed that diazepam attenuates delta and theta activity and enhances EEG power density in the frequency range of sleep spindles and in the higher frequency bands within non-REM sleep in cats.^[29m] Thus, in spite of the species-specific changes in sleep–wake behavior, benzodiazepines seem to induce comparable alterations in the sleep EEG.

Most studies on the effects of the long-acting benzodiazepine nitrazepam on sleep in soundly sleeping subjects report a shortened sleep latency, a reduction in the number of body movements, and an increase in total sleep time and stage 2. Furthermore, nitrazepam produces a delay in the occurrence of the first REM episode and thereby decreases the time of REM sleep.^[27e,g, 30]

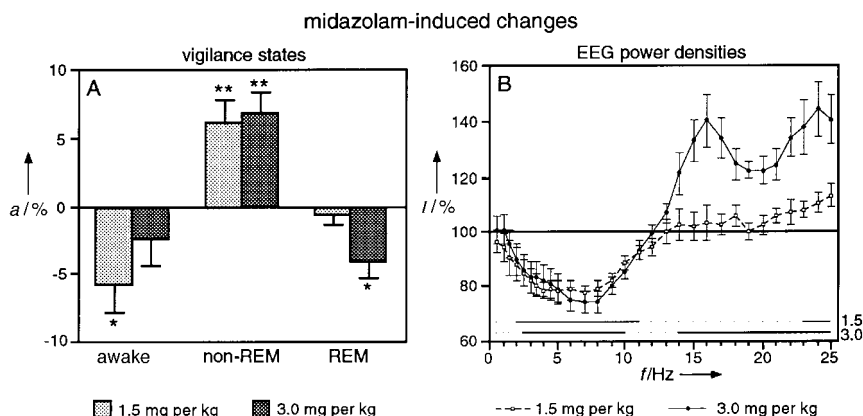


Figure 4. Influence of two doses of midazolam, administered intraperitoneally to rats at the beginning of the light period, on the percentage *a* of time in each vigilance state (A) and on the average EEG power density within non-REM sleep for the frequencies between 0.5 and 25 Hz (B) during the first 6 h after injection. Values are mean values with standard error of the mean ($n = 8$ for each dose). The vigilance-state data are expressed as deviations from the data with the placebo (percentage of recording time with midazolam minus percentage of recording time with placebo). The EEG data are expressed as a percentage of the corresponding placebo values (for each frequency band an intensity of 100% indicates the average EEG power density within non-REM sleep with placebo). Significant differences from the placebo data are indicated by one ($P < 0.05$) and two asterisks ($P < 0.01$, two-sided, paired *t*-test) for the vigilance states and with bars at the bottom of the graph for EEG power density ($P < 0.05$, two-sided, paired *t*-test run on normalized and logarithmically transformed values). The data are reproduced from references [29h, 43d].

Flunitrazepam, another benzodiazepine with a long elimination half-life, has consistently been found to increase total sleep time, which results from a shortened sleep latency, a reduction in the number of awakenings and body movements, and a marked increase in stage 2. In contrast, stage 1, SWS, and REM sleep are decreased, the last effect being due to a prolongation of REM latency and to a reduction in the number of REM sleep episodes.^[30a, 31a–d] Flunitrazepam has also been shown to attenuate EEG power density in the lower frequencies (≤ 9 Hz) and to elevate activity in the spindle frequency range within non-REM sleep.^[31c,d] Separate analysis of SWA revealed that flunitrazepam decreases mean SWA, while barely affecting the temporal development within and across non-REM sleep episodes.^[31e,f] Similar effects on sleep architecture and sleep EEG power have been observed for another long-acting benzodiazepine, flurazepam.^[27d, 31b,d, 32a–d] Computer signal analyses demonstrated that flurazepam reduces the amplitude as well as the number of slow waves and increases the occurrence of spindles.^[32e–g]

The benzodiazepine bromazepam, which has a mediate elimination half-life, has been shown to reduce the number of body movements, increase stage 2 as well as the spindle rate, decrease stage 1, SWS, and REM sleep, and delay the latency to REM sleep as a function of dose.^[30a] One study, in which the influence of a single dose of temazepam on nocturnal sleep was investigated, demonstrated a decrease in the number of awakenings, an increase in the percentage of stage 2, and a lowering of the percentage of wakefulness, stage 1, and SWS. Neither non-REM nor REM sleep latency was affected in this study.^[33a] In contrast, when given shortly before daytime sleep following sleep deprivation as well as before night sleep after an early evening nap, temazepam appeared to shorten sleep latency and to delay the latency to REM sleep. Under both conditions, temazepam tended to increase total sleep time and stage 2 and to decrease SWS. Furthermore, spectral analysis of the non-REM sleep-specific EEG showed that temazepam reduced power in the lower frequencies during both conditions and enhanced activity in the spindle frequencies during daytime sleep.^[33b]

The intake of the short-acting benzodiazepine midazolam at bedtime reportedly induces a shortening of subjective sleep latency and a reduction in the perceived time in wakefulness and in the number of awakenings.^[34a] In a more elaborate study, midazolam was administered shortly before a bedtime that was advanced by four hours to assess its effects at a time of day when sleep propensity is low. Midazolam shortened sleep latency, promoted stage 2, and decreased stage 3, but had little influence on REM sleep. Moreover, midazolam depressed EEG power density in the low-frequency range (≤ 9 Hz) and augmented the activity in the spindle frequency region,^[34b] while hardly influencing the time course of SWA and spindle activity within and across non-REM sleep episodes.^[34c]

Most studies on the hypnotic effects of triazolam found an increased total sleep time, caused by a shortened sleep onset latency, an increase in stage 2, and a reduction in the duration and number of awakenings. Furthermore, triazolam has little effect on SWS, but seems to decrease REM sleep, which is mainly due to a delay in REM latency.^[30f, 31d, 35] Spectral

analysis of the EEG within non-REM sleep revealed similar alterations as evoked by other benzodiazepines.^[31d–f] Also in accordance with the findings for other benzodiazepines, triazolam has been observed to increase the occurrence of spindles and to decrease the number of slow waves.^[35d]

Taken together, the reactivity to benzodiazepines differs between species. In rats and humans benzodiazepine hypnotics increase the ability to fall and to stay asleep and promote non-REM or pre-REM sleep. In the cat, the same drugs induce alertness. Nevertheless, in each of these species they increase the occurrence of spindles and depress slow waves during non-REM sleep and decrease REM sleep, which is related to a suppression of the REM sleep initiation and possibly also to a disruption of its maintenance.

4.3. Zolpidem

In the rat, the imidazopyridine derivative zolpidem, which binds selectively to the benzodiazepine type I receptor, has been demonstrated to shorten the latency to non-REM sleep, to increase non-REM sleep time, to have little effect on pre-REM sleep, and to decrease REM sleep as a function of dose. The last effect is associated with a prolongation of the appearance of the first REM episode and with a transient reduction in the number of REM episodes. The promotion of non-REM sleep and the suppression of REM sleep have been observed during both the light and dark periods.^[26a, 29i, 36]

Similar to the effects of benzodiazepines, zolpidem initially induces wakefulness in the cat. Thereafter, it reportedly promotes both non-REM and pre-REM sleep in a dose-related manner.^[36a]

The experiments focussed on the effects of zolpidem on night sleep in young, healthy subjects revealed only moderate hypnotic effects. Some reports yielded a dose-dependent, slight increase in total sleep time, which was associated with a shortening of sleep onset latency. Most studies revealed no influence on the number of awakenings or on the time in the non-REM sleep substages, but found a tendential decrease in REM sleep or a slight delay in REM latency.^[37a–d] Although zolpidem has minimal effects on time in each of the non-REM sleep stages, spectral analysis of the EEG within non-REM sleep found a marked attenuation of power in the low-frequency bands (≤ 10 Hz) and an enhancement in the frequency range of sleep spindles.^[37d] More pronounced effects of zolpidem were observed on sleep during the daytime, when the propensity and need for sleep are relatively low. During such a condition, it appears to increase total sleep time, mainly caused by a decrease in the number of awakenings and an increase in stage 3, and to decrease REM sleep, without significantly affecting the latencies to either non-REM or REM sleep, in a dose-related fashion.^[37a] The observed increase in visually scored stage 3 may be related to the selective binding of zolpidem to benzodiazepine type I receptors and their regional distribution. Furthermore, the effects of zolpidem on sleep have been shown to increase with age. The administration of zolpidem to noninsomniac middle-aged subjects prior to bedtime reduces wakefulness and the number of awakenings, decreases stage 1, increases stage 2,

and, without affecting total time in REM sleep, delays the latency to REM sleep as a function of dose.^[37a] In geriatric subjects, without sleep complaints, zolpidem has been found to shorten the subjective and objective sleep onset latency, to reduce time in wakefulness after sleep onset, to increase the percentage of stage 2, and to decrease the percentage of stage 1 as well as REM sleep in a dose-dependent fashion.^[37c]

Thus, except for the finding that it does not promote pre-REM sleep in the rat, zolpidem affects sleep in a benzodiazepine-like fashion. In cats, zolpidem transiently produces wakefulness, whereas in both rats and humans it is able to induce and maintain non-REM sleep, facilitates spindling, and, though not detectable by visual scoring, depresses slow components in the EEG during non-REM sleep, and initially inhibits the appearance of REM sleep.

4.4. Zopiclone

The cyclopyrrolone derivate zopiclone, which is structurally related to zolpidem, probably binds at a physically distinct domain on the GABA_A receptor that is closely linked to a benzodiazepine binding site.^[20b, 38a] Zolpidem administered to rats during the light period decreases wakefulness, caused by a shortening of the latency to and an increase of the time spent in non-REM sleep, as a function of dose. Furthermore, it decreases pre-REM and REM sleep, which is generated by a delay in the latency of both stages and a reduction in the number of pre-REM and REM sleep episodes.^[38a,b]

In the cat, zopiclone has been shown to increase wakefulness, at the expense of all sleep stages, particularly non-REM and REM sleep, in a dose-related manner.^[38c,d]

Administration of zopiclone to young, soundly sleeping subjects has only minimal effects on nocturnal sleep. It merely seems to decrease stage 1, to increase stage 2, and to prolong the latency to REM sleep.^[39a-f] In noninsomniac, middle-aged subjects zopiclone additionally decreases wakefulness and the number of awakenings.^[39g] Zopiclone appears to have more pronounced effects in a phase-advanced sleep schedule: When given prior to a bedtime that was advanced by four to six hours, zopiclone has been shown to shorten sleep onset latency and to increase total sleep time owing to an increase in stage 2.^[34b, 39h] Although it hardly affects visually scored SWS, spectral analysis of the EEG within non-REM sleep yielded a prominent reduction in power density in the low-frequency range (≤ 10 Hz) and an enhanced activity in the spindle frequencies both during phase-advanced and nocturnal sleep.^[34b, 39d] Furthermore, zopiclone induced a general decrease in SWA and an increase in spindle activity, without disrupting the inter- or intraepisodic time course.^[34a] Period-crossing analysis showed that zopiclone decreases the number of high-amplitude slow waves and increases the number of low-amplitude slow waves.^[39i] The elevation in spindle activity appears to be brought about by an increased spindle density.^[39j]

Taken together, the effects of zopiclone on sleep are to a large extent comparable to those evoked by short-acting benzodiazepines. In cats, zopiclone transiently promotes wakefulness, while in humans and rats it is able to induce and consolidate non-REM sleep, facilitates the occurrence of

spindles, attenuates low-frequency EEG signals, and suppresses the initiation of REM sleep.

4.5. Neuroactive Steroids

Various steroid hormones modulate GABA_A-mediated transmission, probably through unique steroid binding sites that are distinct from those for barbiturates and benzodiazepines.^[20a,b, 40] Particularly the ring A reduced metabolites of progesterone, 3 α -hydroxy-5 α -dihydroprogesterone (allopregnanolone) and 3 α -hydroxy-5 β -dihydroprogesterone (pregnanolone), and of deoxycorticosterone (DOC), tetrahydro-DOC (THDOC), are potent naturally occurring agonistic modulators of GABA_A receptors. At low nanomolar concentrations these steroids augment GABA-induced GABA_A receptor currents by increasing both the frequency and duration of chloride channel opening. Similar to barbiturates, at high concentrations they are able to directly activate GABA_A receptors in the absence of GABA.^[41]

Already in the 1940s progesterone was found to exert anesthetic actions, in that peripheral administration of high doses of progesterone causes the loss of the righting reflex in rats.^[42a] Progesterone has recently been shown to influence sleep in the rat.^[42b] It shortens the latency to non-REM sleep, decreases wakefulness due to a selective promotion of pre-REMS (Figure 5A), and increases the duration of the non-REM episodes as a function of dose. At a high dose, progesterone suppresses REMS by a prolongation of REM latency and a reduction in the number of REM episodes. Spectral analysis of the EEG within non-REM sleep yielded an attenuation of low-frequency (≤ 7 Hz) activity and enhancements in the spindle and higher frequency bands (Figure 5B). In young, healthy subjects, a single oral dose of 300 mg of micronized progesterone at bedtime was found to increase stage 2, to tendentially decrease stage 4 and REM sleep, and to depress EEG activity in the lower frequencies, while augmenting the activity in the frequencies above 15 Hz within non-REM sleep.^[42c] In both studies progesterone produced an elevation in the levels of allopregnanolone and, to a lesser extent, of pregnanolone in the brain and/or plasma.

The observations that progesterone evokes benzodiazepine-like changes in sleep and that the temporal development of the alterations in sleep and in the concentrations of allopregnanolone and pregnanolone parallel strongly suggest that progesterone affects sleep through its bioconversion into neuroactive metabolites. In line with this postulate, the GABA_A receptor blocker picrotoxin appeared effectively to attenuate most of the changes in sleep evoked by progesterone in the rat.^[42d] Further support for this notion comes from studies on the influence of exogenous pregnanolone and allopregnanolone. In the rat, administration of various doses of pregnanolone and a synthetic analogue, CCD-3693, during the dark period rapidly promotes non-REM sleep in a dose-related manner, without disrupting REM sleep.^[29i] Unfortunately, pre-REM sleep was not distinguished in this study. The administration of allopregnanolone at the beginning of the light period was found to shorten non-REM sleep latency and to significantly increase pre-REM sleep, without interfering with REM sleep (Figure 5C), as a function of dose. Moreover,

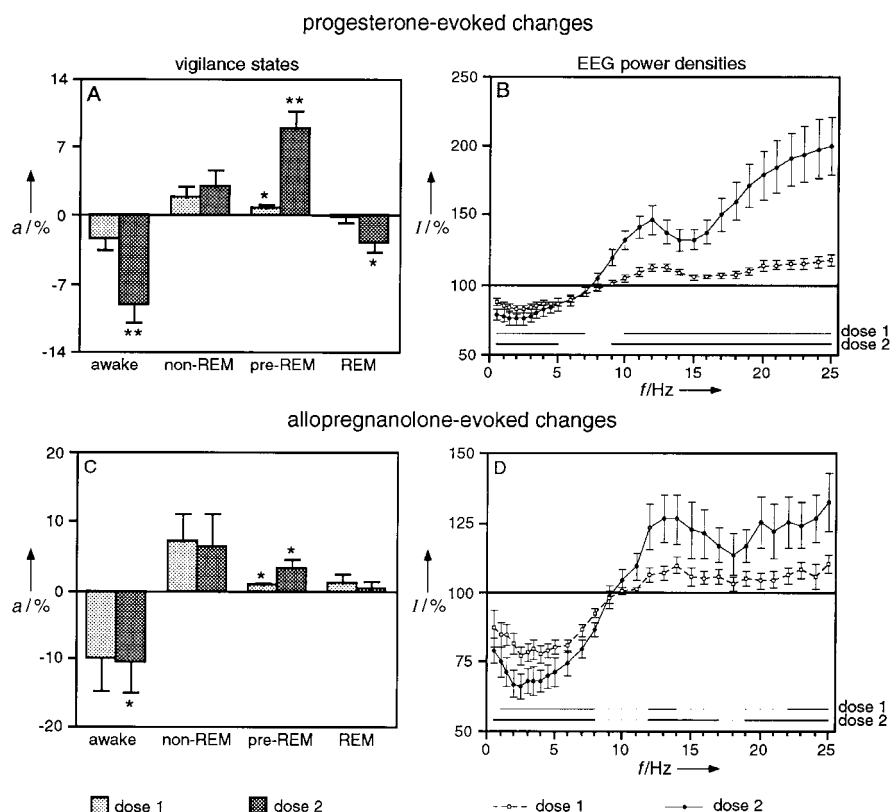


Figure 5. Influence of two doses of progesterone (A, B) and of allopregnanolone (C, D), administered intraperitoneally to rats at the beginning of the light period, on percentage *a* of time in each vigilance state and on average EEG power densities within non-REM sleep during the first 12 h after administration of progesterone and during the first 2 h after administration of allopregnanolone. Values are mean values with standard errors of the mean ($n=8$). See the legend to Figure 4 for more information. Both substances were dissolved in 35% hydroxypropyl- β -cyclodextrin solution, and, to attain a slower release, allopregnanolone was thereafter mixed with corn oil. The doses employed were 90 (dose 1) and 180 mg per kg (dose 2) of progesterone and 7.5 (dose 1) and 15 mg per kg (dose 2) of allopregnanolone. The data are reproduced from references [42b,e].

it depressed slow frequency components (≤ 8 Hz) and augmented EEG power density in the spindle and higher frequency bands (Figure 5D).^[42e] Intriguingly, this study showed that doses of allopregnanolone and progesterone that produce comparable elevations in the brain levels of allopregnanolone have quantitatively and qualitatively similar effects on sleep. Pregnanolone has also been demonstrated to increase sleep propensity in humans. Short polygraphic recordings made during resting conditions at 30-minute intervals revealed that pregnanolone, administered early in the morning to young healthy subjects, increases the number of sleep attempts and the sleep time compared with predosing recordings.^[42f]

Much less attention has been given to the soporific effects of THDOC. One study investigated the effects of THDOC, administered during the light period, on sleep in rats and found a dose-dependent decrease of non-REM sleep latency and an increase in non-REM sleep time.^[42g] As pre-REM sleep was not separated from non-REM sleep, it is unknown whether THDOC particularly promotes pre-REM sleep. Studies on the influence of the THDOC precursor DOC on sleep in humans did not find alterations.^[42h,i] One possible explanation for the lack of effect is that DOC may not be able to enter the brain.

Although the given findings await confirmation and need to be extended, they strongly suggest that steroidogenic agonistic modulators of GABA_A receptors evoke a sleep profile reminiscent of that induced by short-acting benzodiazepines. Similar to benzodiazepines, these steroids appear to be able to increase the ability to fall and to stay asleep, to promote non-REM or pre-REM sleep, to enhance the occurrence of spindles, and to attenuate slow EEG waves during non-REM sleep. In contrast to benzodiazepines, they do not seem to inhibit the initiation of REM sleep. However, since a high dose of progesterone has been demonstrated to clearly interfere with REM sleep in the rat, it can not be excluded that higher doses of its neuroactive metabolites exert a similar effect.

5. Effects of GABA_A Receptor Agonists on Sleep

GABA_A agonists, such as muscimol and 4,5,6,7-tetrahydroisoxazolo-pyridin-3-ol (THIP), are structural analogues of GABA that interact directly with the GABA binding site on the GABA_A receptor complex and thereby increase the membrane conductance for chloride ions.

In the rat, peripheral administration of muscimol during the light period exerts little effect on sleep latency, but increases non-REM sleep and, to a lesser extent, REM sleep as a function of dose (Figure 6A) and tends to increase the duration of the non-REM and REM episodes. EEG spectral analysis revealed that muscimol enhances low-frequency activity within non-REM sleep (Figure 6B). The mean elevation of SWA appeared to be associated with an overall increase of SWA within the non-REM sleep episodes.^[29h] The partial agonist THIP, administered during the light period, has also been demonstrated to increase non-REMS (Figure 6C), to tendentially lengthen the duration of the non-REM episodes, and to augment slow frequency components in the EEG within non-REM sleep (Figure 6D).^[43a] Qualitatively similar, but more pronounced effects of THIP were observed when administered during the dark period.^[43b] In young, noninsomniac subjects a single oral dose of THIP, given half an hour before bedtime, increased the sleep efficiency index (ratio of total sleep time to time in bed) and time in SWS in comparison to a placebo (Figure 7A). Moreover, it enhanced SWA and attenuated EEG activity in the frequency range of sleep spindles within non-REM sleep (Figures 7B, C).^[43c] These findings suggest that at least the GABA_A agonists muscimol and THIP are able to increase the maintenance and intensity of non-REM sleep, without disrupting REM sleep.

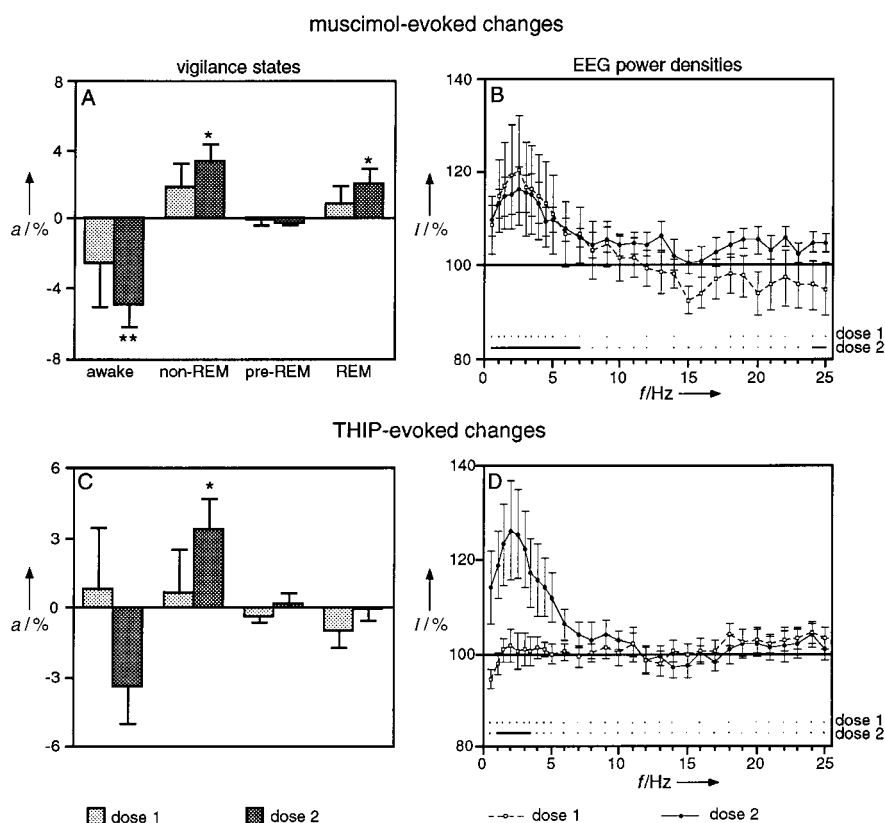


Figure 6. Effects of two doses of muscimol (A, B) and of THIP (C, D), administered intraperitoneally to rats at the beginning of the light period, on percentage *a* of time in each vigilance state and on average EEG power densities within non-REM sleep during the first 6 h after injection. Values are mean values with standard errors of the mean ($n = 8$ for each substance). See the legend to Figure 4 for more information. The doses employed were 0.2 (dose 1) and 0.4 mg per kg (dose 2) of muscimol and 2 (dose 1) and 4 mg per kg (dose 2) of THIP. The data are reproduced from references [29h, 43a].

Since GABA_A agonists and benzodiazepines mimic and potentiate the action of endogenous GABA at the GABA_A receptor, one would expect that GABA_A agonists have effects similar to benzodiazepines and that their effects should be enhanced by benzodiazepines. With regard to their influence on sleep parameters, this is clearly not the case. While muscimol and THIP particularly promote deep non-REM sleep, benzodiazepines increase sleep propensity, promote a state with the EEG characteristics of shallow sleep, and suppress SWS and REM sleep. Moreover, studies in which benzodiazepines and muscimol were coadministered to rats found that these compounds do not augment each other's effects on sleep architecture,^[29c,e, 43d] but instead even attenuate each other's effects on the EEG signals within non-REM sleep.^[43d] These findings, which are at variance with the classical view, indicate that the

has neither been observed in sleep investigations nor in absence-epilepsy studies. One may also postulate that the hypnotic effects of benzodiazepines are not mediated by

influence of agonists and agonistic modulators of GABA_A receptors on electrical brain activity differs substantially. This notion is supported by observations made in studies on non-convulsive, absence-epilepsy (petit-mal) and on drug discrimination. Whereas GABA_A agonists trigger or exacerbate absence-epilepsy in epilepsy-prone animals,^[44a] various agonistic modulators suppress spontaneous as well as GABA_A agonist induced absence-epileptic seizures.^[29g, 44b] Rats trained to discriminate benzodiazepines from saline react the same to other benzodiazepines as well as to barbiturates, allopregnanolone, and THDOC^[45a,b], but not to muscimol or THIP.^[45c]

A possible explanation for the divergent effects of GABA_A agonists and benzodiazepines is that these agents activate different GABA_A receptor subtypes. Whereas muscimol and THIP are likely to act on all GABA_A receptors, the responsiveness to benzodiazepines depends on the precise receptor composition. If this postulate were true, one might expect that the massive activation by GABA analogues dominates the response and masks the modulation evoked by benzodiazepines. As outlined above, this

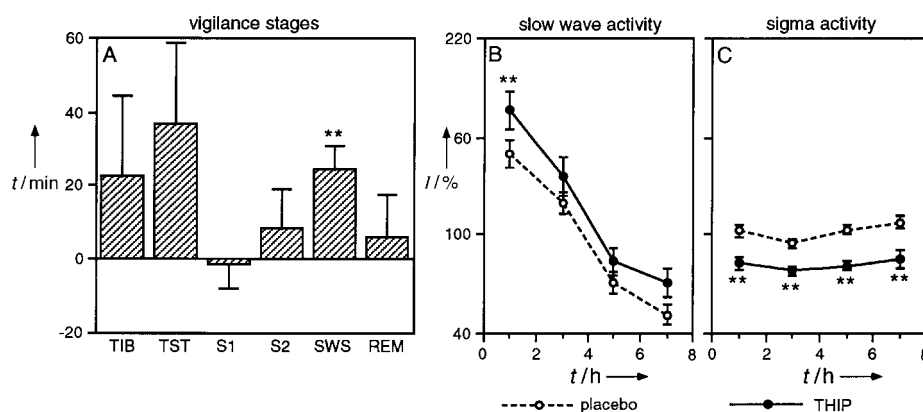


Figure 7. Influence of 20 mg of THIP, given orally shortly before bedtime to young healthy subjects, on visually scored sleep parameters (A) and on average slow wave activity (B) and sigma activity (C) within non-REM sleep for two-hour intervals. Values are mean values with standard errors of the mean ($n = 10$). The sleep states are expressed as deviations from the data with the placebo (time after administration of THIP [min] minus time after administration of the placebo [min]). Average slow wave activity (0.8–4.3 Hz) and sigma activity (12.5–14.8 Hz), which are plotted in the middle of the two-hour intervals, are expressed as percentage of the average power densities within non-REM sleep during the entire night with placebo. TIB = total time in bed; TST = total sleep time; S1 = stage 1; S2 = stage 2; SWS = slow wave sleep; REM = rapid eye movement sleep. Significant differences between the treatments are indicated by two asterisks ($P < 0.01$; Wilcoxon matched pairs signed rank test for vigilance states, and two-sided, paired *t*-test for EEG power densities). The data are reproduced from reference [43c].

GABA_A receptors. This is not very likely since other agonistic modulators of GABA_A receptors exert comparable effects on sleep as benzodiazepines, and flumazenil, an antagonist of the benzodiazepine binding site, has been shown to totally antagonize nearly all benzodiazepine-induced sleep alterations.^[31c] Sleep-related processes are associated with the liberation of GABA in specific brain regions. Thus, an alternative and obvious explanation for the different effects of GABA_A agonists and benzodiazepines is that the former stimulate GABA_A receptors throughout the brain, while benzodiazepines potentiate the action of selectively released GABA on GABA_A receptors. Furthermore, GABA and GABA analogues may exert differential net effects on GABA_A receptor function under in vivo conditions. The action of liberated GABA is temporally and spatially confined by rapid uptake into neurons and glial cells.^[46] In contrast, both muscimol and THIP are poor substrates for uptake mechanisms and may therefore produce more tonic hyperpolarizations than synaptically released GABA, which is likely to have a considerable impact on neural electric activity. In line with the postulate that the distinct effects of muscimol and THIP are caused by an unphysiological tonic activation of GABA_A receptors, the GABA re-uptake inhibitor tiagabine has recently been shown to facilitate absence-epileptic seizures^[47a] and to enhance low-frequency components in the EEG within non-REM sleep in the rat.^[47b]

Taken together, the few available studies on the hypnotic effects of muscimol and THIP suggest that these GABA_A agonists have minimal effects on sleep initiation, but are able to increase sleep maintenance and to promote deep sleep, while having no disrupting influence on REM sleep. Moreover, in humans THIP selectively depresses EEG power density in the spindle frequencies. It is at present unclear whether this is due to a reduction in spindle rate, amplitude, and/or duration.

6. Summary and Outlook

The reviewed data demonstrate a clear link between the hypnotic properties of drugs and their action at the GABA_A receptor complex. However, depending on the site of binding, various substances exert different effects on sleep.

The previously and currently marketed sleeping pills that act at the GABA_A receptor—barbiturates, benzodiazepines, zolpidem, and zopiclone—produce an agonistic modulation and thereby effectually increase the ability to fall and to stay asleep. A common disadvantage of these drugs is the lacking capacity to induce physiological sleep. The most natural method to promote sleep is sleep deprivation. As described in Section 2, sleep deprivation is consistently followed by an increase in deep sleep, as reflected by an increase in SWS and SWA. Benzodiazepines, zolpidem, and zopiclone modulate sleep in the opposite fashion, as they suppress SWS and/or SWA. In addition, all these substances as well as barbiturates facilitate the occurrence of sleep spindles, which are a sign of shallow sleep. Furthermore, these drugs decrease REM sleep.

Beside changing the natural sleep pattern, the aforementioned substances exert other relevant side effects. Barbitu-

rates are now obsolete in the treatment of insomnia, owing to their toxicity. Accidental or suicidal poisoning with barbiturates may be lethal. Benzodiazepines are much safer than barbiturates and were for a long time termed “lucky pills”, until the risk of dependency and addiction became evident. Nowadays the prescription of benzodiazepines is restricted in many countries. In Germany, for example, benzodiazepines are the only class of drugs for which an official usage guideline was released by an expert group on behalf of the federal government. One major point is the recommendation that benzodiazepines should not be prescribed long-term. Since insomnia is frequently chronic, doctors and patients have the problem that they must discontinue successful treatment and undergo the risk of a relapse. The newer hypnotics zolpidem and zopiclone, which exert qualitatively similar effects on sleep as benzodiazepines, were claimed to have a lower tolerance and dependency potential. However, recent observations suggest that particularly patients with a history of substance abuse as well as patients with psychiatric disorders are at risk for abuse of zolpidem and zopiclone.^[48a]

The finding that certain naturally occurring steroid metabolites are agonistic modulators of GABA_A receptors gives rise to the question of whether such substances are putative hypnotics. The results reviewed here indicate that the effects of such neurosteroids on sleep largely resemble those of benzodiazepines. The only difference is that they may not suppress REM sleep. Research in mice indicates that tolerance develops rapidly. Similar to the case of the benzodiazepine temazepam, the sedative response to an acute dose of the neuroactive steroid minaxolone is lost in mice after treatment with the drug for seven days.^[48b] Thus, endogenous neurosteroids may play a role in physiological sleep–wake regulation, but they seem unsuitable as sleeping pills.

In contrast to agonistic modulators of GABA_A receptors, the GABA_A agonists muscimol and THIP enhance SWA and exert minimal effects on REM sleep. Although only few studies have been done with these compounds, it is evident that they mimic the effects of a physiological increase in the need for sleep as evoked by sleep deprivation. Possibly, GABA_A agonists may have prospects in the treatment of sleep that is too light and nonrefreshing. As SWS and SWA decrease during normal aging, especially the elderly may benefit from compounds with such a working profile. Further research is necessary to delineate the effects of GABA_A agonists in insomniacs. Moreover, the effects of long-term treatment and drug withdrawal need to be investigated.

This work was supported by a grant from the Deutsche Forschungsgemeinschaft (M.L.).

Received: September 18, 1998

Revised version: January 11, 1999 [A300IE]

German version: *Angew. Chem.* **1999**, *111*, 3024–3037

- [1] a) R. T. Wilkinson in *The Physiology of Human Survival* (Eds.: O. G. Edholm, A. L. Bacharach), Academic Press, New York, **1965**, pp. 399–430; b) W. B. Webb, *Biol. Psychol.* **1986**, *22*, 169–172; c) J. A. Horne, *Sleep* **1988**, *11*, 528–536.
- [2] Review: H. Moldofsky, *Int. J. Immunopharmacol.* **1995**, *17*, 649–654.
- [3] Review: W. B. Mendelson, *The Use and Misuse of Sleeping Pills. A Clinical Guide*, Plenum, New York, **1980**.

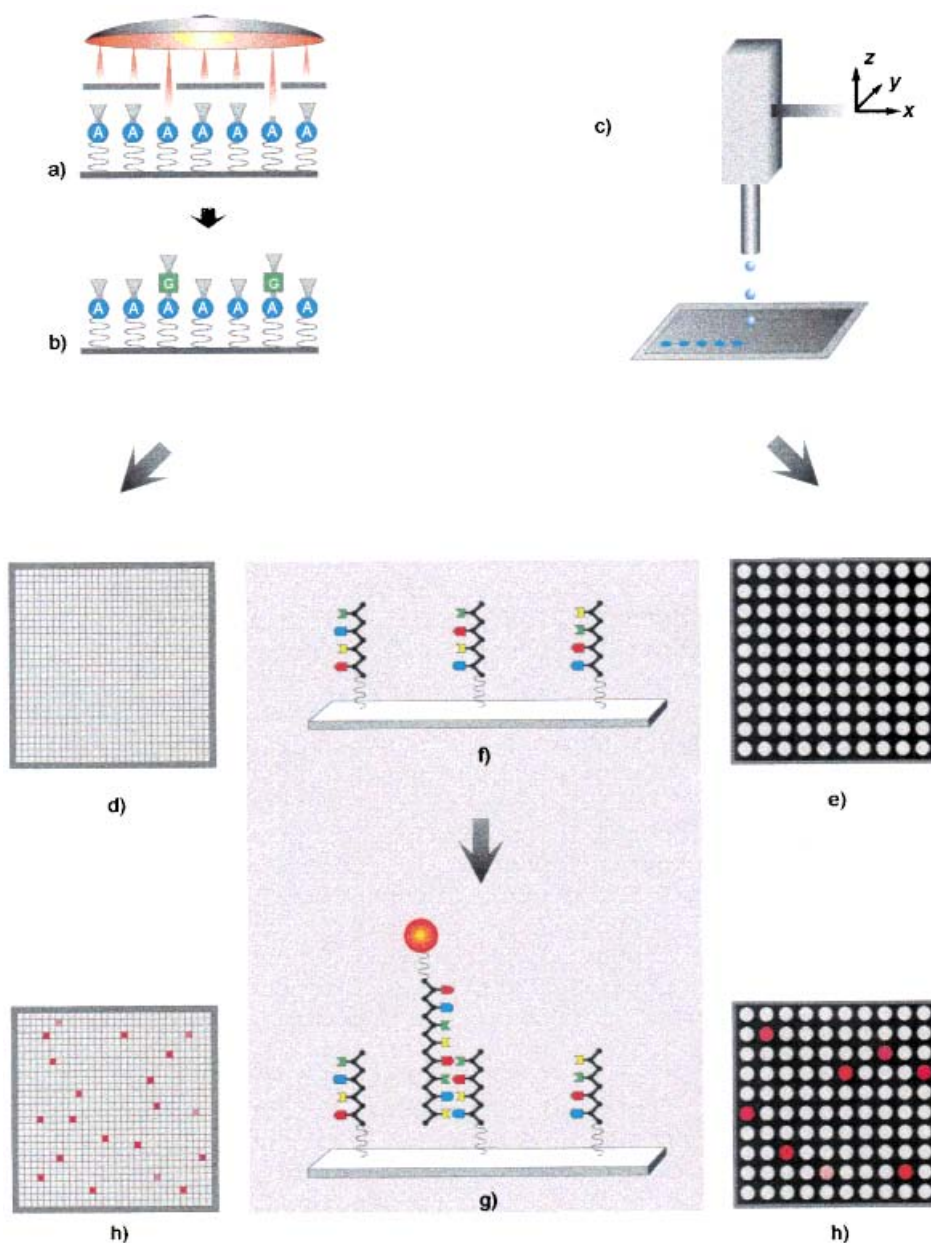
- [4] a) J. Dingemans, *Pharm. World Sci.* **1995**, *17*, 67–75; b) J. A. C. E. Silva, M. Chase, N. Sartorius, T. Roth, *Sleep* **1996**, *19*, 412–416.
- [5] a) J. K. Walsh, C. L. Engelhardt, *J. Clin. Psychiatry* **1992**, *53*, 10–17; b) G. Blennow, A. Romelsjö, H. Leifman, A. Leifman, G. Karlsson, *Am. J. Public Health* **1994**, *84*, 242–246.
- [6] a) M. Lader, *Psychopharmacology* **1992**, *108*, 248–255; b) A. N. Wadsworth, D. McTavish, *Drugs Aging* **1993**, *3*, 441–459; c) J. M. Monti, P. Attali, D. Monti, A. Zipfel, B. de la Giclais, P. L. Morselli, *Pharmacopsychiatry* **1994**, *27*, 166–175; d) M. Lader, *J. Neurol.* **1997**, *244*, S18–S22; e) S. Noble, H. D. Langtry, H. M. Lamb, *Drugs* **1998**, *55*, 279–302.
- [7] a) H. Blake, R. W. Gerard, *Am. J. Physiol.* **1937**, *119*, 692–703; b) C. J. Frederickson, A. Rechtschaffen, *Sleep* **1978**, *1*, 69–82; c) S. Grahnstedt, R. Ursin, *Electroencephalogr. Clin. Neurophysiol.* **1980**, *48*, 222–229; d) D. Neckelmann, R. Ursin, *Sleep* **1993**, *16*, 467–477.
- [8] A. Rechtschaffen, A. Kales, *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*, US Government Printing Office, Washington, DC, **1968**.
- [9] C. Gottesmann, *Neurosci. Biobehav. Rev.* **1996**, *20*, 367–387.
- [10] a) I. Feinberg, T. C. Floyd, *Psychophysiology* **1979**, *16*, 283–291; b) A. A. Borbély, H. U. Neuhaus, *J. Comp. Physiol.* **1979**, *133*, 71–87; c) M. Lancel, H. van Riezen, A. Glatt, *Sleep* **1992**, *15*, 102–118.
- [11] D. J. Dijk, C. A. Czeisler, *J. Neurosci.* **1995**, *15*, 3526–3538, and references therein.
- [12] a) R. E. Mistlberger, B. M. Bergmann, W. Waldenar, A. Rechtschaffen, *Sleep* **1983**, *6*, 217–233; b) I. Tobler, A. A. Borbély, G. Groos, *Neurosci. Lett.* **1983**, *42*, 49–54; c) R. A. Cohen, H. E. Albers, *Neurology* **1991**, *41*, 726–729; d) L. Trachsel, D. M. Edgar, W. F. Seidel, H. C. Heller, W. C. Dement, *Brain Res.* **1992**, *589*, 253–261.
- [13] a) M. W. Church, J. D. March, S. Hibi, K. Benson, C. Cavness, I. Feinberg, *Electroencephalogr. Clin. Neurophysiol.* **1975**, *39*, 1–7; b) A. A. Borbély, H. U. Neuhaus, *J. Comp. Physiol.* **1979**, *133*, 71–87; c) A. A. Borbély, F. Baumann, D. Brandeis, I. Strauch, D. Lehmann, *J. Comp. Physiol.* **1981**, *51*, 71–87; d) A. A. Borbély, I. Tobler, M. Hanagasioglu, *Behav. Brain Res.* **1984**, *14*, 171–182; e) I. Tobler, A. A. Borbély, *Electroencephalogr. Clin. Neurophysiol.* **1986**, *64*, 74–76; f) M. Lancel, G. A. Kerkhof, *Physiol. Behav.* **1989**, *45*, 289–297; g) D. J. Dijk, D. P. Brunner, A. A. Borbély, *Am. J. Physiol.* **1990**, *258*, R650–R661.
- [14] a) I. Feinberg, T. Maloney, J. D. March, *Sleep* **1992**, *15*, 400–403; b) E. Werth, D. J. Dijk, P. Achermann, A. A. Borbély, *Am. J. Physiol.* **1996**, *271*, R501–R510.
- [15] a) I. Tobler, R. Scherschlicht, *Behav. Brain Res.* **1990**, *37*, 109–118; b) M. Lancel, H. van Riezen, A. Glatt, *Brain Res.* **1991**, *548*, 206–214; c) M. Lancel, H. van Riezen, A. Glatt, *Sleep* **1992**, *15*, 102–118.
- [16] Review: A. A. Borbély, I. Tobler, *Physiol. Rev.* **1989**, *69*, 605–670.
- [17] Review: D. L. Bliwise, *Sleep* **1993**, *16*, 40–81.
- [18] a) S. Fahn, L. J. Côté, *J. Neurochem.* **1968**, *15*, 209–213; b) T. L. Perry, K. Berry, S. Hansen, S. Diamond, C. Mok, *J. Neurochem.* **1971**, *18*, 513–519.
- [19] a) E. Roberts, S. Frankel, *J. Biol. Chem.* **1950**, *187*, 55–63; b) F. E. Bloom, L. L. Iversen, *Nature* **1971**, *229*, 628–630.
- [20] Review: a) R. L. Macdonald, R. W. Olsen, *Annu. Rev. Neurosci.* **1994**, *17*, 569–602; b) W. Sieghart, *Pharmacol. Rev.* **1995**, *47*, 181–234; c) R. A. Deisz in *The GABA receptors* (Eds.: S. J. Enna, N. G. Bowery), Humana, Totowa, NJ, **1997**, pp. 157–207.
- [21] A. B. Young, D. Chu, *Drug Dev. Res.* **1990**, *21*, 161–167.
- [22] Review: a) H. Lüddens, E. R. Korpi, P. H. Seeburg, *Neuropharmacology* **1995**, *34*, 245–254; b) F. A. Stephenson, *Biochem. J.* **1995**, *310*, 1–9; c) G. A. R. Johnston, *Pharmacol. Ther.* **1996**, *69*, 173–198.
- [23] a) D. B. Pritchett, H. Sontheimer, B. D. Shivers, S. Ymer, H. Kettenmann, P. R. Schofield, P. H. Seeburg, *Nature* **1989**, *338*, 582–585; b) E. R. Sigel, R. Baur, G. Trube, H. Möhler, P. Malherbe, *Neuron* **1990**, *5*, 703–711.
- [24] a) R. L. Macdonald, J. L. Barker, *Neurology* **1979**, *29*, 432–447; b) J. Bormann, *Trends Neurosci.* **1988**, *11*, 112–116.
- [25] a) R. E. Study, J. L. Barker, *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 7180–7184; b) R. L. Macdonald, C. J. Rogers, R. E. Twyman, *J. Physiol.* **1989**, *417*, 483–500.
- [26] a) C. Gottesmann, G. Gandolfo, C. Arnaud, P. Gauthier, *Eur. J. Neurosci.* **1998**, *2*, 409–414; b) R. Scherschlicht, J. Marias, J. Schneeberger, M. Steiner in *Sleep 1980. 5th Eur. Congr. Sleep Res.* (Ed.: W. P. Koella), Karger, Basel, **1981**, pp. 147–155; c) D. J. Hinman, M. Okamoto, *Sleep* **1984**, *7*, 69–76; d) T. Hara, K. Masuda, H. Miyake in *Advances in Sleep Research* (Ed.: E. D. Weitzman), Spectrum Publications, New York, **1975**, pp. 131–154; e) C. Gottesmann, G. Gandolfo, B. Zernicki, *J. Physiol.* **1984**, *79*, 365–372, and references therein; review: f) W. Schallek, W. Schlosser, *Mod. Probl. Pharmacopsychiatry* **1979**, *14*, 157–173; g) M. Steriade, D. A. McCormick, *Science* **1993**, *262*, 679–685; h) A. Nuñez, R. Curró Dossi, D. Contreras, M. Steriade, *Neuroscience* **1992**, *48*, 75–85.
- [27] a) B. K. Lester, R. Guerrero-Figueroa, *Psychophysiology* **1966**, *2*, 224–236; b) G. Rosadini, P. Masturzo, G. Rodriguez, G. Murialdo, V. Montano, M. L. Bonura, A. Polleri, *Acta Endocrinol.* **1983**, *103*, 309–314; c) F. Baekland, *Psychopharmacologia* **1967**, *11*, 388–396; d) E. Hartmann, *Psychopharmacologia* **1968**, *12*, 346–353; e) I. Haider, I. Oswald, *Br. J. Psychiatry* **1971**, *118*, 519–522; f) I. Oswald, R. J. Berger, R. A. Jaramillo, K. M. G. Keddie, P. C. Olley, G. B. Plunkett, *Br. J. Psychiatry* **1963**, *109*, 66–78; g) H. E. Lehmann, T. A. Ban, *Int. J. Clin. Pharmacol.* **1968**, *1*, 424–427; h) B. K. Lester, J. D. Coulter, L. C. Cowden, H. L. Williams, *Psychopharmacologia* **1968**, *13*, 275–286; i) M. F. Allnutt, P. J. O'Connor, *Aerosp. Med.* **1971**, *42*, 1006–1010.
- [28] J. L. Barker, N. L. Harrison, A. P. Mariani, *Life Sci.* **1986**, *39*, 1959–1968.
- [29] a) J. M. Monti, H. Altier, L. D'Angelo in *Pharmacology of the States of Alertness* (Eds.: P. Passouant, I. Oswald), Pergamon, Oxford, **1979**, pp. 65–71; b) L. T. Meltzer, K. A. Serpa, *Drug Dev. Res.* **1988**, *14*, 151–159; c) W. B. Mendelson, J. V. Martin, *Life Sci.* **1990**, *47*, PL99–PL101; d) D. M. Edgar, W. F. Seidel, W. C. Dement, *Psychopharmacology* **1991**, *105*, 374–380; e) W. B. Mendelson, D. Monti, *Life Sci.* **1993**, *53*, PL81–PL87; f) M. Lancel, T. A. M. Crönlein, P. Müller-Preuß, F. Holsboer, *Brain Res.* **1994**, *646*, 85–94; g) H. Depoortere, D. Françon, E. L. J. M. van Luijcklaar, W. H. I. M. Drinkenburg, A. M. L. Coenen, *Pharmacol. Biochem. Behav.* **1995**, *51*, 571–576; h) M. Lancel, T. A. M. Crönlein, J. Faulhaber, *Neuropsychopharmacology* **1996**, *15*, 63–74; i) D. M. Edgar, W. F. Seidel, K. W. Gee, N. C. Lan, G. Field, H. Xia, J. E. Hawkins, S. Wieland, R. B. Carter, P. L. Wood, *J. Pharmacol. Exp. Ther.* **1997**, *282*, 420–429; j) J. Lanoir, E. K. Killam, *Electroencephalogr. Clin. Neurophysiol.* **1968**, *25*, 530–542; k) P. Polc, W. Haefely in *Sleep 1974. 2nd Europ. Congr. Sleep Res.* (Eds.: P. Levin, W. P. Koella), Karger, Basel, **1975**, pp. 303–305; l) H. Depoortere, M. Decobert, P. Granger, F. Riou-Merle, *Neuropsychobiology* **1986**, *16*, 157–162; m) T. Hashimoto, C. Hamada, T. Wada, N. Fukuda, *Neuropsychobiology* **1992**, *26*, 89–99.
- [30] a) J. M. Gailard, P. Schulz, R. Tissot, *Pharmacopsychiatry* **1973**, *6*, 207–217; b) H. Lechner, *Prog. Brain Res.* **1965**, *18*, 225–226; c) I. Oswald, R. G. Priest, *Br. Med. J.* **1965**, *2*, 1093–1095; d) H. Gastaut, H. Lob, J. J. Papy, *Electroencephalogr. Clin. Neurophysiol.* **1967**, *23*, 288; e) K. Adam L. Adamson, V. Brezinová, W. M. Hunter, I. Oswald, *Br. Med. J.* **1976**, *1*, 1558–1560; f) C. Ogura, K. Nakazawa, K. Majima, H. Ueda, Y. Umezawa, W. M. Wardell, *Psychopharmacology* **1980**, *68*, 61–65.
- [31] a) J. M. Monti, H. Altier, *Psychopharmacologia* **1973**, *32*, 343–349; b) G. Cerone, F. Cirignotta, G. Coccagna, F. Ferro Milone, P. Lion, A. Lorizio, E. Lugaresi, M. Mantovani, A. Muratorio, L. Murri, R. Mutani, A. Roccio, *Eur. Neurol.* **1974**, *11*, 172–179; c) J. M. Gailard, R. Blois, *Sleep* **1989**, *12*, 120–132; d) A. A. Borbély, P. Mattmann, M. Loepe, I. Strauch, D. Lehmann, *Human Neurobiol.* **1985**, *4*, 189–194; e) P. Achermann, A. A. Borbély, *Human Neurobiol.* **1987**, *6*, 203–210; f) A. A. Borbély, P. Achermann, *Eur. J. Pharmacol.* **1991**, *195*, 11–18.
- [32] a) A. Kales, J. D. Kales, M. B. Scharf, T. L. Tan, *Arch. Gen. Psychiatry* **1970**, *23*, 219–225; b) M. W. Johns, J. P. Masterton, *Pharmacology* **1974**, *11*, 358–364; c) I. Feinberg, G. Fein, J. M. Walter, L. J. Price, T. C. Floyd, J. D. March, *Arch. Gen. Psychiatry* **1979**, *36*, 95–102; d) I. Karacan, W. Orr, T. Roth, M. Kramer, J. Thornby, S. Bingham, D. Kay, *Psychopharmacology* **1981**, *73*, 332–339; e) I. Feinberg, G. Fein, J. M. Walker, L. J. Price, T. C. Floyd, J. D. March, *Science* **1977**, *198*, 847–848; f) L. C. Johnson, K. Hanson, R. G. Bickford, *Electroencephalogr. Clin. Neurophysiol.* **1976**, *40*, 67–77; g) L. C. Johnson, D. M. Seales, P. Naitoh, M. W. Church, M. Sinclair, *Electroencephalogr. Clin. Neurophysiol.* **1979**, *47*, 309–321.
- [33] a) F. Ferrillo, V. Balestra, F. Carta, G. Nuvoli, C. Pintus, G. Rosadini, *Neuropsychobiology* **1984**, *11*, 72–76; b) D. J. Dijk, D. G. M. R.

- Beersma, S. Daan, R. H. van den Hoofdakker, *Eur. J. Pharmacol.* **1989**, *171*, 207–218.
- [34] a) A. A. Borbély, G. Balderer, L. Trachsel, I. Tobler, *Arzneimittel-Forsch./Drug Res.* **1985**, *35*, 1696–1699; b) L. Trachsel, D. J. Dijk, D. P. Brunner, C. Klene, A. A. Borbély, *Neuropsychopharmacology* **1990**, *3*, 11–18; c) D. Aeschbach, D. J. Dijk, L. Trachsel, D. Brunner, A. A. Borbély, *Neuropsychopharmacology* **1994**, *11*, 237–244.
- [35] T. M. Itil, B. Saletu, J. Marasa, *Pharmacopsychiatry* **1974**, *240*, 265–280; b) T. Roth, M. Kramer, J. L. Schwartz, *Curr. Ther. Res.* **1974**, *16*, 117–123; c) A. N. Nicholson, B. M. Stone, *Br. J. Clin. Pharmacol.* **1980**, *9*, 187–194; d) L. C. Johnson, C. L. Spinweber, *Electroencephalogr. Clin. Neurophysiol.* **1981**, *52*, 89–97.
- [36] a) H. Depoortere, B. Zivkovic, K. G. Lloyd, D. J. Sanger, G. Perrault, S. Z. Langer, G. Bartholini, *J. Pharmacol. Exp. Ther.* **1986**, *237*, 649–658; b) C. Gottesmann, S. Trefouret, H. Depoortere, *Pharmacol. Biochem. Behav.* **1994**, 359–362.
- [37] a) A. N. Nicholson, P. A. Pascoe in *Imidazopyridines in Sleep Disorders* (Eds.: J. P. Sauvanet, S. Z. Langer, P. L. Morselli), Raven, New York, **1988**, pp. 231–240; b) R. Lund, E. Rütther, W. Wober, H. Hippus in *Imidazopyridines in Sleep Disorders* (Eds.: J. P. Sauvanet, S. Z. Langer, P. L. Morselli), Raven, New York, **1988**, pp. 193–203; c) L. Merlotti, T. Roehrs, G. Koshorek, F. Zorick, J. Lamphere, T. Roth, *J. Clin. Psychopharmacol.* **1989**, *9*, 9–14; d) D. P. Brunner, D. J. Dijk, M. Münch, A. A. Borbély, *Psychopharmacology* **1991**, *104*, 1–5; e) M. B. Scharf, D. W. Mayleben, M. Kaffeman, R. Krall, R. Ochs, *J. Clin. Psychiatry* **1991**, *52*, 77–83.
- [38] a) J. M. Stutzmann, O. Piot, M. Reibaud, A. Doble, J. C. Blanchard, *Encephale* **1992**, *18*, 393–400; b) P. Gauthier, C. Arnaud, J. M. Stutzmann, C. Gottesmann, *Psychopharmacology* **1997**, *130*, 139–143; c) H. Depoortere, P. Granger in *Sleep 1982. 6th Eur. Congr. Sleep Res.* (Ed.: W. P. Koella), Karger, Basel, **1983**, pp. 285–287; d) L. Julou, M. C. Bardone, J. C. Blanchard, C. Garret, J. M. Stutzmann, *Pharmacology* **1983**, *27*, 46–58.
- [39] a) O. B. Godtlibsen, J. F. Dreyfus, *Waking Sleeping* **1980**, *4*, 319–325; b) M. Billiard, A. Besset, C. de Lustrac, L. Brissaud, *Sleep* **1987**, *10*, 27–34; c) N. Hayashida, Y. Nakatawa, T. Sakamoto, N. Uchimura, K. Kuroda, Y. Hashizume, S. Tsuchiya, Y. Tsutsumi, *Jpn. J. Psychiatry Neurol.* **1993**, *47*, 893–899; d) Y. Kim, H. Zhuang, M. Tsutsumi, A. Okabe, M. Kurachi, Y. Kamikawa, *Sleep* **1993**, *16*, 655–661; e) K. Mann, H. Bauer, C. Hiemke, J. Röschke, H. Wetzel, O. Benkert, *Eur. Neuropsychopharmacol.* **1996**, *6*, 163–168; f) H. Yamadera, M. Kato, Y. Tsukahara, N. Kajimura, T. Okuma, *Neuropsychobiology* **1997**, *35*, 152–155; g) A. N. Nicholson, B. M. Stone, *Sleep* **1987**, *10*, 35–39; h) O. Kanno, H. Watanabe, H. Kazamatsuri, *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1993**, *17*, 229–239; i) N. A. Wright, A. Beyavin, R. G. Borland, A. N. Nicholson, *Sleep* **1986**, *9*, 348–352; j) M. Jobert, E. Poiseau, P. Jähmig, H. Schulz, S. Kubicki, *Neuropsychobiology* **1992**, *26*, 100–107.
- [40] Review: a) S. I. Deutsch, J. Mastropaolo, A. Hitri, *Clin. Neuropharmacol.* **1992**, *15*, 352–364; b) R. W. Olsen, D. W. Sapp in *GABA_A Receptors and Anxiety: From Neurobiology to Treatment* (Eds.: G. Biggio, E. Sanna, E. Costa), Raven, New York, **1995**, pp. 57–74; c) R. Rupperecht, *J. Psychiatr. Res.* **1997**, *31*, 297–314.
- [41] a) H. Callachan, G. A. Cottrell, N. Y. Hather, J. J. Lambert, J. M. Nooney, J. A. Peters, *Proc. R. Soc. London* **1987**, *231*, 359–369; b) N. L. Harrison, M. D. Majewska, J. W. Harrington, J. L. Barker, *J. Pharmacol. Exp. Ther.* **1987**, *214*, 346–353; c) J. A. Peters, E. F. Kirkness, H. Callachan, J. L. Lambert, A. J. Turner, *Br. J. Pharmacol.* **1988**, *94*, 1257–1269.
- [42] a) H. Selye, *Endocrinology* **1942**, *30*, 437–453; b) M. Lancel, J. Faulhaber, F. Holsboer, R. Rupperecht, *Am. J. Physiol.* **1996**, *271*, E763–E772; c) E. Friess, H. Tagaya, L. Trachsel, F. Holsboer, R. Rupperecht, *Am. J. Physiol.* **1997**, *272*, E885–E891; d) M. Lancel, J. Faulhaber, F. Holsboer, R. Rupperecht, *Psychopharmacology* **1999**, *141*, 213–219; e) M. Lancel, J. Faulhaber, T. Schiffelholz, E. Romeo, F. Di Michele, F. Holsboer, R. Rupperecht, *J. Pharmacol. Exp. Ther.* **1997**, *282*, 1213–1218; f) H. Schulz, M. Jobert, K. W. Gee, D. W. Ashbrook, *Neuropsychobiology* **1996**, *34*, 106–112; g) W. B. Mendelson, J. V. Martin, M. Perlis, R. Wagner, M. D. Majewska, S. M. Paul, *Psychopharmacology* **1987**, *93*, 226–229; h) J. C. Gillin, L. S. Jacobs, F. Snyder, R. I. Henkin, *Electroencephalogr. Clin. Neurophysiol.* **1974**, *36*, 283–289; i) A. Steiger, R. Rupperecht, D. Spengler, J. Guldner, U. Hemmeter, B. Rothe, K. Damm, F. Holsboer, *J. Psychiatr. Res.* **1993**, *27*, 275–284.
- [43] a) M. Lancel, J. Faulhaber, *NeuroReport* **1996**, *7*, 2241–2245; b) M. Lancel, *Sleep* **1997**, *20*, 1099–1104; c) J. Faulhaber, A. Steiger, M. Lancel, *Psychopharmacology* **1997**, *130*, 285–291; d) M. Lancel, J. Faulhaber, T. Schiffelholz, S. Mathias, R. A. Deisz, *J. Neurophysiol.* **1997**, *77*, 1624–1629.
- [44] a) M. Vergnes, C. Marescaux, G. Micheletti, A. Depaulis, L. Rumbach, J. M. Warter, *Neurosci. Lett.* **1984**, *44*, 91–94, and references therein; b) C. Marescaux, G. Micheletti, M. Vergnes, L. Rumbach, J. M. Warter, *Eur. J. Pharmacol.* **1985**, *113*, 19–24.
- [45] a) H. S. Garcha, I. C. Rose, I. P. Stoleran, *Psychopharmacology* **1985**, *87*, 233–237; b) N. A. Ator, K. A. Grant, R. H. Purdy, S. M. Paul, R. R. Griffiths, *Eur. J. Pharmacol.* **1993**, *241*, 237–243; c) R. J. Rauch, I. P. Stoleran, *J. Psychopharmacol.* **1987**, *2*, 71–80.
- [46] L. L. Iverson, J. S. Kelly, *Biochem. Pharmacol.* **1975**, *24*, 933–938.
- [47] a) A. M. L. Coenen, E. H. M. Blezer, E. L. J. M. van Luijtelaar, *Epilepsy Res.* **1995**, *21*, 89–94, and references therein; b) M. Lancel, J. Faulhaber, R. A. Deisz, *Br. J. Pharmacol.* **1998**, *123*, 1471–1477.
- [48] a) A. Ströhle, I. A. Antonijevic, A. Steiger, A. Sonntag, *Der Nervenarzt* **1999**, *70*, 72–75; b) F. H. Marshall, S. C. Stratton, J. Mullings, E. Ford, S. P. Worton, N. R. Oakley, R. M. Hagan, *Pharmacol. Biochem. Behav.* **1997**, *58*, 1–8.

DNA Microarrays**

Christof M. Niemeyer* and Dietmar Blohm

Two milestones characterize the way from the Southern Blot,^[1] the first “array”, to the nylon-filter-based screening of clone libraries, to today’s DNA microarrays^[2,3] that already host several million DNA fragments.^[2e] The first was the use of nonporous solid supports, in particular glass surfaces, for the employment of fluorescence detection and miniaturization (Scheme 1). Up to 10000 DNA fragments, prepared by enzymatic or chemical syntheses, have been covalently immobilized on activated glass supports by means of automated dispensing or plotting devices.^[2d, f, m, 4] The second landmark was the development of a combinatorial photolithographic process by Affymetrix,^[2e] which was originally destined for peptide syntheses.^[5] Highly structured lateral oligonucleotide libraries on glass supports are accessible by initially modifying the surface with photolabile protection groups.^[6] Illumination through a microstructured photomask leads to the deprotection of selected areas, to which the first phosphoramidite building block is covalently attached. Since the coupled nucleotides also contain photolabile protection groups the iterative repetition of the process generates new patterns, which leads to two-dimensionally structured oligonucleotide arrays. As an example, an array comprised of 256 octanucleo-



Scheme 1. Comparison of microarray formats. High-density oligonucleotide arrays (d) are attainable using Affymetrix photolithographic on-chip synthesis (a, b). The deposition of DNA fragments, previously synthesized by chemical or enzymatic methods using automated spotting or dispensing devices, allows the production of microarrays with a lower density of hybridization spots (c, e). However, this technique allows for the immobilization of long pieces of DNA, for instance, obtained from clone libraries or by PCR. Following the hybridization of fluorophore-labeled cRNA or cDNA samples (f, g), the resulting hybridization patterns (h) are analyzed using a fluorescence scanner.

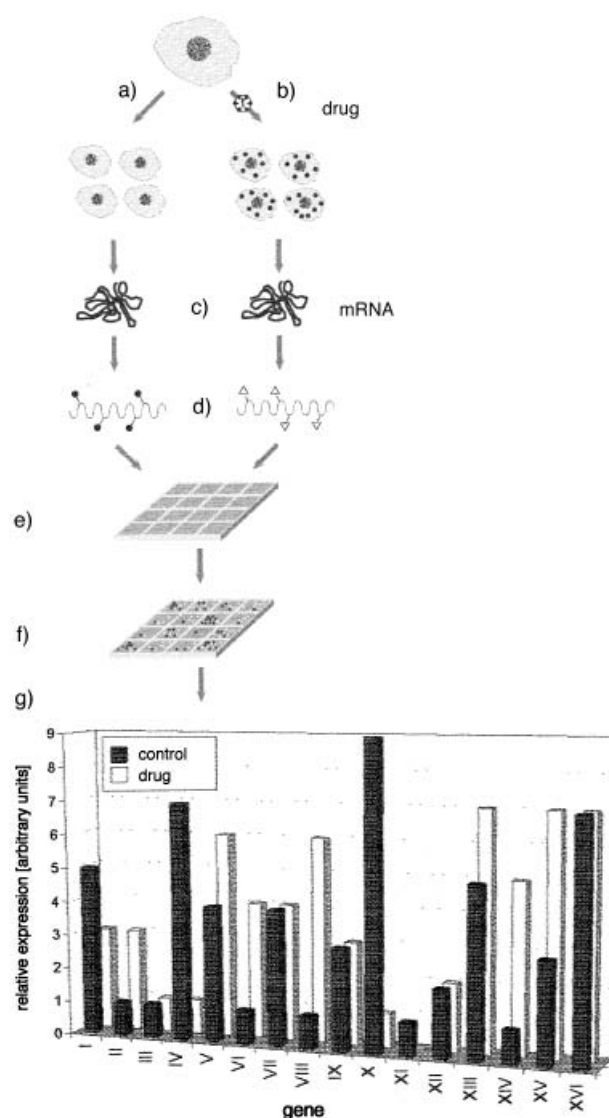
[*] Dr. C. M. Niemeyer, Prof. Dr. D. Blohm
Universität Bremen, FB2-UFT
Biotechnologie und Molekulare Genetik
Leobener Strasse, D-28359 Bremen
(Germany)
Fax: (+49) 421-218-7578
E-mail: cmn@biotec.uni-bremen.de

[**] We thank S. Hahner and M. Adler for help with the figures and critical discussions.

tides on a surface area of 1.3×1.3 cm was synthesized by 16 reaction cycles in four hours.^[7] Currently available fabrication routines allow the production of arrays containing more than 300 000 DNA oligomers to a length of up to 25 nucleotides. A microfluidics station, fluorescence GeneArray scanner, as well as processing and analysis software is required to run the GeneChip microarrays. The complete system is priced at about 175 000 US Dollars.^[2e] As an alternative, the in-situ chemical synthesis of oligonucleotides on glass supports has been developed by Southern and co-workers.^[8] Microarrays have been prepared that contain about 2000 different 17-mer oligonucleotides^[8h] by using a stepwise movable device that allows the application of synthesis reagents to small areas of only a few square micrometers.

One initial motivation for the elaboration of DNA microarrays resulted from efforts during the early stages of the Human Genome Project aimed at developing powerful alternative methodologies for the sequencing of nucleic acids. "Sequencing by hybridization" (SBH) was considered as a promising approach.^[9] This method allows the de-novo determination of an unknown nucleic acid sequence by means of hybridization analysis by using a comprehensive DNA array containing all possible 65 536 ($=4^8$) octanucleotides. During the experimental exploration it turned out that SBH is associated with severe unexpected practical problems. However, the DNA arrays were found to be suitable for immediate applications in the fields of gene expression analysis,^[2c, e, f, m, 3] resequencing, and mutational analysis.^[2h] The particular strength of microarray analysis results from the highly redundant measurement of many parallel hybridization events, which leads to an extraordinary level of assay validation. The probe redundancy does not mean that identical probe molecules are attached on several sites of the chip, but rather the presence of multiple probes of different sequence with specificity for the same nucleic acid target.

Total mRNA or, if there is insufficient sensitivity, polyadenylated RNA (poly(A)⁺-RNA) is isolated, for instance, from different tissues for gene expression analysis. The material is enzymatically transcribed to cDNA and amplified either through a polymerase chain reaction (PCR) or isothermal amplification to incorporate labels, such as fluorophores. The sample material is then hybridized with a microarray containing DNA probes complementary to the genes of interest. Either short DNA oligonucleotides or long single-stranded cDNA fragments are used as array probes. A common experimental variation of enhanced performance is the differential expression analysis (Scheme 2). In this method the two mRNA samples to be compared are labeled with fluorophores that give rise to different colors. The competition of the two samples for the array-bound probe oligomers can be directly deduced from the colors obtained by hybridization. This process allows estimation of the relative abundance of particular transcripts. The analysis of the transcription activity of individual genes is not only useful to study whether and how external parameters influence cellular gene expression activity. Moreover, fundamental growth and differentiation processes, such as mitosis and meiosis, can be investigated.^[2k] As a consequence of its relatively low genome



Scheme 2. Differential expression analysis, illustrated for the screening of drug effects. Cells are cultivated without (a) and (b) in the presence of a drug. The isolated mRNA (c) is amplified and labeled with fluorophores of different colors (d). A mixture of the two nucleic acid samples is hybridized to a microarray (e) containing probe oligomers complementary to the genes of interest. The competition for the array-bound probes leads to mixed colors (f), symbolized schematically by the varying occurrence of the two labels, which can be quantified (g) by means of a fluorescence scanner.

complexity the yeast *Saccharomyces cerevisiae* is currently the eucaryotic model organism of choice. However, it becomes apparent that microarrays containing probes for all approximately 100 000 human genes will soon be available.^[2a] Such arrays will further increase the importance of expression monitoring for the pharmaceutical industry as they will allow both detection of disease-causing genes as potential targets, and analysis of drug effects by means of "high-throughput-screening" (HTS).^[2i]

In addition to the basic research-oriented expression analysis, the second main application of microarrays is the determination of nucleic acid sequences actually known with respect to mutational screenings.^[2h] For this purpose, the microarrays accommodate subsets of probes containing the fully complementary oligonucleotides and also homologous

probe molecules with single base exchanges in a central position. This format leads to the generation of highly characteristic hybridization patterns, thus enabling the determination of both mis-hybridization and the detection of base mutations.^[2h] Genotyping microarrays currently being developed are capable of simultaneously reading several tens to hundreds of thousands of bases in order to allow for an efficient high-throughput. The analysis of point mutations (single nucleotide polymorphism, SNP) is not only important for population genetics,^[2i] the identification of organisms, and in clinical diagnostics of cancer^[2e] and viral diseases such as AIDS.^[2e] Single nucleotide polymorphism analysis is also of great significance for the concept of pharmacogenomics.^[2i] In addition, the reading of single nucleotides is used for the resequencing of highly variable genes. A well known example is the breast and ovarian cancer gene *brac1*, for which over 400 distinct mutations have been reported.^[2h]

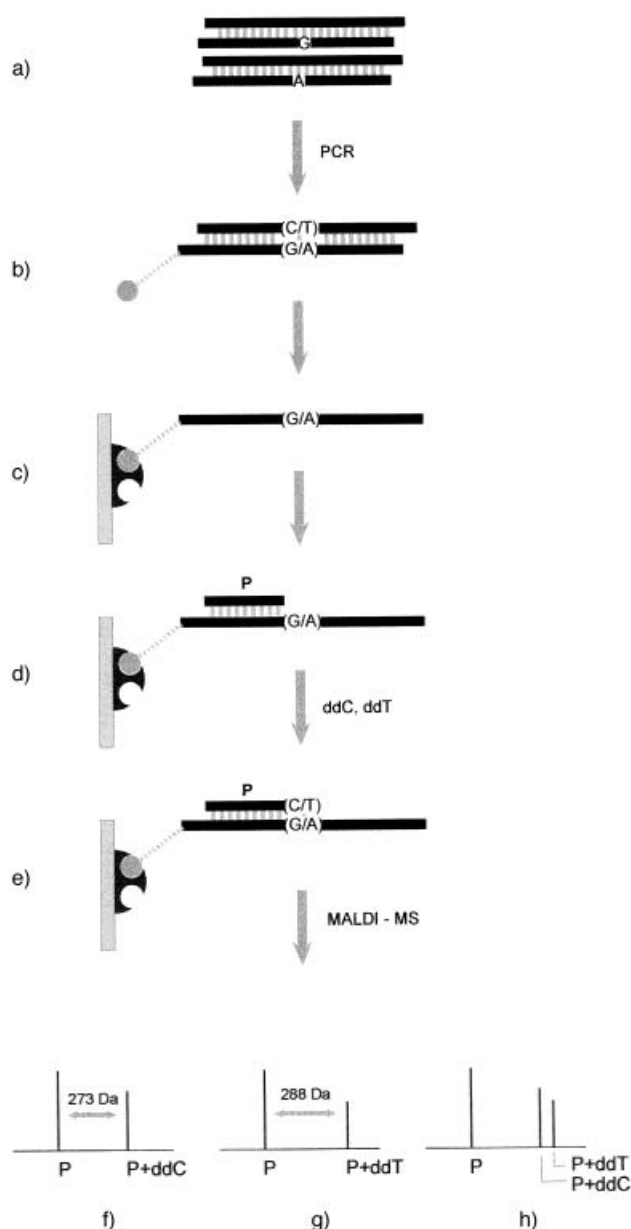
Despite the impressive technical advances in microarray development, there are still many basic questions within this new field of research, for instance, concerning the topology of DNA-functionalized surfaces and the details of the molecular interactions that occur at the interphase. DNA monolayers formed through self-assembly of thiol-modified oligonucleotides on gold substrates have recently been characterized.^[10] Conventional hybridization assays using radiolabeled oligonucleotides as well as X-ray photoelectron spectroscopy (XPS),^[10a] neutron reflectivity,^[10b] electrochemical methods such as cyclic voltammetry,^[10c-f] and scanning force microscopy^[10c, 10g] have been used for this purpose. These studies reveal insights into the density of surface coverages and the orientation of the DNA fragments attached. For example, the single-stranded oligonucleotides within the monolayers are oriented horizontally to the surface, which suggests multiple contacts occur with the surface.^[10a, 10b] In contrast, terminally attached double helical fragments are oriented almost perpendicular to the solid surface.^[10b, 10f] Interestingly, single-stranded oligomers can also be “put upright” by treating the DNA-functionalized surface with short-chain thioalkanoles.^[10a, b]

Southern and co-workers are also carrying out basic research with oligonucleotide arrays.^[2b, 8] For instance, they have investigated how the shape, length, and base composition of the double helices during the formation process affects the efficiency of hybridization.^[8c-f] Also studied were the dependency of surface densities and of the lengths of oligonucleotides and spacers on steric effects.^[8g] A severe problem of solid-phase hybridization is caused by the fact that the efficiency of duplex formation depends on both the melting temperature of the nucleic acids and the formation of intramolecular secondary structure. This is of general importance for microarray analytics, which requires uniform signal intensities that are independent of the nucleic acid sequence. To solve this problem the addition of quarternary ammonium additives to the hybridization buffer,^[11] the incorporation of synthetic nucleotide analogues into the solid phase-bound oligomers,^[12] and the semiempiric design of suitable sequence stretches^[13] are being considered. Such studies are not only relevant for experimental microarray technology but also for other applications such as antisense techniques. For example, microarrays have been used to determine the sequence- and

length-dependent hybridization efficiency of about 2000 surface-bound oligomers in order to select suitable antisense oligonucleotides capable of effectively binding a mRNA target,^[8h] and to examine the intramolecular folding of an mRNA molecule.^[8k]

Great efforts in microarray technology are devoted to technical improvements of reliable and highly sensitive detection methods, for instance, to enable the analysis of even trace amounts of mRNA, possibly without the necessity of a previous amplification step. In the field of DNA microarrays fluorophore labels have practically replaced radiolabels that were commonly used for highly sensitive detection and quantification purposes.^[2d, 2e] The fluorescence scanners currently available allow the quantitation of sub-attomol amounts of fluorophores with a dynamic range of more than three decades.^[2d] However, the use of labels in the detection of nucleic acid hybridization is generally associated with drawbacks. Homogeneously labeled sample materials are required, and stringent washing steps are necessary to remove unbound materials subsequent to hybridization. Instead of this end-point determination, a real-time hybridization analysis would be advantageous for obtaining additional data from the sequence- and temperature-dependent binding kinetics of individual oligomer probes attached to the surface. Optical^[14] or mass-sensitive methods,^[15] often based on layers of metallic transducers, are currently being investigated for their suitability as label-free detection methods. Although not yet sufficiently sensitive, the use of impedance spectroscopy^[16] is very attractive since it would open a way to realize the visions of DNA chips with integrated electronics being used for signal analysis. In this context, studies concerning the hybridization of nucleic acids on microchips as directed by electric fields^[17] shall be mentioned, which have recently been applied to SNP detection.^[17d] Mass spectrometry^[18] is a particularly powerful method for the “read out” of microarrays. Sequenom has developed an SNP analysis^[18b] that is based on the enzymatic elongation of oligonucleotides bound to the solid phase subsequent to hybridization. The products are analyzed by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS; Scheme 3). An entirely automated processing enables daily throughputs of about 10 000 samples to be attained. Since MALDI detection allows the determination of the molecular weight of DNA oligomers with an accuracy of a few Daltons, the method is also convenient for Sanger sequencing at mass ranges up to 20 kDa, which is equal to about 60 nucleotides.^[18c, 18d]

The current “gold rush” atmosphere in the field is probably a result of both the fascinating bioanalytical potential for basic research and also the excellent economic prospects of DNA microarray technology for the various industrial applications. To overcome the gap between desire and reality, however, serious technical obstacles remain to be solved, which range from the highly reproducible chip production to the necessity of performing the many thousands of hybridization reactions under identical reaction conditions. A current frontier in microarray analytics is the detection of length polymorphisms of micro- and minisatellite DNA, which is essential for forensics and paternity analyses. A solution to this problem



Scheme 3. Mass spectrometric analysis of SNPs. Genomic DNA (a) of a heterozygous proband containing a single point mutation (G→A) is amplified and functionalized with a biotin group by PCR (b). The DNA is denatured and immobilized at a streptavidin-coated surface (c), and an oligonucleotide probe P is added and hybridizes immediately upstream of the point mutation (d). Following, the enzymatic elongation of the probe with nucleotide terminators (ddC and ddT) is carried out, and the products are analyzed by MALDI-MS. The spectra shown schematically illustrate the cases of a healthy (f) and sick (g) homozygous as well as of a heterozygous proband (h).

may be provided by HTS based on mass spectrometry.^[18c] Further improvements in detection sensitivity of microarray analytics might result from current advances in the area of single-molecule detection, and also chip-based amplification methods.^[19] To take advantage of the full power of the novel microarray technology, however, it is necessary to emphasize the role of bioinformatics. As a result of the gigantic amounts of data emerging from array hybridizations, comprehensive hard- and software solutions are required for both the a-priori

design of experiments and chips, and the analysis and standardization of the results. The latter is essential to allow for data mining by basic and commercial genome researchers,^[2k] particularly if the next array generations already envisioned^[2e] in fact accommodate several millions of oligomer probes. An increasingly important parameter that has not yet been substantially taken into account is the role of translation. This means that mRNA expression data needs to be correlated with the assortment of proteins actually present in the cell. Thus, it remains to be seen whether future developments of protein, antibody,^[20] or even cell arrays^[2a] will help to correlate genome and proteome^[21] research. This may lead to a comprehension of the entire cellular processes, which will enable the exploitation and standardization of the multi-dimensional relations between genotype and phenotype.

German version: *Angew. Chem.* **1999**, *111*, 3039–3043

Keywords: analytical methods • gene technology • microarrays • nucleic acids • oligonucleotides

- [1] E. M. Southern, *J. Mol. Biol.* **1975**, *98*, 5003.
- [2] A series of review articles has recently been published in a supplement of *Nature Genetics*: a) E. S. Lander, *Nat. Genet.* **1999**, *21*, 3; b) E. M. Southern, K. Mir, M. Shchepinov, *Nat. Genet.* **1999**, *21*, 5; c) D. J. Duggan, M. Bittner, Y. Chen, P. Meltzer, J. M. Trent, *Nat. Genet.* **1999**, *21*, 10; d) V. G. Cheung, M. Morley, F. Aguilar, A. Massimi, R. Kucherlapati, G. Childs, *Nat. Genet.* **1999**, *21*, 15; e) R. J. Lipshutz, S. P. Fodor, T. R. Gingeras, D. J. Lockhart, *Nat. Genet.* **1999**, *21*, 20; f) D. D. L. Bowtell, *Nat. Genet.* **1999**, *21*, 25; g) K. A. Cole, D. B. Krizman, M. R. Emmert-Buck, *Nat. Genet.* **1999**, *21*, 38; h) J. G. Hacia, *Nat. Genet.* **1999**, *21*, 42; i) C. Debouck, P. N. Goodfellow, *Nat. Genet.* **1999**, *21*, 48; k) D. E. Bassett, Jr., M. B. Eisen, M. S. Boguski, *Nat. Genet.* **1999**, *21*, 51; l) A. Chakravarti, *Nat. Genet.* **1999**, *21*, 56; m) for early contributions of european groups, see A. Vente, B. Korn, G. Zehetner, A. Poustka, H. Lehrach, *Nat. Genet.* **1999**, *22*, 22.
- [3] J. D. Hoheisel, *Trends Biotechnol.* **1997**, *15*, 465.
- [4] M. Schena, D. Shalon, R. W. Davis, P. O. Brown, *Science* **1995**, *270*, 467.
- [5] S. Fodor, J. L. Read, M. C. Pirrung, L. Stryer, A. Tsai Lu, D. Solas, *Science* **1991**, *251*, 767.
- [6] Recent publications concerning: a) the chemistry of photolithographical DNA synthesis, see G. H. McGall, A. D. Barone, M. Diggelmann, S. P. A. Fodor, E. Gentalen, N. Ngo, *J. Am. Chem. Soc.* **1997**, *119*, 5081; M. C. Pirrung, L. Fallon, G. H. MacGall, *J. Org. Chem.* **1998**, *63*, 241; M. Beier, J. D. Hoheisel, *Nucleosides Nucleotides* **1999**, in press; b) the surface immobilization and the synthesis of linkers, see M. Beier, J. D. Hoheisel, *Nucleic Acids Res.* **1999**, *27*, 1970.
- [7] A. C. Pease, D. Solas, E. J. Sullivan, M. T. Cronin, C. P. Holmes, S. P. A. Fodor, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 5022.
- [8] a) E. M. Southern, U. Maskos, J. K. Elder, *Genomics* **1992**, *13*, 1008; b) U. Maskos, E. M. Southern, *Nucleic Acids Res.* **1992**, *20*, 1679; c) U. Maskos, E. M. Southern, *Nucleic Acids Res.* **1992**, *20*, 1675; d) U. Maskos, E. M. Southern, *Nucleic Acids Res.* **1993**, *21*, 4663; e) E. M. Southern, S. C. Case-Green, J. K. Elder, M. Johnson, K. U. Mir, L. Wang, J. C. Williams, *Nucleic Acids Res.* **1994**, *22*, 1368; f) J. C. Williams, S. C. Case-Green, K. U. Mir, E. M. Southern, *Nucleic Acids Res.* **1994**, *22*, 1365; g) M. S. Shchepinov, S. C. Case-Green, E. M. Southern, *Nucleic Acids Res.* **1997**, *25*, 1155; h) N. Milner, K. U. Mir, E. M. Southern, *Nat. Biotechnol.* **1997**, *15*, 537; k) M. Sohail, S. Akhtar, E. M. Southern, *RNA* **1999**, *5*, 646.
- [9] a) W. Bains, G. Smith, *J. Theor. Biol.* **1988**, *135*, 303; b) R. Drmanac, I. Labat, I. Brunker, R. Crkvenjakov, *Genomics* **1989**, *4*, 114; c) K. Khrapko, L. Y. A. Khorlyn, V. Shick, V. Florentiev, A. D. Mirzabekov, *FEBS Lett.* **1989**, *256*, 118; d) C. R. Cantor, A. Mirzabekov, E. Southern, *Genomics* **1992**, *13*, 1378.

- [10] a) T. M. Herne, M. J. Tarlov, *J. Am. Chem. Soc.* **1997**, *119*, 8916; b) R. Levicky, T. M. Herne, M. J. Tarlov, S. Satija, *J. Am. Chem. Soc.* **1998**, *120*, 9798; c) A. B. Steel, T. M. Herne, M. J. Tarlov, *Anal. Chem.* **1998**, *70*, 4670; d) S. O. Kelley, J. K. Barton, N. M. Jackson, M. G. Hill, *Bioconjugate Chem.* **1997**, *8*, 31; e) S. O. Kelley, J. K. Barton, N. M. Jackson, L. McPherson, A. Potter, E. M. Spain, M. J. Allen, M. G. Hill, *Langmuir* **1998**, *14*, 6781; f) S. O. Kelley, N. M. Jackson, M. G. Hill, J. K. Barton, *Angew. Chem.* **1999**, *111*, 991; *Angew. Chem. Int. Ed.* **1999**, *38*, 941; g) for a study of DNA microarrays on glass supports by scanning force microscopy, see L. T. Mazzola, S. P. Fodor, *Biophys. J.* **1995**, *68*, 1653.
- [11] K. A. Jacobs, R. Rudersdorf, S. D. Neill, J. P. Dougherty, E. L. Brown, E. F. Fritsch, *Nucleic Acids Res.* **1988**, *16*, 4637.
- [12] Mixed oligomers containing ribo- and deoxyribonucleotides: J. D. Hoheisel, *Nucleic Acids Res.* **1996**, *24*, 430; modified uridine and adenosine bases in the *brca1* analysis: J. G. Hacia, S. A. Woski, J. Fidanza, K. Edgemon, N. Hunt, G. McGall, S. P. Fodor, F. S. Collins, *Nucleic Acids Res.* **1998**, *26*, 4975; alkyldeoxycytidine-modified nucleotides (H. K. Nguyen, E. Bonfils, P. Auffray, P. Costaglioli, P. Schmitt, U. Asseline, M. Durand, J. C. Maurizot, D. Dupret, N. T. Thuong, *Nucleic Acids Res.* **1998**, *26*, 4249) show uniform duplex stabilities in the presence of chaotropic agents: H. K. Nguyen, O. Fournier, U. Asseline, D. Dupret, N. T. Thuong, *Nucleic Acids Res.* **1999**, *27*, 1492; peptide nucleic acids (PNAs) are ideal probe molecules since the duplex stability is only scarcely influenced by the presence of secondary structures: H. F. Arlinghaus, M. N. Kwoka, K. B. Jacobson, *Anal. Chem.* **1997**, *69*, 3747; J. Weiler, H. Gausepohl, N. Hauser, O. N. Jensen, J. D. Hoheisel, *Nucleic Acids Res.* **1997**, *25*, 2792; see also ref. [3].
- [13] The hybridization efficiencies, determined experimentally for a set of array-bound oligomers, are used to generate heuristic rules by means of bioinformatic procedures employing neuronal networks. The next generation of oligomers is designed by following these rules: D. J. Lockhart, H. Dong, M. C. Byrne, M. T. Follettie, M. V. Gallo, M. S. Chee, M. Mittmann, C. Wang, M. Kobayashi, H. Horton, E. L. Brown, *Nat. Biotechnol.* **1996**, *14*, 1675.
- [14] Surface plasmon resonance: a) S. J. Wood, *Microchem. J.* **1992**, *47*, 330; b) analysis of enzymatic DNA manipulations: P. Nilsson, B. Persson, M. Uhlen, P. A. Nygren, *Anal. Biochem.* **1995**, *224*, 400; c) ellipsometry: D. E. Gray, S. C. Case-Green, T. S. Fell, P. J. Dobson, E. M. Southern, *Langmuir* **1997**, *13*, 2833; d) optical grating coupler: F. F. Bier, F. W. Scheller, *Biosens. Bioelectron.* **1996**, *11*, 669; e) resonance mirror: H. J. Watts, D. Yeung, H. Parkes, *Anal. Chem.* **1995**, *67*, 4283; f) reflectometric interference spectroscopy: J. Piehler, A. Brecht, G. Gauglitz, M. Zerlin, C. Maul, R. Thiericke, S. Grabley, *Anal. Biochem.* **1997**, *249*, 94.
- [15] Nucleic acid hybridization can be detected by means of the piezoelectric quartz crystal microbalance (QCM): Y. Okahata, Y. Matsunobu, K. Ijio, M. Mukae, A. Murakami, K. Makino, *J. Am. Chem. Soc.* **1992**, *114*, 8299; b) S. Yamaguchi, T. Shimomura, *Anal. Chem.* **1993**, *65*, 1925; c) K. Ito, K. Hashimoto, Y. Ishimori, *Anal. Chim. Acta* **1996**, *327*, 29; d) hybridization using QCM-bound DNA multilayers: F. Caruso, E. Rodda, D. N. Furlong, K. Niikura, Y. Okahata, *Anal. Chem.* **1997**, *69*, 2043; e) detection of single mismatches by means of QCM-bound PNA probes: J. Wang, P. E. Nielsen, M. Jiang, X. Cai, J. R. Fernandes, D. H. Grant, M. Ozsoz, A. Beglieter, M. Mowat, *Anal. Chem.* **1997**, *69*, 5200; f) hybridization with QCM-bound DNA dendrimers: J. Wang, M. Jiang, T. W. Nilsen, R. C. Getts, *J. Am. Chem. Soc.* **1998**, *120*, 8281; g) detection of the enzymatic activity of a DNA polymerase at surfaces of a QCM: K. Niikura, M. Hisao, Y. Okahata, *J. Am. Chem. Soc.* **1998**, *120*, 8537; for electrochemical analysis of hybridization, see J. Wang, *Chem. Eur. J.* **1999**, *5*, 1681.
- [16] R. Hintsche, M. Paeschke, A. Uhlig, R. Seitz, *Frontiers in Biosensors: Fundamental Aspects* (Eds.: F. W. Scheller, F. Schaubert, J. Fredrowitz), Birkhäuser, **1997**, p. 267.
- [17] This principle has been developed by the US company Nanogen: a) C. F. Edman, D. E. Raymond, D. J. Wu, E. Tu, R. G. Sosnowski, W. F. Butler, M. Nerenberg, M. J. Heller, *Nucleic Acids Res.* **1997**, *25*, 4907; b) R. G. Sosnowski, E. Tu, W. F. Butler, J. P. O'Connell, M. J. Heller, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 1119; c) J. Cheng, E. L. Sheldon, L. Wu, A. Uribe, L. O. Gerrue, J. Carrino, M. J. Heller, J. P. O'Connell, *Nat. Biotechnol.* **1998**, *16*, 541; d) P. N. Gilles, D. J. Wu, C. B. Foster, P. J. Dillon, S. J. Chanock, *Nat. Biotechnol.* **1999**, *17*, 365.
- [18] a) Review: E. Nordhoff, F. Kirpekar, P. Roepstorff, *Mass Spectrom. Rev.* **1996**, *15*, 67; b) enzymatic elongation of immobilized oligomers with dideoxy terminators allows the detection of SNPs even in heterozygous probands: G. S. Higgins, D. P. Little, H. Köster, *Biotechniques* **1997**, *23*, 710; c) MALDI-MS sequencing of the human *p53* gene: D. J. Fu, K. Tang, A. Braun, D. Reuter, B. Darnhofer-Demar, D. P. Little, M. J. O'Donnell, C. R. Cantor, H. Köster, *Nat. Biotechnol.* **1998**, *16*, 381; d) nucleic acids of more than 500 kDa can be detected by means of an infrared laser: S. Berkenkamp, F. Kirpekar, F. Hillenkamp, *Science* **1998**, *281*, 260; e) MALDI-MS analysis of length polymorphisms: A. Braun, D. P. Little, D. Reuter, B. Müller-Mysok, H. Köster, *Genomics* **1997**, *46*, 18; P. L. Ross, P. Belgrader, *Anal. Chem.* **1997**, *69*, 3966.
- [19] a) Single-molecule detection using fluorescence spectroscopy (review: S. Weiss, *Science* **1999**, *283*, 1676) has recently been applied to the analysis of DNA hybridization (W. Trabesinger, G. J. Schutz, H. J. Gruber, H. Schindler, T. Schmidt, *Anal. Chem.* **1999**, *71*, 279) and RNA transcription (A. M. Femino, F. S. Fay, K. Fogarty, R. H. Singer, *Science* **1998**, *280*, 585); b) surface-immobilized DNA can be amplified by isothermal "rolling circle amplification": P. M. Lizardi, X. Huang, Z. Zhu, P. Bray-Ward, D. C. Thomas, D. C. Ward, *Nat. Genet.* **1998**, *19*, 225.
- [20] Peptide arrays (R. Frank, *Tetrahedron* **1992**, *48*, 9217) are used, for instance, for the screening of antibodies: A. Kramer, J. Schneider-Mergener, *Methods. Mol. Biol.* **1998**, *87*, 25; photolithographical immobilization of immunoglobulins: L. F. Rozsnyai, D. R. Benson, S. P. A. Fodor, P. G. Schultz, *Angew. Chem.* **1992**, *104*, 801; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 759; "DNA-directed immobilization" (DDI) uses DNA arrays as immobilization matrices for antibodies and enzymes, and thus, allows the fabrication of mixed arrays containing both nucleic acids and proteins: C. M. Niemeyer, L. Boldt, B. Ceyhan, D. Blohm, *Anal. Biochem.* **1999**, *268*, 54; protein microarrays for the screening of gene expression: A. Lueking, M. Horn, H. Eickhoff, K. Bussow, H. Lehrach, G. Walter, *Anal. Biochem.* **1999**, *270*, 103.
- [21] Proteome research (reviews: A. Persidis, *Nat. Biotechnol.* **1998**, *16*, 393; R. Parekh, *Nat. Biotechnol.* **1999**, *17*, Suppl. 19; A. Dove, *Nat. Biotechnol.* **1999**, *17*, 233; F. Lottspeich, *Angew. Chem.* **1999**, *111*, 2630; *Angew. Chem. Int. Ed.* **1999**, *38*, 2476) is based on the separation of total protein mixtures using two-dimensional (2D) gel electrophoresis (P. H. O'Farrell, *J. Biol. Chem.* **1975**, *250*, 4007). This leads, in analogy to the Southern Blot^[1], to 2D-protein arrays containing more than 10000 spots.

Self-Assembled, Sub-Micrometer Diameter Semipermeable Capsules

David E. Bergbreiter*

Self-assembly is an elegant and simple approach to the design of new materials relevant to problems in catalysis, sensor design, biological chemistry, and materials science.^[1] The many applications of two-dimensional arrays such as those derived from thiol-self-assembly on gold and other metals illustrate the potential of macroscopic organized molecular assemblies.^[2] However, while self-assembly has proven to be a very versatile and useful method for modifying the reactivity and chemistry of two-dimensional macroscopically planar surfaces, less attention has been paid to the use of self-assembly to modify the surfaces of one and zero dimensional fibers and particles. This oversight is now being addressed. The work highlighted here illustrates the potential of self-assembly both as a method for modifying surfaces of particles and as a method in the fabrication of micrometer- and submicrometer-sized hollow spheres. This work by Möhwald et al. and Wooley et al. spans a range of materials and length scales and promises to provide chemists with new sorts of materials that should be useful in applications in areas as diverse as biological chemistry, synthesis, and catalysis.^[3–7]

Micrometer- and submicrometer-sized containers are not new; nature uses them in various ways in intracellular apparatus. Chemists too use structures such as liposomes in applications such as drug delivery and in other chemistry. Still smaller materials such as micelles are easily prepared, but they have only modest stability as discrete nanoscopic objects. More stable dendritic structures comparable in size to micelles can also be prepared.^[8] Moreover, since dendrimers are covalently assembled in a step-by-step approach from smaller molecules they can be engineered to have considerable chemical diversity. However, dendrimer synthesis is a tedious, costly process. Recent work by Möhwald et al. and Wooley et al.^[3–7] shows how synthetically less complex self-assembly approaches can be used to prepare particles or spherical hollow shells. This work shows that self-assembly can be a powerful, but simple, synthetic method for the fabrication and surface modification of nanometer- to micrometer-sized hollow spheres and particles.

The approaches of Möhwald et al. to the synthesis of surface modified sub-micrometer particles and spheres relies on surface modification chemistry developed for two-dimensional surfaces by Decher.^[9] This chemistry uses a series of layer-by-layer deposition steps as shown in Figure 1. This polyelectrolyte self-assembly has proven to be broadly applicable as a method for the modification of two-dimensional surfaces and has been used successfully in many ways on a wide variety of substrates.

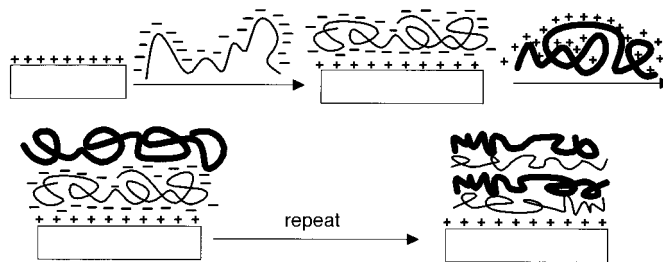


Figure 1. Layer-by-layer ionic self-assembly on a planar surface.

Möhwald et al. have shown that micrometer- and sub-micrometer-sized particles can be modified by ionic self-assembly in the same way Decher modifies planar surfaces by electrostatic self-assembly. For example, the approach by Möhwald et al. begins with a colloidal organic polymer support.^[10] Micrometer-sized melamine–formaldehyde colloidal particles 2 or 3.3 μm in diameter were used as substrates. These polymer particles were suspended in a dilute aqueous solution containing 0.5 M NaCl and 1 mg mL^{-1} of sodium polystyrene sulfonate (NaPSS). After repeated centrifugation and washing, a second, cationic polyelectrolyte, poly(allylamine hydrochloride) (PAH), was added. Repetition of this process leads to multiple bilayers on the melamine–formaldehyde support. In this chemistry the anionic polyelectrolyte sodium polystyrene sulfonate initially self-assembles onto the cationic melamine–formaldehyde particle. Since all the sulfonated groups are not consumed by electrostatic interactions with the particle surface there are sulfonate groups in random, polydisperse sections of the polymer that are available for further ion exchange with the cationic polyelectrolyte. Thus, polyvalent ionic interactions with the support entropically favor deposition of the polymer onto the sub-micrometer particular support, and the first deposition of an anionic polyelectrolyte sets the stage for subsequent deposition of a second, positively charged polyelectrolyte. This sequential deposition of polyelectrolytes eventually produces a multilayer mat of polyelectrolyte polymers on the underlying particle.

Möhwald et al. have also shown^[4,5] that functionalized polystyrene latex particles are also suitable substrates for ionic self-assembly chemistry. In this work a cationic polyelectrolyte, an anionic polyelectrolyte, and finally a cationic polyelectrolyte were first sequentially adsorbed onto negatively charged, 640-nm diameter polystyrene latex particles. This initial set of deposition experiments produced a uniformly positively charged outer surface that could then be used in sequential adsorption of negatively charged 25-nm SiO_2 particles and cationic poly(diallyldimethylammonium chloride) (PDADAC) polyelectrolyte. Layers with thicknesses ranging from tens to hundreds of nanometers were prepared with this procedure. The alternating surface charge postulated in these syntheses was verified by electrophoretic mobility

[*] Prof. D. E. Bergbreiter
Department of Chemistry, Texas A&M University
P.O. Box 30012, College Station, TX 77842-3012 (USA)
Fax: (+1) 409-845-4719
E-mail: bergbreiter@tamu.edu

measurements of particles at intermediate stages in the synthesis.

The coated particles obtained from the work of Möhwald et al. can then be transformed into hollow spheres (Figure 2). In reference [3] exposure of the coated particles to an acidic



Figure 2. A confocal micrograph of an 8- μm hollow sphere illustrating the stability and deformability of a [(PSS/PAH)₄PSS] hollow shell.^[3]

solution ($\text{pH} < 1.6$) dissolves the acid-sensitive melamine–formaldehyde colloidal core. Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) images of nine-layer [(PSS/PAH)₄PSS] hollow shells that were obtained show that the resulting hollow capsules are approximately 4 μm in diameter. The TEM studies indicate that the nine-layer polyelectrolyte film is about 20 nm thick. Mass spectroscopic studies of the dissolved melamine–formaldehyde products show that oligomers consisting of 5–10 monomers of tetramethylol–melamine are produced. Molecular dynamics simulations indicated that these oligomers are about 1 nm in diameter. This observation indicates that the shells formed by this chemistry are permeable.

They have also described several procedures for forming hollow spheres from SiO_2 /poly(diallyldimethylammonium chloride) nanocomposite-coated particles. With polystyrene latex cores, calcining thermally destroys the core (Figure 3).

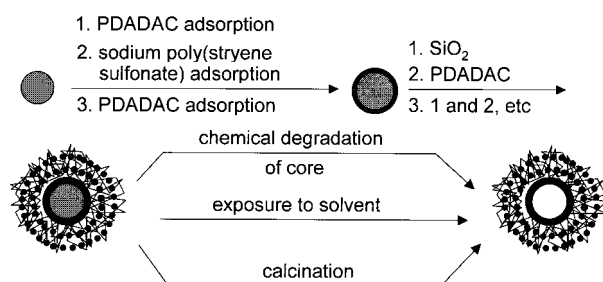


Figure 3. Procedures for preparing hollow spheres with a hybrid SiO_2 /PDADAC shell (solvent extraction of core or chemical degradation of the core).

This thermal process generates product spheres that are mostly whole but also produces some ruptured spheres. Milder procedures for core removal generate more whole spheres. For example, dissolution of the core by a good solvent (THF) leads to more unruptured hollow spheres. When a chemically reactive core such as the melamine–formaldehyde

colloid is used in place of polystyrene, acid treatment such as that described in reference [3] can be used to chemically dissolve the core to form hollow spheres.

Still smaller particles may be prepared as reported recently by Wooley's group.^[6, 7] This work uses a conceptually different synthetic approach that relies on the synthesis of block copolymers and the assembly of these block copolymers into polymeric micelles. Such micellarization isprecedented and produces materials whose dimensions are smaller than those of colloids prepared by emulsion polymerization. By varying the conditions of micellarization polymeric micelles with diameters in the 10–100 nm range can be prepared from polymers such as polyisoprene or polystyrene for the core and polymers such as poly(acrylic acid) and poly(*tert*-butyl acrylate) for the shells. Such polymer micelles can be designed to have significant stability, interesting morphologies, and can be chemically manipulated by cross-linking.^[11–13] The innovative feature of the work by Wooley et al. is the subsequent cross-linking of these block copolymer micelles to form shell- or core-cross-linked particles whose reactive interiors can be chemically degraded to give hollow spheres with nanometer-sized cavities.^[7]

Wooley et al. describe their shell-cross-linked polymeric micelles as knedels.^[14] The cross-linked shell of these knedels is semi-permeable similar to the shells of the hollow micrometer-sized spheres Möhwald et al. have prepared. By using controlled anionic polymerization, Wooley and co-workers have prepared a variety of diblock copolymers. These diblock copolymers are then assembled into polymeric micelles by using the general concepts associated with the formation of polymer micelles that have been developed over a number of years by others. By design, Wooley et al. have chosen block copolymer systems where either the exterior or interior diblock contains polymerizable groups or cross-linkable groups. For example, when knedels with a poly(acrylic acid) and a polyisoprene core are prepared the shell can be chemically cross-linked by treatment with an activating agent and a diamine (Figure 4). Ongoing work has shown that suitable cores can be chemically removed to yield smaller hollow spheres than are available by the methods Möhwald et al. have developed.^[7] In this latest work, Wooley's group used polymeric micelles derived from poly(isoprene-*b*-acrylic

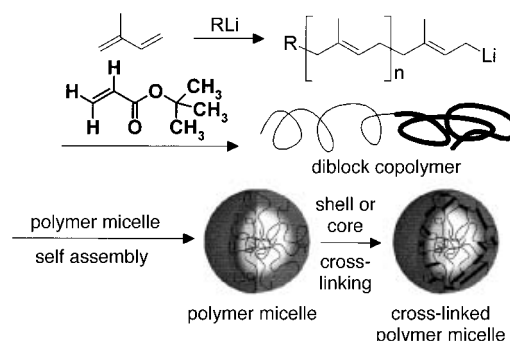


Figure 4. Shell cross-linked knedel nanospheres prepared from an amphiphilic diblock copolymer by 1) assembly of the amphiphilic diblock copolymer into multi-molecular micelles and 2) intramicellar cross-linking of the shell domain through reactions along the hydrophilic segment of the diblock copolymer.

acid) that were cross-linked with α,ω -diamino(polyethylene glycol).^[15] Ozonolysis was then used to chemically degrade the polyisoprene core into small molecules that diffuse into solution and leave a hollow-sphere product. The hollow spheres were characterized by dynamic light scattering and were visualized by TEM and atomic force microscopy (AFM). Control experiments showed that noncross-linked polymeric micelles disintegrated on ozonolysis, which shows that a cross-linked shell was required. The diameter of the hollow-sphere products is controllable and dependent both on the degree of polymerization of the diblock copolymers originally used to form the micelle and on the nature of the cross-linking diamine used to prepare the Knedel.

Applications of these materials have been proposed but not yet realized. However, the authors have each described some general ideas. Drug delivery seems to be an especially likely application and may be especially interesting since shells can be designed or fabricated that will be biocompatible and permeable. However, other applications could also be envisioned. These materials are not likely to be permeable to macromolecular reagents or catalysts so reagents, substrates, and catalysts can be prepared that will be localized inside or outside of these hollow shells. It should thus be possible to incorporate enzymatic catalysts or other catalysts into these hollow shells and to mix these shell-immobilized enzymes with other shells containing other catalysts or reagents. Since the immobilized reagents in such systems are precluded from diffusing into contact with one another such systems could capitalize on some of the early ideas espoused by others working with solid-phase organic synthesis where so-called "wolf and lamb" systems were designed in which mixtures of incompatible species were rendered compatible by diffusional restraints.^[16]

Hollow shells could also be useful in other areas such as combinatorial synthesis, catalysis, sensor chemistry, and in materials chemistry. For example, if a library of precatalysts were enclosed in these hollow shells and if these catalysts were then used to produce a colored product that was constrained to remain in the nanoscopic reactor, hollow spheres could serve to differentiate good, efficient catalysts from their less efficient cousins. The small size of these materials and the potential chemical versatility of the shells makes them candidates as synthesis supports because of shell permeability and high surface area. The permeability of these

shells and the potential to load shells with recognition elements that cannot readily diffuse out of the shell also make them potentially useful in sensor chemistry. The shells or particles themselves can also presumably be immobilized on various surfaces, which leads to new sorts of chemically responsive functional grafts. Regardless of what specific applications are developed, the synthetic versatility and simplicity inherent in the syntheses of sub-micrometer diameter semipermeable capsules by Möhwald et al. and Wooley et al. make intriguing new materials available for further use in basic and applied chemistry.

German version: *Angew. Chem.* **1999**, *111*, 3044–3046

Keywords: colloids • micelles • nanostructures • polymers • self-assembly

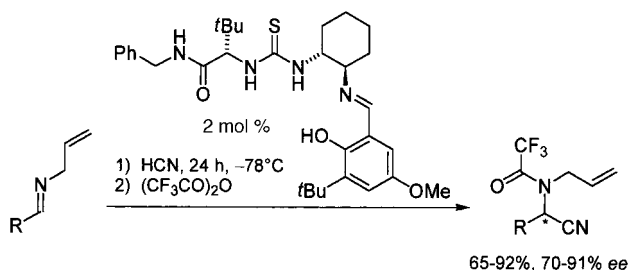
- [1] a) S. Schacht, Q. Huo, I. G. Voigt-Martin, G. D. Stucky, F. Schüth, *Science* **1996**, *273*, 768–771; b) D. Y. Zhao, P. D. Yang, Q. S. Huo, B. F. Chmelka, G. D. Stucky, *Curr. Opin. Solid State Mater. Sci.* **1998**, *3*, 111–121.
- [2] X. M. Zhao, Y. N. Xia, G. M. Whitesides, *J. Mater. Sci.* **1997**, *7*, 1069–1074.
- [3] E. Donath, G. B. Sukhorukov, F. Caruso, S. A. Davis, H. Möhwald, *Angew. Chem.* **1998**, *110*, 2323–2327; *Angew. Chem. Int. Ed.* **1998**, *37*, 2202–2205.
- [4] F. Caruso, H. Lichtenfeld, M. Giersig, H. Möhwald, *J. Am. Chem. Soc.* **1998**, *120*, 8523–8524.
- [5] F. Caruso, R. A. Caruso, H. Möhwald, *Science* **1998**, *282*, 1111–1114.
- [6] a) K. B. Thurmond II, T. Kowalewski, K. L. Wooley, *J. Am. Chem. Soc.* **1996**, *116*, 7239–7240; b) K. B. Thurmond II, T. Kowalewski, K. L. Wooley, *J. Am. Chem. Soc.* **1997**, *117*, 6656–6665; c) H. Huang, T. Kowalewski, E. E. Remsen, R. Gertzmann, K. L. Wooley, *J. Am. Chem. Soc.* **1997**, *117*, 11653–11659.
- [7] H. Huang, E. E. Remsen, T. Kowalewski, K. L. Wooley, *J. Am. Chem. Soc.* **1999**, *121*, 3805–3806.
- [8] O. A. Matthews, A. N. Shipway, J. F. Stoddart, *Prog. Polym. Sci.* **1998**, *23*, 1–56.
- [9] G. Decher, *Science* **1997**, *277*, 1232–1237.
- [10] R. M. Fitch, *Polymer Colloids*, Academic Press, San Diego, CA, 1997.
- [11] P. Munk, P. Karel, Z. Tuzar, S. E. Webber, *CHEMTECH* **1998**, *28*, 20–28.
- [12] K. Khougaz, M. Moffitt, L. Zhang, A. Eisenberg, *Macromol. Symp.* **1996**, *106*, 435–438.
- [13] Y. Y. Won, H. T. Davis, F. S. Bates, *Science* **1999**, *283*, 960–963.
- [14] K. L. Wooley, *Chem. Eur. J.* **1997**, *3*, 1397–1399.
- [15] H. Huang, E. E. Remsen, K. L. Wooley, *Chem. Commun.* **1998**, 1415–1416.
- [16] A. Patchornik, *CHEMTECH* **1987**, *17*, 58–63.

Asymmetric Catalytic Aminoalkylations: New Powerful Methods for the Enantioselective Synthesis of Amino Acid Derivatives, Mannich Bases, and Homoallylic Amines

Michael Arend*

The economic importance of enantiomerically pure compounds has grown considerably during the last years and will increase even further.^[1] Therefore, the development of efficient asymmetric syntheses with chiral catalysts is a main focus of modern industrial and basic research. As a result, there are meanwhile powerful asymmetric catalytic variants for many basic reactions.^[2] However, until recently this did not include the important class of aminoalkylation reactions,^[3] if one leaves aside aminoalkylations of Grignard, organolithium, or organozinc compounds catalyzed by chiral ligands (Lewis bases).^[4]

Attempts to activate and to modify other nucleophiles such as ester enolates^[5a,b] or HCN^[5c] chirally with ligands or Lewis bases (diether,^[5a,b] dipeptide^[5c]) and to aminoalkylate them enantioselectively were only partly successful. These methods either require a stoichiometric amount of the chiral ligand or provide good *ee* values solely in special cases. However, recently it has been shown impressively that the potential of this methodology is definitely not exhausted yet. Thus, a relatively efficient and broadly applicable asymmetric variant of the Strecker synthesis could be developed by optimization of a Lewis base catalyst using combinatorial methods (Scheme 1).^[5d]



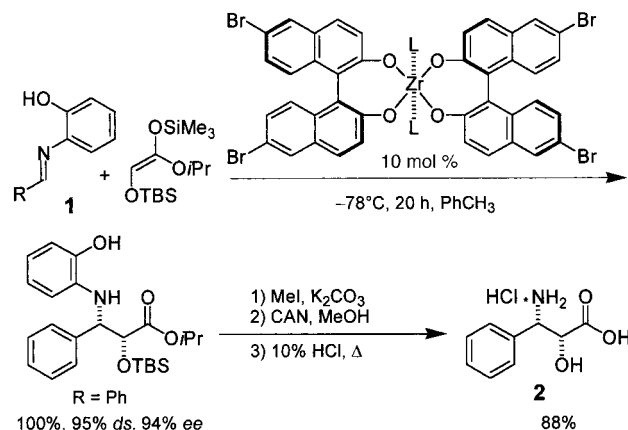
Scheme 1. Base-catalyzed enantioselective variant of the Strecker synthesis (R = alkyl, aryl).^[5d]

More recent publications demonstrate the extraordinary potential of an alternative synthetic strategy: the use of chiral Lewis acid catalysts for the activation and chiral modification of Mannich reagents (generally imino compounds). In this way, not only HCN or its synthetic equivalents^[6] but also numerous other nucleophiles could be aminoalkylated asymmetrically (e.g. trimethylsilyl enol ethers derived from esters^[7-9a] or ketones,^[9] alkenes,^[10] allyltributylstannane,^[11a] allyltrimethylsilanes,^[9a, 11b] and ketones^[12]). Thus, efficient routes for the enantioselective synthesis of a variety of

valuable synthetic building blocks were created (e.g. α -aminonitriles,^[6] α - or β -amino acid derivatives,^[7-10] homoallylic amines,^[9a, 10-11] or β -amino ketones^[9, 12]).

Most of the hitherto published methods employ imino compounds that can act as bidentate ligands and form chelate complexes with the chiral Lewis acid catalysts. On the other hand, simple Mannich reagents usually furnish significantly lower *ee* values.^[9c, 12] One can easily explain this by the restriction of the configurational diversity in the chelate complexes,^[9d] favoring a stereochemically uniform course of the reaction.

Thus, *N*-(2-hydroxyphenyl)imines **1** (R = alkyl, aryl) together with zirconium catalysts (binaphthol derivatives) generated in situ were used successfully for the asymmetric synthesis of α -aminonitriles^[6a] and simple β -amino acid derivatives^[7a,c] or for the diastereo- and enantioselective preparation of α -hydroxy- β -amino acid derivatives.^[7b] The advantages of the methodology include good yields and stereoselectivities, a relatively broad scope, and also the fact that the *N*-(2-methoxyphenyl) moiety is easily removed by oxidation with cerium ammonium nitrate (CAN).^[6a, 7] A good example for the potential of this approach is depicted in Scheme 2.^[7b] A related method employs *N*-4-trifluoromethylbenzoylhydrazones for the enantioselective aminoalkylation



Scheme 2. Asymmetric catalytic aminoalkylation as the key step in the diastereo- and enantioselective synthesis of (2*R*,3*S*)-3-phenylisoserine hydrochloride (**2**).^[7b] TBS = *tert*-butyldimethylsilyl, L = 1,2-dimethylimidazole.

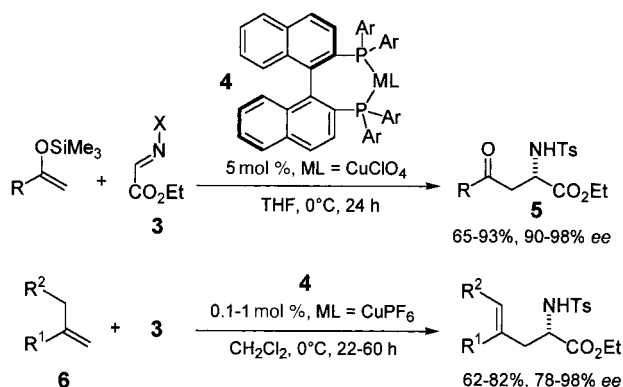
of ketene acetals. The resulting hydrazine derivatives are obtained in moderate yields, but in part with good *ee* values, and can be transformed into β -amino acid esters without racemization by cleavage of the N–N bond with samarium(II) iodide.^[8]

The imines **3** (X = 4-H₃CC₆H₄SO₂ (Ts),^[9a,b,d, 10] aryl^[9c]) derived from glyoxylic acid, preformed^[9b-d, 10] or generated in situ from *N*,*O*-acetals,^[9a] can also form chelate complexes

[*] Dr. M. Arend

Fachbereich Chemie und Chemietechnik der Universität
Warburger Strasse 100, D-33098 Paderborn (Germany)
Fax: (+49) 5251-60-3245
E-mail: ma@fb13a.uni-paderborn.de

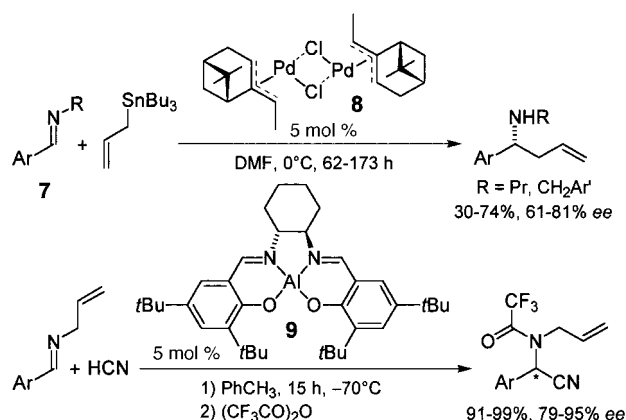
with chiral Lewis acids. Among other things, excellent results were obtained in the enantioselective aminoalkylation of silyl enol ethers with the 2,2'-bis(diarylphosphanyl)-1,1'-binaphthyl (BINAP) catalysts **4** (usually copper complexes).^[9] A typical example is the synthesis of Mannich bases **5** depicted in Scheme 3.^[9d] Because of their comparatively high electrophilicity imines **3** could even be used successfully for the asymmetric aminoalkylation of unactivated alkenes **6** (ene reactions, see Scheme 3).^[10]



Scheme 3. Enantioselective catalytic aminoalkylation of silyl enol ethers^[9d] and alkenes^[10b] with imines **3** (X = Ts) and BINAP catalysts **4** (Ar = 4-MeC₆H₄).

All methods discussed so far employ special Mannich reagents (bidentate ligands) and BINAP-derived Lewis acids, which generally count among the most powerful chiral catalysts.^[13] However, preliminary experiments show that in principle simple imines **7** can also be used successfully for asymmetric catalytic aminoalkylations. Nevertheless, BINAP catalysts such as **4** do not seem to be suitable for this kind of reaction.^[9c, 11a] On the other hand, the asymmetric allylation of the simple imines **7** with allyltrimethylsilane^[11b] or allyltributylstannane^[11a] (Scheme 4) catalyzed by the β -pinene derivative **8** furnished comparatively good results. Moreover, it was demonstrated on the basis of Strecker syntheses^[6b,c] that other catalysts such as the chiral salen complex **9**^[6b] (Scheme 4) are also well suited for enantioselective aminoalkylations with simple imines.

During the past two years impressive progress has been made in the field of catalytic asymmetric aminoalkylation.



Scheme 4. Asymmetric catalytic aminoalkylation of allyltributylstannane^[11a] and HCN^[6b] with simple imines. Al represents Al^{III}Cl.

Nevertheless, this chemistry is still in its infancy. An important reason for this is that in many cases the common techniques (even if they have been applied successfully to formally closely related reactions such as aldol additions) are only imperfectly or not at all applicable to aminoalkylations.^[3b, 12] Hence, the hitherto known methods for asymmetric aminoalkylation are mostly limited to special cases. Furthermore, they often require low reaction temperatures, relatively large amounts of the catalyst, or long reaction times to give good yields or ee values. However, it can be assumed that in the future both the scope and efficiency of enantioselective aminoalkylations can be enhanced considerably by the development of tailor-made catalysts. There is no doubt that modern methodologies such as the design of chiral catalysts using combinatorial techniques will play a key role in this process.^[5d, 6c, 14]

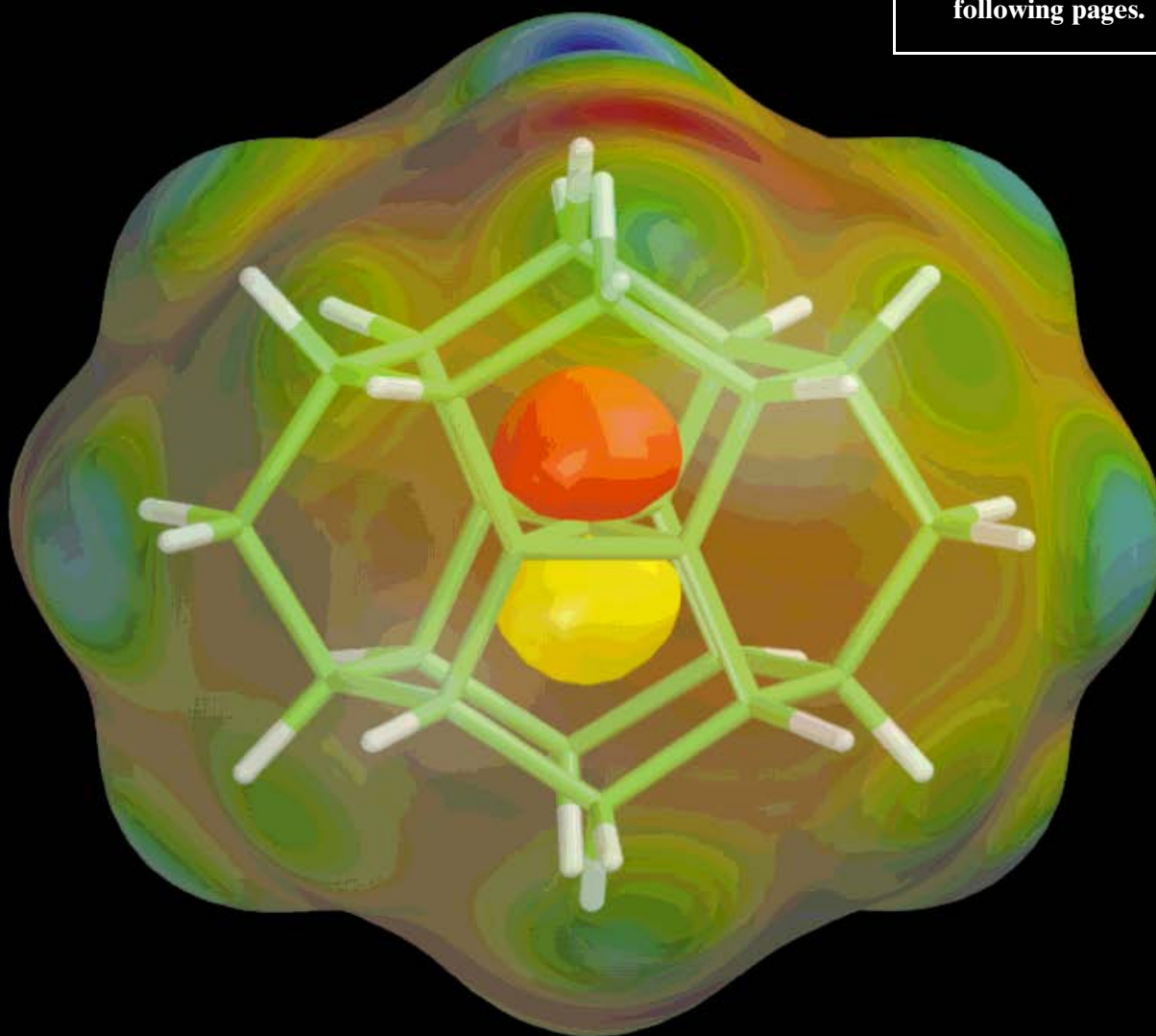
German version: *Angew. Chem.* **1999**, *111*, 3047–3049

Keywords: amino acids • asymmetric catalysis • asymmetric synthesis • chiral auxiliaries • Mannich bases

- [1] S. C. Stinson, *Chem. Eng. News* **1998**, 76(38), 83.
- [2] M. Wills, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3101.
- [3] a) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1097; *Angew. Chem. Int. Ed.* **1998**, *37*, 1045; b) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069.
- [4] a) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407; b) D. Enders, U. Reinhold, *Tetrahedron: Asymmetry* **1997**, *8*, 1895; c) N. Risch, M. Arend, *Methoden Org. Chem. (Houben-Weyl) 4th ed. 1952–, Vol. E21b* **1995**, p. 1833.
- [5] a) T. Kambara, M. A. Hussein, H. Fujieda, A. Iida, K. Tomioka, *Tetrahedron Lett.* **1998**, *39*, 9055; b) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060; c) M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996**, *118*, 4910; d) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901.
- [6] a) H. Ishitani, S. Komiyama, S. Kobayashi, *Angew. Chem.* **1998**, *110*, 3369; *Angew. Chem. Int. Ed.* **1998**, *37*, 3186; b) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315; c) C. A. Krueger, K. W. Kuntz, C. D. Dzierba, W. G. Wirsching, J. D. Gleason, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 4284.
- [7] a) H. Ishitani, T. Kitazawa, S. Kobayashi, *Tetrahedron Lett.* **1999**, *40*, 2161; b) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* **1998**, *120*, 431; c) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153.
- [8] S. Kobayashi, Y. Hasegawa, H. Ishitani, *Chem. Lett.* **1998**, 1131.
- [9] a) D. Ferraris, T. Dudding, B. Young, W. J. Drury III, T. Lectka, *J. Org. Chem.* **1999**, *64*, 2168; b) D. Ferraris, B. Young, C. Cox, W. J. Drury III, T. Dudding, T. Lectka, *J. Org. Chem.* **1998**, *63*, 6090; c) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, *120*, 2474; d) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 4548.
- [10] a) W. J. Drury III, D. Ferraris, C. Cox, B. Young, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 11006; b) S. Yao, X. Fang, K. A. Jørgensen, *Chem. Commun.* **1998**, 2547.
- [11] a) H. Nakamura, K. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 4242; b) K. Nakamura, H. Nakamura, Y. Yamamoto, *J. Org. Chem.* **1999**, *64*, 2614.
- [12] S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 307.
- [13] L. Pu, *Chem. Rev.* **1998**, *98*, 2405.
- [14] a) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885; b) A. Berkessel, D. A. Héroult, *Angew. Chem.* **1999**, *111*, 99; *Angew. Chem. Int. Ed.* **1999**, *38*, 102; c) K. Ding, A. Ishii, K. Mikami, *Angew. Chem.* **1999**, *111*, 519; *Angew. Chem. Int. Ed.* **1999**, *38*, 497; d) M. B. Francis, E. N. Jacobsen, *Angew. Chem.* **1999**, *111*, 987; *Angew. Chem. Int. Ed.* **1999**, *38*, 937.

**A neutral saturated hydrocarbon with
a planar-tetracoordinate atom?**

**Find out more on the
following pages.**



**A saturated hydrocarbon with an ionization
energy comparable to that of alkali metals?**

Planar-Tetracoordinate Carbon in a Neutral Saturated Hydrocarbon: Theoretical Design and Characterization**

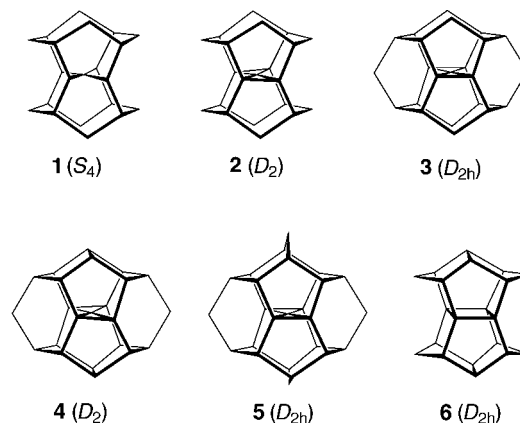
Danne R. Rasmussen and Leo Radom*

It is more than a century since van't Hoff and Le Bel independently concluded that the four bonds to tetracoordinate carbon in organic molecules are oriented in an approximately tetrahedral arrangement.^[1] About 30 years ago, however, Hoffmann and co-workers^[2] raised the question of whether it would be possible to design and synthesize compounds with a planar arrangement of bonds at tetracoordinate carbon. This has been achieved both theoretically^[3] and experimentally^[4, 5] in systems where the planar-tetracoordinate carbon atom has metal substituents. In contrast, as noted in a recent important paper by Keese et al.,^[6] "despite considerable computational efforts no structures with a planar-tetracoordinate C(C)₄ substructure have been found."^[7] We report here the design of the first neutral saturated hydrocarbon containing a planar-tetracoordinate carbon and its theoretical characterization through molecular orbital calculations.

Ab initio molecular orbital calculations^[8] show that the energy cost of constraining the bonds at tetracoordinate carbon to be planar is enormously high.^[9] For example, the lowest energy planar structure of methane is found to lie approximately 520 kJ mol⁻¹ higher in energy than the normal tetrahedral form.^[10] However, the energy needed to break the H₃C–H bond is approximately 100 kJ mol⁻¹ lower than this. Clearly, methane will fall apart before it can be flattened. A similar situation is seen for the central carbon of neopentane,^[10] where we estimate flattening to cost 880 kJ mol⁻¹. It appears that a very high energy difference between planar and tetrahedral geometries is the norm for tetracoordinate carbon in organic molecules. One important consequence of this high energy barrier is that it ensures that racemization of chiral compounds through planar bonding arrangements at carbon is generally energetically prohibitive, and this leads to preservation of enantiomeric integrity. As has been indicated previously,^[2, 3, 5c, 9] the large energy penalty is a consequence of the unusual bonding arrangement for planar carbon, in which the highest occupied molecular orbital (HOMO) is a *p*-type lone pair of loosely bound electrons, leaving only six electrons to bind the four substituents.

We have been interested in recent years in designing a neutral saturated hydrocarbon containing a planar-tetracoor-

dinate carbon atom, the driving force necessarily being structural rather than electronic. Our strategy to achieve this end has been based on variants of the alkaplane family of molecules,^[11] which may be described as strained hydrocarbon cage compounds. We have used ab initio molecular orbital calculations,^[8] carried out with the Gaussian 94^[12] and GAMESS programs,^[13] to investigate the structures and properties of these molecules. The geometries of alkaplanes **1–5** were determined by optimization at the MP2 level using an enhanced 6-31G(d) basis;^[14] energies were calculated at the MP2/6-311+G(2d,p) level.



The simplest alkaplanes may be described in terms of an equatorial plane that contains the potentially planar quaternary carbon atom and is capped above and below by cycloalkane moieties (e.g. octaplane **1**).^[11a] The angle δ between the bonds at the quaternary carbon atom and the best plane through that carbon atom is found to be 5.1° in octaplane, compared with 35.3° in a perfectly tetrahedral arrangement and 0.0° in an exactly planar arrangement. Thus, octaplane contains a nearly but not exactly planar tetracoordinate carbon atom.

Modification of the equatorial plane in octaplane by forming two new C–C bonds between opposite pairs of adjacent α -carbon atoms leads to spiro[2.2]octaplane (**2**)^[10] with a δ angle of 3.1°. This indicates an even closer approach to planarity, but there is still some deviation from an exactly planar arrangement.

However, if the top and bottom caps in **2** are linked by methylene bridges, leading to dimethanospiro[2.2]octaplane (**3**), our calculations indicate that exact planarity at the central quaternary carbon atom is achieved. The calculated potential functions^[15] corresponding to out-of-plane bending in **1–3** (Figure 1) show the clear progression from a distinctly nonplanar situation with a moderately large inversion barrier in **1** to exact planarity in **3**.^[16] Compound **3** is the first neutral saturated hydrocarbon to be found either theoretically or experimentally to contain a planar-tetracoordinate carbon atom.

The optimized structure for **3** is displayed in Figure 2. This *D*_{2h} structure is verified by numerical frequency analysis using double differencing to be a minimum on the potential energy surface.^[17] This calculation confirms that **3** indeed prefers an exactly planar bonding arrangement at the central carbon atom. An examination of the structure reveals that the longest

[*] Prof. L. Radom, D. R. Rasmussen
Research School of Chemistry
Australian National University
Canberra, ACT 0200 (Australia)
Fax: (+61) 2-62490750
E-mail: radom@rsc.anu.edu.au

[**] We are indebted to Professor Mark Gordon for the MP2 frequency calculation on dimethanospiro[2.2]octaplane, which was made possible by a United States Department of Defense Grand Challenge grant. We thank the Australian National University Supercomputer Facility and the Maui High Performance Computer Center for generous allocations of time on the Fujitsu VPP 300 and IBM SP supercomputers, respectively.

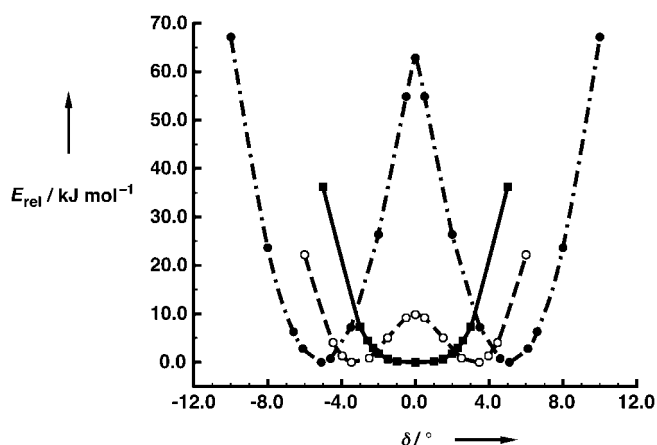


Figure 1. Calculated potential energy curves^[15] describing the lowest mode for distortion from planarity at the central quaternary carbon atom. The relative energy E_{rel} [kJ mol⁻¹] is plotted against the angle of distortion from planarity δ [°] for octaplane (**1**, ●), spiro[2.2]octaplane (**2**, ○), and dimethanospiro[2.2]octaplane (**3**, ■).

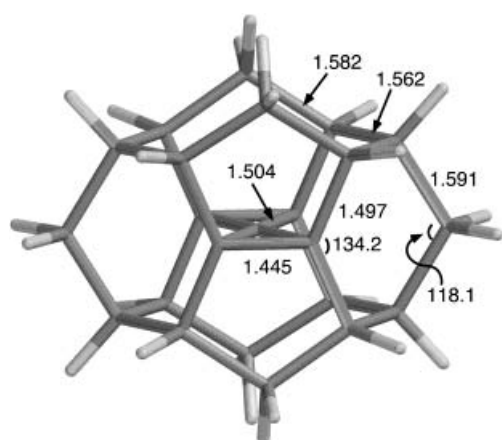


Figure 2. Calculated structure for **3** with bond lengths [Å] and angles [°].

C–C bonds are 1.582 and 1.591 Å. This suggests that there are no glaringly long C–C bonds, which might have reflected inherent instability in the molecule. In fact, the structure shows some correspondence to a synthetically known [4.4.4.5]fenestrane derivative that bears the most flattened tetracoordinate carbon atom ($\delta = 11.5^\circ$) observed experimentally in an organic molecule to date.^[18] The internal bonds to the central carbon atom in this fenestrane system are about 1.50 Å, while some peripheral bonds are as long as 1.60 Å.

The fact that the calculated vibrational frequencies for **3** are all real shows that there are finite barriers to any decomposition mode. However, it does not indicate the size of these barriers. This would require explicit calculations of possible reaction pathways, which is a major undertaking for a system the size of **3**.^[19, 20] We have nevertheless carried out a preliminary exploration of a number of the lowest vibrational modes of **3**. We find that, despite the high degree of strain particularly at the central carbon atom, **3** appears to lie in a relatively deep potential well.

We have examined structures for two other members of the dimethanospiroalkaplane family, dimethanospiro[2.2]biocaplane (**4**) and dimethanospiro[2.2]binonaplane (**5**). Both molecules are closely related to **3** but may prove more

accessible synthetic targets. The biocaplane **4** is particularly interesting because of its similarity to pagodane (**6**), a well-known cage hydrocarbon involved in the synthesis of dodecahedrane from isodrin.^[21] Our calculations indicate that **4** is slightly nonplanar at the central carbon atom ($\delta = 2.2^\circ$), with a difference in energy between the planar and tetrahedral forms of only 4.4 kJ mol⁻¹. On the other hand, the binonaplane **5** is found, according to a potential curve analysis like that used for **3**, to contain an exactly planar tetracoordinate carbon atom, as does **3**, and has the advantage from a synthetic point of view of not containing any eight-membered rings.

The HOMO of **3** is predominantly a *p*-type lone pair orbital at the central quaternary carbon atom, which is surrounded by the hydrocarbon cage (Figure 3). As a consequence, **3**, like the

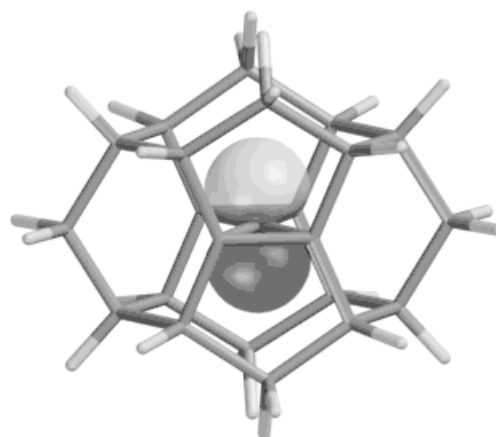


Figure 3. An isosurface of the HOMO of **3** (0.08 e Å⁻³).

simpler members of the alkaplane family **1**^[11] and **2**,^[10] has an extremely low predicted ionization energy^[22] of about 5 eV, which is comparable to that of the alkali metals lithium (5.39 eV) and sodium (5.14 eV). Our calculations suggest in addition that the electron is removed from the central atom with little change to the surrounding cage, thus protecting the ionized atom in a lipophilic sphere.

The unusual bonding at the central planar-tetracoordinate carbon atom in **3** gives rise to a new organic moiety which can be expected to have remarkable properties and functions. Advantage might be taken in this respect of the unique combination of metallike properties (such as readily ionizable electrons) and organic properties (such as strong covalent bonding, which helps preserve integrity). We hope that such considerations will add impetus to attempts to synthesize dimethanospiro[2.2]octaplane (**3**).

Received: April 6, 1999 [Z13240IE]

German version: *Angew. Chem.* **1999**, *111*, 3052–3054

Keywords: ab initio calculations • cage compounds • hydrocarbons • ionization potentials • planar-tetracoordinate carbon

[1] a) J. H. van't Hoff, *Arch. Neerl. Sci. Exactes Nat.* **1874**, *9*, 445–454; English translation: J. H. van't Hoff in *Classics in the Theory of Chemical Combinations*, Vol. I (Ed.: O. T. Benfey), Dover, New York, **1963**, pp. 151–160; b) J. A. Le Bel, *Bull. Chim. Soc. Fr.* **1874**, *22*, 337–

- 347; English translation: J. A. Le Bel in *Classics in the Theory of Chemical Combinations*, Vol. 1 (Ed.: O. T. Benfey), Dover, New York, **1963**, pp. 161–171.
- [2] a) R. Hoffmann, R. Alder, C. F. Wilcox, Jr., *J. Am. Chem. Soc.* **1970**, *92*, 4992–4993; b) R. Hoffmann, *Pure Appl. Chem.* **1971**, *28*, 181–194.
- [3] See, for example, a) J. B. Collins, J. D. Dill, E. D. Jemmis, Y. Apeloig, P. von R. Schleyer, R. Seeger, J. A. Pople, *J. Am. Chem. Soc.* **1976**, *98*, 5419–5427; b) K. Krogh-Jespersen, D. Cremer, D. Poppinger, J. A. Pople, P. von R. Schleyer, J. Chandrasekhar, *J. Am. Chem. Soc.* **1979**, *101*, 4843–4851; c) K. Sorger, P. von R. Schleyer, *J. Mol. Struct. Theochem.* **1995**, *338*, 317–346.
- [4] See, for example, a) F. A. Cotton, M. Millar, *J. Am. Chem. Soc.* **1977**, *99*, 7886–7891; b) H. Dietrich, W. Mahdi, W. Storck, *J. Organomet. Chem.* **1988**, *349*, 1–10; c) S. Harder, J. Boersma, L. Brandsma, A. van Heteren, J. A. Kanters, W. Bauer, P. von R. Schleyer, *J. Am. Chem. Soc.* **1988**, *110*, 7802–7806; d) S. L. Buchwald, E. A. Lucas, W. M. Davies, *J. Am. Chem. Soc.* **1989**, *111*, 397–398; e) S. T. Chacon, M. H. Chisholm, K. Folting, J. C. Huffman, M. J. Hampden-Smith, *Organometallics* **1991**, *10*, 3722–3735; f) A. D. Horton, A. G. Orpen, *Angew. Chem.* **1992**, *104*, 912; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 876–878.
- [5] See also a) M. Albrecht, G. Erker, C. Krüger, *Synlett* **1993**, 441–448; b) R. Gleiter, I. Hyla-Kryspin, S. Niu, G. Erker, *Angew. Chem.* **1993**, *105*, 753; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 754–756; c) D. Röttger, G. Erker, *Angew. Chem.* **1997**, *109*, 840–856; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 813–827; d) J. Schottek, G. Erker, R. Fröhlich, *Eur. J. Inorg. Chem.* **1998**, 551–558.
- [6] B. W. Ding, R. Keese, H. Stoeckli-Evans, *Angew. Chem.* **1999**, *111*, 387–388; *Angew. Chem. Int. Ed.* **1999**, *38*, 375–376.
- [7] For representative studies, see a) K. B. Wiberg, *Tetrahedron Lett.* **1985**, 26, 5967–5970; b) W. C. Agosta in *The Chemistry of Alkanes and Cycloalkanes* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1992**, pp. 927–962; c) M. Thommen, R. Keese, *Synlett* **1997**, 231–240.
- [8] W. J. Hehre, L. Radom, P. von R. Schleyer, J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, **1986**.
- [9] a) M. S. Gordon, M. W. Schmidt, *J. Am. Chem. Soc.* **1993**, *115*, 7486–7492; b) M. J. M. Pepper, I. Shavitt, P. von R. Schleyer, M. N. Glukhovtsev, R. Janoschek, M. Quack, *J. Comput. Chem.* **1995**, *16*, 207–225.
- [10] Detailed results and more extensive references will be published elsewhere: D. R. Rasmussen, M. P. McGrath, L. Radom, unpublished results.
- [11] a) M. P. McGrath, L. Radom, *J. Am. Chem. Soc.* **1993**, *115*, 3320–3321; b) J. E. Lyons, D. R. Rasmussen, M. P. McGrath, R. H. Nobes, L. Radom, *Angew. Chem.* **1994**, *106*, 1722; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1667–1668.
- [12] M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, *Gaussian 94, Revision E.2*, Gaussian, Inc., Pittsburgh PA, **1995**.
- [13] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis, J. A. Montgomery, Jr., *J. Comput. Chem.* **1993**, *14*, 1347–1363.
- [14] With the 6-31G(d) basis, we have used five pure d functions rather than the usual six cartesian functions. Detailed calculations on model systems (methane, neopentane, and spiropentane) indicate that the binding at the central C(C)₄ substructure is not well described by small basis sets.^[10] In particular, we find that diffuse functions on the central atom significantly lower the relative energies of the planar versus the tetrahedral species. The 6-311+G(2d,p) basis was found to be the smallest basis set which adequately approaches the basis set limit for this energy difference. As might have been expected, calculations on alkaplanes indicate that the full 6-311+G(2d,p) basis can be well approximated by using a 6-31G(d) basis which is enhanced to 6-311+G(2d) level at the central carbon atom and to the 6-311+G(d) level at the four α -carbon atoms, thus significantly reducing the size of the calculations. Optimization in the full 6-311+G(2d,p) basis (765 basis functions for **3**) is beyond our current computational resources.
- [15] Energies for the potential functions were calculated at the MP2/6-311+G(2d,p) level using the full 6-311+G(2d,p) basis on all atoms. Geometries were optimized at the HF/6-31G(d) level.
- [16] Calculations at the B3-LYP/6-311+G(3df,2p) level predict a double-well potential for **3**, but with a barrier of just 0.1 kJ mol⁻¹.
- [17] This 435 basis function calculation took 32000 node hours on a Cray T3E at the CEWES High Performance Computing Center! D. R. Rasmussen, M. S. Gordon, L. Radom, unpublished results.
- [18] V. B. Rao, C. F. George, S. Wolff, W. C. Agosta, *J. Am. Chem. Soc.* **1985**, *107*, 5732–5739.
- [19] A noteworthy potential decomposition pathway involves opening of the central spiropentane unit to give allene- and ethylene-type moieties.^[20] However, it would seem difficult for this to occur within the extremely rigid constraints of the cage system.
- [20] a) R. Herges, personal communication; b) R. Herges, *Angew. Chem.* **1994**, *106*, 261; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 255–276.
- [21] H. Prinzbach, K. Weber, *Angew. Chem.* **1994**, *106*, 2329; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2239–2257, and references therein.
- [22] Ionization energies for the alkaplanes **1–3** were obtained at the RMP2/6-31G(d)//RHF/6-31G(d) level and found to be 4.6, 4.3, and 4.2 eV, respectively. Test calculations on molecules where experimental data are available suggest that ionization energies calculated at this level of theory are generally underestimated by about 0.3–0.7 eV.^[11b]

meso Myths: What Drives Assembly of Helical versus meso-[M₂L₃] Clusters?*

Jide Xu, Tatjana N. Parac, and Kenneth N. Raymond*

Metallohelicates are the simplest supramolecular structures formed by the self-assembly of metal centers and bridging ligands.^[1,2] With each metal center viewed as a polyhedral vertex, metallohelicates [M₂L₃] are two-vertex structures. Currently the scope and power of the supramolecular chemistry of metal coordination compounds is being explored, particularly with regard to the selective preparation of more complex architectures based on the structures containing multiple vertices.^[3]

Triple helicates of M₂L₃ stoichiometry may be formed by bridging bis-bidentate ligands bound to two octahedral metal centers. This generates chiral (Λ or Δ) metal centers.^[2] If there is mechanical coupling between the two centers, the chirality at one can be transmitted to the second, thereby generating the homochiral ($\Lambda\Lambda$ or $\Delta\Delta$) helicate. The magnitude of this coupling has been measured in one case.^[4] In contrast, the

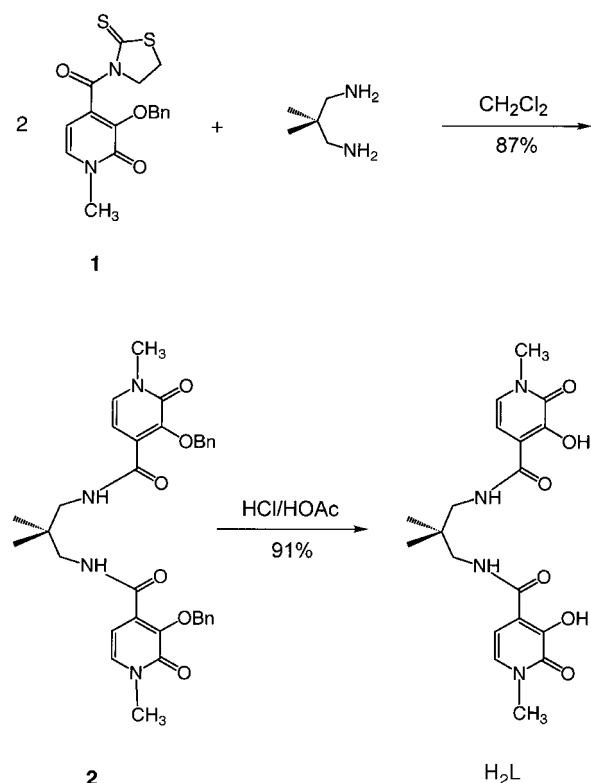
[*] Prof. Dr. K. N. Raymond, Dr. J. Xu, Dr. T. N. Parac
Department of Chemistry, University of California
Berkeley, CA 94720 (USA)
Fax: (+1) 510-486-1460
E-mail: raymond@socrates.berkeley.edu

[**] Coordination Number Incommensurate Cluster Formation, Part 10. This research was supported by NSF grant CHE-9709621 and by exchange grants NSF INT-9603212 and NATO SRG951516. We wish to gratefully acknowledge Dr. Frederick J. Hollander for help in the crystal structure determinations and Dr. Stephane Petoud for help with the least squares refinements. We also thank an anonymous referee for stimulating a further analysis of the equilibria. Part 9: Ref. [3h].

heterochiral ($\Delta\Delta$) complex is an achiral *meso* structure.^[5] What determines the formation of either the helical or *meso* forms?

In one case it has been proposed that the length of the alkyl spacer between two bidentate chelating units of the bridging ligand can determine whether the resulting complex will have a helical or *meso* structure. Based on the principle that the most favorable conformation of a linear alkyl chain has a zigzag structure, it was suggested that a chain with an even number of atoms would favor a helix, while a chain with an odd number of atoms would favor a *meso* structure.^[6] An alternative hypothesis came from a recent study in which an enantiomerically pure catechol-based tetradentate ligand led exclusively to the formation of a $\Delta\Delta$ triple helicate. It was suggested that a chiral ligand backbone will force the formation of a helicate and disfavor the formation of a *meso* complex.^[7] Here we contradict the generality of any such hypothesis with an example of *both* helical and *meso* complexes formed from the same ligand. We further demonstrate that in this complex the interconversion of helicate to mesocate is driven by formation of a host–guest solvate.

The bis-hydroxypyridinone ligand H_2L was synthesized in an overall 79% yield according to established general synthetic methods (Scheme 1).^[8] The two methyl groups in



Scheme 1. Synthesis of the ligand H_2L .

its symmetric spacer were designed as spectroscopic tags to allow monitoring of the solution structure of the metal complexes by NMR spectroscopy. In the helical complex, both metal centers have the same chirality and the two methyl groups are equivalent, related by C_2 symmetry. In the case of

the *meso* complex the two methyl groups are symmetrically inequivalent. Remarkably, the solution NMR results are confirmed by the single-crystal structure analyses, which show that in the solid state the $[Al_2L_3]$ complex is a helicate, while $[Ga_2L_3]$ forms a mesocate. The crystal structures of the $[Al_2L_3]$ ^[9] and $[Ga_2L_3]$ ^[10] complexes (Figure 1) are markedly

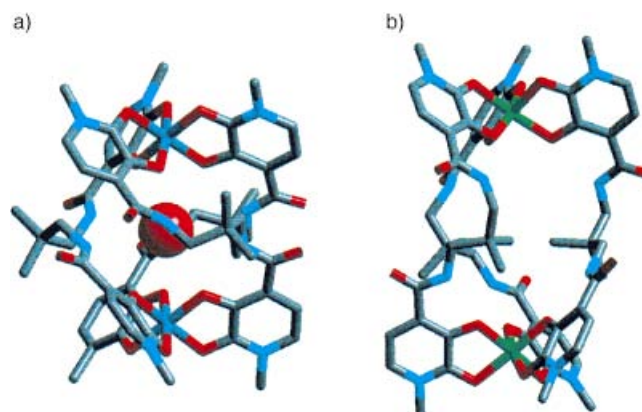


Figure 1. Crystal structures of a) $H_2O \cdot (\Delta\Delta, \Delta\Delta)-[Al_2L_3]$ and b) $(\Delta\Delta)-[Ga_2L_3]$ (hydrogen atoms are omitted for clarity). The $[Al_2L_3]$ helicate has a guest molecule of water in the cluster cavity. The red sphere represents the guest water oxygen atom. The wireframes represent the complexes with carbon atoms shown in gray, nitrogen atoms in deep blue, oxygen atoms in red, aluminium atoms in pale blue, and gallium atoms in green.

different: the distance between the two metal centers in the helicate $[Al_2L_3]$ is 7.13 Å, while in the mesocate $[Ga_2L_3]$ it is 9.74 Å. In addition, the helicate encapsulates a water molecule within its cavity, while no encapsulated guest is found in the mesocate $[Ga_2L_3]$, which has no significant void volume within the cluster.

The water guest in $[Al_2L_3]$ is located in the center of the helicate and is close (2.9–3.0 Å) to the six phenolic oxygen donor atoms of the ligands.^[11] The host–guest interaction brings the two Al^{III} centers closer and stabilizes the helicate structure. Indeed, the $[Al_2L_3]$ complex synthesized from wet methanol (containing ca. 1% water) solution yielded the pure helicate form;^[12] the helical host–guest complex is the favored thermodynamic product.

While the solid-state structure of $[Ga_2L_3]$ contains only the *meso* form, ^1H NMR spectra of $[Ga_2L_3]$ in $[D_6]DMSO$ show the presence of both helical and *meso* forms. The two singlets for the methyl groups at $\delta = 0.40$ and 0.85 are assigned as the resonances of the two diastereotopic methyl groups of the *meso* complex, while an additional singlet at $\delta = 0.50$ indicates that the helical form of this complex is also present in solution. The variable temperature NMR spectra (Figure 2) display the dynamic behavior of the $[Ga_2L_3]$ complex: at higher temperatures the amount of the mesocate decreases relative to the helicate. Cooling the solution to room temperature restores the original ratio of *meso* to helical complexes, indicating that these two structures are in thermodynamic equilibrium. The relative concentrations of mesocate and helicate of the $[Ga_2L_3]$ complex were determined by integrating the intensities of their methyl resonances.^[13, 14] The data show that

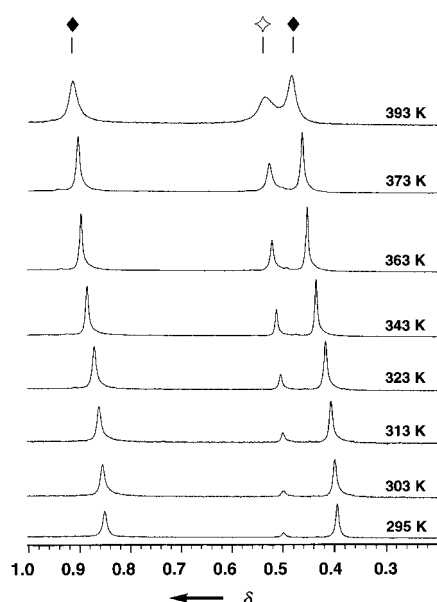


Figure 2. Variable temperature NMR spectra of $[\text{Ga}_2\text{L}_3]$ in $[\text{D}_6]\text{DMSO}$ ($\blacklozenge$: resonances of *meso* form, $\diamond$: resonance of helix form).

there are two temperature-dependent equilibria (1 a), one of which shows a first-order dependence on D_2O concentration. Our interpretation is that the helicate complex encapsulates either water or DMSO as a guest (G).



$$K = \frac{[\text{helicate}]}{[\text{mesocate}][\text{G}]} \quad (1b)$$

For $\text{G} = \text{DMSO}$ the equilibrium constant according to Equation (1 b) will be called K_{DMSO} , for $\text{G} = \text{D}_2\text{O}$ the constant will be called K_{water} . The ratios of helicate to mesocate are shown in Figure 3 as a function of both D_2O concentration and temperature. Since the model has two equilibrium constants, K_{DMSO} and K_{water} , there are four thermodynamic parameters, ΔH_{DMSO} , ΔH_{water} , ΔS_{DMSO} , and ΔS_{water} that define the system. A weighted least-squares fit^[14] to the helicate/

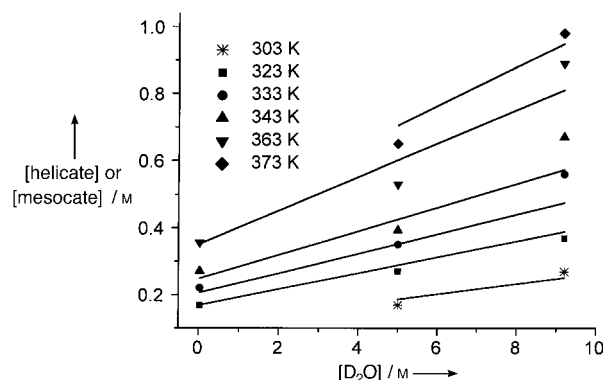


Figure 3. Plots of the helicate/mesocate ratio of $[\text{Ga}_2\text{L}_3]$ in $[\text{D}_6]\text{DMSO}$ as a function of temperature and D_2O concentration. There are two temperature-dependent equilibria: one dependent on $[\text{D}_2\text{O}]$ and one independent. Both are interpreted as due to a host–guest complex formed by the helicate.

mesocate ratios, with the relationship shown in Equation (2), gave the following values: $\Delta H_{\text{DMSO}} = 18(3) \text{ kJ}$, $\Delta S_{\text{DMSO}} = 19(9) \text{ J K}^{-1}$, $\Delta H_{\text{water}} = 18(3) \text{ kJ}$, $\Delta S_{\text{water}} = 25(9) \text{ J K}^{-1}$. The lines

$$\frac{[\text{helicate}]}{[\text{mesocate}]} = \frac{[\text{DMSO}]}{[\text{D}_2\text{O}]} e^{-\frac{(\Delta H_{\text{DMSO}}/RT + \Delta S_{\text{DMSO}}/R)}{}} + e^{-\frac{(\Delta H_{\text{water}}/RT + \Delta S_{\text{water}}/R)}{}} \quad (2)$$

in Figure 4 are calculated from these parameters. Like other host–guest interactions,^[3f] this is entropy driven. We interpret the relatively low helicate/mesocate ratio found in DMSO to be due to the poor fit of the large guest inside the host.

The ^1H NMR spectra of the $[\text{Al}_2\text{L}_3]$ complex in $[\text{D}_6]\text{DMSO}$ also indicates dynamic behavior, although markedly slower than that of the corresponding $[\text{Ga}_2\text{L}_3]$ complex. The singlet at $\delta = 0.39$, which corresponds to two equivalent methyl groups in the helicate, slowly converts into two singlets at $\delta = 0.36$ and 0.82 , which correspond to the two diastereotopically inequivalent methyl groups on the mesocate. This conversion is very slow at ambient temperature, requiring about ten days to reach equilibrium. Figure 4 shows the proton NMR spectra of the $[\text{Al}_2\text{L}_3]$ helicate in $[\text{D}_6]\text{DMSO}$ immediately after dissolution (a) and the same solution after 10 days (b). After this period of time there is a new set of resonances, due to the mesocate, in addition to those of the helicate. At 295 K the ratio of helicate to mesocate is 0.62.

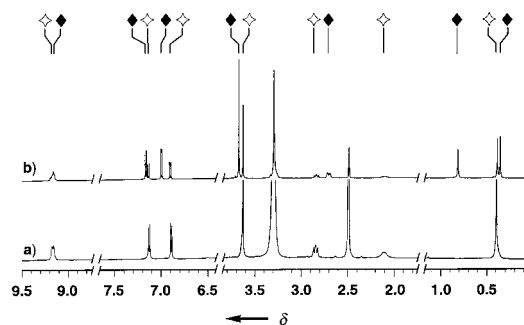


Figure 4. ^1H NMR spectra of $[\text{Al}_2\text{L}_3]$ helix in $[\text{D}_6]\text{DMSO}$ solution immediately after dissolution (a), and the same solution after 10 days (b). ($\blacklozenge$: resonances of *meso* form, $\diamond$: resonance of helix form).

The helicate to mesocate isomerization requires inversion at only one metal center. We have previously shown that inversion of Ga^{III} -catecholamide helicates is fast on the NMR time scale and proceeds through an intramolecular Bailar twist.^[4] In general, coordination isomerization in mononuclear Al^{III} and Ga^{III} complexes proceeds through the same mechanism.^[15] We therefore assume that inversion of the $[\text{Al}_2\text{L}_3]$ helicate also proceeds through an intramolecular Bailar twist. Furthermore, it is known that the rearrangement rates are consistently faster for Ga^{III} -tris-chelates than for the corresponding Al^{III} complexes. Most Ga^{III} complexes reach the fast NMR exchange limit below 273 K, while fast inversion of Al^{III} complexes sometimes requires temperatures of up to 373 K.^[16] Indeed, when the $[\text{Al}_2\text{L}_3]$ complex is held above 333 K the equilibrium between the helicate and mesocate is established within a few minutes.

In summary, we have shown that the ligand H_2L forms both helicate and mesocate complexes: the $[\text{Ga}_2\text{L}_3]$ complex crystallizes as a mesocate, the $[\text{Al}_2\text{L}_3]$ complex as a helicate

hydrate. Both the Ga and Al complexes form helicate–mesocate equilibria in $[D_6]DMSO$ with the mesocate enthalpically favored. The helicate structure is markedly stabilized by forming a host–guest complex in which solvent is encapsulated. In both the Ga and Al complexes the inversion at the metal centers proceeds by a nondissociative mechanism.^[17] The mechanical coupling between metal centers, which determines the degree to which a homochiral (helicate) or heterochiral (mesocate) complex forms, will generally require full molecular modeling for a quantitative prediction. Even then, the formation of host–guest complexes, as occurs here within the large cavity of the helicate complex, can drive the equilibrium to the otherwise less stable structure.

Experimental Section

General: All NMR spectra were measured on a 500 MHz Bruker DRX-500 spectrometer (TMS as standard). All compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy and elemental analysis.

2: To a solution of 3-benzyloxy-4-(2-thioxothiazolidin-1-yl)carbonyl-2(1*H*)-pyridinone^[8] (**1**, 1.44 g, 4 mmol) in CH_2Cl_2 was added neat 2,2-dimethyl-1,3-propanediamine (184 mg, 1.8 mmol). The mixture was stirred overnight at room temperature. After evaporation of the solvent, the residue was purified by flash column chromatography (SiO_2 , eluent CH_2Cl_2 with 2–6% CH_3OH) to give **2** as white foam (0.92 g, 87%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.876 (s, 6H), 3.127 (d, br, 4H), 3.565 (s, 6H), 5.301 (s, 4H), 6.507 (dd, 2H), 7.135 (d, 2H), 7.246 (d, 2H), 7.21–7.50 (m, 6H), 7.850 (t, 2H, J = 6.6 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 23.0, 36.2, 37.5, 46.4, 74.1, 104.7, 128.4, 128.7, 130.5, 131.8, 136.2, 146.0, 159.4, 163.7.

H₂L: Compound **2** (587 mg, 1 mmol) was dissolved in a 1:1 mixture of 12*M* HCl and glacial acetic acid (20 mL) and stirred at room temperature for two days. Filtration followed by removal of the solvent gave a beige residue which was recrystallized from methanol/diethyl ether solution to give **H₂L** as a white powder in 91% yield. ^1H NMR (500 MHz, $[D_6]DMSO$): δ = 0.88 (s, 6H); 3.17 (d, J = 6.3 Hz, 4H); 5.6 (s, 6H); 6.53 (d, J = 7.3 Hz, 2H, ArH) 7.21 (d, J = 7.3 Hz, 2H, ArH); 8.53 (t, J = 6.5 Hz, 2H, NH); 11.40 (s, 2H, phenol OH); ^{13}C NMR (500 MHz, $[D_6]DMSO$): δ = 23.30, 36.84, 36.85, 46.10, 102.87, 117.65, 127.84, 147.17, 158.09, 165.70; elemental analysis (%) calcd. for $C_{19}H_{24}N_4O_6 \cdot H_2O$ (422.445): C 54.02, H 6.20, N 13.26; found: C 54.14, H 6.11, N 12.99.

$[Al_2L_3] \cdot 3H_2O$: A solution of aluminum acetylacetonate complex (0.1 mmol) in CH_3OH was added to a stirring solution of **H₂L** (0.16 mmol) in CH_3OH . The resulting mixture was heated under reflux overnight under an atmosphere of nitrogen. The beige microcrystalline solid that precipitated from the solution was collected by filtration, washed with methanol, and dried in a vacuum oven (yield 87%). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.476 (s, 18H), 2.115 (d, ^2J = 14 Hz, 6H), 3.041 (dd, ^2J = 14 Hz, ^3J = 10 Hz, 6H), 3.683 (s, 18H), 6.774 (d, J = 7.2 Hz, 6H, ArH), 7.164 (d, J = 7.2 Hz, 6H, ArH), 9.311 (d, J = 10 Hz, 6H, NH); elemental analysis (%) calcd. for $Al_2C_{57}H_{66}N_{12}O_{18} \cdot 3H_2O$: C 52.05, H 5.51, N 12.78; found: C 51.84, H 5.61, N 12.52. Crystals of $[Al_2L_3] \cdot 2CHCl_3 \cdot CH_3OH \cdot 2H_2O \cdot 2C_6H_{12}$ suitable for analysis by X-ray diffraction were obtained by diffusion of cyclohexane into a 3:1 chloroform/wet methanol (with ca. 1% water) solution.

$[Ga_2L_3] \cdot H_2O$: This complex was prepared by a procedure similar to that for $[Al_2L_3] \cdot 3H_2O$, except $[Ga(acac)_3]$ was used instead of $[Al(acac)_3]$. Separation and purification were performed similarly. Yield: 81%. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.529 (s, 9H), 1.002 (s, 9H), 2.938 (d, ^2J = 14 Hz, 6H), 3.577 (dd, ^2J = 14 Hz, ^3J = 7 Hz, 6H), 3.757 (s, 18H), 6.743 (d, J = 7.2 Hz, 6H, ArH), 7.284 (d, J = 7.2 Hz, 6H, ArH), 9.294 (s, br, 6H, NH); elemental analysis (%) calcd. for $Ga_2C_{57}H_{66}N_{12}O_{18} \cdot H_2O$: C 50.16, H 5.02, N 12.32; found: C 49.94, H 5.16, N 12.12. X-ray-quality crystals of $[Ga_2L_3] \cdot 4CHCl_3 \cdot 2CH_3OH \cdot 0.5C_6H_{12}$ were obtained by diffusion of cyclohexane into a 3:1 chloroform/wet methanol (with ca. 1% water) solution.

Received: February 8, 1999

Revised version: July 9, 1999 [Z13007IE]

German version: *Angew. Chem.* **1999**, *111*, 3055–3058

Keywords: helical structures • mesocates • self-assembly • supramolecular chemistry

- [1] J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, **1995**.
- [2] C. Piguet, G. Bernardinelli, G. Hopfgartner, *Chem. Rev.* **1997**, *97*, 2005–2062.
- [3] a) D. L. Caulder, K. N. Raymond, *J. Chem. Soc. Dalton Trans.* **1999**, 1185, and references therein; b) T. Beissel, R. E. Powers, K. N. Raymond, *Angew. Chem.* **1996**, *108*, 1166; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1084; c) D. L. Caulder, K. N. Raymond, *Angew. Chem.* **1997**, *109*, 1508; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1440; d) C. Brückner, R. E. Powers, K. N. Raymond, *Angew. Chem.* **1998**, *110*, 1937; *Angew. Chem. Int. Ed.* **1998**, *37*, 1837; e) D. L. Caulder, R. E. Powers, T. N. Parac, K. N. Raymond, *Angew. Chem.* **1998**, *110*, 1940; *Angew. Chem. Int. Ed.* **1998**, *37*, 1840; f) T. N. Parac, D. L. Caulder, K. N. Raymond, *J. Am. Chem. Soc.* **1998**, *120*, 8003; g) R. W. Saalfrank, V. Seitz, D. L. Caulder, K. N. Raymond, M. Teichert, D. Stalke, *Eur. J. Inorg. Chem.* **1998**, 1317; h) X. Sun, D. W. Johnson, D. L. Caulder, R. E. Powers, K. N. Raymond, E. H. Wang, *Angew. Chem.* **1999**, *111*, 1386; *Angew. Chem. Int. Ed.* **1999**, *38*, 1303.
- [4] a) B. Kersting, M. Meyer, R. E. Powers, K. N. Raymond, *J. Am. Chem. Soc.* **1996**, *118*, 7221; b) M. Meyer, B. Kersting, R. E. Powers, K. N. Raymond, *Inorg. Chem.* **1997**, *36*, 5179.
- [5] Since a helix is by definition chiral “meso helicate” is an oxymoron and will not be used. Instead we will use the term “meso complex” or “mesocate”.
- [6] a) M. Albrecht, S. Kotila, *Angew. Chem.* **1995**, *107*, 2285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2134; b) M. Albrecht, M. Schneider, H. Röttle, *Chem. Ber.* **1997**, *130*, 615.
- [7] E. J. Enemark, T. D. P. Stack, *Angew. Chem.* **1995**, *107*, 1082; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 996.
- [8] J. Xu, K. N. Raymond, P. W. Durbin, B. Kullgren, *J. Med. Chem.* **1995**, *38*, 2606.
- [9] Crystal data for $[Al_2L_3] \cdot 2CHCl_3 \cdot CH_3OH \cdot 2H_2O \cdot 2C_6H_{12}$ ($Al_2C_{57}H_{66}N_{12}O_{18} \cdot 2CHCl_3 \cdot CH_3OH \cdot 2H_2O \cdot 2C_6H_{12}$): M_r = 1736.36, monoclinic, $C2/c$ (no. 15), a = 17.2348(1), b = 20.7011(3), c = 21.4044(3) Å, β = 91.742(1)°, V = 7633.1(1) Å³, Z = 4, T = 132 K, ρ_{calcd} = 1.305 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 0.317 mm⁻¹, $F(000)$ = 3112.00. Data for the crystal of dimensions 0.30 × 0.25 × 0.17 mm³ were collected on a Siemens SMART diffractometer equipped with a CCD area detector (2θ = 46.5°), ω scans, graphite-monochromated $\text{MoK}\alpha$ radiation (λ = 0.71073 Å). Of the 15974 reflections collected, 5458 were unique (R_{int} = 0.026). The structure was solved by direct methods (SHELXL-97) and was refined on F^2 . Data were corrected for Lorentz and polarization effects and anomalous dispersion. An empirical absorption correction was applied using XPREP (ellipsoidal model, T_{max} = 0.909 and T_{min} = 0.847). All non-hydrogen atoms except the disordered solvent (chloroform and cyclohexane) were refined anisotropically. Hydrogen atoms were assigned to idealized positions. The conventional R_1 = 0.0526, wR_2 = 0.1361 for 5458 observations ($I > 2.00\sigma(I)$) 526 parameters; maximum and minimum residual electron density in the final difference Fourier map were +0.433 and -0.375 e Å⁻³.^[10b]
- [10] a) Crystal data for $[Ga_2L_3] \cdot 4CHCl_3 \cdot 2CH_3OH \cdot 0.5C_6H_{12}$ ($Ga_2C_{57}H_{66}N_{12}O_{18} \cdot 4CHCl_3 \cdot 2CH_3OH \cdot 0.5C_6H_{12}$): M_r = 1930.36, triclinic, $P\bar{1}$ (no. 2), a = 13.6579(2), b = 17.1346(3), c = 18.5746(1) Å, α = 81.992(1), β = 78.198(1), γ = 78.201(1)°, V = 4143.47(4) Å³, Z = 2, ρ_{calcd} = 1.581 g cm⁻³, T = 143 K, $F(000)$ = 2028.00, $\mu(\text{MoK}\alpha)$ = 1.114 mm⁻¹. Data for the crystal of dimensions 0.30 × 0.25 × 0.10 mm³ were collected on a Siemens SMART diffractometer equipped with a CCD area detector (2θ = 46.5°), ω scans, graphite-monochromated $\text{MoK}\alpha$ radiation (λ = 0.71073 Å). Of the 17438 reflections collected, 11616 were unique (R_{int} = 0.024). The structure was solved by direct methods (SHELXL-97) and was refined on F^2 . Data were corrected for Lorentz and polarization effects and anomalous dispersion. An empirical absorption was applied using XPREP (ellipsoidal model, T_{max} = 0.868 and T_{min} = 0.757). All non-hydrogen atoms except the disordered solvent (chloroform and cyclohexane) were refined anisotropically. Hydrogen atoms were assigned to idealized positions. Final R_1 = 0.0599, wR_2 =

0.1557 for 11596 observations ($I > 2.00\sigma(I)$) 1066 parameters; maximum and minimum residual electron density in the final difference Fourier map were +0.878 and -1.123 e Å⁻³. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-118969 and -118970. 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).

- [11] The distances from the encapsulated water oxygen atom to the six endohedral oxygen atoms of the hydroxypyridinonate binding units in [Al₂L₃] are: 2.905(6), 2.905(6), 2.915(3), 2.915(3), 2.996(6), 2.996(6) Å.
- [12] A quantity of 1% of H₂O in [D₆]DMSO solution corresponds to about 0.5 M, which is a large excess of water compared to the concentration of the complex. The hydrated complex, which requires one water molecule as the guest, can be easily formed in this wet [D₆]DMSO solution.
- [13] The equilibrium ratios of helicate to mesocate were determined by integration of the ¹H NMR spectra (500 MHz) of 1.0 mM [M₂L₃] complex in [D₆]DMSO solution.
- [14] A nonlinear least-squares refinement minimized the function (3), where $w_i = 1/\sigma_i^2 = (1/0.06 y_i)^2$, $y_{\text{calcd}} = K_{\text{DMSO}}[\text{DMSO}] + K_{\text{water}}[\text{D}_2\text{O}]$.

$$R = \sum_{i=1}^n w_i (y_{\text{obs}} - y_{\text{calcd}})^2 \quad (3)$$

K_{DMSO} and K_{water} are functions of their respective ΔH and ΔS values as described in the text. The weighted R_w factor which is equal to $[R/(\sum w_i y_{\text{obs}}^2)]^{1/2}$ is 0.0855. The reported standard deviations are from the variance-covariance matrix.

- [15] a) R. C. Fay, T. S. Piper, *Inorg. Chem.* **1964**, 3, 348; b) J. R. Hutchison, J. G. Gordon, R. H. Holm, *Inorg. Chem.* **1971**, 10, 1004.
- [16] S. S. Eaton, G. R. Eaton, R. H. Holm, E. L. Muetterties, *J. Am. Chem. Soc.* **1973**, 95, 1116.
- [17] Heating the [M₂L₃] complex in the presence of excess ligand did not result in the exchange of “free” and bound ligand, as determined by ¹H NMR spectroscopy.

Self-Assembly of a Three-Dimensional [Ga₆(L²)₆] Metal–Ligand “Cylinder”**

Darren W. Johnson, Jide Xu, Rolf W. Saalfrank,* and Kenneth N. Raymond*

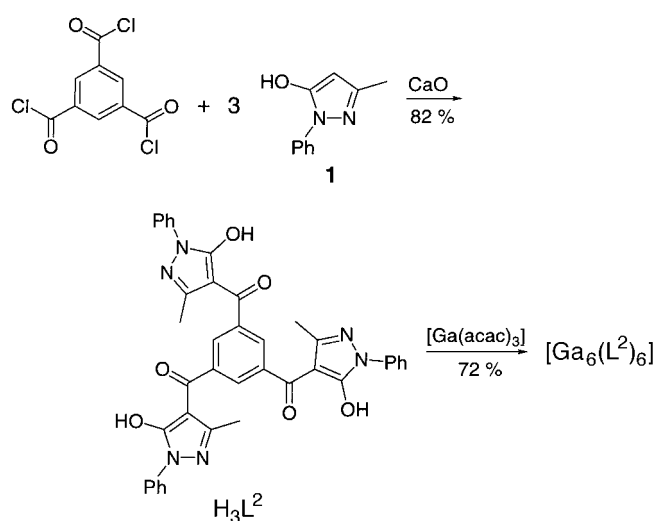
There are many lovely examples of supramolecular high-symmetry metal–ligand clusters.^[1–5] Typically these have resulted from the self-assembly of a twofold symmetric ligand and a carefully chosen metal ion. However, there are far fewer

[*] Prof. Dr. R. W. Saalfrank
Institut für Organische Chemie der Universität Erlangen-Nürnberg
Henkestrasse 42, D-91054 Erlangen (Germany)
Fax: (+49) 9131-852-1155
Prof. Dr. K. N. Raymond, D. W. Johnson, Dr. J. Xu
Department of Chemistry, University of California
Berkeley, CA 94720 (USA)
Fax: (+001) 510-486-1460
E-mail: raymond@socrates.berkeley.edu

[**] Coordination Number Incommensurate Cluster Formation, Part 12. This research was supported by NSF grant CHE-9709621 and by exchange grants NSF INT-9603212 and NATO SRG951516. We gratefully acknowledge Drs. Frederick J. Hollander and Dana L. Caulder for their help in the crystal structure determination, Dr. Andreas J. Terpin for helpful discussions, and Prof. Christian Brückner for assistance in the molecular modeling studies. Part 11: Ref. [30].

examples of *T* symmetry [M_xL_y] clusters containing a three-fold symmetric ligand.^[6–10] [M₆L₆] and higher stoichiometry rings have been assembled from triethanolamine,^[11] and Fujita and co-workers have synthesized [M₆L₄] metalla-macrotricycles,^[12] as well as a [M₃L₂] cage-like complex,^[13] from rigid, C₃-symmetry ligands.

A rational design for the synthesis of high-symmetry, metal–ligand clusters has been reported;^[14] one example is a (HNEt₃)₈[Ti₄(L¹)₄] tetrahedral cluster comprising a three-fold symmetric, tris-bidentate catecholamide ligand.^[6] In an attempt to generalize this methodology for assembling [M₄L₄] tetrahedra, we prepared H₃L² (Scheme 1), a rigid, threefold symmetric, tris-bidentate, pyrazolone-based ligand. Here we describe the serendipitous formation of a [Ga₆(L²)₆] “cylinder” having idealized D₃ symmetry, a new geometry for metal–ligand clusters comprising threefold symmetric ligands.



Scheme 1. Synthesis of the metal–ligand “cylinder” [Ga₆(L²)₆].

The venerable class of pyrazolone ligands has recently been used in the self-assembly of M₂L₃ helicates containing lanthanum(III) ions.^[15–18] Scheme 1 depicts the synthesis of the threefold symmetric, tris-β-diketone ligand H₃L². Treatment of 3-methyl-1-phenyl-2-pyrazoline-5-one (**1**) with 1,3,5-benzenetricarbonyl trichloride and calcium oxide in dioxane at 85 °C under an inert atmosphere affords the C₃-symmetric ligand H₃L² in high yield. This ligand reacts with a variety of metal acetylacetonate salts to generate high-symmetry, three-dimensional metal–ligand clusters.^[19]

In particular, a microcrystalline material precipitated out of a DMSO solution of H₃L² and [Ga(acac)₃] (acac = acetylacetonate) during a period of 16 h at 90 °C. This compound analyzed as a cluster with the composition [Ga_n(L²)_n] and gave, at first glance, a confusing ¹H NMR spectrum for a high-symmetry molecule. In a metal–ligand cluster with *T* molecular symmetry (i.e. [Ga₄(L²)₄] stoichiometry), all four ligands are equivalent and one would expect to see only one set of signals shifted with respect to the free ligand.^[6, 20] Surprisingly, a tripling in the number of signals was observed in both the ¹H and ¹³C NMR spectra (Figure 1). This implies

that each arm of the ligand is inequivalent and thus the C_3 symmetry of the ligand (L^2)³⁻ is disrupted upon metal complexation. None of the isomers of a tetrahedron (i.e. S_4 or C_3 symmetry) would generate a spectrum of this type.^[21, 22] Additionally, the parent ion in the positive-ion FAB mass spectrum of the complex corresponds to $[Ga_6(L^2)_6]$ (m/z 4472.4).^[23]

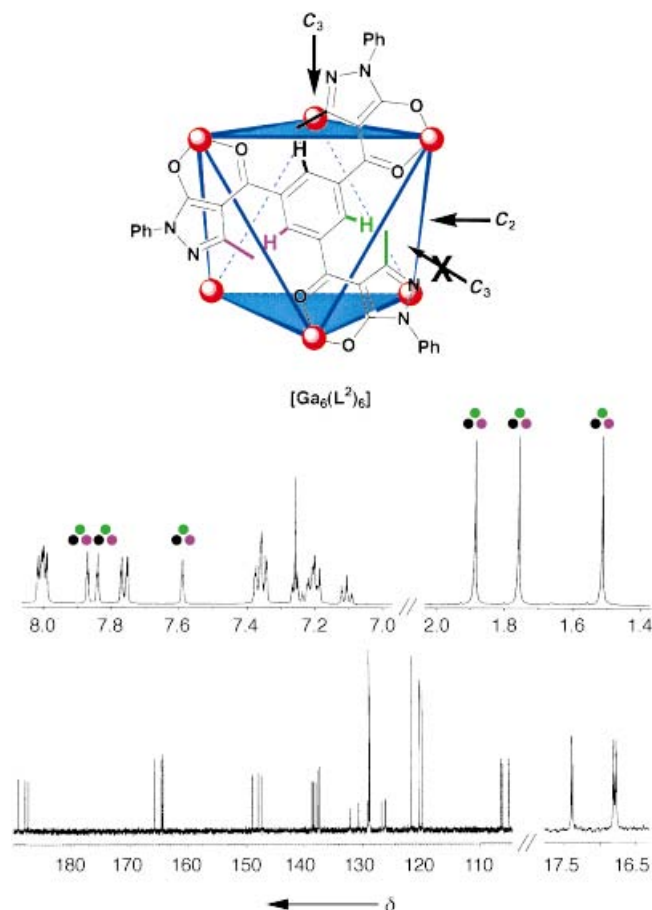


Figure 1. ^1H (top) and ^{13}C NMR spectra (bottom) of $[Ga_6(L^2)_6]$ in $CDCl_3$ showing the tripling of all ligand resonances upon complexation. The three inequivalent methyl protons and phenyl protons are labeled in color on the spectra to highlight these well-resolved signals.

The hexanuclear structure (Figure 1) justifies both the surprising stoichiometry elucidated by FAB-MS and the complicated NMR spectra. The ^1H and ^{13}C NMR spectra in $CDCl_3$ show a tripling of all ligand signals in the complex with respect to the free ligand. In particular, the three singlets in this portion of the spectrum correspond to the phenyl protons (Figure 1, shown in black, purple, and green) of the 1,3,5-trisubstituted phenyl backbone. In the putative $[Ga_6(L^2)_6]$ structure (Figure 1) the threefold axis and perpendicular twofold axes of the D_3 point group relate all six ligands by symmetry. However, there is no C_3 axis passing through the ligand backbone, therefore each arm of the ligand is inequivalent.

Single-crystal X-ray diffraction was used to confirm unequivocally this cylindrical geometry. Indeed, $[Ga_6(L^2)_6]$ crystallizes as a metal–ligand cylinder (Figure 2) in the space group $P2_1/n$ with four molecules per unit cell.^[24] While the

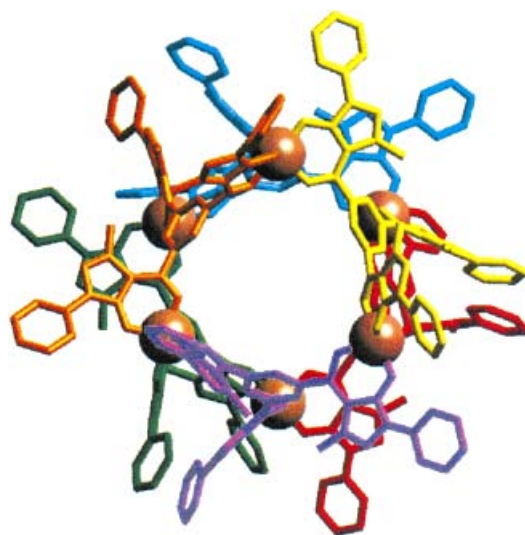


Figure 2. Wire frame and sphere representation of the crystal structure of $[Ga_6(L^2)_6]$ as viewed down the pseudo threefold axis of the cluster. For clarity each ligand is represented in a different color, with gallium ions represented by tan spheres.

molecule has no crystallographic symmetry it can be described as having idealized D_3 molecular symmetry.^[25] The gallium atoms define a distorted trigonal antiprism in which six ligands make up the equatorial faces of the cylinder with a hole at the top and the bottom. The antiprism is compressed along the pseudo C_3 axis, with average gallium...gallium distances of 9.82 Å (ranging from 9.71 to 9.95 Å) at the top and bottom, while the average gallium...gallium distance around the equator of the structure is 8.78 Å (ranging from 8.62 to 8.94 Å). Thus the pseudo threefold faces of the “holes” are larger than those occupied by the (equatorial) ligands. Due to this, the distance from the top of the prism to the bottom (Figure 3), as measured from the center of the top

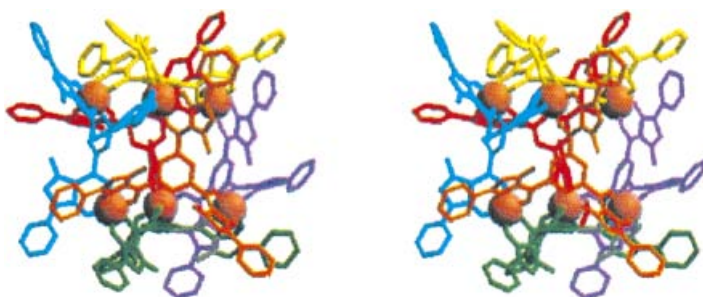


Figure 3. A stereo representation of the crystal structure of $[Ga_6(L^2)_6]$ viewed down the pseudo twofold axis of the cluster. For clarity each ligand is represented in a different color, with gallium ions represented by tan spheres.

hole to the center of the bottom hole is 6.70 Å, whereas the average face-to-face distance between opposite equatorial sides of the antiprism is 7.88 Å. The average twist angle of the trigonal antiprism is 36.2°; a perfect trigonal antiprism would have a twist angle of 60° and a trigonal prism would have a twist angle of 0°.

The molecule exists as a racemic mixture of homochiral, hexanuclear clusters ($\Delta\Delta\Delta\Delta\Delta\Delta$ or $\Lambda\Lambda\Lambda\Lambda\Lambda\Lambda$) in the solid

state and in solution. There is no interconversion of the various possible isomers on the NMR time scale between -40°C and 120°C . Probably the interconversion of these species is slow due to strong chiral coupling between the metal centers. This is under investigation in this and related systems.^[22, 26, 27]

Molecular modeling^[28] indicates that an $[\text{M}_4\text{L}_4]$ tetrahedron could also form with $(\text{L}^2)^{3-}$, although the metal ions would be closer to one another in the tetrahedron ($8.5\text{ \AA}$) than in the cylinder ($9.82\text{ \AA}$) causing the methyl group of the pyrazolone functionality to be in close proximity to the phenyl backbone. Hence ΔH favors the cylinder, while ΔS favors the tetrahedron. We are currently investigating analogous compounds to try to make larger rings, and perhaps tetrahedra, in order to determine the relative magnitude of these thermodynamic forces.

In summary, we have presented the successful formation of a new geometry of metal–ligand clusters, which we describe as cylinders. The $[\text{Ga}_6(\text{L}^2)_6]$ molecule was discovered while attempting to synthesize a $[\text{M}_4\text{L}_4]$ tetrahedron and has been unequivocally characterized by various techniques, including X-ray crystallography. This molecule has a pocket size similar to that of the cyclodextrins and could thus exhibit interesting host–guest chemistry, similar to that seen in compounds we have previously reported.^[20, 29–31]

Experimental Section

General: All chemicals were used as received from Aldrich unless otherwise noted. The synthesis of H_3L^2 is given in the Supporting Information. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-500 spectrometer. Mass spectra and elemental (C,H,N) analyses were performed at the Elemental Analysis Facility, College of Chemistry, UC Berkeley.

$[\text{Ga}_6(\text{L}^2)_6]$: A solution of gallium(III) acetylacetonate (0.37 g, 1 mmol) in DMSO (10 mL) was added to a suspension of $\text{H}_3\text{L}^2 \cdot \text{H}_2\text{O}$ (0.73 g, 1.05 mmol) in DMSO (30 mL). The reaction mixture was stirred under nitrogen at 90°C for 16 h. The microcrystalline product precipitated during the reaction was collected by filtration, washed with DMSO, and dried in vacuo at 80°C overnight. X-ray quality red block crystals were grown from a solution of the compound in DMF in the course of two days (yield 72 %): ^1H NMR (CDCl_3): $\delta = 1.51$ (s, 3H), 1.76 (s, 3H), 1.89 (s, 3H), 7.12 (t, $J = 7.4\text{ Hz}$, 1H), 7.22 (t, $J = 8.0\text{ Hz}$, 2H), 7.22 (t, $J = 8.0\text{ Hz}$, 1H), 7.27 (t, $J = 7.4\text{ Hz}$, 1H), 7.37 (t, $J = 7.7\text{ Hz}$, 2H), 7.38 (t, $J = 7.9\text{ Hz}$, 2H), 7.61 (s, 1H), 7.78 (d, $J = 7.8\text{ Hz}$, 2H), 7.86 (s, 1H), 7.89 (s, 1H), 8.02 (d, $J = 7.6\text{ Hz}$, 2H), 8.03 (d, $J = 7.6\text{ Hz}$, 2H); ^{13}C NMR (CDCl_3): $\delta = 16.77$, 16.80, 17.38, 104.89, 106.02, 106.30, 119.87, 120.34, 121.68, 126.10, 126.21, 126.76, 128.78, 128.91, 128.92, 129.09, 130.67, 132.06, 137.39, 137.42, 137.55, 137.99, 138.37, 138.60, 147.40, 148.02, 148.91, 164.22, 164.47, 165.66, 187.30, 187.92, 189.12; positive-ion FAB-MS: m/z (nitrobenzyl alcohol (NBA) matrix): calcd for $[\text{Ga}_6(\text{L}^2)_6\text{H}]^+$: 4472.4, found 4474; calcd for $[\text{Ga}_6(\text{L}^2)_6\text{H}_2]^{2+}$: 2236.7, found 2237; elemental analysis (%), crystals grown out of $\text{CHCl}_3/\text{pentane}$: calcd for $[\text{Ga}_6(\text{L}^2)_6] \cdot 4(\text{C}_5\text{H}_{12})$: C 64.64, H 4.81, N 10.28; found: C 64.55, H 4.82, N 10.21.

Received: April 12, 1999 [Z132751E]

German version: *Angew. Chem.* **1999**, *111*, 3058–3061

Keywords: cage compounds • cluster compounds • gallium • self-assembly • supramolecular chemistry

- [1] J. M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, **1995**, and references therein.
- [2] D. L. Caulder, K. N. Raymond, *J. Chem. Soc. Dalton Trans.* **1999**, 1185, and references therein; “Ligand and Metal Control of Self-Assembly in Supramolecular Chemistry”: R. W. Saalfrank, B. Demleitner in

Perspectives in Supramolecular Chemistry, Vol. 5, Transition Metals in Supramolecular Chemistry (Ed.: J. P. Sauvage), WILEY-VCH, Weinheim, **1999**, pp. 1–51, and references therein.

- [3] C. Piguet, G. Bernardinelli, G. Hopfgartner, *Chem. Rev.* **1997**, *97*, 2005, and references therein.
- [4] P. J. Stang, B. Olenyuk, *Acc. Chem. Res.* **1997**, *30*, 502, and references therein.
- [5] B. Olenyuk, A. Fechtenkötter, P. J. Stang, *J. Chem. Soc. Dalton Trans.* **1998**, *11*, 1707, and references therein.
- [6] C. Brückner, R. E. Powers, K. N. Raymond, *Angew. Chem.* **1998**, *110*, 1937; *Angew. Chem. Int. Ed.* **1998**, *37*, 1837.
- [7] M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi, K. Ogura, *Nature* **1995**, *378*, 469.
- [8] A. J. Amoroso, J. C. Jeffery, P. L. Jones, J. A. McCleverty, P. Thornton, M. D. Ward, *Angew. Chem.* **1995**, *107*, 1577; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1443.
- [9] P. J. Stang, B. Olenyuk, D. C. Muddiman, R. D. Smith, *Organometallics* **1997**, *16*, 3094.
- [10] S. L. James, M. P. Mingos, A. J. P. White, D. J. Williams, *Chem. Commun.* **1998**, *21*, 2323.
- [11] R. W. Saalfrank, I. Bernt, E. Uller, F. Hampel, *Angew. Chem.* **1997**, *109*, 2596; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2482.
- [12] M. Fujita, S. Y. Yu, T. Kusukawa, H. Funaki, K. Ogura, K. Yamaguchi, *Angew. Chem.* **1998**, *110*, 2192; *Angew. Chem. Int. Ed.* **1998**, *37*, 2082.
- [13] M. Fujita, S. Nagao, K. Ogura, *J. Am. Chem. Soc.* **1995**, *117*, 1649.
- [14] K. N. Raymond, D. L. Caulder, R. E. Powers, T. Beissel, M. Meyer, B. Kersting, *Proc. of the 40th Robert A. Welch Found. on Chem. Res.* **1996**, *40*, 115.
- [15] L. Yang, R. Yang, *Polyhedron* **1995**, *14*, 507.
- [16] B. S. Jensen, *Acta Chem. Scand.* **1959**, *13*, 1668.
- [17] X. C. Dong, F. C. Liu, Y. L. Zhao, *Acta Chim. Sin. Engl. Ed.* **1983**, *41*, 848.
- [18] J. Xu, S. Petoud, C. Brückner, **1999**, unpublished results.
- [19] Various clusters have been synthesized containing V, Fe, Ga, In, Th, and La. For brevity we only describe the first fully characterized of these systems, $[\text{Ga}_6(\text{L}^2)_6]$, in this communication. For details on the corresponding lanthanum and thorium containing clusters see: J. Xu, K. N. Raymond, **1999**, unpublished results.
- [20] D. L. Caulder, R. E. Powers, T. Parac, K. N. Raymond, *Angew. Chem.* **1998**, *110*, 1940; *Angew. Chem. Int. Ed.* **1998**, *37*, 1840.
- [21] T. Beissel, R. E. Powers, K. N. Raymond, *Angew. Chem.* **1996**, *108*, 1166; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1084.
- [22] T. Beissel, R. E. Powers, T. N. Parac, K. N. Raymond, *J. Am. Chem. Soc.* **1999**, *121*, 4200.
- [23] There is a low intensity peak in the positive-ion FAB mass spectrum corresponding to a $[\text{Ga}_4(\text{L}^2)_4]$ species. This is the proper stoichiometry for a tetrahedron, however there is no other evidence for formation of this compound in solution (NMR spectroscopic measurements and TLC). We conclude that this a mass spectrometer fragmentation species.
- [24] Crystal data for $[\text{Ga}_6(\text{C}_{39}\text{H}_{27}\text{N}_6\text{O}_6)_6] \cdot 13.5\text{DMF} \cdot 3.5\text{H}_2\text{O} \cdot x(\text{solvent})$ were collected using a Siemens SMART diffractometer equipped with a CCD area detector;^[32] crystal size $0.30 \times 0.10 \times 0.08\text{ mm}$; $T = -132^{\circ}\text{C}$; graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073\text{ \AA}$); monoclinic, $P2_1/n$ (no. 14), $a = 24.8178(3)$, $b = 39.0554(7)$, $c = 31.3024(5)\text{ \AA}$, $\beta = 93.721^{\circ}$, $V = 30277(1)\text{ \AA}^3$, $Z = 4$, $\mu = 0.601\text{ mm}^{-1}$, $F(000) = 11146$, $\rho_{\text{calcd}} = 1.192\text{ Mg m}^{-3}$, $2\theta_{\text{max}} = 37.9^{\circ}$. Of the 79 223 reflections collected, 23 948 were unique ($R_{\text{int}} = 0.1412$). Final $R_1 = 0.139$ for 12 941 reflections with $F_o > 4\sigma(F_o)$ (12 941 Friedel unique data, 2070 parameters, 1706 restraints, $2.04^{\circ} < 2\theta < 37.9^{\circ}$); for all 23 948 data, $wR_2 = 0.3613$, $GOF = 1.768$; max./min. residual density $+1.176/-0.663\text{ e \AA}^{-3}$. (The largest difference peaks correspond to noise near severely disordered solvent). Details of the disorder in the structure are contained in the Supporting Information. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-117432. 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; email: deposit@ccdc.cam.ac.uk).

- [25] Crystal data for the analogous $[\text{In}_6\text{L}_2]_6$ cluster have been collected. The molecule crystallizes in space group $P3$ and has crystallographically imposed C_3 symmetry. The details of this structure will be contained in a future report.
- [26] J. Xu, D. W. Johnson, K. N. Raymond, *XXIII International Symposium on Macrocyclic Chemistry* **1998**, PSA-55.
- [27] A. J. Terpin, D. W. Johnson, M. Ziegler, K. N. Raymond, **1999**, unpublished results.
- [28] CAChe Version 4.0, Oxford Molecular Group, Inc., U.S.A. **1997**. The gallium ions were modeled as having a fixed coordination geometry. The geometry minimization of the structure was performed using MM3 force field parameters.
- [29] T. Parac, D. L. Caulder, K. N. Raymond, *J. Am. Chem. Soc.* **1998**, *120*, 8003.
- [30] M. Scherer, D. L. Caulder, D. W. Johnson, K. N. Raymond, *Angew. Chem.* **1999**, *111*, 1689; *Angew. Chem. Int. Ed.* **1999**, *38*, 1587.
- [31] R. W. Saalfrank, R. Burak, A. Breit, D. Stalke, R. Herbst-Irmer, J. Daub, M. Porsch, E. Bill, M. Mütther, A. X. Trautwein, *Angew. Chem.* **1994**, *106*, 1697; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1621.
- [32] SMART Area Detector Software Package, V4.050, Siemens Industrial Automation, Inc., Madison, **1995**.

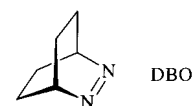
“Inverted” Solvent Effect on Charge Transfer in the Excited State**

Werner M. Nau* and Uwe Pischel

The mechanism of charge-transfer (CT) processes^[1, 2] is vital to the understanding of many photochemical^[3] and photo-biological^[4] reactions. It is paradigmatic for CT-induced photo-reactions that their rates increase with solvent polarity, a phenomenon which has been most extensively examined through the fluorescence quenching of singlet-excited states.^[5–7] The faster quenching in polar solvents is attributed to a stabilization of the primary reaction intermediates resulting from CT.^[8] When free ions are formed, this stabilization derives from the reduced Coulombic attraction between ions in polar solvents which decreases with the inverse of the dielectric constant (ϵ) according to the Born formula.^[8–10] When excited CT complexes or exciplexes are involved, the stabilization is related to the large induced dipole moment^[11–14] and follows a $(\epsilon-1)/(2\epsilon+1)$ dependence according to the Kirkwood–Onsager continuum model.^[5, 8–10, 15, 16]

The quenching of n, π^* -excited ketones by amines and sulfides is a well-examined case of a CT-induced photoreaction,^[17, 18] which displays the expected solvent effect. Herein, we have examined the fluorescence quenching of the n, π^* -excited azoalkane 2,3-diazabicyclo[2.2.2]oct-2-ene (DBO)^[19]

by amines and sulfides, which presents a closely related example of a CT-induced photoreaction. This photoreaction is slowed down in polar solvents. To the best of our knowledge, this is the first observation of an “inverted” solvent effect on the rate constants for CT-induced quenching. It is presumed that the initial reaction step involves the formation of an exciplex with partial CT character. Counterintuitively, the exciplex is stabilized to a lesser degree by polar solvents than the reactants.



The rate constants for fluorescence quenching of DBO by triethylamine and diisopropyl sulfide in different solvents (Table 1) were on the order of 10^6 – $10^8 \text{ M}^{-1} \text{ s}^{-1}$ and varied over one order of magnitude for each quencher. Linear Stern–Volmer behavior was observed in the steady-state experi-

Table 1. Rate constants k_q for the quenching of singlet-excited DBO and triplet-excited benzophenone by amines and sulfides in different solvents.

Solvent	E_T [a]	k_q [$10^7 \text{ M}^{-1} \text{ s}^{-1}$]			
		NEt_3	SiPr_2	$^1\text{DBO}^* \text{ [b]}$	$^3\text{Ph}_2\text{CO}^* \text{ [d]}$
perfluorohexane	30.4	24		23	
cyclohexane	33.2	14		6.7	9.0
Freon-113	33.2	18		5.0	14
benzene	34.8	7.2	170	1.8	19
ethyl acetate	38.1	5.6		1.4	
1,4-dioxane	36.0	6.1		1.3	
acetone	42.2	6.2		1.0	
acetonitrile	46.0	4.4	380	0.67	59

[a] Data from: C. Reichardt, E. Harbusch-Görnert, *Lieb. Ann. Chem.* **1983**, 721–743 except for Freon-113 (C. Laurence, P. Nicolet, M. Lucon, T. Dalati, C. Reichardt, *J. Chem. Soc. Perkin Trans. 2* **1989**, 873–876) and perfluorohexane (estimated from Equation (4) of the latter reference). [b] Determined from steady-state or time-resolved fluorescence quenching; error in data is 10%. [c] From: A. A. Gorman, C. T. Parekh, M. A. J. Rodgers, P. G. Smith, *J. Photochem.* **1978**, *9*, 11–17. [d] From: S. Inbar, H. Linschitz, S. G. Cohen, *J. Am. Chem. Soc.* **1982**, *104*, 1679–1682.

ments, and time-resolved measurements (for benzene and acetonitrile) gave consistent results. Most interesting, the quenching rates decreased with increasing solvent polarity (cf. Reichardt’s E_T parameter^[20] in Table 1), that is, they were *highest* in perfluorohexane and cyclohexane and *lowest* in acetonitrile.^[21] The peculiar solvent effect of singlet-excited DBO is opposite to that established in the literature, both for n, π^* -excited ketones (cf. data for triplet-excited benzophenone in Table 1) and π, π^* -excited aromatic molecules as acceptors.^[5–7]

A mechanistic interpretation of the “inverted” solvent effect must take three pertinent features into account: a) The fluorescence quenching involves CT from the donor molecule to the excited DBO, as evidenced by the dependence of the quenching rate constant on the ionization potential of the donor (Table 2). The CT nature of the fluorescence quenching of DBO has also been firmly established for the weaker olefin donors.^[22–24] Incidentally, a first indication for the unusual solvent effect (isooctane and acetonitrile) was noted by Engel et al. for olefin quenching,^[23] but the underlying reasons were not discussed. b) Ion pair formation is unlikely to occur with

[*] Dr. W. M. Nau, Dipl.-Chem. U. Pischel
Departement Chemie der Universität
Klingelbergstrasse 80, CH-4056 Basel (Switzerland)
Fax: (+41) 61-267-3855
E-mail: nau@ubaclu.unibas.ch

[**] This work was supported by the Swiss National Science Foundation and the German Fonds der Chemischen Industrie. We thank Dr. Bruno Hellrung for the cyclovoltammetric measurement. W.M.N. is grateful to Prof. D. Klapstein for the support at St. Francis Xavier University, where parts of this study were undertaken during tenure of the W. F. James Chair.

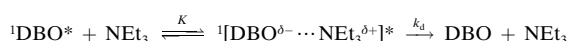
Table 2. Dependence of the rate constants k_q for fluorescence quenching of DBO on the ionization potential of the donor.

Donor	IP [eV] ^[a]	k_q [$10^7 \text{ M}^{-1} \text{ s}^{-1}$] ^[b]
tetrahydrofuran	9.42	0.23 ^[c]
diisopropylsulfide	8.26 ^[d]	0.67
triethylamine	7.50	7.2
tri- <i>n</i> -propylamine	7.23	8.5
tri- <i>n</i> -butylamine	7.15 ^[e]	9.2
<i>N,N</i> -dimethylaniline	7.12	24
triphenylamine	6.86	21

[a] Adiabatic ionization potentials taken from: R. C. Weast, D. R. Lide, M. J. Astle, W. H. Beyer, *CRC Handbook of Chemistry and Physics*, CRC Press, Boca Raton, FL, 1990. [b] Determined from time-resolved fluorescence quenching in benzene; error in data is 10%. [c] From: W. Adam, J. N. Moorthy, W. M. Nau, J. C. Scaiano, *J. Org. Chem.* **1997**, 62, 8082–8090. [d] Vertical ionization potential taken from: G. Wagner, H. Bock, *Chem. Ber.* **1974**, 107, 68–77. [e] From: X. Allonas, P. Jacques, *Chem. Phys.* **1997**, 215, 371–378.

the examined quenchers since full electron transfer between singlet-excited DBO and triethylamine should be *endergonic* by about 38 kJ mol^{−1}.^[25] The same reaction is *exergonic* by about 25 kJ mol^{−1} for triplet-excited benzophenone.^[25] This energetics is consistent with the absolute quenching rate constants of DBO, which fall 2–3 orders of magnitude below the diffusion-controlled limit.^[26] The formation of free ions was also excluded (< 1%) by time-resolved photoconductivity measurements in acetonitrile,^[27] and, most importantly, the observed solvent effect argues against rate-determining electron transfer. c) The reaction quantum yields for DBO with triethylamine are very low, for example, 4.4% in benzene and 2.7% in acetonitrile, which demonstrates that deactivation of singlet-excited DBO predominates.

The combined arguments point to the involvement of an exciplex with partial CT character in the fluorescence quenching of DBO. Such exciplexes are well-established for other photoreactions,^[28–32] including the quenching of DBO by olefins,^[22–24] and that of triplet-excited azoalkanes by amines.^[33] In keeping with the present mechanistic understanding of related photoreactions,^[6, 7, 34] we propose a reversible formation and subsequent deactivation of this exciplex (Scheme 1).



Scheme 1. Exciplex-induced deactivation of DBO by triethylamine.

The kinetics of quenching k_q according to Scheme 1 increases with the equilibrium constant for exciplex formation K and the rate of deactivation k_d .^[6, 7, 23, 26] When dissociation of the exciplex occurs faster than deactivation, a typical preequilibrium and steady-state scenario results,^[7] where $k_q = Kk_d$. We will now demonstrate that the equilibrium constant for exciplex formation K may display an “inverted” solvent effect, which suffices to account for the experimental results, regardless of any superimposed solvent dependence and the nature of the deactivation step. This finding contrasts the general presumption that exciplex formation is facilitated in polar solvents.^[5, 8–11, 13, 14]

According to the full expression of the Kirkwood–Onsager solvation model,^[15, 16, 20, 35, 36] the polar solvent stabilization ($\Delta G_{\text{solvant}}$) of an exciplex (or generally an adduct) AB relative to the reactants (A and B) is proportional to a structural constant C , which incorporates the difference of the square of the individual dipole moments μ divided by the cube of the corresponding molecular radii r [Eq. (1)].

$$\Delta G_{\text{solvant}} = \frac{N_A}{4\pi\epsilon_0} \left(\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} - \frac{\mu_{AB}^2}{r_{AB}^3} \right) \left(\frac{\epsilon - 1}{2\epsilon + 1} \right) = C \left(\frac{\epsilon - 1}{2\epsilon + 1} \right) \quad (1)$$

The reaction constant C may be negative or positive, resulting in a relative stabilization or destabilization of the exciplex with increasing solvent polarity, or it may vanish as in the case of the pyrene excimer ($\mu_{AB} = \mu_A = \mu_B = 0$) to result in an insensitivity on the solvent.^[11] Most aromatic exciplexes have much higher dipole moments than the reactants and in these cases the normal solvent dependence is expected (negative C), since $\mu_{AB} \gg \mu_A$ and $\mu_{AB} \gg \mu_B$.^[11, 13, 14] In fact, the dipolar solvent stabilization of the reactants is neglected in most treatments of solvent effects on exciplex formation.^[5, 8–11] However, the possibility of an inverted solvent dependence becomes a real one, when the reactant has a significant dipole moment and when the dipole moment of the exciplex falls short of its maximum value of about 14 D^[11, 13, 14] due to partial CT, that is, $\mu_{AB} \geq \mu_A$. In such cases, the molecular size effect will tend to offset any increase in dipole moment, since $r_{AB} > r_A$, and when a small reactant (small r_A) is involved, the inverted solvent effect may become sizable. These boundary conditions, namely a small, strongly dipolar reactant, and an exciplex with only partial CT are unquestionably met in the fluorescence quenching of DBO by amines and sulfides.

The absence of exciplex emission^[37] precluded an experimental estimate of the exciplex dipole moment.^[11, 38, 39] Hence, we have used the semiempirical UHF-PM3 method^[40] to assess the resulting dipole moments of the exciplexes between n,π^* -excited states and amines. CT interaction entails molecular orbital overlap between the donor HOMO and the acceptor LUMO or, in the case of an excited acceptor, its lowest SOMO. In the case of n,π^* -excited states and amines, CT interaction should take place between the lone pair of the amine and the electron-deficient, singly occupied lone pair orbital of the carbonyl oxygen or azo nitrogen atoms. The minimized exciplex structures (in the triplet state due to the restriction of the UHF method) confirmed this mode of CT interaction (Figure 1). These are the first calculated exciplex structures between n,π^* -excited states and amines.^[41]

The UHF-PM3 geometries were employed in single-point CI-PM3 calculations^[40] (including the lone pairs and closest π and π^* as active orbitals) to obtain estimators for the dipole moments of singlet-excited DBO (3.2 D), triplet-excited benzophenone (2.2 D), triethylamine (1.0 D), the singlet exciplex of DBO (4.4 D), and the triplet exciplex of benzophenone (7.3 D). We contend that the pertinent trends of the dipole moments produced by the semiempirical method are meaningful. First, the calculated and experimental dipole moments for the ground states of triethylamine (1.0 versus 0.86 D)^[42] and DBO (3.4 versus 3.5 D),^[43] but also the triplet-excited state of benzophenone (2.2 versus 2.1 D)^[44] are in excellent agreement. Second, the calculated dipole moment of

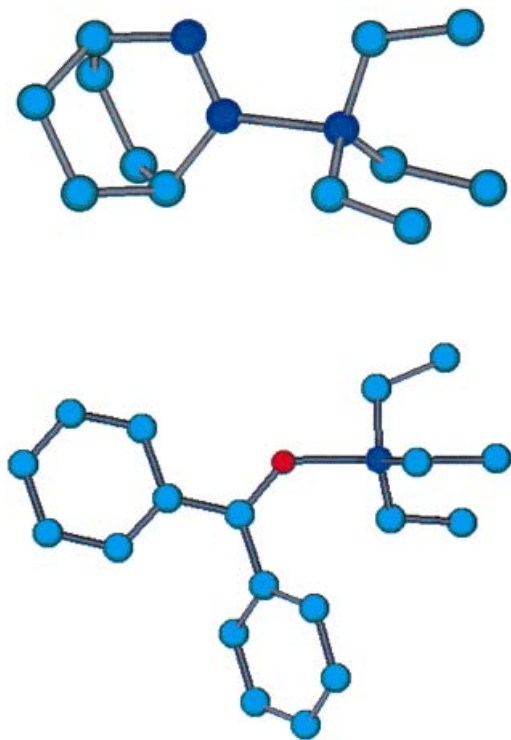


Figure 1. Calculated geometries (UHF-PM3 method) of the triplet exciplexes between DBO and triethylamine (top) and benzophenone and triethylamine (bottom).

the DBO exciplex (4.4 D) meets the expectation for a partial CT.^[5, 36] Third, the larger increase in dipole moment for the benzophenone exciplex (7.3 D) agrees with the more favorable energetics for electron transfer (see above). The molecular radii of the reactants can be taken from the literature^[45] or calculated accordingly by using 1,4-diazabicyclo[2.2.2]octane as a model for DBO ($r_A = 3.07 \text{ \AA}$). Those of the complexes were estimated by volume additivity, that is, $r_{AB}^3 = r_A^3 + r_B^3$.

The use of the above parameters in Equation (1) affords a positive reaction constant for singlet-excited DBO ($C = +0.101 \text{ D}^2 \text{ \AA}^{-3}$), that is, a relative destabilization of the exciplex in polar solvents, but a stabilization for triplet-excited benzophenone ($C = -0.466 \text{ D}^2 \text{ \AA}^{-3}$). These results are in agreement with the experimentally observed “normal” solvent effect for benzophenone and the “inverted” solvent effect for DBO (Table 1). Note that the solvent effect for exciplex formation of benzophenone operates in the same direction as that expected for electron transfer, such that a mechanistic discrimination is not possible on the basis of the observed solvent dependence alone. The calculated differential solvation energy ($\Delta\Delta G_{\text{solvant}}$) of the DBO-NEt₃ exciplex in acetonitrile versus cyclohexane amounts to 1.7 kJ mol^{-1} (factor of 2 difference), while the experimental data (factor 3.2) suggest a value of 2.9 kJ mol^{-1} . Given the simplicity of the solvation model (e.g., spherical approximation, continuum model), this agreement between experiment and theoretical expectation is satisfactory, but reveals also the limitations for making accurate quantitative predictions.

The applicability of the simple Kirkwood–Onsager Equation (1) for assessing solvent effects on the CT-induced

quenching of singlet-excited DBO was subject to additional computational and experimental tests. The reaction constant C should decrease for better donors as a consequence of increased CT in the exciplex, which should result in a larger μ_{AB} in Equation (1). Indeed, triethylamine exhibits a smaller solvent effect than the weaker donor diisopropylsulfide, for example, the ratio of rate constants in cyclohexane and acetonitrile decreases from 10 for the sulfide to 3.2 for the amine (Tables 1 and 2). The expected effect is also reproduced by the computational method described above.^[46] The calculated C value for diisopropylsulfide ($+0.234 \text{ D}^2 \text{ \AA}^{-3}$) is larger than for triethylamine ($+0.101 \text{ D}^2 \text{ \AA}^{-3}$), although the molecular radii of the donors are virtually the same ($r_B = 3.49$ versus $3.44 \text{ \AA}$).^[47]

In conclusion, the fluorescence quenching of the azoalkane DBO by amines and sulfides provides an example for an “inverted” solvent effect on a CT-induced photoreaction. The effect, which can be semiquantitatively rationalized by the Kirkwood–Onsager solvation model [Eq. (1)], appears to be related to the large dipole moment and small molecular size of DBO and the partial degree of CT in the exciplex intermediate. Similar effects must be considered when predicting solvent effects in related CT-induced photoreactions. They are particularly important when exciplexes with partial CT character are involved, which have been postulated for an increasing number of photoreactions and may precede the electron transfer step.^[8, 28–32]

Received: March 22, 1999 [Z13193IE]

German version: *Angew. Chem.* **1999**, *111*, 3126–3129

Keywords: azo compounds • charge transfer • fluorescence spectroscopy • photochemistry • solvent effects

- [1] D. Rehm, A. Weller, *Ber. Bunsen-Ges. Phys. Chem.* **1969**, *73*, 834–839.
- [2] R. A. Marcus, *Angew. Chem.* **1993**, *105*, 1161–1172; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1111–1121.
- [3] J. Mattay, *Angew. Chem.* **1987**, *99*, 849–870; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 825–847.
- [4] H. Kurreck, M. Huber, *Angew. Chem.* **1995**, *107*, 929–947; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 849–866.
- [5] H. Beens, A. Weller in *Organic Molecular Photophysics* (Ed.: J. B. Birks), Wiley, London, **1975**, pp. 159–215.
- [6] J. E. Baggott, M. J. Pilling, *J. Chem. Soc. Faraday Trans. 1* **1983**, *79*, 221–234.
- [7] R. Rathore, S. M. Hubig, J. K. Kochi, *J. Am. Chem. Soc.* **1997**, *119*, 11468–11480.
- [8] A. Weller, *Z. Phys. Chem. (Wiesbaden)* **1982**, *133*, 93–98.
- [9] G. J. Kavarnos, *Top. Curr. Chem.* **1990**, *156*, 21–58.
- [10] G. J. Kavarnos, *Fundamentals of Photoinduced Electron Transfer*, VCH, New York, **1993**.
- [11] H. Beens, H. Knibbe, A. Weller, *J. Chem. Phys.* **1967**, *47*, 1183–1184.
- [12] H. Knibbe, D. Rehm, A. Weller, *Ber. Bunsen-Ges. Phys. Chem.* **1969**, *73*, 839–845.
- [13] A. Weller in *The Exciplex* (Eds.: M. Gordon, W. R. Ware), Academic Press, New York, **1975**, pp. 23–38.
- [14] N. Mataga in *The Exciplex* (Eds.: M. Gordon, W. R. Ware), Academic Press, New York, **1975**, pp. 113–144.
- [15] J. G. Kirkwood, *J. Chem. Phys.* **1934**, *2*, 351–361.
- [16] L. Onsager, *J. Am. Chem. Soc.* **1936**, *58*, 1486–1493.
- [17] S. G. Cohen, A. Parola, G. H. Parsons, *Chem. Rev.* **1973**, *73*, 141–161.
- [18] H. Miyasaka, M. Kiri, K. Morita, N. Mataga, Y. Tanimoto, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1569–1582.
- [19] The azoalkane DBO has an exceedingly long-lived singlet state (up to 800 ns), a singlet energy of about 318 kJ mol^{-1} , and it does not undergo

- intersystem crossing (W. M. Nau, W. Adam, J. C. Scaiano, *J. Am. Chem. Soc.* **1996**, *118*, 2742–2743).
- [20] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim, **1988**.
- [21] Protic solvents caused again an increase in the rate constants, for example, the rate constants in aqueous solution were virtually the same as in cyclohexane. This effect can be due to specific solvation (hydrogen bonding) and the larger singlet-excitation energy of n, π^* -excited states in protic solvents, cf. λ_{max} of DBO in hexane (378 nm) versus water (364 nm).
- [22] T. R. Evans, *J. Am. Chem. Soc.* **1971**, *93*, 2081–2082.
- [23] P. S. Engel, A. Kitamura, D. E. Keys, *J. Org. Chem.* **1987**, *52*, 5015–5021.
- [24] W. Adam, A. Nikolaus, *Eur. J. Org. Chem.* **1998**, 2177–2179.
- [25] For the quantitative prediction of the free enthalpy of electron transfer^[41] we used $E_{\text{ox}}(\text{NEt}_3) = 0.96 \text{ V}$ (vs. saturated calomel electrode (SCE)),^[33] $E_{\text{p,red}}(\text{DBO}) = -2.8 \text{ V}$ (vs. SCE in acetonitrile/hanging mercury drop electrode (HMDE), this work), $E^*(\text{DBO}^*) = 3.30 \text{ eV}$,^[19] $E_{\text{red}}(\text{Ph}_2\text{CO}) = -1.83 \text{ V}$ (vs. SCE in acetonitrile),^[28] $E^*(\text{Ph}_2\text{CO}^*) = 3.00 \text{ eV}$,^[28] taking the Coulomb term as -0.06 eV in acetonitrile.
- [26] K. Kikuchi, Y. Takahashi, T. Katagiri, T. Niwa, M. Hoshi, T. Miyashi, *Chem. Phys. Lett.* **1991**, *180*, 403–408.
- [27] X. Allonas, Ecole Nationale Supérieure de Chimie de Mulhouse, unpublished results.
- [28] P. J. Wagner, R. J. Truman, A. E. Puchalski, R. Wake, *J. Am. Chem. Soc.* **1986**, *108*, 7727–7738.
- [29] J. Gersdorf, J. Mattay, H. Görner, *J. Am. Chem. Soc.* **1987**, *109*, 1203–1209.
- [30] P. Jacques, *J. Photochem. Photobiol. A* **1991**, *56*, 159–163.
- [31] I. R. Gould, R. H. Young, L. J. Mueller, S. Farid, *J. Am. Chem. Soc.* **1994**, *116*, 8176–8187.
- [32] P. Jacques, X. Allonas, M. von Raumer, P. Suppan, E. Haselbach, *J. Photochem. Photobiol. A* **1997**, *111*, 41–45.
- [33] W. Adam, J. N. Moorthy, W. M. Nau, J. C. Scaiano, *J. Am. Chem. Soc.* **1997**, *119*, 6749–6756.
- [34] T. M. Bockman, S. M. Hubig, J. K. Kochi, *J. Am. Chem. Soc.* **1998**, *120*, 2826–2830.
- [35] Y. P. Tsentalovich, H. Fischer, *J. Chem. Soc. Perkin Trans. 2* **1994**, 729–733.
- [36] M. Hild, H.-D. Brauer, *Ber. Bunsen-Ges. Phys. Chem.* **1996**, *100*, 1210–1216.
- [37] Emission from singlet exciplexes involving n, π^* -excited states has never been observed to our knowledge.
- [38] E. Lippert, *Z. Naturforsch. A* **1955**, *10*, 541–545.
- [39] N. Mataga, Y. Kaifu, M. Koizumi, *Bull. Chem. Soc. Jpn.* **1956**, *29*, 465–471.
- [40] J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209–220.
- [41] U. Maharaj, I. G. Czizmadia, M. A. Winnik, *J. Am. Chem. Soc.* **1977**, *99*, 946–948.
- [42] M. G. Ivanov, E. Z. Zhuravlev, Y. Dergunov, T. P. Elizarova, *Zh. Obshch. Khim.* **1990**, *60*, 1209–1212.
- [43] M. D. Harmony, T. L. Talkington, R. N. Nandi, *J. Mol. Struct.* **1984**, *125*, 125–130.
- [44] H. Shimamori, H. Uegaito, K. Houdo, *J. Phys. Chem.* **1991**, *95*, 7664–7667.
- [45] M. Terazima, K. Okamoto, N. Hirota, *J. Phys. Chem.* **1993**, *97*, 13387–13393.
- [46] For diisopropylsulfide the UHF-PM3 calculation gave $\mu_{\text{B}} = 2.1 \text{ D}$ and for the corresponding exciplex $\mu_{\text{AB}} = 4.0 \text{ D}$.
- [47] In an effort to observe a “normal” solvent effect we examined also triphenylamine, which is a better donor than triethylamine (Table 2). However, the solvent effect for this better amine donor was very similar as for triethylamine. Although this result may be in part related to the increase in molecular size of triphenylamine, which would tend to balance the donor strength effect in Equation (1), a C value could not be estimated. The UHF-PM3 calculation does not produce minimum exciplex structures in the case of aromatic amines, which differ from aliphatic amines in that they act as “ π ” rather than “ n ” donors (cf. P. Jacques, X. Allonas, *Chem. Phys. Lett.* **1995**, *233*, 533–537).

An Inorganic Tire-Tread Lattice: Hydrothermal Synthesis of the Layered Vanadate $[\text{N}(\text{CH}_3)_4]_5\text{V}_{18}\text{O}_{46}$ with a Supercell Structure**

Bryan E. Koene, Nicholas J. Taylor, and Linda F. Nazar*

There has been much recent interest in preparing new vanadium oxides owing to their promise as anodes in secondary lithium batteries and electrochromic devices.^[1–3] The catalytic properties of vanadium oxides also make these materials viable candidates as heterogeneous catalysts. An inviting synthetic route that deviates from traditional solid-state high-temperature synthesis is hydrothermal chemistry at relatively low temperatures (120–250 °C) and pressures with organic cations as templating agents. Recent developments in this field have proven that it is a viable method for the preparation of many novel two-dimensional materials, especially vanadium oxides. To date, only five truly unique host inorganic lattices have been synthesized, although each lattice can be formed with one of several organic cations in most cases. The lattices, indicated by square brackets, include $[\text{V}_4\text{O}_{10}]^-$ in the presence of tetramethylammonium (TMA) ions;^[4] $[\text{V}_4\text{O}_{10}]^{2-}$ in the presence of ethylenediamine (en), piperazine (pip),^[5] or diaminopropane;^[6] and $[\text{V}_6\text{O}_{14}]^{2-}$ in the presence of 1,4-Diazabicyclo[2.2.2]octan (dabco).^[7] Other frameworks that are very closely related to $[\text{V}_6\text{O}_{14}]^{2-}$ were also recently reported, namely, $(\text{TMA})_2[\text{V}_6\text{O}_{14}]$ ^[8] and $[\text{Zn}(\text{en})_2]^{2+}[\text{V}_6\text{O}_{14}]$.^[9] The mechanism by which these inorganic and organic components assemble under hydrothermal conditions is currently the subject of intense research but is not yet understood. Cooperative organization of organic and inorganic phases has been alluded to in some cases. The organic cation also acts as a reducing agent in the synthesis of transition metal oxides, and this complicates the dissolution and nucleation processes.

We report here the highly unusual layered vanadate $(\text{TMA})_5\text{V}_{18}\text{O}_{46}$, whose structure is sufficiently distinct from those of other metal oxides that it has no precedent in the literature. The lattice is self-assembled from two distinct $[\text{V}_9\text{O}_{23}]$ building blocks, neither of which is known to form repeating lattices on its own, to form a supercell arrangement. One building block is neutral, and the other carries localized electrons and is negatively charged. The organic cations reside between the layers. Formation of this unusual lattice arrangement appears to be driven by thermodynamic factors that minimize strain in the “mixed” alternating lattice.

$(\text{TMA})_5\text{V}_{18}\text{O}_{46}$ was prepared by mixing V_2O_5 (182 mg, 1.0 mmol), V_2O_3 (50 mg, 0.33 mmol), $[\text{N}(\text{CH}_3)_4]\text{Cl}$ (110 mg,

[*] Prof. L. F. Nazar, B. E. Koene, N. J. Taylor
Department of Chemistry
University of Waterloo
Waterloo, ON, N2L3G1 (Canada)
Fax: (+1) 519-746-0435
E-mail: lfnazar@uwaterloo.ca

[**] This work was supported by the NSERC (Canada) through the operating and strategic research programs. G. R. Goward and J. Britten are thanked for confirming the structure with an independent determination.

1.0 mmol), and $[\text{N}(\text{CH}_3)_4]\text{OH}$ (5.0 mmol), and then adjusting the pH to 5.0 by the dropwise addition of HNO_3 . The mixture was heated under autogeneous pressure in a Teflon-lined autoclave at 170°C for 2 d. The resulting product was a mixture of black crystalline phases, of which approximately 10% was the title compound. The characteristic long, hexagonally distorted morphology of the crystals allowed them to be readily separated from the other phases. Another layered vanadate $((\text{TMA})\text{V}_4\text{O}_{10})$ was recovered from this reaction mixture (40%), along with the well-known polyoxovanadate cluster $(\text{TMA})_6\text{V}_{15}\text{O}_{36}\cdot\text{Cl}\cdot 4\text{H}_2\text{O}$ (40%), and a fourth, unknown phase (10%). These black, octagonal crystals have a very long unit cell length along one axis ($69.5\text{ \AA}$) and a high degree of disorder perpendicular to the layers. They appear to be a larger disordered supercell of the title compound, although further details await structural refinement.

The asymmetric unit cell of $(\text{TMA})_5\text{V}_{18}\text{O}_{46}$ is shown in Figure 1a without the TMA cations. Several unusual structural characteristics indicate that the structure is intermediate between two different phases. First, the 18 unique vanadium atoms are arrayed in a “block” motif in the layers, in contrast to regular ordering of polyhedra in the lattice in all other structurally characterized metal oxides prepared by solid-state routes or hydrothermal synthesis. The lattice is best considered as consisting of two periodic “intergrowth” segments that have similarities to other known vanadates. The two segments that form strips within the layers are shown more clearly in a polyhedral motif perpendicular to the layers (Figure 1b). The building blocks are compared to other known phases in Figure 2, in which a portion of the $(\text{TMA})_5\text{V}_{18}\text{O}_{46}$ structure (Figure 2b) is shown along three orthogonal directions together with the unit cells of $\alpha\text{-V}_2\text{O}_5$ and $(\text{TMA})\text{V}_4\text{O}_{10}$. The section of the lattice between V3 and V10 (Block A) resembles $\alpha\text{-V}_2\text{O}_5$, although the square pyramids share corners with chains of polyhedra disposed in an opposite orientation, unlike $\alpha\text{-V}_2\text{O}_5$, in which the corresponding corner-sharing square pyramids have the same orientation (Figure 2a). This topology is, however, similar to the network of $\text{V}_{2-x}\text{Mo}_x\text{O}_5$ if the sites in the latter are regarded as square-pyramidal.^[10] The resultant block is slightly curved, viewed

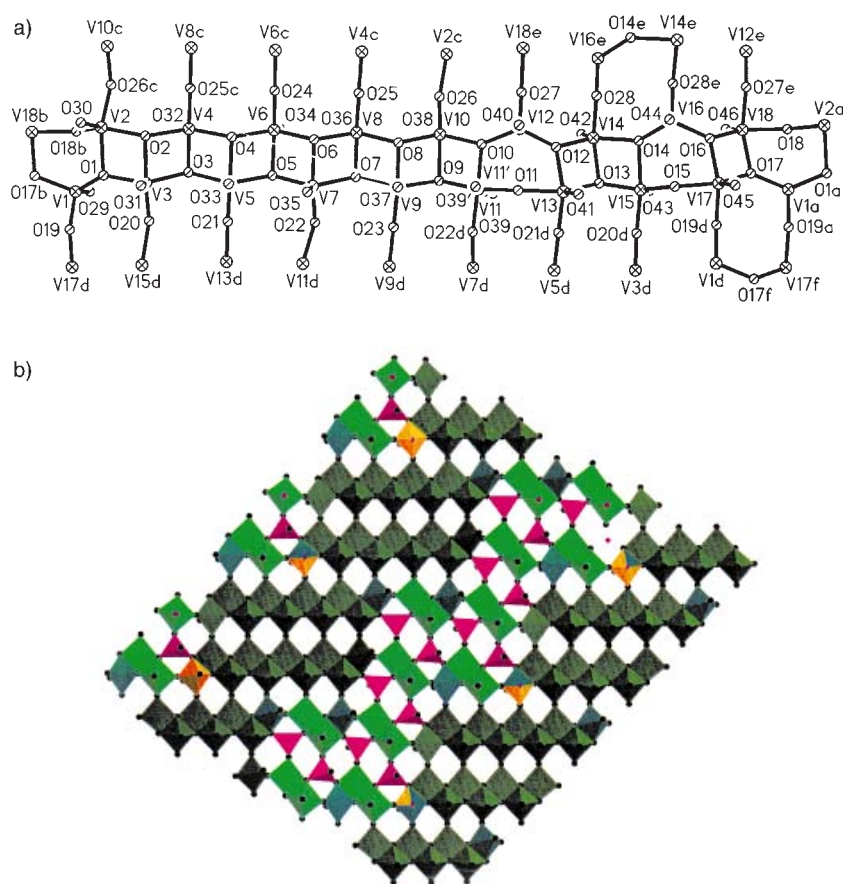


Figure 1. a) Asymmetric unit cell of $[\text{N}(\text{CH}_3)_4]_5\text{V}_{18}\text{O}_{46}$. In the disorder about V11/V11', the square pyramid is flipped by 180° for about $1/4$ of its occurrence in the lattice; four inversion centers exist on positions occupied by O25, O27 and adjacent to O14, O17. Symmetry codes: a: $1+x, 1+y, 1+z$; b: $-1+x, -1+y, -1+z$; c: $1-x, 1+y, 1+z$; d: $1-x, 1-y, 1-z$; e: $2-x, 1-y, 2-z$. b) View of $[\text{N}(\text{CH}_3)_4]_5\text{V}_{18}\text{O}_{46}$ in polyhedral motif, perpendicular to the layers.

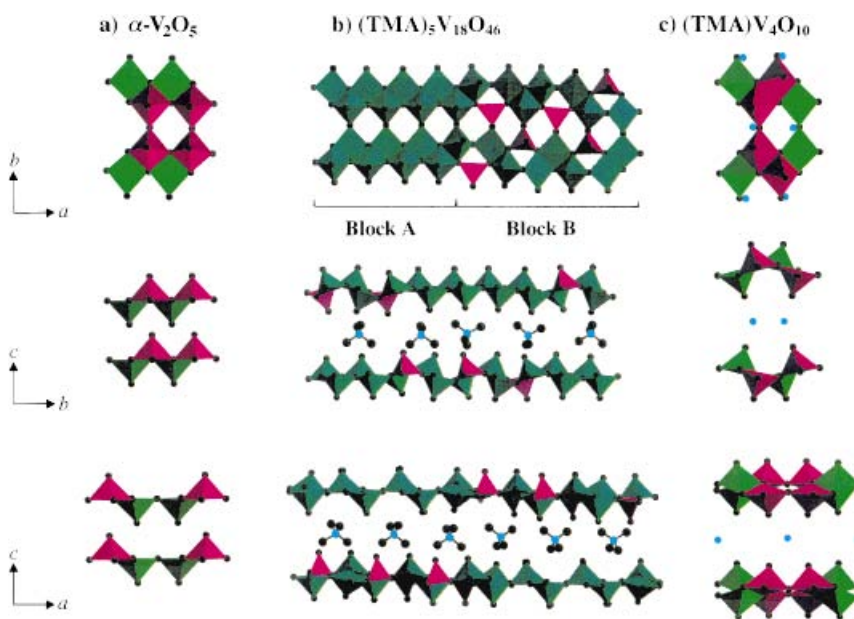


Figure 2. Polyhedral depiction of the structure of $[\text{N}(\text{CH}_3)_4]_5\text{V}_{36}\text{O}_{92}$ along the three different crystal axes, shown with respect to the labeling adopted for the V_2O_5 axes, in comparison with other vanadium oxides; a) $\alpha\text{-V}_2\text{O}_5$; b) $(\text{TMA})_5\text{V}_{18}\text{O}_{46}$; c) $(\text{TMA})\text{V}_4\text{O}_{10}$.

parallel to the layers, whereas the corresponding view of the α -V₂O₅ layers shows they are completely flat.

The second block, between V11 and V1a (Block B), is more irregular. The three tetrahedra at V1, V12, and V15 can be considered to be very highly distorted square pyramids with very long equatorial bonds to oxygen atoms O18, O11, and O15, respectively (≈ 2.8 Å). If the square pyramids were regular (i.e., if the equatorial bonds were all of the same length), this block would effectively have the same topology as (TMA)-V₄O₁₀ (Figure 2c). Alternatively, if these sites are classified as tetrahedral, this block can be considered to be a disordered combination of the framework structures of (H₂dabco)V₆O₁₄⁷⁻ and (H₂pip)V₄O₁₀⁵⁻, since the pairs of square pyramids with an *anti* disposition alternate with those of *syn* disposition along the chain direction. A common characteristic of Block B and the related polyhedral networks is edge-sharing square pyramids disposed in the same direction, an arrangement which is exclusively found in layered vanadates prepared by hydrothermal methods, as opposed to high-temperature solid-state reactions. Hydrothermal synthesis does not always result in such an organization, however, as the alkylidiammonium [V₄O₁₀]²⁻ vanadates^[5] have edge-sharing VO₅ square pyramids alternatingly oriented in different directions.

The similarly oriented adjacent square pyramids in Block B are tilted substantially away from one another to give highly puckered layers due to the repulsion of the adjacent axial oxygen atoms. Hence, the layers of (TMA)₄₅V₁₈O₄₆ are slightly curved in Block A, in which the layers are similar to α -V₂O₅ (V3–V1), but are puckered in Block B, as in (TMA)V₄O₁₀, in which repulsion between axial oxygen atoms is observed (V11–V18). The ultimate result of such repulsion effects are polyoxovanadium clusters, in which similarly oriented square pyramids are exclusively observed (i.e., all axial oxygen atoms point outwards, and the central vanadium cation in the square pyramidal base interacts with an anion at the center of the cluster). Müller et al.^[11] showed that the repulsive interaction between the terminal oxygen atoms directly influences the curvature of the shell. In a similar way, the corrugated layers we observe may be influenced by such interactions. Hence, the subtle, but distinct, curvature of Block A may represent an intermediate step en route to cluster formation.

The average oxidation state of vanadium in the title compound of V^{4.83+} is manifested in an unusual distribution of V⁴⁺ in the structure. The relative localization of the negative charge over the 15 square-pyramidal sites in the unit cell of the latter can be calculated from valence bond sums (Table 1). The partially reduced vanadium ions (V^{<5+}) are localized as weakly interacting dimer pairs on V13/V14 and

V17/V18, giving rise to average oxidation states of 4.1/4.3 and 4.5/4.7, respectively, from valence sum calculations. These are highlighted in the view along the direction perpendicular to the layers (Figure 1b). The structural distortion is apparently driven by pinching of the structure at the dimer “defects”. This also results in an alternating three-dimensional tire-tread pattern of the strips along the direction perpendicular to the layers (Figure 3). Thus, the neutral strips containing “V₂O₅”-type blocks are interleaved with the structurally distorted

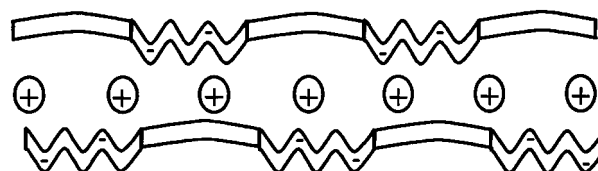


Figure 3. Schematic representation of [N(CH₃)₄]₅V₁₈O₄₆ illustrating the structure in a direction parallel to the layers; the slightly curved portions represent Block A, and the puckered portions with the localized negative charges Block B.

strips containing negatively charged blocks with localized reduced vanadium centers. This gives rise to the superlattice structure of Block A/Block B moieties about 12 Å in width. This probably arises to relieve the structural strain that would arise from either lattice alone. Note that neither building block alone is known to form a repeating lattice.

While crystallization of this unique framework is apparently driven by the relief of lattice strain, its assembly is presumably controlled by kinetic factors. Furthermore, the presence of preformed “building blocks” in solution at some stage in the nucleation process is implicated by the structure. Block A, for example, may arise from preferential dissolution of α -V₂O₅ along the direction of the corner-joined ribbons. The reverse of this process, “oxolation”,^[12] is thought to take part in the growth of xerogel V₂O₅ from vanadate solutions. The structure of Block B is related to that of (TMA)V₄O₁₀ (vide supra), which also crystallized from the mother liquor. Note that the oxidation state of vanadium in the latter compound is +4.75, whereas the average oxidation state in the [V₅O₂₃]⁵⁻ units that constitute Block B is lower (+4.55). In addition, although the release of the species, the pH value, and the temperature undoubtedly play a part in the rate of nucleation and crystal growth, redox chemistry is also a factor. Here, as in all hydrothermally prepared transition metal oxides, crystallization is partly controlled by the rate of reduction of the V₂O₅ in the synthesis liquor, which usually occurs by reaction with the organic compound in solution (TMA). In this case, the presence of V₂O₃ provides another source. We propose that partial reduction of the vanadium centers by reaction with V₂O₃ during incipient nucleation of the [V₄O₁₀]-like lattice building blocks may give rise to Block B units, which then crystallize to form a repeating lattice by self-assembly with Block A.

Experimental Section

Crystal data for [N(CH₃)₄]₅V₁₈O₄₆: A crystal of dimensions 0.036[101] × 0.14[001] × 0.18[101] × 0.36[111] × 0.125[013] mm was selected for data

Table 1. Valency of vanadium in [(CH₃)₄N]₅V₁₈O₄₆(1) from valence bond sum calculations.

V atom	Valency	V atom	Valency
V1–V11	5.00 ± 0.1		
V13	4.40	V16	4.92
V14	4.09	V17	4.48
V15	4.98	V18	4.23

collection on a Siemens P4 automated diffractometer ($\text{MoK}\alpha$, $\lambda = 0.71073 \text{ \AA}$, $T = 295 \text{ K}$); space group $P1$; $a = 12.660(3)$, $b = 15.359(3)$, $c = 16.963(3) \text{ \AA}$, $\alpha = 78.72(3)$, $\beta = 74.37(3)$, $\gamma = 83.33(3)^\circ$, $V = 3108.0(11) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calc}} = 2.145 \text{ g cm}^{-3}$. Cell parameters from 25 reflections ($20 < 2\theta < 28^\circ$), 8459 reflections collected by ω -scan method ($\Delta\omega = 1.2^\circ$): $4 < 2\theta < 46^\circ$, $0 \leq h \leq 13$, $-16 \leq k \leq 16$, $-17 \leq l \leq 18$; 4627 reflections observed [$F \geq 4\sigma(F)$]. After data reduction (Lorentzian and polarization corrections; absorption correction by face-indexed analytical method; min./max. equivalent transmission factors: 0.6994, 0.9129) and merging ($R_{\text{int}} = 0.0235$), the structure was solved by direct methods with SHELXTL PLUS, and refined by full-matrix least-squares methods. Anisotropic thermal factors were refined for V and O atoms only. $\Delta\rho = -0.59$, $+1.11 \text{ e \AA}^{-3}$ associated with disorder on V11/V11' (see legend to Figure 1). Final residuals: $R(F) = 0.0487$, $wR_2(F) = 0.0492$. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-410088.

Received: August 28, 1998

Revised version: June 10, 1999 [Z12349IE]

German version: *Angew. Chem.* **1999**, *111*, 3065–3068

Keywords: hydrothermal synthesis • polyoxometalates • template synthesis • vanadium

- [1] C. R. Walk in *Lithium Batteries* (Ed.: J. P. Gabano), Academic Press, New York, **1983**.
- [2] F. Garcia-Alvarado, J. M. Tarascon, B. Wilkens, *J. Electrochem. Soc.* **1992**, *139*, 3206.
- [3] W. Li, J. R. Dahn, D. S. Wainwright, *Science* **1994**, *264*, 1115.
- [4] a) E. A. Boylan, T. Chirayil, J. Hinz, P. Zavalij, M. S. Whittingham, *Solid State Ionics* **1995**, *90*, 1; b) P. Zavalij, M. S. Whittingham, E. A. Boylan, V. K. Pecharsky, R. A. Jacobson, *Z. Kristallogr.* **1996**, *211*, 464.
- [5] a) D. Riou, G. Férey, *Inorg. Chem.* **1995**, *34*, 6520; b) D. Riou, G. Férey, *J. Solid State Chem.* **1995**, *120*, 137.
- [6] a) D. Riou, G. Férey, *J. Solid State Chem.* **1995**, *120*, 137; b) Y. Zhang, C. J. O'Connor, A. Clearfield, R. C. Haushalter, *Chem. Mater.* **1996**, *8*, 595; c) Y. Zhang, R. C. Haushalter, A. Clearfield, *Inorg. Chem.* **1996**, *35*, 4950.
- [7] L. F. Nazar, B. E. Koene, J. F. Britten, *Chem. Mater.* **1996**, *8*, 327.
- [8] T. G. Chirayil, E. A. Boylan, M. Mamak, P. Y. Zavalij, M. S. Whittingham, *Chem. Commun.* **1997**, 33.
- [9] Y. Zhang, F. R. DeBord, C. J. O'Connor, R. C. Haushalter, A. Clearfield, J. Zubietta, *Angew. Chem.* **1996**, *108*, 1067; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 989.
- [10] L. Kihlberg, *Acta Chem. Scand.* **1967**, *21*, 2495.
- [11] A. Müller, R. Rohlfing, E. Krickemeyer, H. Bögge, *Angew. Chem.* **1993**, *105*, 916; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 909.
- [12] J. Livage, *Proceedings of the 1st International Conference on Composites: Design for Performance* (Lake Louise, Canada) **1977**, 45–52.

Combinatorial Methods for the Synthesis of Aluminophosphate Molecular Sieves**

Kwangwook Choi, David Gardner, Nicole Hilbrandt, and Thomas Bein*

The optimization of existing hydrothermal procedures for the synthesis of microporous materials and the discovery of new phases depends on effective processing and structural screening methodologies. In view of the tremendous impact of combinatorial techniques in the areas of organic,^[1] biochemical,^[2] and inorganic^[3] chemistry, it appears attractive to develop a combinatorial approach for the hydrothermal synthesis of microporous materials. Akporiaye and co-workers demonstrated the application of combinatorial methods for the hydrothermal synthesis of zeolites with a multiple autoclave,^[4] the recovery and identification of the obtained phases required individual sample manipulation. Recently, Maier and co-workers reported the microgram-scale hydrothermal synthesis of microporous materials in an array format on a Si wafer which allowed for automated X-ray diffractometry.^[5]

We have developed a new methodology based on automatic dispensing of reagents into autoclave blocks, followed by synthesis, isolation, and automated structure analysis without any manipulation of individual samples. Our reaction chambers ("multiclaves") are Teflon blocks (36 mm diameter, with 8 holes (6 mm diameter) or 19 holes (4.5 mm diameter), 25 mm in hole depth) that provide an inert reaction environment. This allows us to use reactant volumes of 150–300 μL per hole. A thin sheet and a lid of Teflon covers the reaction vessel, which is then sealed inside a specially designed stainless steel autoclave. The reagents are dosed directly into the multiclaves using a commercially available pipette robot, or a custom-built robot^[6] which can inject multiple liquid reagents. After hydrothermal synthesis, the washing of the sample array by filtration and preparation of libraries is done with a custom-designed centrifuge apparatus,^[7] which allows almost quantitative product recovery. The resulting products are identified in transmission using either a standard X-ray powder diffractometer or a rotating anode diffractometer with CCD detector. In both cases, an automated xy stage is used for sample translation. The advantages of our methodology include reduced reagent consumption by direct dosing at the microliter scale, production of multi-milligram sample

[*] Prof. T. Bein,^[+] K. Choi, D. Gardner, Dr. N. Hilbrandt
Department of Chemistry
Purdue University
West Lafayette, IN 47906 (USA)
Fax: (+1) 765-494-0239
E-mail: tbein@chem.purdue.edu

[+] New address:
Institut für Organische Chemie der Universität München (LMU)
Butenandtstrasse 5–13(E)
D-81377 München (Germany)
Fax: (+49) 89-2180-7624
E-mail: tbein@cup.uni-muenchen.de

[**] Funding from the US National Science Foundation, the Purdue Research Foundation (K.C.), and the Humboldt Foundation (N.H.) is greatly appreciated. We thank Dr. P. Fanwick for his support during the X-ray data collection.

quantities, and almost complete sample recovery, which enables determination of yields.

Here we present the synthesis of aluminophosphate phases applying combinatorial strategies. Of particular interest is the influence of combined organometallic ($[\text{Co}(\text{Cp})_2]\text{OH}$, Cp = cyclopentadienyl) and organic structure-directing agents (here Pr_2NH) on the resulting aluminophosphate phases, based on the different size and flexibility of the organometallic component. Aluminophosphates of the types AFI ($\text{AlPO}_4\text{-5}^{[8]}$) and AST ($\text{AlPO}_4\text{-16}^{[9]}$) were synthesized previously using cobalticinium salts as templates. In a typical synthesis, the aluminophosphate gels were prepared by mixing an Al source with H_3PO_4 and water followed by addition of different templating molecules, including cobalticinium salts.

In this study, we examined the effect of the molar fraction of the two templates, at a fixed total concentration of 1.0 mol per mole of Al_2O_3 . Furthermore, the influence of increasing amounts of each single template was studied. Table 1 lists the molar compositions of the various starting gels in each hole of a reactor block. In all samples, the molar ratio of framework precursors and water, $\text{Al}_2\text{O}_3\text{:P}_2\text{O}_5\text{:H}_2\text{O}$, was fixed to 1:1:190, and the reaction was carried out at 160 °C for 24 h.

Table 1. Chemical composition of the representative sample library shown in Figure 3.

Hole	Composition ^[a]		Hole	Composition ^[a]	
	x	y		x	y
1	1.0	0	11	0.4	0
2	0.8	0.2	12	0.3	0
3	0.6	0.4	13	0.2	0
4	0.4	0.6	14	0.1	0
5	0.3	0.7	15	0	0.9
6	0.2	0.8	16	0	0.8
7	0.1	0.9	17	0	0.7
8	0	1.0	18	0	0.6
9	0.8	0	19	0	0.4
10	0.6	0			

[a] $1 \text{ Al}_2\text{O}_3\text{:}1 \text{ P}_2\text{O}_5\text{:}x [\text{Co}(\text{Cp})_2]\text{OH}\text{:}y \text{ Pr}_2\text{NH}\text{:}190 \text{ H}_2\text{O}$.

Figure 1 displays a CCD camera image of the transmission powder diffractogram of the AFI-type phase as well as the corresponding circularly integrated presentation. The data collection time is 10 min or less per spot by using a rotating anode diffractometer with a CCD detector (Nonius). Increased resolution of the library diffractograms can be obtained with a commercial powder diffractometer (Scintag; standard Cu tube, $0.3 \times 4 \text{ mm}$ emission profile, equipped with a liquid N_2 cooled germanium solid-state detector, data taken in transmission). Figure 2 shows selected diffractograms of some of the observed phases which were obtained with a step size of 0.01° .

As seen in Table 1, holes 2–7 were used for the mixed template system ($x[\text{Co}(\text{Cp})_2]\text{OH} + y\text{Pr}_2\text{NH}$). Holes 1 and 9–14 cover only the effect of $[\text{Co}(\text{Cp})_2]\text{OH}$ concentration, while holes 8 and 15–19 cover the effect of Pr_2NH concentration. The resulting phases associated with the various template concentrations are displayed in Figure 3. The different levels of template inclusion in the case of $[\text{Co}(\text{Cp})_2]\text{OH}$ are indicated by the gradients in the resulting physical library.

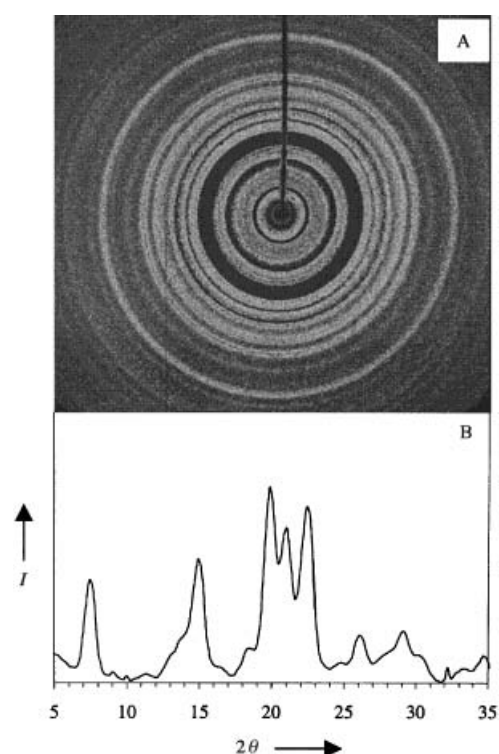


Figure 1. A) CCD camera image of the X-ray diffractogram of as-synthesized AFI-type product (Table 1, hole 4); the data collection time is 10 min per diffractogram. B) The corresponding circularly integrated diffractogram.

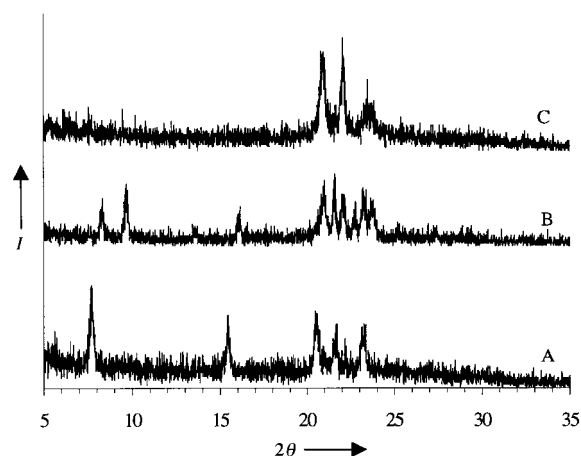


Figure 2. Selected diffractograms of the resulting phases recorded with a germanium solid-state detector. The data collection time is 60 min per diffractogram. A) The AFI structure (Table 1, hole 7), B) the AEL structure (hole 8), C) the tridymite structure (hole 16).

In the mixed template synthesis, starting with 100 mol % cobalticinium ion, no crystalline phase was observed after 24 h. Both AFI and AST types were observed at 20 mol % Pr_2NH . The AFI and AST structures have 12-membered channels and cages that are large enough to accommodate the larger $[\text{Co}(\text{Cp})_2]^+$ ion (Figures 4A and B). The formation of the pure AFI structure requires at least 40 mol % Pr_2NH under the conditions employed. A drastic switch to another phase is only observed on changing to 100 mol % Pr_2NH , when the AEL structure type emerges (Figure 3). The AEL

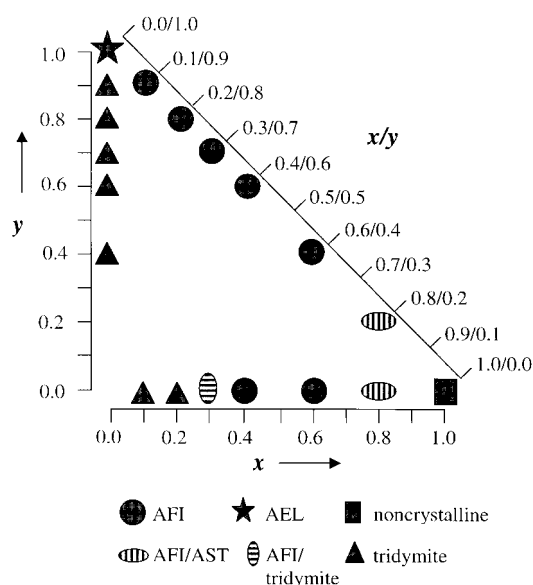


Figure 3. The effect of single and mixed templates on the resulting aluminophosphate phases. The chemical composition of starting gel was $1\text{ Al}_2\text{O}_3:1\text{ P}_2\text{O}_5:x[\text{Co}(\text{Cp})_2]\text{OH}:y\text{ Pr}_2\text{NH}:190\text{ H}_2\text{O}$; the molar compositions with hole numbers are listed in Table 1.

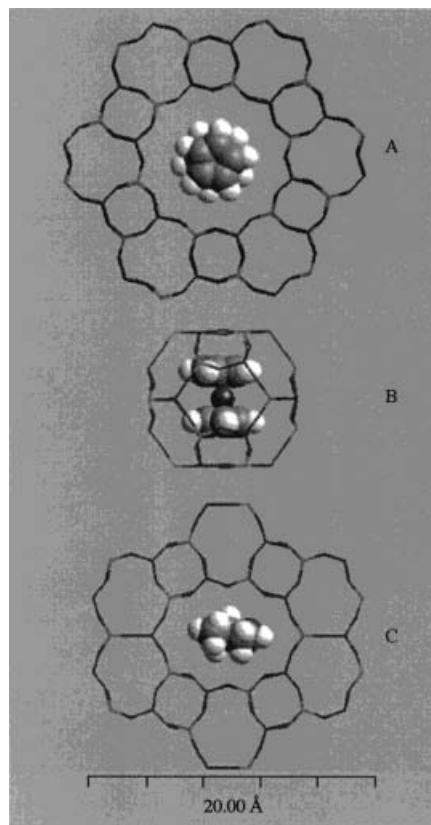


Figure 4. Structures of the different aluminophosphate phases with template molecules, modeled with Cerius2 software. A) AFI structure with $[\text{Co}(\text{Cp})_2]\text{OH}$, B) AST structure with $[\text{Co}(\text{Cp})_2]\text{OH}$, C) AEL structure with Pr_2NH .

structure offers a one-dimensional 10-ring channel system which is large enough to contain the Pr_2NH molecule but too small for the accommodation of cobalticinium (Figure 4C). These observations clearly demonstrate the important effect

of template size (when the other synthesis parameters are kept constant) on the structure of the resulting aluminophosphate phase.

In addition, the influence of the concentration of single templates ($[\text{Co}(\text{Cp})_2]\text{OH}$ or Pr_2NH) on the resulting products was studied. The amount of $[\text{Co}(\text{Cp})_2]\text{OH}$ was varied from 0.1 to 1.0 mol per mole of Al_2O_3 . As shown in Figure 3, a minimum amount of 30 mol% of cobalticinium ion is required to form a microporous framework in this system (at lower concentrations, tridymite is formed). The AFI structure was observed at template concentrations between 0.4–0.6 mol per mole of Al_2O_3 ; however, the use of more than 0.8 mol of $[\text{Co}(\text{Cp})_2]\text{OH}$ per mole of Al_2O_3 resulted in noncrystalline material. With Pr_2NH as template under these conditions, concentrations up to 0.9 mol per mole of Al_2O_3 result in a dense phase (tridymite). However, a sudden structural change occurs when the template concentration is increased to 1.0 mol per mole of Al_2O_3 , resulting in the AEL phase as mentioned above.

An interesting feature in the mixed template system is the observation of a pure AFI-type structure when the molar ratios of $[\text{Co}(\text{Cp})_2]\text{OH}:\text{Pr}_2\text{NH}$ were either 0.2:0.8 or 0.1:0.9. In comparison, only dense phase (tridymite) was observed when either $[\text{Co}(\text{Cp})_2]\text{OH}$ or Pr_2NH was used alone at these template concentrations. This indicates that there is some synergy or interaction between the two template molecules to crystallize the AFI-type structure, although the molecular origin of this effect is not yet clearly understood.

Our methodology demonstrates a powerful, realistic combinatorial approach for the hydrothermal synthesis of microporous materials. Using inert reactor materials and a direct dosing system for reagents at the micromole scale, this approach permits the preparation and characterization of libraries of solids without any manipulation of individual samples. Low reagent consumption and efficient sample recovery make it feasible to explore many reaction conditions and templating agents for the discovery of new phases, and to perform additional characterization by, for example, thermogravimetric analysis or electron microscopy with material from the same library.

Experimental Section

Synthesis of $[\text{Co}(\text{Cp})_2]\text{OH}$: $[\text{Co}(\text{Cp})_2]\text{PF}_6$ was synthesized using a procedure similar to that previously reported by Sheats et al.^[10] Cyclopentadiene, CpH , was prepared from the dimer.^[11] The solutions of $[\text{Co}(\text{Cp})_2]\text{OH}$ were prepared by a modified ion-exchange method.^[8] $[\text{Co}(\text{Cp})_2]\text{PF}_6$ (3.24 g, 10 mmol) was dissolved in water (1.5 L). This solution was passed through a column containing Dowex-50W cation exchange resin. The resin containing the cobalticinium cation was washed with water and a 1M HCl solution until all the yellow cobalticinium chloride, $[\text{Co}(\text{Cp})_2]\text{Cl}$, was eluted from the column. The $[\text{Co}(\text{Cp})_2]\text{Cl}$ was dried under vacuum and then dissolved in water (4 L). The yellow solution was passed through a column containing Dowex-SBR-OH anion exchange resin. The concentration of the $[\text{Co}(\text{Cp})_2]\text{OH}$ solution was determined by titration with 0.00990M sulfuric acid. A 0.5M $[\text{Co}(\text{Cp})_2]\text{OH}$ solution was used in the synthesis of the molecular sieve.

Aluminophosphate synthesis: In a typical synthesis the aluminophosphate gel was prepared by mixing alumina sol (45 μL , Condea vista, 10.6 wt % of Al_2O_3) and 29.2% H_3PO_4 (29.5 μL , $d = 1.128$). After vigorous shaking for 2 h, aliquots (10–100 μL) of 0.5M aqueous template solutions ($[\text{Co}(\text{Cp})_2]\text{OH}$ and Pr_2NH) were injected into the AlPO_4 mixture. The water contents

were corrected for by adding distilled water in some cases. The gel was shaken at room temperature for 12 h for homogenization and aging. The multiclave was placed in an oven for 24 h at 160 °C. The products were washed and isolated as an array by a custom-designed centrifuge apparatus. The sample array collected on filter paper was transferred to an X-ray sample holder for X-ray analysis. Automated X-ray diffraction analysis was carried out with a computer-controlled xy stage on either a Scintag XDS 2000 diffractometer equipped with a liquid N₂ cooled germanium solid-state detector using CuK α radiation, or on a rotating anode diffractometer with a Nonius CCD detector using MoK α radiation. In both cases, the diffractograms were obtained in the transmission mode. Data collection time varied from 10 to 60 min per spot depending on the detector. The data collection time for the standard powder diffractometer can be significantly reduced by using a more powerful X-ray source within the same setup. Powderize, a program from Nonius, was employed to integrate the CCD images.

Received: April 7, 1999 [Z 13253 IE]

German version: *Angew. Chem.* **1999**, *111*, 3070–3073

Keywords: aluminophosphates • combinatorial chemistry • hydrothermal synthesis • molecular sieves • solid-state chemistry

- [1] *Acc. Chem. Res.* **1996**, *29*, 112–170 (special issue).
- [2] G. Lowe, *Chem. Soc. Rev.* **1995**, *24*, 309–317.
- [3] X. D. Xiang, X. Sun, G. Briceno, Y. Lou, K. A. Wang, H. Chang, W. G. Wallace-Freedman, S. W. Chen, P. G. Schultz, *Science* **1995**, *268*, 1738–1740; for a review on combinatorial materials science, see: B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *111*, 2648–2689; *Angew. Chem. Int. Ed.* **1999**, *38*, 2494–2532.
- [4] D. E. Akporiaye, I. M. Dahl, A. Karlsson, R. Wendelbo, *Angew. Chem.* **1998**, *110*, 629–631; *Angew. Chem. Int. Ed.* **1998**, *37*, 609–611.
- [5] J. Klein, C. W. Lehmann, H.-W. Schmidt, W. F. Maier, *Angew. Chem.* **1998**, *110*, 3557–3561; *Angew. Chem. Int. Ed.* **1998**, *37*, 3369–3372.
- [6] The custom-built robot is a modified xy chart recorder which has a nozzle head that can hold four to six reagent lines. Each reagent line is made up of a unique reagent reservoir, an independently operable micropump, and a nozzle that has a sapphire tip with an orifice of 0.12 mm in diameter. The entire apparatus is controlled by a personal computer and was programmed using LabView.
- [7] The custom-designed centrifuge apparatus consists of two different filter papers (glass microfibre and normal filter paper), a PVC block with a matching hole pattern, a filtrate reservoir, and a PVC cylinder. Two pieces of filter paper were placed between the multiclave and the PVC block that was connected to the filtrate reservoir. For washing, the multiclave and the PVC block were turned upside down, and water was added into the holes of the PVC block and then forced into the multiclave by centrifugation. These steps were repeated several times before isolation of the final library.
- [8] K. J. Balkus, A. G. Gabrielov, S. Shepelev, *Microporous Mater.* **1995**, *3*, 489–495.
- [9] L. Schreyeck, P. Caullet, J. C. Mougénel, J. Patarin, J. L. Paillaud, *Microporous Mater.* **1997**, *11*, 161–169.
- [10] J. E. Sheats, M. D. Rausch, *J. Org. Chem.* **1970**, *35*, 3245–3249.
- [11] L. T. Reynolds, G. Wilkinson, *J. Inorg. Nucl. Chem.* **1959**, *9*, 86.

“Scaffold-Hopping” by Topological Pharmacophore Search: A Contribution to Virtual Screening**

Gisbert Schneider,* Werner Neidhart, Thomas Giller, and Gerard Schmid

In the process of drug discovery the crucial step to initiate a medicinal chemistry program is to identify molecular entities that interact with a specific target, namely an enzyme, a receptor, or an ion channel. The usual experiment one carries out to identify these lead structures is the so-called “blind screening”. Although today automation has made this process fast for large target families, there are still particular cases for which the set-up of the screen is expensive and time-consuming. This is especially true when a very complex device is used for measuring the interaction of chemical compounds with a protein, as for instance in functional receptor assays. In these latter cases as soon as a few lead structures have been identified a very appealing complementary approach is to derive a pharmacophore model from the known active structure (the “seed” or “query” structure) and perform a computer-based similarity search to speed up the process of lead identification.^[1]

Several such “virtual screening” techniques have been invented on the basis of two- or three-dimensional representations of molecular structures and various definitions of biophores/pharmacophores.^[2] The underlying idea is to define a measure of molecular similarity and collect the most similar compounds to a given seed from a large collection of prospective candidates. Despite recent advances in predicting three-dimensional molecular structures,^[3] current high-throughput similarity searches are primarily based on two-dimensional (2D) topology.^[4] Herein we present the successful application of a novel straightforward technique to “scaffold-hopping”, that is, identification of isofunctional molecular structures with significantly different molecular backbones.

Topological cross-correlation of generalized atom types is a simple molecular descriptor that leads to a compact, molecular size independent description of potential pharmacophores.^[5] The general idea of this representation scheme is to count the distances between atom pairs and then to regard the histogram of counts as a simplifying but exhaustive pharmacophore fingerprint of the molecule. Distances are expressed as the number of bonds along the shortest path connecting two nodes (non-hydrogen atoms) in the molecular graph (Figure 1). Each node is checked as to whether it can be assigned one of the following generalized atom types: hydrogen-bond donor (D), hydrogen-bond acceptor (A), positively

[*] G. Schneider, W. Neidhart, T. Giller, G. Schmid
F. Hoffmann-La Roche Ltd
Pharmaceuticals Division
CH-4070 Basel (Switzerland)
Fax: (+41) 61-6889041
E-mail: gisbert.schneider@roche.com

[**] We wish to thank our colleagues Petra Schneider, Eric Ertel, Hans-Joachim Böhm, Eva-Maria Gutknecht, Christian Hubschwerlen, Man-Ling Lee, Martin Stahl, and Manfred Kansy for helpful discussions and encouragement.

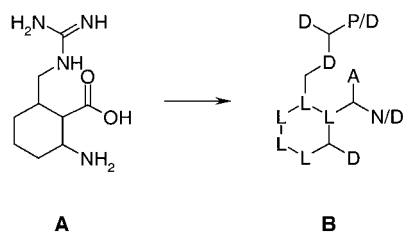


Figure 1. Conversion of a two-dimensional molecular representation (**A**) into the molecular graph (**B**), in which generalized atom types are assigned as implemented in CATS. See text for more information.

charged (P), negatively charged (N), or lipophilic (L). The numbers of all 15 possible pairs of generalized atom types (DD, DA, DP, DN, DL, AA, AP, AN, AL, PP, PN, PL, NN, NL, LL) are determined, and the resulting histogram counts are divided by the total number of non-hydrogen atoms to obtain scaled vectors. Distances of up to ten bonds were considered in the present study, which led to a 150 (15 × 10) dimensional vector representation of a molecular compound.

Large virtual compound libraries can be searched on the basis of this correlation-vector representation for structures similar to a given molecule with a defined biological activity. Each library molecule is compared to the query vector (derived from the query structure). Here we used the euclidian distance measure $D(A,B)$ [Eq. (1)] to express the similarity between two molecules A and B.

$$D(A,B) = \sqrt{\sum_{i=1}^{150} (v_i^A - v_i^B)^2} \quad (1)$$

v^A and v^B are the correlation vectors derived from molecules A and B, respectively. As a result the library compounds are ordered by their distance-to-seed value, and a ranking list of virtual hits is constructed. This technique is referred to as “CATS” (chemically advanced template search) herein. Molecules with a low distance-to-seed value are expected to exhibit an overall distribution of pairs of generalized atom types that reflects the characteristics of the query molecule. The in vivo or in vitro activity of potential hits can then be tested for using a biological assay.

Correlation vectors are not new to the field of computer-based similarity searches, for example, they were used as an encoding scheme for molecular surface properties and amino acid sequences.^[5, 6] The special attraction of CATS is its exhaustive 2D pharmacophore/biophore model based on the cross-correlation of generalized atom types. As a consequence problems associated with three-dimensional model building and multiple conformers can be avoided.^[7] All potential ligand–receptor contact points are described by five interaction types (D, A, P, N, L) and expressed as a scaled histogram of two-point pharmacophores. By defining this topological descriptor for a similarity search we minimize the risk of using a misleading three-dimensional pharmacophore model, which can easily happen if, for example, the conformation of the receptor-bound ligand is unknown or several different conformations appear equally possible.^[2] We are well aware that ignoring three-dimensional conformation bears the danger of missing essential information required to capture relevant pharmacophores and enantiomers. The

heuristic CATS pharmacophore representation can, however, easily be extended to the third dimension.

As a simple retrospective test of CATS we used the thrombin inhibitor PPACK as a query structure to search for other known thrombin inhibitors in the MEDCHEM library (version 1997, as distributed by Daylight Chemical Information Systems Inc., Irvine, CA, USA) containing approximately 33000 molecules.^[8] The CATS system was able to rank 15 out of 29 (52%) annotated thrombin inhibitors among the top 100 potential hits. For comparison, the commercially available search tool MERLIN (Daylight Chemical Information Systems Inc., Irvine, CA, USA)—which is based on Daylight’s definition of topological fingerprints—retrieved only 12 (41%) known inhibitors among the top 100. In addition, CATS found five inhibitors not reported by MERLIN, whereas MERLIN retrieved only two thrombin inhibitors not found by CATS among the top 100. As a result of this preliminary analysis in which CATS retrieved a larger number of relevant structures than a conventional fingerprint-based search we concluded that CATS seems to be a useful tool for database mining.

In a prospective test CATS was applied to the prediction of novel cardiac T-type Ca^{2+} channel blocking agents by exploring the Roche in-house compound depository. Mibefradil (**1**), a known T-channel blocking agent ($\text{IC}_{50} = 1.7 \mu\text{M}$) (Figure 2),^[9] was used as the seed structure for CATS. The 12 highest-ranking molecules were tested using a cell culture

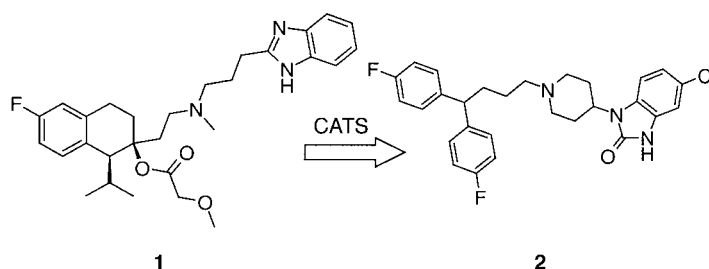


Figure 2. Query structure **1** (mibefradil) and a high-ranking isofunctional structure **2** (clopimozid) derived from **1** by CATS.

assay for their ability to inhibit cellular Ca^{2+} influx.^[10] Nine compounds (75%) showed significant activity ($\text{IC}_{50} < 10 \mu\text{M}$), of which one compound (**2**, clopimozid^[11]) had an $\text{IC}_{50} < 1 \mu\text{M}$. The IC_{50} values of the next best structures (not shown) were: 1.7, 2.2, 3.2, and 3.5 μM . These hits have structural scaffolds that differ significantly from the query structure **1**. However, essential function-determining points are preserved, which form the basis of a relevant pharmacophore pattern.

From the experimental results we conclude that CATS can be useful for identifying novel molecular structures with substantial biological activity. The procedure might help to save time and efforts to create targeted libraries and obtain rational molecular designs.^[12]

Received: May 17, 1999 [Z13432IE]
German version: *Angew. Chem.* **1999**, *111*, 3068–3070

Keywords: computer chemistry • drug research • structure–activity relationships • virtual screening

- [1] a) *Molecular Similarity in Drug Design* (Ed.: P. M. Dean), Chapman & Hall, Glasgow, **1995**; b) G. Schneider, W. Schrödl, G. Wallukat, J. Müller, E. Nissen, W. Röspeck, P. Wrede, R. Kunze, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 12179–12184; c) P. Willett, J. M. Barnard, G. M. Downs, *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 983–996.
- [2] a) G. W. Milne, M. C. Nicklaus, S. Wang, *SAR QSAR Environ. Res.* **1998**, *9*, 23–38; b) H. Briem, I. D. Kuntz, *J. Med. Chem.* **1996**, *39*, 3401–3408.
- [3] a) J. Sadowski, J. Gasteiger, *Chem. Rev.* **1993**, *93*, 2567–2581; b) R. S. Bohacek, C. McMartin, *Curr. Opin. Chem. Biol.* **1997**, *1*, 157–161.
- [4] a) R. D. Brown, Y. C. Martin, *SAR QSAR Environ. Res.* **1998**, *8*, 23–39; b) H. Matter, *J. Med. Chem.* **1997**, *40*, 1219–1229.
- [5] G. Schneider, P. Wrede, *Prog. Biophys. Mol. Biol.* **1998**, *70*, 175–222, and references therein.
- [6] a) G. Moreau, P. Broto, *Nouv. J. Chim.* **1980**, *4*, 757–764; b) M. Wagener, J. Sadowski, J. Gasteiger, *J. Am. Chem. Soc.* **1995**, *117*, 7769–7775; c) S. Anzali, W. W. K. R. Mederski, M. Osswald, D. Dorsch, *Bioorg. Med. Chem. Lett.* **1997**, *8*, 11–16; d) D. D. Jones, *J. Theor. Biol.* **1975**, *50*, 167–183.
- [7] M. Vieth, J. D. Hirst, C. L. Brooks III, *J. Comput. Aided Mol. Des.* **1998**, *12*, 563–72.
- [8] a) C. Kettner, E. Shaw, *Methods Enzymol.* **1981**, *80*, 824–826; b) P. D. Grootenhuis, M. Karplus, *J. Comput. Aided Mol. Des.* **1996**, *10*, 1–10.
- [9] a) S. I. Ertel, E. A. Ertel, *Trends Pharmacol. Sci.* **1997**, *18*, 37–42; b) D. Sarsero, T. Fujiwara, P. Molenaar, J. A. Angus, *Br. J. Pharmacol.* **1998**, *125*, 109–119.
- [10] The cloned T-type Ca^{2+} channel was expressed in HEK293 cells, and the inhibition by the compounds was monitored using a fluorescence assay. T. Giller, unpublished results.
- [11] J. Qar, J. P. Galizzi, M. Fosset, M. Lazdunski, *Eur. J. Pharmacol.* **1987**, *141*, 261–268.
- [12] D. R. Liu, P. G. Schultz, *Angew. Chem.* **1999**, *111*, 36–56; *Angew. Chem. Int. Ed.* **1999**, *38*, 36–54.

exhibit environmentally friendly and resource-saving behavior due to the lack of workup requirements for intermediates, and which use generally accessible starting materials,^[5] were not mentioned in the leading reviews.^[6] Rather, the complexity of the starting materials in these reviews require complicated multistep syntheses and thus question both sustainability and broader applications. The execution of the present cascade reactions in the absence of liquid phases avoids product workup because of the 100% yield and is thus truly resource-saving and environmentally friendly.

If the primary or secondary enamine esters **1a–d** or the enamine ketone **4** are treated with *trans*-1,2-dibenzoyl ethene (**2**) in solution or in a ball-mill without liquid phase, the pyrroles **3** or indole **5** are obtained in moderate or quantitative yields (Table 1), despite the multistep course of reaction (Scheme 1). A thermal after-treatment is only required in the case of **3c** in order to complete the elimination of water (from **8c**, see Scheme 2).

Table 1. Reactions of **1** and **4** with **2** to give **3** and **5**, respectively.

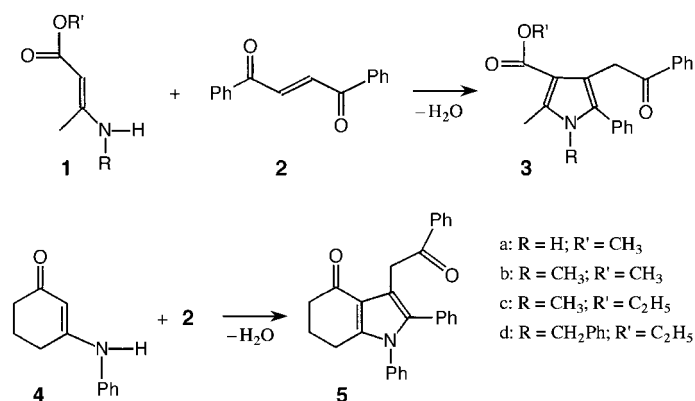
Com-pound	M.p. [°C] (starting material)	Yield [%]		M.p. [°C] (product)	Milling time [h] (T [°C])
		in solution	in crystal		
1a	81–83	68	100	144–146	3 (25)
1b	67–68	81	100	152	3 (25)
1c	1–2	78 ^[a]	100 ^[a]	122–124	3 (–20)
1d	21	55	100	130–131	3 (0)
4	182	46	100	240–241	3 (25)

[a] After short heating (150 °C) of the 1:1 mixture (78%; solution) or 2:3 mixture (solid) of **3c** and **8c**.

Cascade Reactions in Quantitative Solid-State Syntheses**

Gerd Kaupp,* Jens Schmeyers, Axel Kuse, and Adnan Atfeh*

Solvent-free reactions of solids with solids profit from crystal packing effects and are usually highly selective.^[1,2] In contrast to gas–solid reactions^[3] no multistep syntheses are known in this field. We report herein on a one-pot synthesis of highly substituted pyrroles (see Scheme 1), which gives moderate yields in solution, but quantitative yields in the solid–solid variant at much lower temperatures, although at least four reaction steps are required in these reactions, not counting proton transfers from N and O. Such reaction cascades^[4] have not yet received due recognition in academic teaching, because some particularly elegant examples, which



Scheme 1. One-pot synthesis of pyrrole derivatives from easily accessible starting materials.

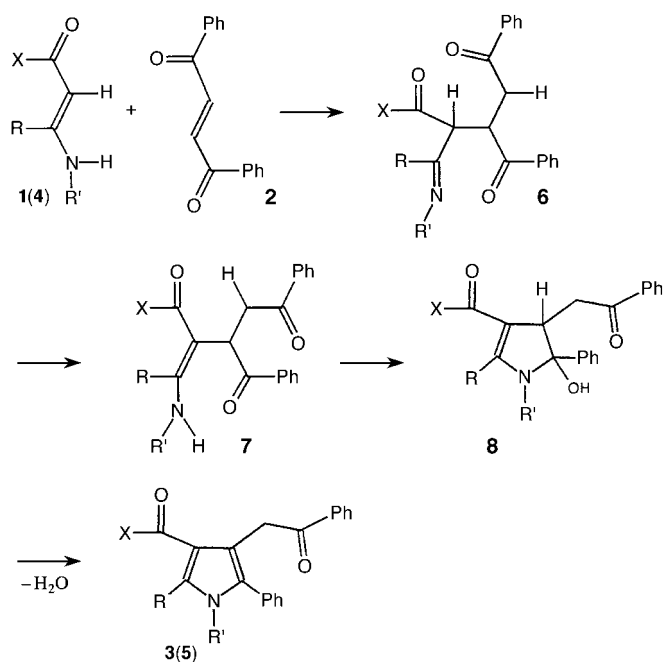
The complex cascade reactions are remarkable in view of their high selectivity (Table 1) and apparently broad versatility.^[7] The constitution of the compounds **3** and **5** is derived from analytical and spectroscopic data.^[8] The neighborhood of the phenyl group to the pyrrole-N atom becomes evident from the $\delta(^{13}\text{C})$ values of C4 and C3 in **3b** (C2 and C3 in **5**), which were determined to be 110.1 and 115.1 (114.2 and 119.2). These values correspond much better to the calculated chemical shifts^[9] of 112.7 and 117.9 (117.4 and 120.0) than those of the isomeric structure in which the phenyl and benzoylmethyl groups are exchanged: 106.5 and 124.7 (127.5

[*] Prof. Dr. G. Kaupp, Dr. J. Schmeyers, Dipl.-Chem. A. Kuse
Universität Oldenburg, FB9-Organische Chemie I (Germany)
Fax: (+49) 441-798-3409
E-mail: kaupp@kaupp.chemie.uni-oldenburg.de
Dr. A. Atfeh
Daaboul & Aktaa Co.
Damaskus (Syria)

[**] This work was supported by the Fonds der Chemischen Industrie, the Deutscher Akademischer Austauschdienst (1995, for A.A.) and the Daaboul & Aktaa Co., Damaskus.

and 126.8). The correspondence with the expectations is excellent. The C–C bond formation is largely preferred over any N–C reaction.

The most reasonable reaction course by four sequential steps is formulated in Scheme 2. After an initial vinylogous Michael addition (including hydrogen transfer) to give **6** and imine/enamine rearrangement to give **7**, the amino group formed adds to the more favorably situated carbonyl function leading to the formation of a five-membered ring to give **8**, from which the pyrrole **3** is obtained by elimination of water.



Scheme 2. Cascade reactions to give **3** (**5**) with four discrete sequential reaction types.

An analogous mechanism can be assumed for **5** starting from **4**. Both, the orientational specificity (an initial Michael addition of the enamine nitrogen, cyclizing addition of the enamine double bond, rearrangement to the enamine, and elimination of water would exchange the positions of phenyl and benzoylmethyl groups in **3** and **5**) and the same preference in solution and in the crystal are remarkable. The moderate yields in solution, which are also influenced by the necessary workup procedures, are sharply contrasted by the quantitative yields of the solid–solid reactions given in Table 1. The peculiarity of slower dehydration for **3c** is found in both media.

As might have been expected, the solid-state reaction cascades succeed at considerably lower temperatures, because of the lack of weakening of the reactivities by solvation, if the crystal lattices do not impede the necessary molecular movements.^[3] The basic mechanistic understanding of solid–solid reactions was established by atomic force microscopy (AFM) and scanning near-field

optical microscopy (SNOM): The experimentally found far-reaching molecular movements that occur in the crystals give rise to clearly distinguishable phase rebuilding, phase transformation, and crystal disintegration in the reaction zone of single-step reactions.^[3, 10] In the case of reaction cascades the conditions are more complicated because of the interaction of numerous physical and chemical processes, and indeed, mechanical help is required in the present cases. Thus, no reaction is detected if finely ground powders of **2** and **4** are mixed and stored, and even the AFM analysis^[3] indicates the lack of surface changes of single crystals of **4** (or **2**) with finely ground dusts **2** (or **4**; strongly aggregated grains of ca. 1 μm in diameter) in the absence of mechanical treatment. Thus, after the mixtures had been left to stand for four days, and the dust was subsequently blown away, clearly resolved molecular terraces were not removed and no significant change whatsoever was detected on the main faces of **4** (or **2**). No opacity was observed, also on the other faces. Such behavior points to difficulties with the phase rebuilding step, which are overcome by using a ball-mill. The continuous mechanical treatment creates new contacts over and over again between the reacting crystals and it is assumed that it is also helpful for promoting the intramolecular reactions that follow by generating reactive conformers of the intermediate products. These interpretations are supported by the unusually long reaction times of 3 h in these cases. These unusual observations are further elucidated by the evaluation of the known crystal structures of **2**^[11] and **4**.^[12] The molecules **2** pack densely in successive layers that interlock slightly (Figure 1). Such packing permits cooperative movements of extended molecules in the crystal lattice at best, but not of adduct molecules from **4** and **2**. Furthermore, the packing of **4** (Figure 2) does not permit molecular movements underneath its surface.

Unlike previously studied solid–solid reactions,^[2, 3, 10] in which molecular movements were detected in the crystal (reaction zone), we find here the interesting feature that efficient mechanical help apparently gives rise to a surface reaction that proceeds molecular layer by molecular layer in acceptable time and leads to a quantitative reaction. Figures 1 and 2 indicate that easily detachable surface molecules of **2**, which are readily accessible on (001) at the ends of the layers,

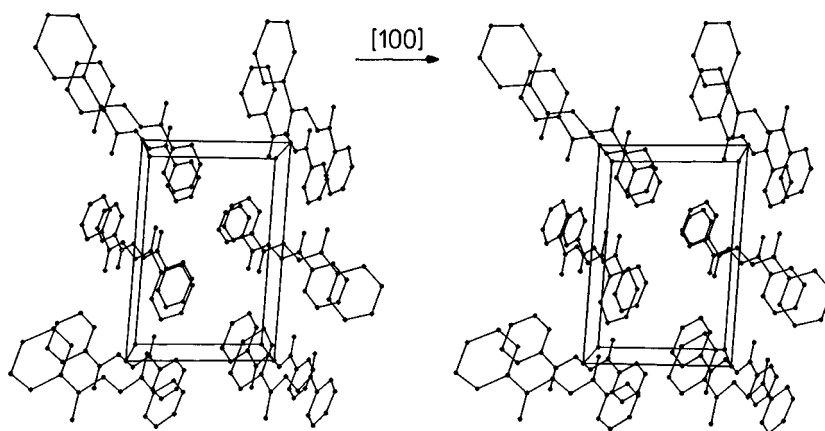


Figure 1. Stereoscopic perspective representation of the crystal packing of **2** ($P2_1/c$) on (010); the layers from bottom to top that are parallel to (100) show the molecules in two orientations that are tilted by 85°; the hydrogens are omitted for clarity; the (001) face is on top.

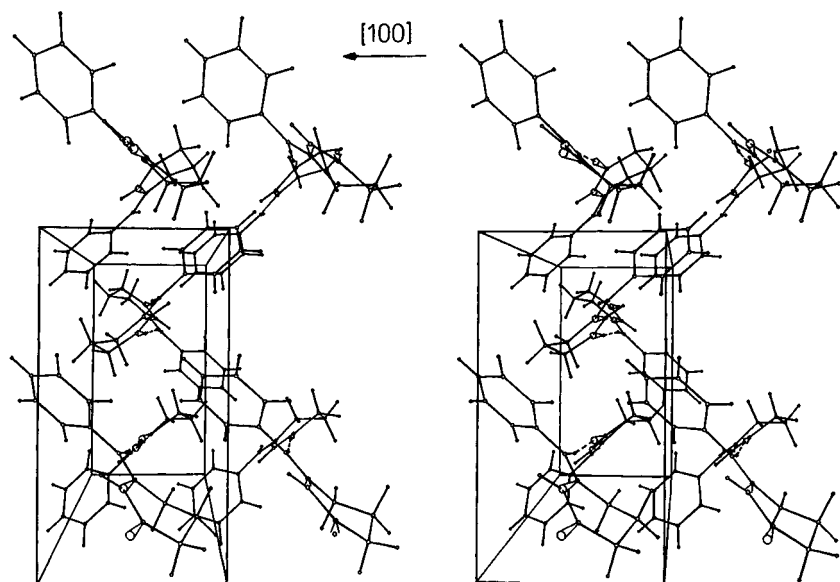
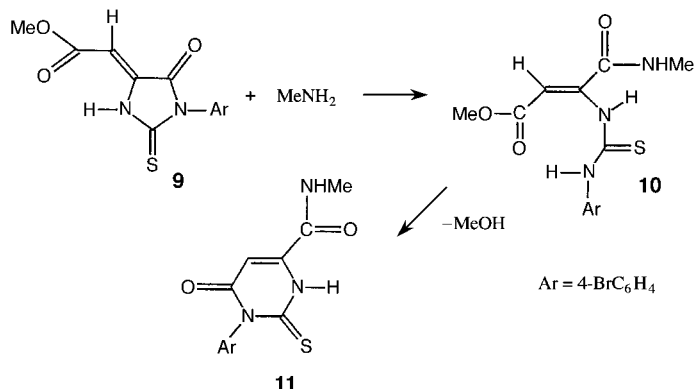


Figure 2. Stereoscopic perspective representation of the crystal packing of **4** ($P2_1/c$) on (001) with marked C=O and C=C double bonds and (dotted) hydrogen bonds [N(H)O distance: 2.851 Å]; the hydrogen-bonded molecular chains are three-dimensionally interlocked; the enamine ketone double bond of the surface molecules in front is sterically shielded.

move to the hydrogen-bridged reaction partner **4** and react with the slightly shielded enamine ketone double bond. Thereafter, the product molecules must detach from the surface of the crystal **4** by breakage of their hydrogen bond, in order to release further reactive molecules at the surface. According to microscopic inspection these processes occur in the ball-mill (mortars and pestles are inefficient here) at 1 μm grains. In view of the recent mechanistic experiences^[3, 10] amorphous product layers would be impeding. We therefore assume that immediate product crystallization and the absence of stable mixed crystals are additional requirements for the reactivity.

In contrast to the previously studied solid-state reactions the present examples cannot be predicted from the crystal structures. Nevertheless, the new mechanism is of considerable importance: it shows that even solid–solid reactions that do not appear promising from crystal structure considerations or that failed previously should be tried in efficient ball-mills, the advantages of which are evidently not restricted to the comfortable handling of sensitive materials.^[10]



Scheme 3. Transformation of the thiohydantoin **9** to give the thioorotic acid amide **11**.

The present results suggest that already known cascade reactions^[5, 6] would be more efficient and perhaps quantitative in the solid-state with efficient milling or in the gas–solid variant than in solution or liquid phase. They also suggest the development of new cascade reactions. The methodological variability of this method is illustrated by the reaction of thiohydantoin **9**^[13] (m.p. 247 °C; 1.0 g), which is easily accessible from dimethylacetylenedicarboxylate, potassium rhodanide, and 4-bromoaniline, with gaseous methylamine (250 mL, 1 bar, left overnight at room temperature), leading to the quantitative formation of the thioorotic acid amide **11** (m.p. 280 °C, decomp; no change after recrystallization from ethanol), (Scheme 3). In this reaction cascade methylamine must add to **9** with ring-opening and formation of the intermediate product **10**. Subsequent cyclization and elimination of methanol without liquefying yields quantitatively the product **11** which is analytically pure after vacuum treatment.

Several quantitative gas–solid cascades and tetrasubstitutions are already known.^[3, 5i, 10] Further environmentally friendly solid-state cascade reactions with 100% yield, with and without mechanical treatment will certainly emerge before long.

Experimental Section

Solution reactions: *trans*-1,2-Dibenzoyl ethylene (**2**) (20 mmol, Aldrich) and **1a–d** (22 mmol; from ethyl acetoacetate and the respective amine) were dissolved in methanol (100 mL) and heated under reflux for 3 h. After cooling to room temperature water was added until crystallization started. It was cooled to 0 °C overnight to complete the crystallization. The crystals were filtered off with suction and dried. In the case of **3c** the methanol was evaporated prior to recrystallization and the solid residue was heated to melting for 5 min, in order to complete the elimination of water.

The related reaction of **4** with **2** was achieved by refluxing in a xylene mixture (30 mL) for 1.5 h. The solvent was evaporated, and the residue crystallized from ethanol.

Solid-state reactions: A heatable/coolable ball-mill (Retsch MM2000) with 10-mL-mill beakers made from stainless steel and two stainless steel balls (6.5 g) was run at 20–30 Hz for 3 h in order to achieve quantitative conversions. Milling of **1a–d** or **4** (2.00 mmol) and **2** (2.00 mmol; m.p. 111 °C) gave dust-dry powders that were heated to 80 °C for removal of the water of reaction. Compound **3c** was obtained as a 2:3 mixture with its precursor **8c** and was obtained in pure form after heating to 150 °C for 5 min in order to complete the elimination and removal of water.

Received: March 2, 1999 [Z13097IE]
German version: *Angew. Chem.* **1999**, *111*, 3073–3076

Keywords: cascade reactions • nitrogen heterocycles • resource savings • solid-state chemistry

- [1] F. Toda in *Comprehensive Supramolecular Chemistry*, Vol. 6 (Eds.: D. D. McNicol, F. Toda, R. Bishop), Pergamon, Oxford, **1996**, pp. 465–516.
- [2] J. Schmeyer, F. Toda, J. Boy, G. Kaupp, *J. Chem. Soc. Perkin Trans. 2* **1998**, 989.

- [3] a) G. Kaupp in *Comprehensive Supramolecular Chemistry*, Vol. 8 (see also color plates 3–22) (Ed.: J. E. D. Davies, J. A. Ripmeester), Elsevier, Oxford, **1996**, pp. 381–423; b) G. Kaupp, *Chemie Unserer Zeit* **1997**, 31, 129–139 (English translation in <http://kaupp.chemie.uni-oldenburg.de>); c) G. Kaupp, A. Kuse, *Mol. Cryst. Liq. Cryst.* **1998**, 313, 361; d) G. Kaupp, J. Schmeyer, M. Haak, T. Marquardt, A. Herrmann, *Mol. Cryst. Liq. Cryst.* **1996**, 276, 315; e) G. Kaupp, A. Herrmann, *J. Prakt. Chem.* **1997**, 339, 256; f) A. Herrmann, G. Kaupp, T. Geue, U. Pietsch, *Mol. Cryst. Liq. Cryst.* **1997**, 293, 261.
- [4] The frequently used terms “tandem” (no time sequence!) or “domino” (table game with 28 divided plates with differing numbers of points) are less appropriate for sequential reactions that do not mutually interfere. On the other hand “cascades” describe sequential or stepwise events.
- [5] a) G. Kaupp, K. Sailer, *J. Prakt. Chem.* **1996**, 338, 47; G. Kaupp, K. Sailer, *Angew. Chem.* **1990**, 102, 917; *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 933; b) G. Kaupp, U. Pogodda, A. Atfah, H. Meier, A. Vierengel, *Angew. Chem.* **1992**, 104, 783; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 768; c) G. Kaupp, in *Photochemical Key Steps in Organic Synthesis* (Eds.: J. Mattay, A. Griesbeck), VCH, Weinheim, **1994**, pp. 224–225; d) S. N. Denisenko, E. Pasch, G. Kaupp, *Angew. Chem.* **1989**, 101, 1397; *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 1381; e) G. Kaupp, *Top. Curr. Chem.* **1989**, 146, 57–98; f) G. Kaupp, H. Voss, H. Frey, *Angew. Chem.* **1987**, 99, 1327; *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 1280; g) G. Kaupp, M. Stark, *Angew. Chem.* **1977**, 89, 555; *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 552; h) G. Kaupp, H. Rösch, *Angew. Chem.* **1976**, 88, 185; *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 163; i) G. Kaupp, U. Pogodda, J. Schmeyer, *Chem. Ber.* **1994**, 127, 2249.
- [6] a) F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, 105, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 131; b) F. Tietze, *Chem. Rev.* **1996**, 96, 115; c) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, 96, 137; d) J. D. Winkler, *Chem. Rev.* **1996**, 96, 167; e) I. Ryu, N. Sonoda, D. P. Curran, *Chem. Rev.* **1996**, 96, 177; f) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, 96, 195; g) K. K. Wang, *Chem. Rev.* **1996**, 96, 207; h) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, 96, 223; i) M. Malacria, *Chem. Rev.* **1996**, 96, 289; j) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, 96, 307; k) B. B. Snider, *Chem. Rev.* **1996**, 96, 339; l) E. Negishi, C. Coperet, S. Ma, S. Y. Liou, F. Liu, *Chem. Rev.* **1996**, 96, 365.
- [7] Recently, *cis*-1,2-diacetylene and **1a** were allowed to react in benzene with analogous result (80% yield): G. Adembri, A. M. Celli, A. Sega, *J. Heterocycl. Chem.* **1997**, 34, 541.
- [8] All new compounds gave correct IR, ¹H, ¹³C NMR, and (highly resolved) mass spectra, for example **3b**: IR (KBr): $\tilde{\nu}$ = 1691 cm^{−1} (C=O); ¹H NMR (CDCl₃, 300 MHz): δ = 8.00 (d, 2H), 7.35 (m, 8H), 4.22 (s, 2H), 3.54 (s, 3H), 3.41 (s, 3H), 2.61 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ = 199.12, 165.93, 137.43, 136.91, 133.13, 132.53, 131.33, 130.66 (2C), 128.43 (2C), 128.36 (2C), 128.01 (2C), 127.87, 115.10, 110.13, 50.24, 36.53, 31.77, 12.01; HR-MS: calcd. for C₂₂H₂₁NO₃: 347.1521; found: 347.1521. **5**: IR (KBr): $\tilde{\nu}$ = 1695 (C=O), 1652 cm^{−1} (C=O); ¹H NMR (CDCl₃, 300 MHz): δ = 8.03 (d, 2H), 7.51 (m, 3H), 7.30 (m, 3H), 7.11 (m, 7H), 4.42 (s, 2H), 2.69 (t, *J* = 6.05 Hz, 2H), 2.48 (t, *J* = 6.6 Hz, 2H), 2.14 (quint, *J* = 6.05 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ = 198.69, 195.12, 144.55, 137.67, 137.51, 132.71, 130.71, 130.31 (2C), 129.07 (3C), 128.48 (2C), 128.39 (2C), 128.19 (2C), 127.92, 127.80 (2C), 127.43, 119.16, 114.19, 38.33, 35.95, 23.70, 23.26; HR-MS: calcd. for C₂₈H₂₃NO₂: 405.1667; found: 405.1698. **11**: IR (KBr): $\tilde{\nu}$ = 3305 (NH, sharp), 1680 (sh, C=O), 1658 (C=O), 1270, 1218 cm^{−1} (C=S); ¹H NMR (CDCl₃/[D₆]DMSO ca. 4/1, 300 MHz): δ = 8.08 (2NH), 7.52 (d, 2ArH), 7.01 (d, 2ArH), 6.40 (s, 1H), 2.82 (s, 3H); ¹³C NMR (CDCl₃/[D₆]DMSO, 75 MHz): δ = 180.2, 164.3, 152.7, 141.2, 131.2 (2C), 130.6 (2C), 124.3, 119.6, 101.4, 25.3; HR-MS: calcd. for C₁₂H₁₀BrN₃O₂S: 340.9684; found: 340.9687.
- [9] SpecTool for Windows, Version 2.1, Chemical Concepts GmbH, Weinheim, **1994**.
- [10] a) G. Kaupp, J. Schmeyer, J. Boy, *Eur. J. Chem.* **1998**, 4, 2467; b) G. Kaupp, J. Boy, J. Schmeyer, *J. Prakt. Chem.* **1998**, 340, 346.
- [11] J. C. J. Bart, G. M. J. Schmidt, *Recl. Trav. Chim. Pays-Bas* **1978**, 97, 231.
- [12] V. Bertolasi, P. Gilli, V. Ferretti, G. Gilli, *Acta Crystallogr. Sect. B* **1998**, 54, 50.
- [13] P. C. Thieme, E. Hädicke, *Justus Liebigs Ann. Chem.* **1978**, 227.

Novel Fluorescent Probes for Singlet Oxygen**

Naoki Umezawa, Kumi Tanaka, Yasuteru Urano, Kazuya Kikuchi, Tsunehiko Higuchi, and Tetsuo Nagano*

Singlet oxygen (¹O₂), an excited state of molecular oxygen, has aroused much interest as a chemical and biological oxidant. The chemical reactivity of ¹O₂ is well characterized since ¹O₂ is useful for organic synthesis and has unique reactivity.^[1] Singlet oxygen is thought to be an important toxic species in vivo^[2] since it can oxidize various kinds of biological molecules such as DNA, proteins, and lipids, and its reactivity toward DNA bases has been especially well characterized by Foote et al.^[3] Furthermore, Sies et al. and other researchers have reported that ¹O₂ plays a role as an activator of gene expression.^[4]

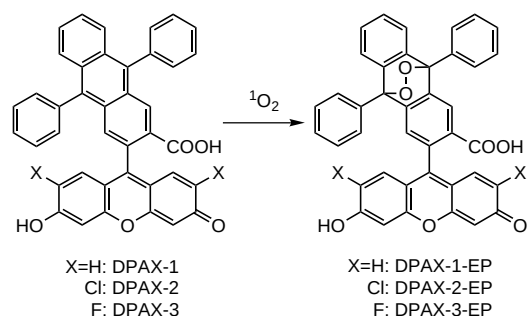
Although many ¹O₂ traps have been reported,^[5] it is still difficult to detect ¹O₂ generated in biological systems because of its short lifetime. The most widely used ¹O₂ trap is 9,10-diphenylanthracene (DPA), which reacts rapidly with ¹O₂ specifically to form a thermostable endoperoxide at a rate of *k* = 1.3 × 10⁶ M^{−1} s^{−1}.^[6] The decrease in absorbance at 355 nm is used as a measure of the formation of the endoperoxide. Many water-soluble DPA derivatives have been developed,^[7] but the quenching of ¹O₂ by water means that they are difficult to apply to biological systems. Steinbeck et al. have achieved the direct detection of ¹O₂ generation from phagocytes with DPA by adapting the method to avoid ¹O₂ quenching.^[8]

DPA derivatives are not very sensitive as probes because the detection is based on the measurement of absorbance. Hence, we designed and synthesized novel fluorometric probes for ¹O₂ in order to improve the sensitivity. In general, fluorescence measurement is more sensitive, and so is easier to use in imaging studies, for example, fura-2 is used in Ca²⁺ imaging.

We designed 9-[2-(3-carboxy-9,10-diphenyl)anthryl]-6-hydroxy-3H-xanthen-3-one (DPAX-1, Scheme 1) as a suitable fluorescent probe. We chose fluorescein as a fluorophore since it has a high fluorescence quantum yield in aqueous solution and is able to be excited at long wavelength. Excitation by visible light is preferable for biological applications as it minimizes cell damage and autofluorescence. We then fused this fluorophore with the reactive moiety of DPA. When DPAX reacts with ¹O₂ to yield DPAX-endoperoxide (DPAX-EP) the conjugation between the DPA structure and xanthene ring is greatly altered, so we expected a change in fluorescence properties.

[*] Prof. T. Nagano, Dr. N. Umezawa, K. Tanaka, Dr. Y. Urano, Dr. K. Kikuchi, Dr. T. Higuchi
Graduate School of Pharmaceutical Sciences
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, 113-0033 (Japan)
Fax: (+81) 3-5841-4855
E-mail: tlong@mol.f.u-tokyo.ac.jp

[**] This work was supported in part by a research grant from the Ministry of Education, Science, Sports, and Culture of Japan. N.U. gratefully acknowledges the Japanese Society for the Promotion of Science for the JSPS Research Fellowship for Young Scientists.



Scheme 1. Reaction of DPAXs with $^1\text{O}_2$.

The fluorescence intensity of fluorescein derivatives is known to be decreased under acidic conditions as a consequence of the protonation of the phenoxide oxygen atom. In order to stabilize the fluorescence intensity at physiological pH we incorporated electron-withdrawing groups, Cl (DPAX-2) and F (DPAX-3), at the 2- and 7-positions of the xanthene chromophore. This modification lowered the pK_a value of the phenolic oxygen atom.

DPAX-1, DPAX-2, and DPAX-3 were synthesized according to Scheme 2. The corresponding endoperoxides were synthesized with chemically generated $^1\text{O}_2$ ($\text{MoO}_4^{2-}/\text{H}_2\text{O}_2$). The fluorescence parameters are shown in Table 1; these values were obtained under basic conditions, as the compounds are highly fluorescent when deprotonated. Absorb-

Table 1. Absorbance and fluorescence properties of DPAXs and DPAX-EPs.^[a]

	λ [nm]	ϵ [$\times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$]	E_m [nm]	Φ_f
DPAX-1	493	6.1	516	0.007
DPAX-1-EP	494	7.9	515	0.53
DPAX-2	507	5.7	524	0.006
DPAX-2-EP	506	8.9	527	0.66
DPAX-3	493	7.6	514	0.006
DPAX-3-EP	494	6.7	515	0.70

[a] All data were obtained at 20 °C in 0.1 M NaOH (0.1 % DMSO).

ance maxima (λ), molar absorption coefficients (ϵ), and emission maxima (E_m) were not altered much between DPAXs and DPAX-EPs. However, the quantum efficiencies of fluorescence (Φ_f) were greatly changed: DPAXs themselves are almost nonfluorescent and DPAX-EPs are highly fluorescent. The maximum absorbance and emission of the chlorinated compound DPAX-2-EP were shifted to longer wavelengths than the other compounds.

We examined the pH profiles of fluorescence intensity for the DPAX-EPs (Figure 1). The fluorescence intensities were greatly decreased under acidic conditions. The pK_a values of DPAX-1-EP, DPAX-2-EP, and DPAX-3-EP were 6.6, 5.7, and

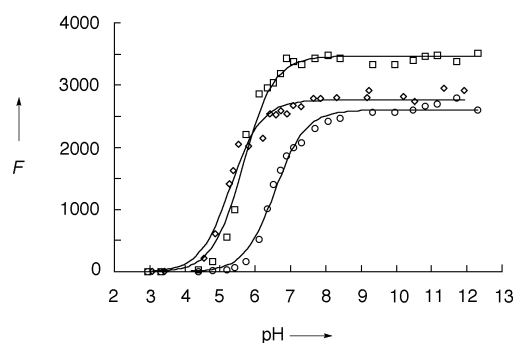
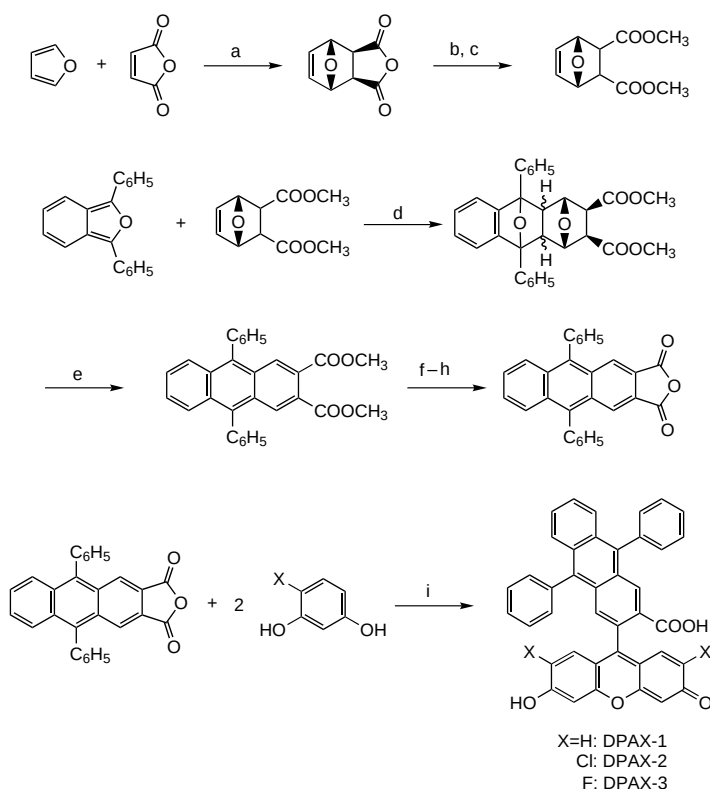


Figure 1. Effect of pH on the fluorescence intensity of DPAX-EPs. DPAX-EPs (1 μM ; 0.1 % DMSO as a cosolvent) were added to sodium phosphate solution (0.1 M) adjusted to various pH values. The fluorescence intensity of the DPAX-EPs was measured at 515, 530, and 515 nm with excitation at 495, 505, and 494 nm, respectively. $\circ$: DPAX-1-EP, $\square$: DPAX-2-EP, $\diamond$: DPAX-3-EP. F = fluorescence intensity (in arbitrary units).

5.3, respectively. In contrast to the rapid decrease of fluorescence intensity of DPAX-1-EP below pH 8, the intensity was stable above pH 7 in the cases of DPAX-2-EP and DPAX-3-EP. These profiles showed that DPAX-2 and DPAX-3 should be useful as probes under neutral conditions.

Then, we tried to detect chemical $^1\text{O}_2$ production using DPAX-2. The $\text{MoO}_4^{2-}/\text{H}_2\text{O}_2$ system was again used as a chemical source of $^1\text{O}_2$. The reaction was performed at pH 10.5, since the $\text{MoO}_4^{2-}/\text{H}_2\text{O}_2$ system only works effectively under basic conditions.^[9] Hydrogen peroxide (final concentration: 20 mM) was added to a buffer solution of DPAX-2 (10 μM ; 0.1 % DMSO) and MoO_4^{2-} (1 mM) every hour; the reaction of MoO_4^{2-} with H_2O_2 is slow and excess H_2O_2 inhibits the reaction. The excitation and emission spectra of DPAX-2 are shown in Figure 2. Each spectrum was measured one hour after the addition of H_2O_2 . The fluorescence intensity



Scheme 2. Synthesis of DPAXs. a) THF, room temperature, 46 %; b) H_2O , room temperature, 98 %; c) CH_3I , Cs_2CO_3 , acetone, room temperature, 56 %; d) CHCl_3 , reflux, quantitative yield; e) H_2SO_4 , CH_2Cl_2 , reflux, 41 %; f) dioxane, KOH, CH_3OH , reflux, 91 %; g) HCl, H_2O , room temperature, quantitative yield; h) Ac_2O , reflux, 97 %; i) $\text{CH}_3\text{SO}_3\text{H}$, 80–85 °C (DPAX-1 (43 %) and DPAX-2 (59 %)) or 150 °C (DPAX-3 (63 %)).

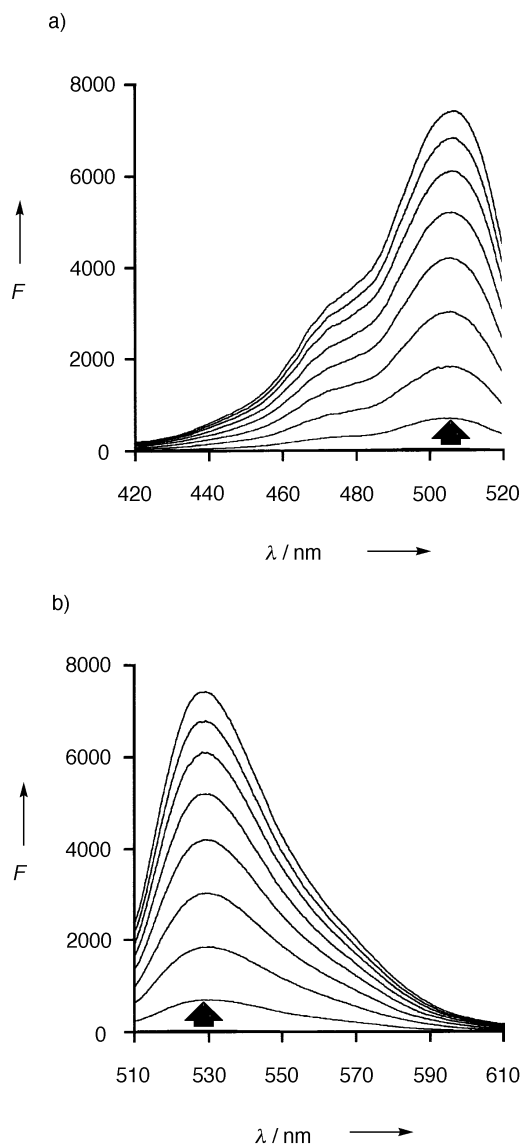


Figure 2. a) Excitation spectra recorded at 530 nm and b) emission spectra recorded at 505 nm of DPAX-2 in the reaction with $^1\text{O}_2$ generated from a $\text{MoO}_4^{2-}/\text{H}_2\text{O}_2$ system. The reaction was performed at 25°C in 0.1 M sodium phosphate buffer at pH 10.5 containing 0.1 mM EDTA.

increased with the generation of $^1\text{O}_2$ in a dose-dependent manner. An increase in fluorescence was also observed at pH 7.4 using 3-(4-methyl-1-naphthyl)propionic acid endoperoxide (EP-1) as a $^1\text{O}_2$ source.^[10] These results showed that DPAX-2 is a useful probe in both basic and neutral aqueous solutions. In addition, we confirmed the production of DPAX-2-EP in these reactions by HPLC. The fluorescence intensity did not change upon reaction with H_2O_2 , superoxide, and nitric oxide, which are reported to be produced in biological samples. The specificity of DPAX-2 for $^1\text{O}_2$ is therefore confirmed.

The detection of $^1\text{O}_2$ in biological samples was also investigated. For this we prepared DPAX-2 diacetate (DPAX-2DA), which is thought to be more permeable to the cell. DPAX-2DA will be hydrolyzed by intracellular esterases to generate DPAX-2. We have tried both DPAX-2

and DPAX-2DA, however, cells were stained similarly in both cases. This observation means that DPAX-2 itself is membrane-permeable.

Received: April 19, 1999 [Z13290IE]
German version: *Angew. Chem.* **1999**, *111*, 3076–3079

Keywords: dyes • endoperoxides • fluorescence spectroscopy • singlet oxygen

- [1] a) M. Prein, W. Adam, *Angew. Chem.* **1996**, *108*, 519–538; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 477–494; b) *Singlet Oxygen* (Eds.: H. H. Wasserman, R. W. Murray), Academic Press, New York, **1979**.
- [2] a) K. Briviba, L. O. Klotz, H. Sies, *Biol. Chem.* **1997**, *378*, 1259–1265; b) B. Epe, *Chem. Biol. Interact.* **1991**, *80*, 239–260; c) J. R. Wagner, P. A. Motchnik, R. Stocker, H. Sies, B. N. Ames, *J. Biol. Chem.* **1993**, *268*, 18502–18506.
- [3] a) C. Sheu, C. S. Foote, *J. Am. Chem. Soc.* **1993**, *115*, 10446–10447; b) C. Sheu, C. S. Foote, *J. Am. Chem. Soc.* **1995**, *117*, 474–477.
- [4] a) S. Basu-Modak, R. M. Tyrrell, *Cancer Res.* **1993**, *53*, 4505–4510; b) K. Scharffetter-Kochanek, M. Wlaschek, K. Briviba, H. Sies, *FEBS Lett.* **1993**, *331*, 304–306; c) M. Wlaschek, K. Briviba, G. P. Stricklin, H. Sies, K. Scharffetter-Kochanek, *J. Invest. Dermatol.* **1995**, *104*, 194–198; d) M. Wlaschek, J. Wenk, P. Brenneisen, K. Briviba, A. Schwarz, H. Sies, K. Scharffetter-Kochanek, *FEBS Lett.* **1997**, *413*, 239–242; e) S. Grether-Beck, S. Olaizola-Horn, H. Schmitt, M. Grewe, A. Jahnke, J. P. Johnson, K. Briviba, H. Sies, J. Krutmann, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 14586–14591.
- [5] a) C. S. Foote, F. C. Shook, R. A. Abakerli, *J. Am. Chem. Soc.* **1980**, *102*, 2503–2504; b) V. Nardello, N. Azaroual, I. Cervoise, G. Vermeersch, J. M. Aubry, *Tetrahedron* **1996**, *52*, 2031–2046; c) M. Botsivari, D. F. Evans, *J. Chem. Soc. Chem. Commun.* **1979**, 1114–1117; d) B. A. Lindig, M. A. J. Rodgers, A. P. Schaap, *J. Am. Chem. Soc.* **1980**, *102*, 5590–5593; e) J. M. Aubry, J. Rigaudy, N. K. Cuong, *Photochem. Photobiol.* **1981**, *33*, 149–153.
- [6] a) E. J. Corey, W. C. Taylor, *J. Am. Chem. Soc.* **1964**, *86*, 3881–3882; b) H. H. Wasserman, J. R. Scheffer, J. L. Cooper, *J. Am. Chem. Soc.* **1972**, *94*, 4991–4996; c) N. J. Turro, M. F. Chow, J. Rigaudy, *J. Am. Chem. Soc.* **1981**, *103*, 7218–7224.
- [7] a) C. Schmitz, J. M. Aubry, J. Rigaudy, *Tetrahedron* **1982**, *38*, 1425–1430; b) V. Nardello, J. M. Aubry, *Tetrahedron Lett.* **1997**, *38*, 7361–7364.
- [8] a) M. J. Steinbeck, A. U. Khan, M. J. Karnovsky, *J. Biol. Chem.* **1992**, *267*, 13425–13433; b) M. J. Steinbeck, A. U. Khan, M. J. Karnovsky, *J. Biol. Chem.* **1993**, *268*, 15649–15654.
- [9] a) J. M. Aubry, B. Cazin, *Inorg. Chem.* **1988**, *27*, 2013–2014; b) J. M. Aubry, B. Cazin, F. Duprat, *J. Org. Chem.* **1989**, *54*, 726–728.
- [10] I. Saito, T. Matsuura, K. Inoue, *J. Am. Chem. Soc.* **1983**, *105*, 3200–3206.

Natural Product Synthesis on Polymeric Supports—Synthesis and Biological Evaluation of an Indolactam Library**

Benjamin Meseguer, Daniel Alonso-Díaz,
Nils Griebenow, Thomas Herget, and
Herbert Waldmann*

The combinatorial synthesis of molecule libraries on polymeric supports is a powerful approach for the rapid identification of new compounds that are efficient tools for the study of biological phenomena and leads for the development of new drugs.^[1] However, its efficiency depends critically on the proper choice of the molecular scaffolds onto which different functional groups are grafted in the process of combinatorial synthesis. The generation of large libraries alone is not sufficient; the underlying basic structure of the individual library members must be biologically relevant. Natural products with proven biological activity offer such relevant molecular frameworks. Therefore, the development of methods for the combinatorial synthesis of compound libraries embodying the molecular architecture of natural products^[2] must be of great relevance to combinatorial, bioorganic, and medicinal chemistry. This calls for the development of synthetic techniques and multistep reaction sequences that proceed with high efficiency on a polymeric support. Here we report on a new method for the synthesis of the protein kinase C (PKC) activator indolactam V and the use of this method in the first solid-phase synthesis of indolactam V analogues. The synthesis is amenable to combinatorial variation of substituents (R^1 – R^3 , see Figure 1), and opens up the opportunity to generate libraries of potential activators and/or inhibitors of PKC.

Protein kinase C plays key roles in signal transduction pathways that regulate numerous cellular responses including gene expression, proliferation, differentiation, apoptosis, and tumor development.^[3] It represents a family of at least eleven closely related serine/threonine kinase isoenzymes and is expressed in all cell types. However, the different isoforms often are distributed in a tissue-specific manner.^[3] Altered PKC activity has been implicated in many disease states, and modulators of PKC activity may be useful in the treatment of, for example, cancer, asthma, rheumatoid arthritis, complications associated with diabetes, psoriasis, and disorders of the

central nervous system.^[3c] Therefore, PKC is considered a promising target for the development of new medicinal lead compounds. Selective activators or inhibitors of the different PKC isoenzymes are also likely to be useful in dissecting signaling pathways in different tissues.^[4] Members of the PKC family are activated and recruited to the plasma membrane by the second messenger diacyl glycerol (DAG). The function of DAG can be mimicked by (exogenously applied) agents such as phorbol esters. In particular, (–)-indolactam V (**1**), the core structure of tumor-promoting teleocidins,^[3,5] has attracted substantial interest as a key component for investigating the structural requirements for the activation of PKC.^[4,6] As shown in Figure 1 the indolactam core structure displays different substituents in a defined pattern, which allows one to set up a multidimensional library based on a natural product derived template with unique spatial properties.

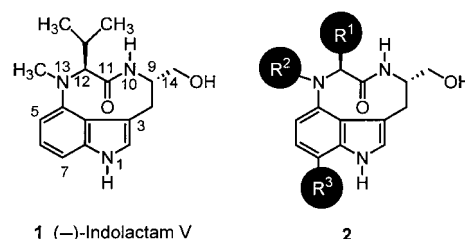


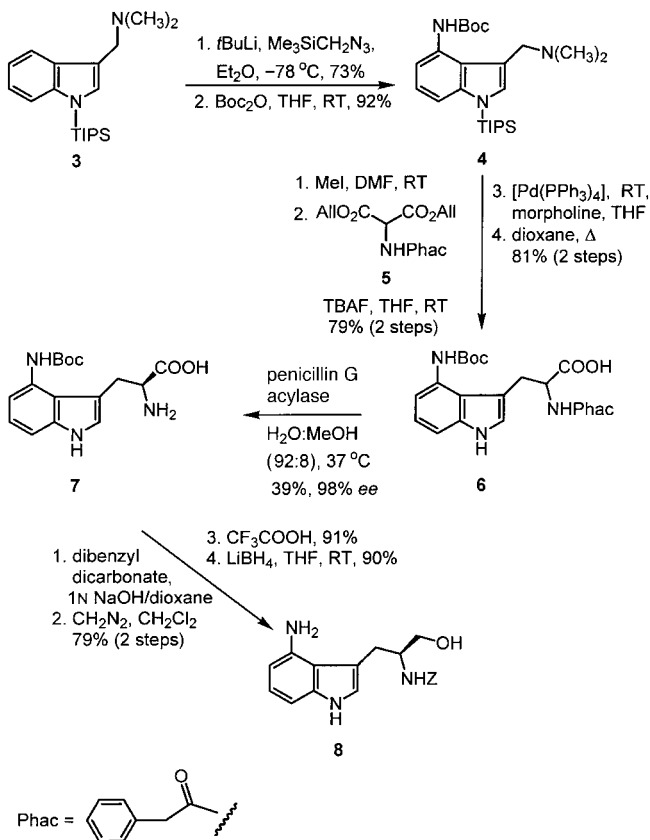
Figure 1. The structure of (–)-indolactam V and the general structure of indolactam V analogues to be built up by combinatorial synthesis.

For the design of the library and the synthetic strategy it had to be taken into account that the structure of substituents at C12 and N13 influences the conformation of the nine-membered lactam ring (twist vs. sofa form), determining the ability of the heterocycles to bind PKC (the twist form represents the active conformation of the indolactams).^[6b] Furthermore, substituents at C7 mediate membrane binding of the PKC activators, and a free OH group is required at C14 for biological activity.^[7] Therefore, indolactam analogues **2** were chosen as promising targets. It was planned to vary substituents R^1 – R^3 by means of appropriate reactions, preferably on a solid support, and to link the indolactam core to the polymeric carrier through the primary OH group.

To construct a central enantiomerically pure building block for the combinatorial introduction of residues R^1 – R^3 on the solid phase, 4-amino-substituted indole derivative **8** was built up as shown in Scheme 1. *N*-TIPS-protected gramine **3** (TIPS = triisopropylsilyl) was regioselectively lithiated in the 4-position,^[8] and an NH_2 group was introduced by treatment of the aryllithium intermediate with trimethylsilylmethyl azide.^[9] After protection of the amino group gramine derivative **4** was elaborated to the corresponding substituted tryptophan. To this end, the tertiary amine was *N*-methylated, followed by fluoride-induced cleavage of the TIPS group. The deprotection was accompanied by elimination of trimethylamine, yielding an *exo*-methylene imine intermediate that was attacked by diallyl phenylacetamidomalonate (**5**) in the sense of a Mannich reaction. The resultant α -alkylated malonic acid diester was deprotected by Pd^0 -mediated allyl transfer to morpholine,^[10] and the malonic acid formed was decarboxy-

[*] Prof. Dr. H. Waldmann, Dr. B. Meseguer, Dr. D. Alonso-Díaz
Max-Planck-Institut für molekulare Physiologie
Otto-Hahn-Strasse 11, D-44227 Dortmund (Germany)
Fax: (+49) 231-133-2499
E-mail: herbert.waldmann@mpi-dortmund.mpg.de
and
Fachbereich 3, Organische Chemie
Universität Dortmund
Dr. Nils Griebenow
Bayer AG, Central Research
Building Q 18, D-51368 Leverkusen (Germany)
Dr. T. Herget
Institut für Physiologische Chemie
Universität Mainz (Germany)

[**] This research was supported by the Fonds der Chemischen Industrie and the Bayer AG.

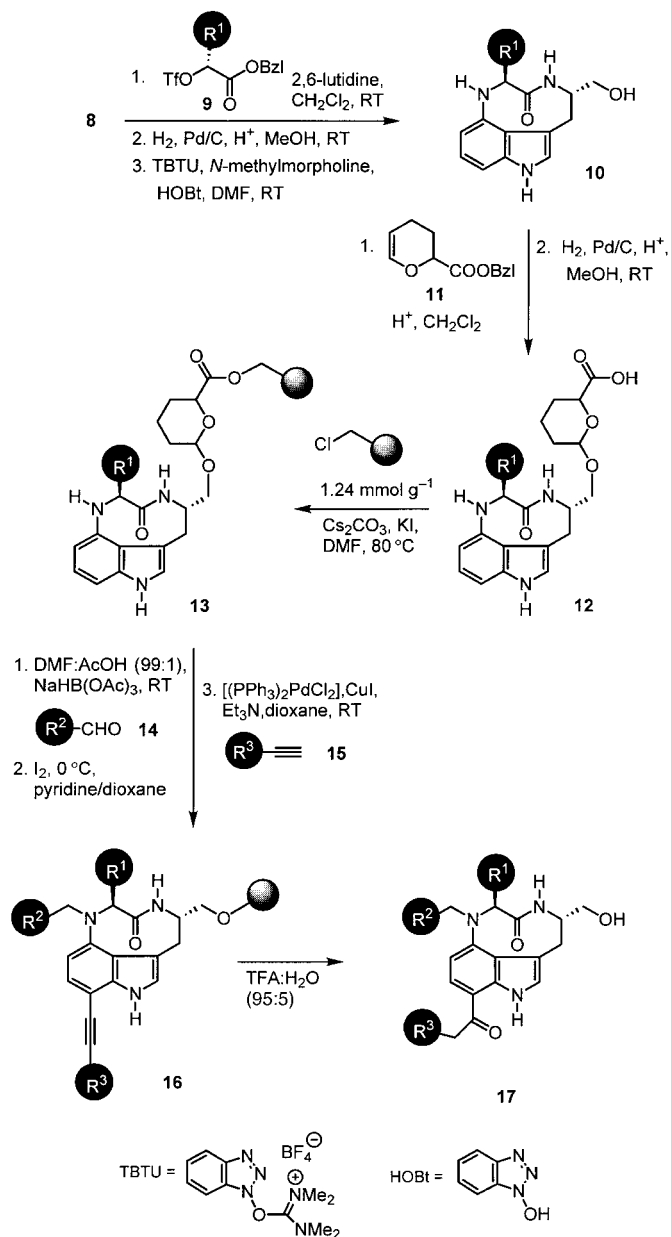


Scheme 1. Enantioselective synthesis of the 4-amino-substituted tryptophan derivative **8**—a formal total synthesis of (–)-indolactam **V** (**1**). All = allyl; Boc = *tert*-butyloxycarbonyl; RT = room temperature; TBAF = tetrabutylammonium fluoride; Z = benzyloxycarbonyl.

lated to give 4-aminotryptophan derivative **6** in high yield. To construct enantiomerically pure indolactam analogues the phenylacetamide group of the N-acylated derivative of racemic amino acid **6** was subjected to enantioselective hydrolysis with penicillin G acylase.^[11] The enzymatic hydrolysis proceeded to 50 % conversion, and from the reaction mixture the desired L-amino acid **7** was obtained in 39 % yield (maximum yield 50 %) and with an enantiomeric excess of more than 98 %.^[12] In addition, the remaining D-amino acid phenylacetamide was isolated as the methyl ester in 40 % yield (two steps; maximum yield 50 %) and with greater than 98 % *ee*. Thus, both enantiomers of 4-*N*-Boc-tryptophan are accessible by this method in a straightforward and efficient manner. L-Amino acid **7** was then converted into selectively masked amino alcohol **8** in 65 % overall yield by protecting-group manipulation and reduction of the intermediately formed methyl ester to the alcohol. 4-Aminoindole derivative **8** has previously been built up as an advanced intermediate in a synthesis of (–)-indolactam V.^[13] Thus the reaction sequence depicted in Scheme 1 represents a novel formal total synthesis of this PKC activator.

Amino alcohol **8** was employed as the central intermediate in the solid-phase synthesis of indolactam **V** analogues. The second stereocenter characteristic of the indolactam nucleus was introduced by alkylation of the aromatic amine with different α -hydroxy acid ester triflates **9**. Subsequent hydrolytic removal of the Z protecting group and the benzyl

ester functionality followed by amide formation yielded nine-membered lactams **10** in high yields (Scheme 2). Direct attachment of indole-derived alcohols **10** to a polystyrene support equipped with a tetrahydropyran (THP) linker^[14a] was unexpectedly inefficient. This problem could, however,



Scheme 2. Solid-phase synthesis of indolactam V analogues **17**. Bzl = benzyl; Tf = trifluoromethanesulfonyl; TFA = trifluoroacetic acid.

be circumvented by acetal formation with prelinker **11**^[14b] followed by hydrogenolysis of the benzyl ester group and coupling of the resulting linker/substrate conjugates **12** to chloromethylated polystyrene beads by nucleophilic esterification. Thereby resins **13** were obtained typically with loading levels of about 0.9–1 mmol g⁻¹,^[15] corresponding to coupling yields of 73–81 % (Table 1).

Resin-linked indole derivatives **13** were then subjected to a four-step sequence to introduce substituents R² and R³ and cleave the desired indolactam **V** analogues from the solid support (Scheme 2). In initial experiments the reaction

Table 1. Results of the synthesis of resin bound indole derivatives **13**.

R ¹	8 → 10		10 → 12		12 → 13	
	compd	yield [%]	compd	yield [%]	compd	yield [%]
CH ₃	10a	76	12a	25	13a	81
<i>i</i> Pr	10b	67	12b	50	13b	73
CH ₂ Ph	10c	65	12c	68	13c	77

sequence was established for compounds **17/1–17/4** (Table 2). To this end, N13 of the indolactam nucleus was N-alkylated by reductive amination with aldehydes **14** and NaHB(OAc)₃ to yield the corresponding immobilized tertiary amines. Subsequently, C7 of the aromatic nucleus was regioselectively iodinated by treatment with iodine in pyridine/dioxane at

Table 2. Results of the solid phase synthesis of indolactam V analogues **17**^[a]

Compd	R ¹	R ²	R ³	Yield [%]
17/1	CH ₂ Ph	<i>n</i> Bu	<i>n</i> Pr	40
17/2	CH ₂ Ph	<i>n</i> Bu	Ph	50
17/3	CH ₃	<i>i</i> Pr	<i>n</i> Pr	43
17/4	CH ₃	<i>i</i> Pr	Ph	47
17/5	<i>i</i> Pr	CH ₃	<i>n</i> Pr	20
17/6	CH ₂ Ph		CH ₂ Ph	13
17/7	CH ₂ Ph			17
17/8	CH ₂ Ph		<i>t</i> Bu	21
17/9	CH ₂ Ph			52
17/10	CH ₂ Ph		Ph	20
17/11	CH ₂ Ph		CH ₂ N(CH ₃) ₂	33
17/12	CH ₂ Ph		CH ₂ Ph	10
17/13	CH ₂ Ph			30
17/14	CH ₂ Ph		Ph	11
17/15	CH ₂ Ph		CH ₂ N(CH ₃) ₂	20
17/16	CH ₂ Ph	CH ₂ CH(CH ₃)Ph	CH ₂ Ph	12
17/17	CH ₂ Ph	CH ₂ CH(CH ₃)Ph		14
17/18	CH ₂ Ph	CH ₂ CH(CH ₃)Ph	<i>t</i> Bu	15
17/19	CH ₂ Ph	CH ₂ CH(CH ₃)Ph	CH ₂ CH ₂ OH	17
17/20	CH ₂ Ph	CH ₂ CH(CH ₃)Ph		56
17/21	CH ₂ Ph	CH ₂ CH(CH ₃)Ph	CH ₂ N(CH ₃) ₂	65
17/22	CH ₂ Ph	<i>n</i> Bu	CH ₂ Ph	20
17/23	CH ₂ Ph	<i>n</i> Bu		22
17/24	CH ₂ Ph	<i>n</i> Bu	<i>t</i> Bu	15
17/25	CH ₂ Ph	<i>n</i> Bu		49
17/26	CH ₂ Ph	<i>n</i> Bu	CH ₂ N(CH ₃) ₂	53
17/27	CH ₂ Ph	CH ₂ CH ₂ Ph	CH ₂ Ph	18
17/28	CH ₂ Ph	CH ₂ CH ₂ Ph		16
17/29	CH ₂ Ph	CH ₂ CH ₂ Ph		53
17/30	CH ₂ Ph	CH ₂ CH ₂ Ph	Ph	17
17/31	CH ₂ Ph	CH ₂ CH ₂ Ph	CH ₂ N(CH ₃) ₂	51

[a] The yields given are based on the total reaction sequence **13** → **17**.

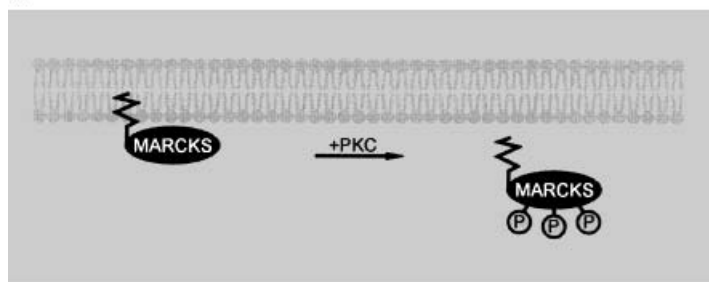
0 °C.^[16] The resulting aryl iodides were subjected to Sonogashira coupling with acetylenes **15** on the polymeric support^[17] to give immobilized alkynes **16**. Finally, the multiply substituted indole derivatives were released from the polymeric carrier by cleavage of the acetal linker with aqueous trifluoroacetic acid. Under these conditions the alkynyl groups attached to C7 unexpectedly were hydrated to give the corresponding ketones **17**.^[18] By means of this four-step sequence indolactam analogues **17/1–17/4** were obtained in yields ranging from 40 to 50 %, that is, with high overall efficiency (average yield per step: 80–84 %). With an efficient solid-phase sequence in hand we then constructed a library of indolactam analogues (Table 2). In particular, resin-bound indole derivative **13c** served as starting material which was derivatized with a series of different aldehydes and alkynes in parallel syntheses^[19] according to the protocol described above. The results given in Table 2 demonstrate that differently substituted aldehydes and alkynes carrying additional functional groups can be applied successfully in the developed solid-phase sequence. With three α -hydroxy acid triflates, seven aldehydes, and eight alkynes, a library of 31 indolactam analogues was synthesized in overall yields ranging from 65 to 10 % (average yield per step 90 to 57 %).

Numerous further aldehydes, alkynes, and α -hydroxy acids are readily available. Furthermore, the aryl iodide intermediates may also be subjected to Pd⁰-mediated Suzuki, Stille, and Heck reactions, opening up the opportunity to introduce various aryl and alkenyl groups. Thus, the developed synthetic route should provide an efficient and flexible access to numerous indolactam and teleocidin analogues.

To investigate if the indolactam analogues formed by the route described above are indeed PKC activators, eleven selected members of the compound libraries were subjected to a cell-based assay system. In this assay Swiss 3T3 fibroblasts are treated with PKC modulators. Activation of PKC causes the phosphorylation of the major PKC substrate, MARCKS (myristoylated alanine-rich C kinase substrate).^[20] The unphosphorylated 80-kDa MARCKS protein is attached to membranes through its N-terminal myristoylated domain and the unphosphorylated phosphorylation domain in the middle of the protein (Figure 2A). MARCKS is a specific PKC substrate.^[21] After activation of PKC, MARCKS becomes phosphorylated in the phosphorylation domain, resulting in rapid and extensive translocation of MARCKS from the membrane to the cytosol. Thus analysis of subcellular MARCKS localization (membrane-bound vs. cytosolic) allows one to determine the activation of PKC. Confluent and quiescent cultures of Swiss 3T3 cells were exposed for 30 min to a saturating concentration of phorbol dibutyrate (PDB, 200 nM) for maximal activation of PKC. The cells were homogenized and the extracts separated into cytosolic and membrane fractions.

The levels of MARCKS protein in these fractions were determined by Western blot analyses using an antiserum raised against recombinant GST-MARCKS protein (GST = glutathione S transferase). This antiserum detects a single band corresponding to MARCKS.^[20] In quiescent cells, only small amounts of MARCKS were detected in the cytoplasmic fraction (Figure 2B; control), while the majority of this

A



B

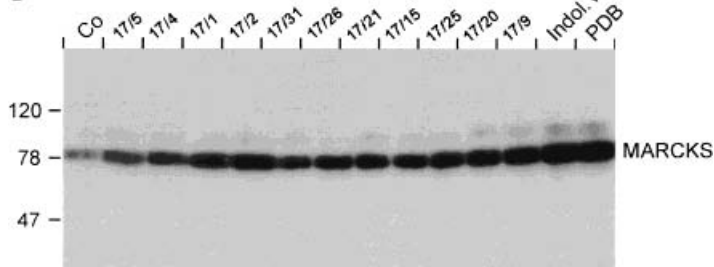


Figure 2. Activation of PKC induces translocation of MARCKS. A) The PKC substrate MARCKS is membrane-bound in its unphosphorylated state. Phosphorylation by PKC causes a rapid and extensive translocation of MARCKS from the membrane to the cytosolic fraction. B) Quiescent Swiss 3T3 cells remained untreated (control) or were treated for 30 min with the substances depicted (200 nM). The cells were washed and homogenized, and the resulting extracts were fractionated by high-speed centrifugation. Cytoplasmic proteins were separated by sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and analyzed by Western blotting employing a polyclonal MARCKS antiserum and enhanced chemiluminescence. The positions of protein markers (in kDa) are shown on the left. Co = control; Indol.V = indolactam V.

protein was found in association with the membrane (data not shown). We then utilized this system to examine the potency of eleven members of our library of indolactam derivatives (200 nM) to activate PKC in 3T3 fibroblasts and to promote MARCKS translocation. All substances tested caused a striking translocation of MARCKS to various degrees (Figure 2B). Scanning of autoradiographs revealed a MARCKS translocation induced by the indolactam V derivatives by three- to fivefold, which was slightly less efficient than with indolactam V itself and with the phorbol ester PDB (both sevenfold, Figure 2B). Preincubation of the Swiss 3T3 cells with 2.5 μ M GF109203X, a specific PKC inhibitor,^[20] completely abrogated the MARCKS translocation (data not shown). Phosphorylation of MARCKS by PKC is a prerequisite for MARCKS translocation.^[20a] Thus, these results demonstrate that the indolactam V analogues are potent PKC activators.

MARCKS is a specific PKC substrate for all conventional and novel PKC isoforms in vitro and in fibroblasts.^[21] Our data concerning the differently pronounced activation of PKC in Swiss 3T3 cells by different indolactam analogues maybe explained by the varying potency of these indolactam analogues for binding to and activating PKC in general. This possibility might open new routes for the establishment of structure–function relationships. Alternatively, the individual indolactam analogues tested may bind the individual members of the PKC family with different efficiency. In this

context it should be noted that the murine Swiss 3T3 fibroblasts used in this study express mainly the conventional PKC isoform α , the novel isoforms δ and ϵ , and the atypical isoform ζ .^[22]

Received: February 15, 1999

Revised version: July 5, 1999 [Z13032IE]

German version: *Angew. Chem.* **1999**, *111*, 3083–3087

Keywords: alkaloids • combinatorial chemistry • drug research • signal transduction • total synthesis

- [1] a) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288; b) J. S. Früchtel, G. Jung, *Angew. Chem.* **1996**, *108*, 19; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17; c) L. A. Thompson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555; d) D. Obrecht, J. M. Villagordo, *Solid-supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*, Pergamon, New York, **1998**.
- [2] In a few cases syntheses of natural product based compound libraries have been described. See a) K. C. Nicolaou, N. Winssinger, J. A. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hansel, *Nature* **1997**, *387*, 268; b) K. C. Nicolaou, N. Winssinger, D. Vourloumis, T. Oshima, S. Kim, J. Pfefferkorn, J.-Y. Xu, T. Li, *J. Am. Chem. Soc.* **1998**, *120*, 10814; c) K. C. Nicolaou, J. A. Pastor, N. Winssinger, F. Murphy, *J. Am. Chem. Soc.* **1998**, *120*, 5132; d) L. A. Thompson, F. L. Moore, Y.-C. Moon, J. A. Ellman, *J. Org. Chem.* **1998**, *63*, 2066; e) S. Chen, K. D. Janda, *J. Am. Chem. Soc.* **1997**, *119*, 8724; f) J. Nielsen, L. O. Lynsø, *Tetrahedron Lett.* **1996**, *37*, 8439.
- [3] a) Y. Nishizuka, *Science* **1986**, *233*, 305; b) Y. Nishizuka, *Science* **1992**, *258*, 607; c) D. Bradshaw, C. H. Hill, J. S. Nixon, S. E. Wilkinson, *Agents Actions* **1993**, *38*, 135.
- [4] For an application of an isoenzyme-selective PKC inhibitor that targets specific tissues, see H. Ishii, M. R. Jirouselz, D. Koya, C. Tatzagi, P. Xia, A. Clermont, S.-E. Bursell, T. S. Kern, L. M. Ballas, W. F. Heath, L. E. Stramm, E. P. Femer, G. L. King, *Science* **1996**, *272*, 728.
- [5] Review: H. Fugitzi, T. Sugimura, *Adv. Cancer Res.* **1987**, *49*, 223.
- [6] a) A. P. Kozikowski, S. Wang, D. Ma, J. Yao, S. Ahmad, R. I. Glazer, K. Bogi, P. Acs, S. Modarres, N. E. Lewin, P. M. Blumberg, *J. Med. Chem.* **1997**, *40*, 1316, and references therein; b) I. Irie, T. Isaka, Y. Iwata, Y. Yanai, Y. Nakamura, F. Koizumi, H. Ohigashi, P. A. Wender, Y. Satomi, H. Nishino, *J. Am. Chem. Soc.* **1996**, *118*, 10733, and references therein; c) O. A. Moreno, Y. Kishi, *J. Am. Chem. Soc.* **1996**, *118*, 8180; d) Y. Endo, M. Hasegawa, A. Itai, K. Shudo, M. Tori, Y. Asakawa, S. Sakai, *Tetrahedron Lett.* **1985**, *26*, 1069; e) G. Zhang, M. G. Kazanietz, P. M. Blumberg, J. H. Hurley, *Cell* **1995**, *81*, 917; f) I. Irie, S. Okuno, S. Kajiyama, K. Koshimizu, H. Nishino, A. Iwashima, *Carcinogenesis* **1991**, *12*, 1883; g) G. Krauter, C. W. Von Der Lieth, R. Schmidt, E. Hecker, *Eur. J. Biochem.* **1996**, *242*, 417; h) Y. Endo, M. Ohno, S. Takehana, P. E. Driedger, S. Stabel, K. Shudo, *Chem. Pharm. Bull.* **1997**, *45*, 424; i) L. Qiao, S. Wang, C. George, N. E. Lewin, P. M. Blumberg, A. P. Kozikowski, *J. Am. Chem. Soc.* **1998**, *120*, 6629; j) Y. Kishi, R. R. Rando, *Acc. Chem. Res.* **1998**, *31*, 163, and references therein.
- [7] Y. Endo, K. Shudo, A. Itai, M. Hasegawa, S. Sakai, *Tetrahedron* **1986**, *42*, 5905.
- [8] M. Iwao, *Heterocycles* **1993**, *36*, 29.
- [9] K. Nishiyama, N. Tanaka, *J. Chem. Soc. Chem. Commun.* **1983**, 1322.
- [10] S. Friedrich-Bochnitschek, H. Waldmann, H. Kunz, *J. Org. Chem.* **1989**, *54*, 751.
- [11] M. Nettekoven, M. Psiorz, H. Waldmann, *Tetrahedron Lett.* **1995**, *36*, 1425.
- [12] The *ee* value was determined by HPLC using a chirobiotic T column (250 $\times$ 4.6 mm; particle size 5 μ m; ASTEC) with $\text{H}_3\text{CCN}/\text{MeOH}/\text{NEt}_3/\text{AcOH}$ (545/455/4/2) as eluent at a flow rate of 1 mL min⁻¹ or 0.4 mL min⁻¹.
- [13] Total syntheses of indolactam V: T. P. Kogan, T. C. Somers, M. C. Kenuti, *Tetrahedron* **1990**, *46*, 6623, and references therein.

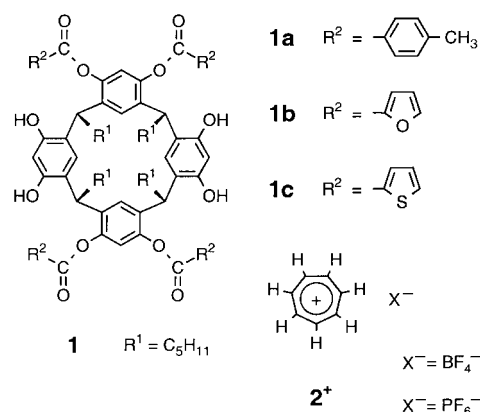
- [14] a) L. A. Thompson, J. A. Ellman, *Tetrahedron Lett.* **1994**, 35, 9333; b) H. P. Hsieh, Y.-T. Wu, S. T. Chen, K.-T. Wang, *Chem. Commun.* **1998**, 649.
- [15] The resin loading was determined by mass balance after cleavage of the compound from the resin with TFA/H₂O (95/5).
- [16] Y. Endo, Y. Sato, K. Shudo, *Tetrahedron* **1987**, 43, 2241.
- [17] S. Berteina, S. Wendeborn, W. K.-D. Brill, A. De Mesmaeker, *Synlett* **1998**, 676, and references therein.
- [18] For a similar observation, see F. Persico, B. D. Wuest, *J. Org. Chem.* **1993**, 53, 95.
- [19] Parallel solid-phase synthesis was performed with a FlexChem reaction block (Robbins Scientific).
- [20] a) T. Herget, E. Rozengurt, *Eur. J. Biochem.* **1994**, 225, 539; b) T. Herget, S. Broad, E. Rozengurt, *Eur. J. Biochem.* **1994**, 225, 549.
- [21] a) T. Herget, S. A. Oehrlin, D. J. C. Pappin, E. Rozengurt, P. J. Parker, *Eur. J. Biochem.* **1995**, 233, 448; b) F. Überall, S. Giselbrecht, K. Hellbert, F. Fresser, B. Bauer, M. Gschwendt, H. H. Grunicke, G. Baier, *J. Biol. Chem.* **1997**, 272, 4072.
- [22] D. R. Olivier, P. J. Parker, *J. Cell Physiol.* **1992**, 240.

Guest-Controlled Formation of a Hydrogen-Bonded Molecular Capsule**

Alexander Shivanyuk,* Erich F. Paulus,* and Volker Böhmer*

Several concave, self-complementary molecules^[1] have been shown to form self-assembled dimeric capsules held together by multiple hydrogen bonds in which various guests can be reversibly entrapped. The encapsulation of a suitable guest is usually necessary for the dimerization, since an empty or incompletely filled cavity would be thermodynamically disadvantageous.^[2] Herein we describe a novel type of dimeric hydrogen-bonded molecular capsules whose formation can be strictly controlled by the amount of guest available for the encapsulation.

C_{2v}-symmetrical tetraesters **1** are easily prepared by regio-selective acylation of resorcarenes with various acid chlorides.^[3] These molecules contain four phenolic hydroxy groups and four ester carbonyl groups as potential hydrogen-bond donors and acceptors and should be able, according to molecular models, to dimerize through eight CO...HO hydrogen bonds forming a closed π -basic cavity. The tropylium cation **2**⁺ as π acceptor was considered to be an appropriate guest and template for such an assembly.



¹H NMR spectra of tetraesters **1a–c** (CDCl₃, 293 K) are sharp and contain one triplet for the methine protons of the bridges and four singlets for the protons of the resorcinol rings^[4] (Figure 1 a). Surprisingly, in the case of **1a** and **1b** the proton exchange between hydroxy groups and water (always present in traces) occurs with such a rate that no signals are observed for the corresponding protons. This indicates that the hydroxy groups are not involved in strong CO...HO hydrogen bonds, but are available for the solvation by water in CDCl₃.

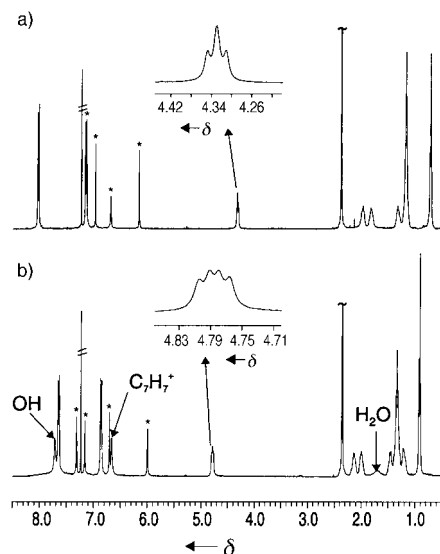


Figure 1. ¹H NMR spectra (400 MHz, CDCl₃, 293 K, c(**1a**) = 10⁻² M) of: a) tetraester **1a**; b) (1aC₇H₇⁺1a)PF₆⁻. The signals for the protons of resorcinol rings are marked with an asterisk.

Compounds **1** solubilize tropylium salts **2**⁺X⁻ in CH₂Cl₂ or CHCl₃. The intensive orange-red color of such solutions (λ_{max} = 463 nm, CH₂Cl₂) is caused by the formation of charge-transfer complexes with C₇H₇⁺.^[5] The complexation with C₇H₇⁺PF₆⁻ also drastically changes the ¹H NMR spectra of resorcarenes **1a–c** (CDCl₃, 293 K). Especially remarkable is the down field shift for the signal of the bridges (Δδ = 0.45) and the change of its multiplicity (Figure 1 b).^[6] Furthermore, the proton exchange between hydroxy groups of **1a, b** and water becomes slow on the NMR time scale, suggesting the formation of strong hydrogen bonds.

[*] Dr. A. Shivanyuk, Dr. V. Böhmer
Fachbereich Chemie und Pharmazie
Abteilung Lehramt Chemie der Universität
Duesbergweg 10–14, D-55099 Mainz (Germany)
Fax: (+49) 6131-395-419.
E-mail: shiva@mail.uni-mainz.de
vboehmer@mail.uni-mainz.de

Dr. E. F. Paulus
Hoechst Marion Roussel
D-65926 Frankfurt/Main (Germany)
E-mail: erich.paulus@hmrag.com

[**] This work was supported by the Deutsche Forschungsgemeinschaft. We thank Mr. H. Kolshorn (Universität Mainz) for the 2D NMR measurements.

Combination of COSY, ^{13}C DEPT, and ^1H - ^{13}C correlation NMR techniques enables an unambiguous assignment of the resonances of the complexed C_7H_7^+ ion (Figure 1b). Its ^1H NMR singlet appears at $\delta = 6.66$, 6.58, and 6.53 in the complexes with **1a**, **1b**, and **1c**, respectively, strongly shifted upfield ($\Delta\delta \approx -2.6$) due to the shielding by the resorcarene aryl rings.^[7] Integration shows that two molecules of resorcarene **1** complex one tropylium cation.^[8]

All these data are in agreement with the encapsulation of the C_7H_7^+ ion in the π -basic cavity of the hydrogen-bonded resorcarene dimers. No changes were observed in the ^1H NMR spectra of **1** upon addition of benzene or toluene as potentially space-filling guests for **1c**, suggesting that host-guest interactions play an important role in the formation of $(1\text{C}_7\text{H}_7^+1)\text{X}^-$.

The ^1H NMR spectrum of the mixture $(1\text{aC}_7\text{H}_7^+1\text{a})\text{PF}_6^-$ and $(1\text{bC}_7\text{H}_7^+1\text{b})\text{PF}_6^-$ exhibits a double set of sharp signals for each resorcarene along with three signals for the protons of C_7H_7^+ (Figure 2). This pattern can be interpreted by the

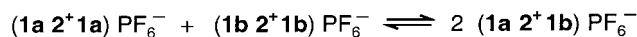
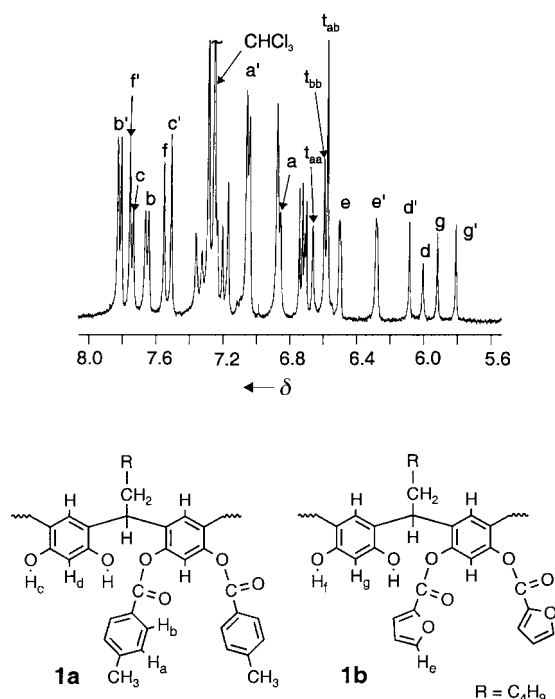


Figure 2. Section of the ^1H NMR spectrum of the mixture $(1\text{aC}_7\text{H}_7^+1\text{a})\text{PF}_6^-$ and $(1\text{bC}_7\text{H}_7^+1\text{b})\text{PF}_6^-$. The signals of the heterodimer $(1\text{aC}_7\text{H}_7^+1\text{b})\text{PF}_6^-$ are marked with a dash. The singlets of the tropylium cation encapsulated in the dimers of **1a**, **1b**, and in the heterodimer are labeled with t_{aa} , t_{bb} , and t_{ab} , respectively.

formation of the kinetically stable hetero-associate $(1\text{aC}_7\text{H}_7^+1\text{b})\text{PF}_6^-$ in a more or less statistical ratio. Accordingly, the ROESY spectrum shows intensive exchange cross peaks between the resolved signals of the homo- and hetero-associates.

The high thermodynamic stability of $(1\text{cC}_7\text{H}_7^+1\text{c})\text{BF}_4^-$ in CH_2Cl_2 is demonstrated by the fact that the absorbance of the charge-transfer band is proportional to the concentration,

($c = 0.35\text{--}5.5\text{ mM}$, $\epsilon_{463} = 398\text{ M}^{-1}\text{ cm}^{-1}$). This proves that no dissociation of the complex occurs upon dilution.

In contrast to other self-assembled molecular capsules,^[9] the degree of dimerization of **1** can be controlled by the amount of tropylium salt. If less than 0.5 equivalents of $\text{C}_7\text{H}_7^+\text{X}^-$ (per equivalent **1**) are solubilized the corresponding amounts of $(1\text{C}_7\text{H}_7^+1)\text{X}^-$ and free **1** are observed.^[10] At the ratios **1**: $(1\text{C}_7\text{H}_7^+1)\text{X}^-$ of 3.0, 1.0, 0.33 the exchange of **1** between the monomer and dimer is slow on the ^1H NMR time scale (200 MHz, CDCl_3 , 293 K) although a slight broadening of the signals takes place.^[11] The addition of CD_3CN (10–20%) to this solution causes the collapse of the signals so that one set of broad resonances is detected for the resorcarene protons. This is obviously caused by hydrogen bonding between hydroxy groups of **1** and acetonitrile molecules.

Exactly one equivalent of **1c** can be solubilized per equivalent of $\text{C}_7\text{H}_7^+\text{BF}_4^-$ in CD_3CN at 293 K resulting in the formation of a colored ($\lambda_{\text{max}} = 475\text{ nm}$) charge-transfer complex. However, the absorbance is not proportional to the concentration in this case ($c(1\text{c}) = c(2^+) = 0.35\text{--}5.5\text{ mM}$), evidently due to the dissociation of the weaker complex. If larger amounts of **1c** are dissolved by heating, the excess of resorcarene crystallizes again upon cooling, suggesting a 1:1 stoichiometry for the complexation in acetonitrile. NMR dilution experiments show that the complex formed is not kinetically stable at 293 K. In this case the signal of C_7H_7^+ undergoes only a relatively small upfield shift ($\Delta\delta = -0.22$ at $c(1\text{c}) = c(2^+) = 10^{-2}\text{ M}$).^[12]

Thus the high (thermodynamic and kinetic) stability of $(1\text{C}_7\text{H}_7^+1)\text{X}^-$ in CDCl_3 arises from the cooperation of eight $\text{CO}\cdots\text{HO}$ hydrogen bonds and the tropylium-resorcinol interactions.

Structural details were obtained from a single-crystal X-ray analysis.^[13] In fact, two molecules of **1c** form in the crystalline state a dimer through eight intermolecular $\text{CO}\cdots\text{HO}$ hydrogen bonds ($\text{O}\cdots\text{O}$ distances 2.76–2.86 Å) (Figure 3). One tropylium cation is encapsulated in the cavity formed in this way and forms angles of 54.8° and 55.0° with the reference planes^[14] of A and B, respectively. In addition two clefts are created by the pendant pentyl chains. One of them (molecule A) is occupied by a BF_4^- ion ($\text{C}_7\text{H}_7^+ - \text{B1} = 7.72\text{ Å}$), while the other one hosts a hexane molecule. This entrapment of the BF_4^- ion between the pentyl chains of resorcarene A leads to the asymmetric location of the tropylium cation in the cavity. The distances of the center of C_7H_7^+ from the centers of the reference planes of A and B are 4.13 and 4.89 Å, respectively.

One unsubstituted resorcinol ring of molecule A (C122 to C127) and one diacylated resorcinol ring of molecule B (C215 to C220) are arranged around the tropylium cation in a sandwichlike manner (Figure 4). The distance of the center of C_7H_7^+ from the plane of the quasi-parallel resorcinol ring C122 to C127 (dihedral angle 5.4°) was found to be 3.57 Å, which is suitable for charge transfer, while the same values for the less π -basic diacylated ring C215 to C220 (23.0° , 5.62 Å) do not suggest any strong interactions. On the other hand the distances between all the carbon atoms of C_7H_7^+ and the planes of the other six resorcinol rings are in accordance with the formation of $\text{CH}\cdots\pi$ bonds (Figure 4).

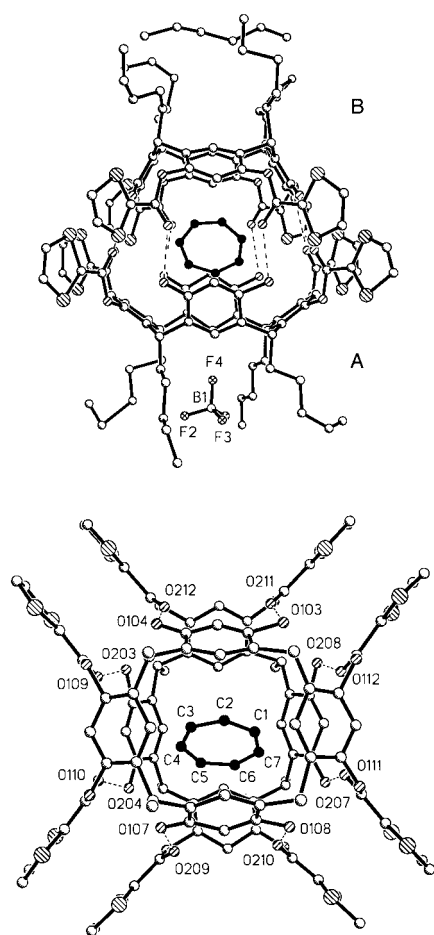


Figure 3. Structure of $(1\text{C}_7\text{H}_7^+1\text{C})\text{BF}_4^-$ in the crystal. Sulfur atoms of the thiophene rings are disordered over two positions. Side view (top): Hydrogen bonds are shown as dotted lines; the carbon atoms of the encapsulated tropylium cation are darkened for clarity. Top view of a resorcarene (bottom): The pentyl chains, the BF_4^- ion, and the hexane molecule are omitted for clarity; the hydrogen-bonded oxygen atoms are labeled; distances [Å]: O103–O211 2.81, O104–O212 2.81, O107–O209 2.86, O108–O210 2.79, O203–O109 2.79, O204–O110 2.76, O207–O111 2.80, O208–O112 2.79.

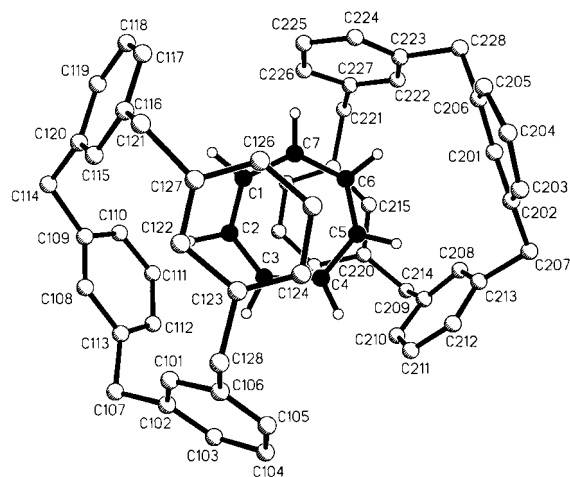


Figure 4. The location of C_7H_7^+ between the molecules A and B. Only the parts, which are important for the host–guest interactions are shown; the shortest distances [Å] between carbon atoms of the tropylium cation and the planes of the aryl rings are: C1–(C115–C120) 3.47, C2–(C108–C113) 3.35, C3–(C101–C106) 3.43, C4–(C208–C213) 3.15, C5–(C208–C213) 3.31, C6–(C201–C206) 3.61, C7–(C222–C227) 3.27.

In conclusion, C_{2v} -symmetrical resorcarenes **1** represent a novel class of self-complementary molecules capable of reversible dimerization controlled by the encapsulation of tropylium cations. It could be unambiguously shown that neither the host–guest interaction alone nor the interaction of the two self-complementary molecules **1** through hydrogen bonds is sufficient by itself to form $(1\text{C}_7\text{H}_7^+1\text{C})\text{X}^-$. Only the cooperative action of both factors leads to the quantitative formation of the 2:1 host–guest complex. Due to charge transfer the self-assembly of $(1\text{C}_7\text{H}_7^+1\text{C})\text{X}^-$ is accompanied by a well-pronounced optical response which is unprecedented so far for molecular capsules.

Received: April 27, 1999 [Z13319IE]
German version: *Angew. Chem.* **1999**, *111*, 3091–3094

Keywords: charge transfer • host–guest chemistry • hydrogen bonds • inclusion compounds • supramolecular chemistry

- [1] M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647–1668.
- [2] R. G. Chapman, J. C. Sherman, *Tetrahedron* **1997**, *53*, 15911–15945.
- [3] A. Shivanyuk, E. F. Paulus, V. Böhmer, W. Vogt, *J. Org. Chem.* **1998**, *63*, 6448–6449.
- [4] A decrease of the temperature to 217 K results in the broadening and splitting of the ^1H NMR spectrum of **1a** (CDCl_3 , 500 MHz) most probably due to a restricted conformational flexibility of the resorcarene skeleton (two C_{2v} -symmetrical boat conformations).
- [5] See for example: M. Lämsä, J. Pursiainen, K. Rissanen, J. Huuskonen, *Acta. Chem. Scand.* **1998**, *52*, 563–570.
- [6] Dynamic ^1H NMR spectroscopy shows that complexation with tropylium rigidifies the conformation of **1a**.
- [7] Although $\text{C}_7\text{H}_7^+\text{BF}_4^-$ and $\text{C}_7\text{H}_7^+\text{PF}_6^-$ are very sparingly soluble in CDCl_3 a singlet at $\delta=9.18$ can be found for the tropylium cation comparable to the value of $\delta=9.23$ in CD_3CN .^[5]
- [8] In order to ensure complete complexation the solid/liquid extraction of $\text{C}_7\text{H}_7^+\text{BF}_6^-$ or $\text{C}_7\text{H}_7^+\text{PF}_6^-$ was carried out for 6–8 h assisted by mechanical stirring.
- [9] a) R. Meuisner, X. Garcias, S. Mecozzi, J. Rebek, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 77–85; b) N. Branda, R. M. Grotzfeld, C. Valdes, J. Rebek, Jr., *J. Am. Chem. Soc.* **1995**, *117*, 85–88; c) O. Mogck, M. Pons, V. Böhmer, W. Vogt, *J. Am. Chem. Soc.* **1997**, *119*, 5706–5712.
- [10] The degree of dimerization of tetrahydroxy cavitands could be controlled by the amount of base used for the deprotonation of the hydroxy groups to form the dianion, while an appropriate space-filling guest (pyrazine) was available in excess: R. G. Chapman, G. Olovsson, J. Trotter, J. C. Sherman, *J. Am. Chem. Soc.* **1998**, *120*, 6252–6260.
- [11] A signal for the free tropylium cation is not observed.
- [12] A similar effect has been observed in the case of 1:1 charge-transfer complexation between $\text{C}_7\text{H}_7^+\text{BF}_4^-$ and dibenzo[24]crown-8 in CD_3CN ($K_{\text{ass}}=10.2\pm0.3\text{M}^{-1}$).^[5] Unfortunately, the low solubility of resorcarenes **1** in acetonitrile prevented the accurate determination of K_{ass} with $\text{C}_7\text{H}_7^+\text{X}^-$.
- [13] Crystallographic data: Intensively red crystals were obtained by slow evaporation of a solution of $(1\text{C}_7\text{H}_7^+1\text{C})\text{BF}_4^-$ in $\text{CH}_2\text{Cl}_2/\text{hexane}$. They were sealed in a Lindemann glass capillary containing some mother liquor. Measurement at 21 °C by a Siemens four-circle diffractometer with CCD, Siemens rotating anode, (50 kV, 120 mA), MoK_α radiation (graphite monochromator, $\lambda=0.7107\text{ Å}$). Lorentz, polarization, and empirical absorption corrections. Direct methods (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467), refinement with full matrix for every resorcarene molecule in the asymmetric unit versus F^2 (G. M. Sheldrick, SHELXL-93, Universität Göttingen). $2(\text{C}_{68}\text{H}_{72}\text{O}_{12}\text{S}_4) \cdot \text{C}_7\text{H}_7^+ \cdot \text{BF}_4^- \cdot \text{C}_6\text{H}_{14}$, $M_r=2683.10$, crystal size $0.24 \times 0.15 \times 0.08\text{ mm}^3$, monoclinic, Cc , $a=23.299(4)$, $b=26.802(4)$, $c=23.218(3)\text{ Å}$, $\beta=92.05(1)^\circ$, $Z=4$, $V=14489\text{ Å}^3$, $\rho_{\text{calcd}}=1.230\text{ g cm}^{-3}$, $2\theta_{\text{max}}=36.0^\circ$, $\mu=0.20\text{ mm}^{-1}$, 1701 parameters, 2210 restraints,

$R = 0.0719$ (for 4529 reflections $I > 2\sigma(I)$), $wR(F^2) = 0.2142$ for all 9201 unique reflections ($R_{\text{int}} = 0.1101$, $R_\sigma = 0.1214$), $S = 0.962$, min./max. residual electron density = $-0.24/0.32 \text{ e } \text{\AA}^{-3}$, $\sigma_{\text{C-C}} = 0.006 \text{ \AA}$. Crystallographic data of this structure (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-119100. 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).

[14] The reference plane of **1** is defined by the four bridging methin carbon atoms.

A Catalytic Enantioselective Electron Transfer Reaction: Titanocene-Catalyzed Enantioselective Formation of Radicals from *meso*-Epoxides**

Andreas Gansäuer,* Thorsten Lauterbach, Harald Bluhm, and Mathias Noltemeyer

In this communication we wish to disclose our results on the use of enantiomerically pure titanocene complexes in the opening of *meso*-epoxides based on our recently developed $[\text{Cp}_2\text{TiCl}_2]$ -catalyzed reductive opening of epoxides^[1] and pinacol couplings.^[2,3] The resulting transformation is to the best of our knowledge the first example of a transition metal catalyzed enantioselective formation of radicals.^[4] Our reaction, in which the crucial β -titanoxy radical intermediate is generated selectively, is conceptually different from the enantioselective opening of *meso*-epoxides by an S_N2 reaction, where the path of the incoming nucleophile has to be controlled. The essential characteristics of a useful catalyst in the enantioselective opening of a *meso*-epoxide are depicted in Figure 1.

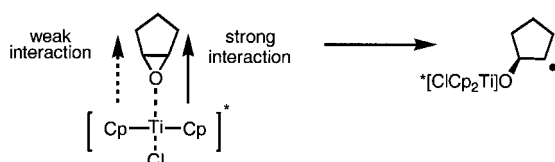


Figure 1. Steric requirements for selective epoxide opening.

To achieve high enantioselectivity the catalyst should allow for distinctly differing interactions of the ligand with the enantiotopic substituents of the epoxide. To implement

rationally designed catalysis the catalyst's chiral pocket must be tailored to allow for recognition of structural elements of the substrate distant from the epoxy group. Efficient chirality transfer to the periphery of the complex is thus essential for successful catalysis. Inspection of the extensive literature on titanocene complexes^[5] suggested that complexes with ligands derived from terpenes are suitable. After consideration of molecular models we decided to use **1**^[6] because its methyl groups seemed to shield the chlorine atoms bound to titanium. The crystal structure of **1**, determined by us for the first time, confirmed our assumptions nicely (Figure 2).

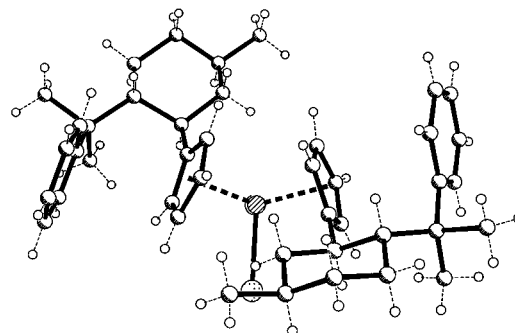
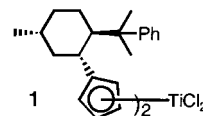


Figure 2. X-ray crystal structure of **1**.

We used epoxides derived from (*Z*)-butenediol dialkyl ethers as substrates for optimizing the reaction conditions. The absolute configuration of the products was established as *S* by comparison with samples derived from (*S*)-malic acid. The reaction conditions are summarized in Scheme 1 and the results in Table 1.



Scheme 1. Optimized conditions for the enantioselective reductive opening with 5 mol % of **1**.

Not only is the enantioselectivity of the electron transfer high (96.5:3.5), but **1** also constituted the catalytically most active complex amongst a series of titanocene complexes. The

Table 1. Enantioselective reduction of *meso*-epoxides in the presence of 5 mol % of **1** (0.1 M in THF, 60 h).

Substrate	Product	Yield [%]	(<i>S</i>):(<i>R</i>) ^[a]
		65	96.5:3.5
		61	96:4
		60	87.5:13.5

[a] Determined by gas chromatography on chiral phases.

[*] Dr. A. Gansäuer, T. Lauterbach, H. Bluhm
Institut für Organische Chemie und Biochemie der Universität
Albertstrasse 21, D-79104 Freiburg (Germany)
Fax: (+49) 761-203-6100
E-mail: agansaeu@organik.chemie.uni-freiburg.de
Dr. M. Noltemeyer
Institut für Anorganische Chemie der Universität Göttingen (Germany)
[**] Financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the BASF AG is gratefully acknowledged. We thank Prof. R. Brückner for constant and generous support of our work.

reason for the high selectivity of epoxide opening with **1** seems to stem from its striking structural feature, the almost perfect coplanarity of the benzene rings and the cyclopentadienyl rings, presumably due to π stacking. This interaction seems to lock the ligands in a conformation necessary for highly selective binding of the substrate. The methyl groups of the terpene moiety point towards the homotopic binding sites of the supposed catalytically active titanium(III) complex.^[7] These binding sites should be located close to the Cl atoms of the almost C_2 -symmetrical titanium(IV) complex, by comparison with other titanocene(III) and titanocene(IV) complexes.^[8] Therefore, **1** meets all requirements we believed to be necessary for a successful catalyst.

Our anticipated mechanism is supported by the reduced enantioselectivity of the opening of **6**. In the case of the *n*-alkyl ethers **2** and **4** the selectivity was similar and high. However, in the case of **6** both *tert*-butyl groups made a rather strong contact with the chiral pocket of **1**, resulting in diminished steric differentiation.

An interesting and demanding problem is the use of bicyclic epoxides in enantio- and diastereoselective C–C bond forming reactions by addition of the β -titanoxy radical to *tert*-butyl acrylate. The results of our investigation are summarized in Table 2. With increasing ring size the enantioselectivity of the epoxide opening increases and reaches synthetically useful

Table 2. Enantioselective C–C bond forming reactions in the presence of 5 mol % of **1** (0.1 M in THF, 48 h).

Substrate	Product	Yield [%]	(<i>R,S</i>):(<i>S,R</i>) ^[a]
		68	87:13 ^[b]
		61	91:9 ^[c]
		65	91:9 ^[d]

[a] Determined by gas chromatography on chiral phases. [b] *trans:cis* > 97:3. [c] *trans:cis* = 81:19, same *ee* value for the two diastereoisomers. [d] *trans:cis* = 87:13.

levels for the six- and seven-membered rings. This indicates a better fit of the larger substrates in the chiral pocket of the catalyst. The diastereoselectivity of the C–C bond forming steps^[9] was higher than with $[Cp_2TiCl_2]$ as catalyst^[3b,c] (**8**: 86:14 vs. 97.5:2.5; **9**: 60:40 vs. 81:19; **10**: 70:30 vs. 87:13) or with stoichiometric amounts of reagent.^[10]

In summary we have demonstrated for the first time that the catalytic opening of *meso*-epoxides by electron transfer can be performed with high enantioselectivity and high diastereoselectivity with **1** as rationally designed catalyst.

Received: April 23, 1999 [Z13306IE]
German version: *Angew. Chem.* **1999**, *111*, 3112–3114

Keywords: enantioselectivity • epoxides • homogeneous catalysis • radical reactions • titanium

- [1] a) A. Gansäuer, M. Pierobon, H. Bluhm, *Angew. Chem.* **1998**, *110*, 107; *Angew. Chem. Int. Ed.* **1998**, *35*, 101; b) A. Gansäuer, H. Bluhm, *Chem. Commun.* **1998**, 2143; c) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849.
- [2] a) A. Gansäuer, D. Bauer, *J. Org. Chem.* **1998**, *63*, 2070; b) A. Gansäuer, D. Bauer, *Eur. J. Org. Chem.* **1998**, 2673.
- [3] Review: A. Gansäuer, *Synlett* **1998**, 801.
- [4] For some enantioselective radical reactions based on different concepts, see a) J. H. Wu, R. Radinov, N. A. Porter, *J. Am. Chem. Soc.* **1995**, *117*, 11029; b) M. P. Sibi, J. Ji, J. H. Wu, S. Gürtler, N. A. Porter, *J. Am. Chem. Soc.* **1996**, *118*, 9200; c) M. Blumenstein, K. Schwartzkopf, J. O. Metzger, *Angew. Chem.* **1997**, *109*, 245; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225; K. Mikami, M. Yamaoka, *Tetrahedron Lett.* **1998**, *39*, 4501.
- [5] R. L. Halterman in *Metalloenes, Vol. 1* (Eds.: A. Togni, R. L. Halterman), WILEY-VCH, Weinheim, **1998**, p. 455.
- [6] R. L. Halterman, K. P. C. Vollhardt, *Organometallics* **1988**, *7*, 883.
- [7] X-ray crystal structure analysis of **1**·CHCl₃ (C₄₃H₅₅Cl₃Ti): *M_r* = 797.0, orthorhombic, space group *P*2₁2₁2₁, *a* = 1290.76(12), *b* = 1310.0(2), *c* = 2517.8(6) pm, *V* = 4.2572 nm³, ρ_{calc} = 1.244 g cm^{−3}, 3454 independent reflections, *R*₁ = 0.0473 for *I* > 2 σ (*I*), *wR*₂ = 0.1101 for all data. The structure was solved by direct methods and refined with anisotropic temperature factors for all non-hydrogen atoms; hydrogen atoms were added in idealized positions and included in the refinement. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-118965. 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).
- [8] a) M. Bochman in *Comprehensive Organometallic Chemistry II, Vol. 4* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, pp. 221, 273; b) T. C. McKenzie, R. D. Scanner, J. E. Bercaw, *J. Organomet. Chem.* **1975**, *102*, 457; c) J. W. Pattiasina, H. J. Heeres, F. van Bolhuis, A. Meetsma, J. H. Teuben, A. L. Spek, *Organometallics* **1987**, *6*, 1004.
- [9] a) B. Giese, *Angew. Chem.* **1989**, *101*, 993; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969; b) B. Giese, K. Heuck, H. Lenhardt, *Chem. Ber.* **1984**, *117*, 2132.
- [10] a) W. A. Nugent, T. V. RajanBabu, *J. Am. Chem. Soc.* **1988**, *110*, 8561; b) T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986.

Noncatalytic Organic Synthesis Using Supercritical Water: The Peculiarity Near the Critical Point

Yutaka Ikushima,* Kiyotaka Hatakeda, Osamu Sato, Toshirou Yokoyama, and Masahiko Arai

As industry is interested in moving away from toxic or environmentally damaging solvents, the finding of an ideal replacement medium for conventional nonpolar solvents offers new opportunities in, for example, reaction engineering, environmental science and technology, and materials science. Supercritical water (scH₂O) heated and pressurized

[*] Dr. Y. Ikushima, Dr. K. Hatakeda, Dr. O. Sato, Dr. T. Yokoyama
National Industrial Research Institute of Tohoku
4-2-1 Nigatake, Miyagino-ku, Sendai 983-8551 (Japan)
Fax: (+81) 22-237-5224
E-mail: ikushima@tniri.go.jp
Dr. M. Arai
Institute for Chemical Reaction Science, Tohoku University
2-1-1 Katahira, Aoba-ku, Sendai 980-8577 (Japan)

beyond its critical point, 374 °C and 22.1 MPa, should be a useful replacement because not only is water the most environmentally acceptable, naturally abundant, and inexpensive solvent, but its physicochemical properties can be changed widely with pressure and temperature;^[1] for example, the static dielectric constant of water is about 80 for the liquid phase and dramatically decreases to 6.0 in the supercritical region at 30 MPa and 400 °C.^[1b] Supercritical water has such unusual properties compared to those of liquid water or of superheated water that nonpolar organic compounds are very soluble or miscible in scH₂O.^[1c] This quality along with its high diffusivity and low viscosity means that scH₂O is expected to function as an ideal replacement for nonpolar organic solvents. Supercritical and superheated H₂O have been used mainly for the “breakdown” of organic reactants, for example, for the oxidative destruction of organic wastes,^[2a] pyrolysis and hydrolysis of coal and biomass materials,^[2b] and geochemical reactions.^[3a] However, there are a few reports on the use of scH₂O as a catalyst or reactant as well as a medium for “organic synthetic reactions”.^[3] Acid-catalyzed organic syntheses will proceed under a scH₂O atmosphere even in the absence of any acid catalysts. This observation may be expected from studies on the structure of water at high temperatures and high pressures, which indicate that the network of hydrogen bonding is significantly changed relative to that under normal conditions.^[4] By using in situ Raman spectroscopy we have shown that the extent and strength of hydrogen bonding decreases peculiarly near the critical point, and promotes the evolution of protons.^[4d]

Herein we report interesting examples of an efficient noncatalytic pinacol rearrangement and of a noncatalytic Beckmann rearrangement in the near-critical region of scH₂O; both reactions are known to be catalyzed by strong acids in conventional solutions. The Beckmann rearrangement of cyclohexanone oxime into ϵ -caprolactam is a commercially important reaction for the production of synthetic fibers and the pinacol rearrangement has attracted attention as a fundamental way of producing aldehydes and ketones. However, both reactions have disadvantages in that highly concentrated monobasic acids or solid acids with short lifetime should be used as catalysts, and by-products of low commercial value are formed frequently.^[5]

Although the rate of the rearrangement of pinacol to pinacolone can be improved by introducing acid catalysts at high concentrations,^[6] it is still very slow and less selective: for example, the first-order rate constants under distillation conditions are at best $3.0 \times 10^{-3} \text{ s}^{-1}$ ^[6a] and $2.9 \times 10^{-3} \text{ s}^{-1}$ ^[6b] with 0.71 M HClO₄ and 2.43 M H₂SO₄, respectively. In addition, the selectivity for pinacolone is only 65–72% even when the reaction is carried out in 6 N concentrated H₂SO₄ solution.^[6c]

Figure 1 shows the background-corrected IR spectra for a mixture of the pinacol rearrangement in scH₂O (390 °C, 25 MPa), superheated H₂O (250 °C, 25 MPa), and ordinary water (20 °C, 0.1 MPa) at a constant reaction time of 108.0 s with our real time, in situ FT-IR measurements. A great change is seen in the spectrum obtained in scH₂O (trace C). A new strong band centered at 1701 cm⁻¹ appears in the scH₂O spectrum, which can be assigned to the CO stretching (ν_1) of the pinacolone formed in this supercritical region. This band is

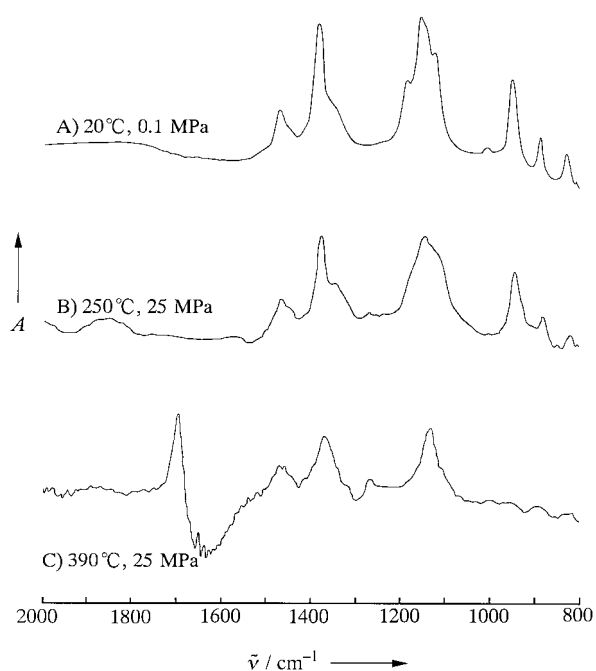


Figure 1. Infrared spectra of the reaction mixture in the noncatalytic pinacol rearrangement in H₂O at different pressures and temperatures. The bands at 1701 and 945 cm⁻¹ correspond to CO stretching (ν_1) in pinacolone and OH bending (ν_2) in pinacol, respectively. The reaction time is 108 s.

not observed in the superheated (trace B) and ordinary water (trace A) phases. In addition the band centered at 945 cm⁻¹, which corresponds to the OH bending (ν_2) of pinacol disappears completely in the scH₂O spectrum. This in situ observation demonstrates for the first time that the rearrangement of pinacol to pinacolone proceeds very rapidly in scH₂O in the absence of any acid catalysts and strongly supports the function of scH₂O as an acid catalyst. Further analysis of the reaction mixture at the end of the reaction by GC-MS and ¹H NMR spectroscopy confirmed that the selectivity for the pinacolone reaches 100% at 390 °C and 25 MPa.

Since the reaction is kinetically first order in pinacol,^[6] the first-order rate constants have been determined by the in situ spectroscopic measurements in the ranges of 20–450 °C and 0.1–35 MPa. The change in the pinacol concentration was monitored by the decrease in the FT-IR absorbance of the ν_2 band of pinacol centered at 945 cm⁻¹. The extinction coefficient of ν_2 determined through the Beer–Lambert law was assumed to be independent of temperature. Variations in pressure did not influence the absorbance at ambient temperatures as evidenced by the unchanged absorptivity of pinacol at a constant concentration of 0.40 M in H₂O over the range of 0.1–35 MPa. Figure 2 shows the first-order rate constants under various conditions: scH₂O, superheated H₂O, and aqueous concentrated acid solutions. A dramatic enhancement in the reaction rate is seen on performing the reaction in scH₂O even in the absence of acid catalysts. The reaction in scH₂O at 25 MPa and 450 °C is over 100 times faster than those in 2.43 M H₂SO₄^[6a] and 0.71 M HClO₄^[6b] under distillation conditions, and it is also 28200 times faster than that in 0.871 M HCl at 46.7 MPa and 70 °C.^[6d] Quantitative formation of pinacolone from pinacol by a classical method requires

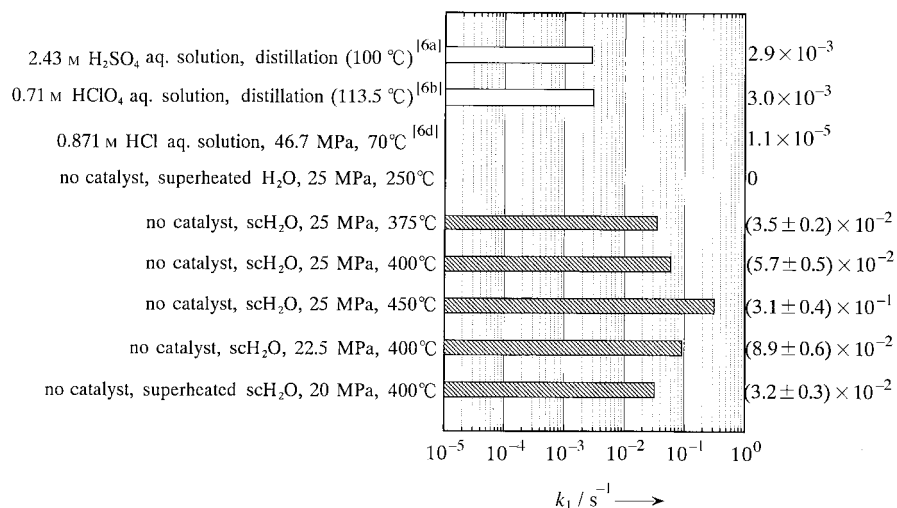


Figure 2. The first-order rate constants k_1 of the pinacol rearrangement to pinacolone. The acid catalyst and its concentration, solvent, pressure, and temperature are stated on the left. For our data 95 % confidence limits are given.

boiling it in 25 % H_2SO_4 for 3 h.^[6c] The reaction is significantly accelerated by raising the temperature in the subcritical and scH_2O region; however, the reaction did not occur in superheated H_2O below 300°C at constant pressures. Up to 60 min were needed to cause quantitative rearrangement of pinacol in superheated D_2O at 275°C .^[6f] Furthermore, no pinacol rearrangement has been reported to have been done in aqueous acid solutions at such high temperatures and pressures that the environment should be changed into the very corrosive state that exists in superheated H_2O ,^[7] and where the ionic behavior including dynamics should be entirely different from that at ambient conditions.^[8] Figure 3 shows the change in the rate constant with pressure at a fixed

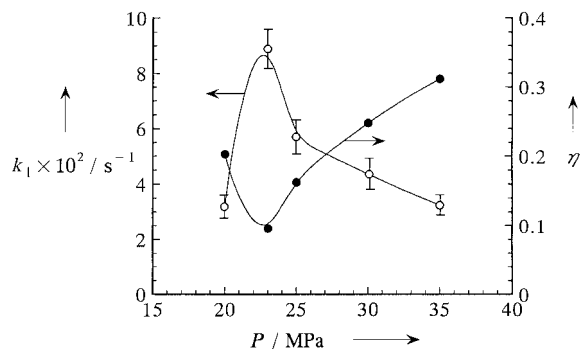


Figure 3. Relationship between the extent of hydrogen bonding η (●) and the first-order rate constant k_1 (○) for the pinacol rearrangement as a function of pressure at a fixed temperature of 400°C . The 95 % confidence limits for the k_1 values are given by bars.

temperature of 400°C . It is thus noted that the rate constant in this pinacol rearrangement becomes maximized at the near-critical pressure of 22.5 MPa. For acid-catalyzed reactions the ion product K_w is of importance.^[3c,i] However, the present results shown in Figures 2 and 3 cannot be explained by the change in K_w . At 400°C and 5 MPa K_w is $10^{-33.18}$ and increases with increasing pressure; for example, to $K_w = 10^{-19.43}$ at 25 MPa, that is, near the critical pressure.^[1d] This pressure

dependence is different from the data shown in Figures 2 and 3, and we should consider microscopic/dynamic factors other than macroscopic/static properties, for example, the ionic product. We are sure that a change of hydrogen bonding is a key factor. The extent of hydrogen bonding η of water is also presented in Figure 3, where $\eta = 0$ is the limit of no hydrogen bonds for hot, low-density vapor and $\eta = 1$ corresponds to water at 25 and 0.1 MPa. Our Raman data concerning the hydrogen bonding of water has been successfully converted into the η scale^[4d] by applying a linear relation between the NMR chemical shift δ of water and the η value.^[9] The η value at the near-critical pressure shows a minimum and is remarkably lower than other superheated or super-

critical conditions. It was thus demonstrated that the extent of hydrogen bonding reduces uniquely near the critical pressure, where dimers and/or monomers are predominant,^[9] but monomers are, in part, further broken down into protons as a result of the large fluctuations in the structure of water.^[4d] The organization of 4–10 water molecules is required to solvate the transferred protons,^[10] and hence the water structure near the critical pressure becomes less able to accommodate the ejected protons. That is, the “local” proton concentration would be extremely high when the transferring proton cannot escape. Furthermore, the “local” concentration of pinacol around the protons would be very large near the critical pressure.^[11] These effects may explain the observed enhancement of the rate of reaction.

To demonstrate that this type of nucleophilic rearrangement in scH_2O is triggered by a decrease in the extent of hydrogen bonding in the near-critical region we have further attempted a Beckmann rearrangement of cyclohexanone oxime into ϵ -caprolactam without acid catalysts in superheated and scH_2O conditions by using a flow system. A new band of CO stretching assigned to the ϵ -caprolactam formed is found in the IR spectrum obtained near the critical point (not shown), whereas no bands for cyclohexanone, which is the hydrolysis product of cyclohexanone oxime, were observed. Furthermore, the ^1H NMR spectrum of the purified chief product obtained at 22.1 MPa and 375°C is in agreement with that of the authentic sample. Therefore, in analogy to the pinacol rearrangement, the Beckmann rearrangement can also proceed without acid catalysts in scH_2O . Figure 4 shows the first-order rate constant versus temperature profile for the formation of ϵ -caprolactam at the critical pressure. One can also see an interesting temperature dependence. In this Beckmann rearrangement the ϵ -caprolactam is found, peculiarly, to be synthesized in the limited temperature range where the rate greatly increases as the temperature approaches the critical temperature. In Figure 4 the extent of hydrogen bonding η in water based on the Raman data^[4d] is also represented. The η value shows a significant decrease above 370°C and shows a minimal value at the critical

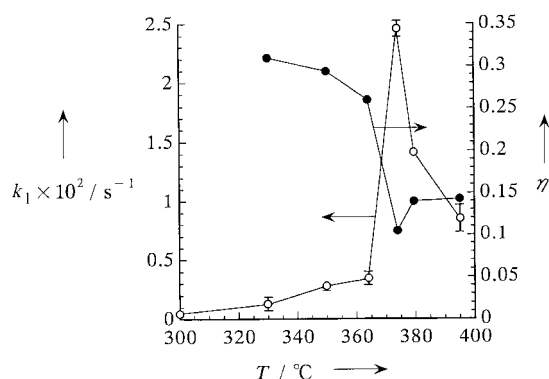
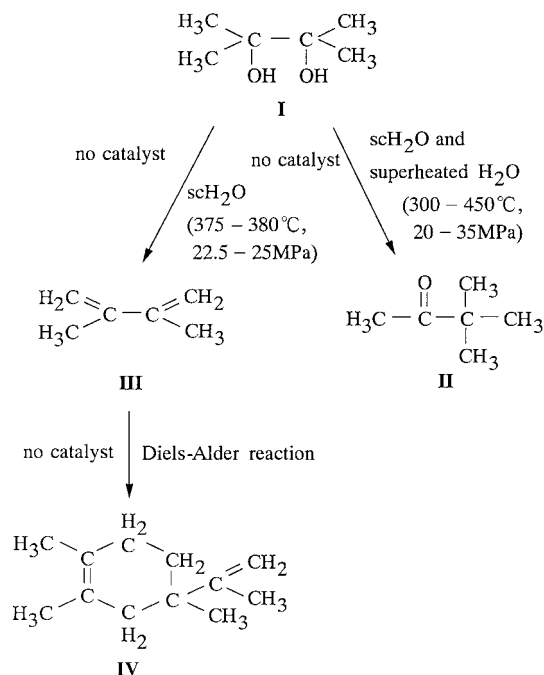


Figure 4. Relationship between the extent of hydrogen bonding η (●) and the first-order rate constant k_1 (○) for the Beckmann rearrangement to ϵ -caprolactam as a function of temperature at the critical pressure of 22.1 MPa. The 95% confidence limits for the k_1 values are given by bars.

temperature. One can thus believe that a marked loss in the ability of water to accept a proton near the critical point is an important cause for the promotion of the Beckmann rearrangement as well as the pinacol rearrangement.

Supercritical water could also be used as a more profitable acid catalyst for dehydration and other reactions if its own "acidity" could be changed. Pinacolone was the sole product under scH_2O and superheated H_2O reaction conditions as described above; however, in the very limited near-critical region of 375–380°C at 22.5–25 MPa, the formation of 1,2,4-trimethyl-4-isopropenyl-cyclohexene (**IV**) rather than of pinacolone (**II**, Scheme 1) from pinacol (**I**) was observed for the first time. The conversion of **I** to **IV** is 50–70%. The analytical result obtained by GC-MS is in accord with that of the authentic sample. We think that pinacol is completely dehydrated into 2,3-dimethyl-1,3-butadiene (**III**), and then the intermolecular Diels–Alder reaction of **III** results in the



Scheme 1. Noncatalytic reaction paths producing pinacolone (**II**, rearrangement) and 1,2,4-trimethyl-4-isopropenyl-cyclohexene (**IV**; Diels–Alder reaction) in scH_2O .

formation of **IV**. Diels–Alder reactions have already been confirmed to occur in scH_2O in the absence of acid catalysts.^[3e] The complete dehydration of **I** to **III** can be achieved with relatively weak acids such as HBr ^[12] by a mechanism different from that in the above-mentioned pinacol–pinacolone rearrangement. Thus, not only the "local" concentration of protons but also the "acidity" of scH_2O itself can be adjusted, especially in the near-critical region. Hence scH_2O is expected to find more important potential applications in organic synthesis. In a very compressible medium such as a supercritical fluid it may be possible, by controlling pressure and temperature, to adjust the mean distance between a solvent and a more massive solute species within a range where the mutual pair function is significantly varied.^[13] It appears that the alternate path for dehydration may be associated with the tuning of the average distance between the protons generated and the substrate molecules, which results in a change in the solvation energy of the substrate.

Experimental Section

The reactions were carried out under ambient to scH_2O conditions by using a high-pressure, high-temperature flow reaction system with a short path length (20 μm) FT-IR cell operable at 500°C and 50 MPa (Figure 5), wherein the reactions could be conducted and monitored. The cell was constructed from Hastelloy C-276 and type IIa diamond windows. This new development of the cell with the short path length diamond windows has

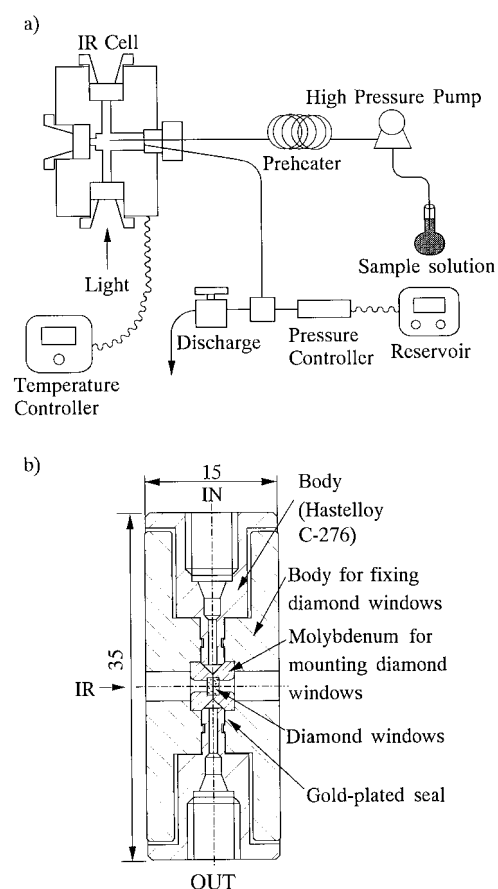


Figure 5. a) Schematic diagram of a high-temperature and high-pressure FT-IR flow reaction system. b) Cross-sectional view of a high-pressure and high-temperature optical IR cell. 15 mm and 35 mm represent the diameter and length, respectively.

enabled broad-range optical access for the first time in the near- and mid-IR region even in a scH_2O atmosphere. Aqueous solutions of pinacol (0.40 M) and cyclohexanone oxime (0.15 M) were introduced into the system with flow rates in the range of 0.07 to 2.0 mL min^{-1} (the reaction time varied from 4 to 215 s) using a high-pressure liquid pump, and pressure control was achieved by a back-pressure regulator. The temperature was then raised to the desired value. Once the system had stabilized, 50 spectra (4 cm^{-1} resolution) were summed in one destination file. Each file was normalized against the spectrum of pure H_2O under the same conditions. Furthermore, all of the products were identified qualitatively by ^1H NMR spectroscopy and GC-MS.

The frequency precision at the band center of the Raman OH symmetric stretch (ν_1) in the spectrum depends on changes in the optical pixel width of the charge-coupled device, and the resulting frequency error of the ν_1 mode is within 2.0 cm^{-1} .^[8]

Received: March 22, 1999 [Z 13199 IE]
German version: *Angew. Chem.* **1999**, *111*, 3087–3091

Keywords: rearrangements • solvent effects • supercritical fluids • vibrational spectroscopy

A 10^{10} Rate Enhancement of Phosphodiester Hydrolysis by a Dinuclear Aminoamidase—Transition-State Analogues as Substrates?*

Hyun Ik Park and Li-June Ming*

The studies of metal complex based chemical models for hydrolytic metalloenzymes^[1–3] have provided insight into the mechanistic roles of the metal ion(s) at the active-site and the coordinated nucleophilic water molecule in those enzymes.^[4] However, these model complexes lack specific recognition and catalysis toward peptide substrates over phosphoester substrates, or vice versa, as a result of the absence of a well-defined active site. Conversely, enzymes have evolved to recognize one particular type of substrate and are able to stabilize the corresponding transition state,^[5] such as the tetrahedral transition state in peptide hydrolysis which is very different from the trigonal bipyramidal transition state in phosphoester hydrolysis.^[4] As a result each class of hydrolytic metalloenzymes can perform only one type of hydrolysis despite the presence of a highly activated ($>10^7$ in terms of $\text{p}K_{\text{a}}$) coordinated water molecule that is ready for nucleophilic attack on the substrate. Moreover, anionic tetrahedral phosphoesters,^[6] phosphonates,^[7] phosphoamidates,^[8] and semiacetals,^[9] resemble the transition-state *gem*-diolate of peptides, esters, and amides formed during hydrolysis and can serve as potential inhibitors for the corresponding enzymes. Thus, it seems unlikely that an enzyme with a single active site can hydrolyze both phosphoester and peptide substrates because the specific recognitions and hydrolytic pathways for these two types of substrates are quite different.

Herein we report a unique example of an “alternative” enzyme catalysis in which a dizinc aminoamidase from *Streptomyces griseus* (sAP) exhibits remarkable hydrolytic activities toward both peptide and phosphodiester substrates. Thus, this enzyme can serve as an alternative dinuclear model system to provide further insight into the catalytic mechanism of metal-centered dinuclear hydrolysis.

The activity profiles obtained during the purification of the sAP^[10, 11] and its thermo-deactivation at 69°C show that the activity toward the hydrolysis of the phosphodiesterase substrate bis-*p*-nitrophenylphosphate (BNPP)^[12] is always parallel to the activities toward the aminoamidase substrates Leu-*p*-nitroanilide (Leu-*p*NA) and Lys-*p*NA (see data in ref. [13] and Table 1). This observation suggests that these two different types of hydrolytic reactions are possibly carried out by a single enzyme, and the decrease in both activities is attributable to thermo-denaturation of the sAP. Both activities are competitively inhibited by the dizinc aminoamidase inhibitors bestatin,^[14] 1-aminobutylphosphonate,^[7] and Leu-

- [1] a) *NBC/NRC Steam Tables* (Eds.: L. Haar, J. S. Gallagher, G. S. Kell), Hemisphere, New York, **1984**; b) *High-Temperature Aqueous Solutions: Thermodynamic Properties* (Eds.: P. R. J. Fernandez, H. R. Corti, M. L. Japer), CRC, Boca Raton, FL, **1992**; c) R. W. Shaw, T. B. Brill, A. A. Clifford, C. A. Eckert, E. U. Franck, *Chem. Eng. News* **1991**, *69*, 2639; d) W. L. Marshall, E. U. Franck, *J. Phys. Chem. Ref. Data* **1981**, *10*, 295.
- [2] a) K. Hatake, Y. Ikushima, S. Ito, O. Sato, N. Saito, *Chem. Lett.* **1997**, 245; b) B. M. Kabyemela, T. Adschiri, R. Malaluan, K. Arai, *Ind. Eng. Chem. Res.* **1997**, *36*, 1552.
- [3] a) M. Siskin, A. R. Katritzky, *Science* **1991**, *254*, 231; b) D. M. Masten, B. R. Foy, D. M. Harradine, R. B. Dyer, *J. Phys. Chem.* **1993**, *97*, 8557; c) A. R. Katritzky, S. M. Allin, *Acc. Chem. Res.* **1996**, *29*, 399; d) J. W. Schoppelrei, M. L. Kieke, T. B. Brill, *J. Phys. Chem.* **1996**, *100*, 7463; e) M. B. Korzenski, J. W. Kolis, *Tetrahedron Lett.* **1997**, *38*, 5611; f) J. An, L. Bagnell, T. Cablewski, C. R. Strauss, R. W. Trainor, *J. Org. Chem.* **1997**, *62*, 2505; g) O. Sato, Y. Ikushima, T. Yokoyama, *J. Org. Chem.* **1998**, *63*, 9100; h) P. E. Savage, *Chem. Rev.* **1999**, *99*, 603; i) K. Chardler, F. Deng, A. K. Dillow, C. L. Liotta, C. A. Eckert, *Ind. Eng. Chem. Res.* **1997**, *36*, 5175.
- [4] a) E. U. Franck, K. Roth, *Discuss. Faraday Soc.* **1967**, *43*, 108; b) W. Kohl, H. A. Lindner, E. U. Franck, *Ber. Bunsenges. Phys. Chem.* **1991**, *95*, 1586; c) H. Ohtaki, T. Radnai, T. Yamaguchi, *Chem. Soc. Rev.* **1997**, *41*; d) Y. Ikushima, K. Hatake, N. Saito, M. Arai, *J. Chem. Phys.* **1998**, *108*, 5855.
- [5] a) M. C. Burguet, A. Aucejo, A. Corma, *Can. J. Chem. Eng.* **1987**, *65*, 944; b) S. Sato, K. Urabe, Y. Izumi, *J. Catal.* **1986**, *102*, 99.
- [6] a) C. A. Bunton, T. Hadwick, D. R. Liewellyn, Y. Pocker, *J. Chem. Soc.* **1958**, 403; b) J. F. Duncan, K. R. Lynn, *J. Chem. Soc.* **1956**, 3512; c) A. Hill, E. W. Flosdorf, *Org. Synth. Coll. Vol.* **1941**, *1*, 462; d) T. Moriyoshi, K. Tamura, *Rev. Phys. Chem. Jpn.* **1970**, *40*, 48; e) J. Boeseken, W. R. van Tonning, *Recl. Trav. Chim. Pays-Bas* **1920**, *39*, 187; f) B. Kuhlman, E. M. Arnett, M. Siskin, *J. Org. Chem.* **1994**, *59*, 3098.
- [7] D. B. Mitton, P. A. Marrone, R. M. Latanision, *J. Electrochem. Soc.* **1996**, *143*, L59, and references therein.
- [8] Y. Ikushima, N. Saito, M. Arai, *J. Phys. Chem. B* **1998**, *102*, 3029; Y. Ikushima, K. Hatake, N. Saito, M. Arai, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1763.
- [9] a) M. M. Hoffmann, S. Conradi, *J. Am. Chem. Soc.* **1997**, *119*, 3811; b) N. Matsubayashi, C. Wakui, M. Nakahara, *Phys. Rev. Lett.* **1997**, *78*, 2573.
- [10] E. T. Ryan, T. Xiang, K. P. Johnston, M. A. Fox, *J. Phys. Chem.* **1996**, *100*, 9395.
- [11] a) Y. Ikushima, N. Saito, M. Arai, *J. Phys. Chem.* **1992**, *96*, 2293; b) J. B. Ellington, J. F. Brennecke, *J. Chem. Soc. Chem. Commun.* **1993**, 1094.
- [12] C. F. R. Allen, A. Bell, *Org. Synth. Coll. Vol.* **1955**, *3*, 312.
- [13] A. A. Clifford, K. Pople, W. J. Gaskill, K. D. Bartle, C. M. Rayne, *Chem. Commun.* **1997**, 595.

[*] Prof. L.-J. Ming, H. I. Park
Department of Chemistry and
Institute for Biomolecular Science
University of South Florida
Tampa, FL 33620-5250 (USA)
Fax: (+1) 813-974-1733
E-mail: ming@chuma.cas.usf.edu

[**] This work was partially supported by a PYF award (1996) from the University of South Florida.

Table 1. The hydrolyses of aminopeptidase substrates and BNPP by sAP (the first active fractions eluted from the ion-exchange column) in 0.1M HEPES buffer at pH 8.0 in the presence of 2 mM Ca^{2+} at 30 °C.

substrate	Heat deactivation ^[a] 7 h [%]	bestatin ^[d]	K_i [μM] ^[b]		k_{cat} [s^{-1}]	Kinetic parameters ^[c]	
			ABP ^[d]	Leu-NHOH ^[c]		K_m [mM]	k_{cat}/K_m [$\text{M}^{-1}\text{s}^{-1}$]
BNPP	22	1.3 ± 0.1	1.5 ± 0.2	40 ± 13	0.45 ± 0.02	4.5 ± 0.4	100
Leu- <i>p</i> NA	21	1.5 ± 0.2	1.9 ± 0.2	38 ± 10	657 ± 54	0.45 ± 0.42	1.46×10^6
Ala- <i>p</i> NA	19	1.2	1.9	30	3.6 ± 0.4	5.0 ± 0.4	720
Lys- <i>p</i> NA	26	2.1	1.9	52	1.5 ± 0.2	7.1 ± 0.8	211

[a] BNPP, 10 mM; Leu-*p*NA, 1 mM; Ala-*p*NA, 10 mM; and Lys-*p*NA, 10 mM in 0.1M HEPES at pH 8.0 and 69 °C. The activities are reported with respect to untreated controls. [b] Obtained from three different inhibitor concentrations.^[5b] The K_i value of BNPP in the hydrolysis of Leu-*p*NA is 5.1 mM. [c] The substrate concentrations were BNPP: 1.0–20 mM; Leu-*p*NA: 0.1–2.0 mM; Ala-*p*NA: 1–20 mM; and Lys-*p*NA: 1–20 mM. The initial rates were obtained from the change of absorbance at 405 nm for peptide substrates ($\epsilon = 10600 \text{ M}^{-1} \text{ cm}^{-1}$) and for BNPP ($\epsilon = 17500 \text{ M}^{-1} \text{ cm}^{-1}$). [d] 1, 2, and 4 μM , pre-incubated with sAP for 3 hours; ABP = 1-aminobutylphosphonate. [e] 25, 50, and 100 μM , without incubation.

hydroxamate^[15] (Table 1). Moreover, the “slow substrate” BNPP itself serves as a competitive inhibitor ($K_i = 5.1 \text{ mM}$) toward the hydrolysis of Leu-*p*NA by sAP. We conclude on the basis of the competitive inhibition patterns that the hydrolysis of BNPP occurs in the dinuclear active site of sAP.

We have previously demonstrated that Co^{2+} binds sequentially to the two metal binding sites of apo-sAP.^[11] The hydrolysis of BNPP by zinc-free sAP exhibits a selective Co^{2+} activation profile (trace $\square$ – $\square$, Figure 1) similar to the

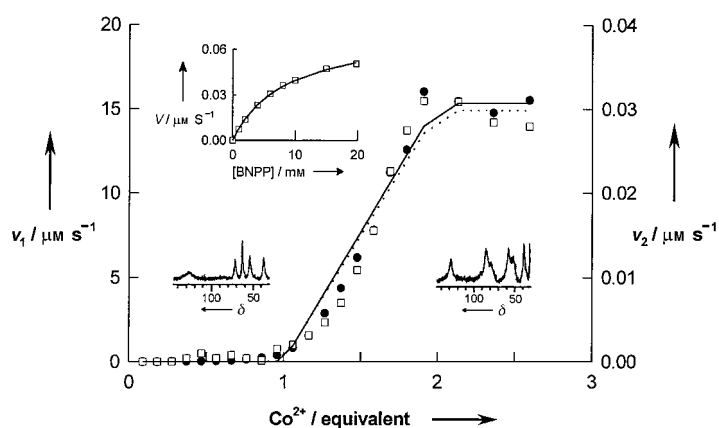


Figure 1. Activation of apo-sAP (0.112 mM in 0.1M MES buffer at pH 6.1) by Co^{2+} towards the hydrolysis of Lys-*p*NA (2.5 mM, $\bullet$, left axis v_1) and BNPP (5 mM, $\square$, right axis v_2) in 0.1M HEPES buffer at 30 °C and pH 8.0 (HEPES = 2[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid). The solid (Lys-*p*NA) and dotted (BNPP) lines are obtained by fitting the data to an ideal selective metal binding mode. The inset is a Michaelis–Menten kinetic plot for BNPP hydrolysis, which gives $k_{\text{cat}} = 0.45 \text{ s}^{-1}$ and $K_m = 4.5 \text{ mM}$. The inset ^1H NMR spectra (Bruker AMX360 at 360.13 MHz, 298 K, 90° pulse, and presaturation for solvent suppression) demonstrate the binding of one (left) and two (right) Co^{2+} ions to apo-sAP.

hydrolysis of a peptide substrate^[11] (trace $\bullet$ – $\bullet$), which suggests that both hydrolyses are carried out in the dinuclear active site of sAP. The sequential binding of Co^{2+} to the dinuclear metal site of apo-sAP has also been concluded by NMR spectroscopy (see insets in Figure 1).^[12] The hydrolysis of BNPP by any phosphodiesterase contaminant can thus be completely excluded from this stoichiometric metal-activation study.

A complete Michaelis–Menten kinetic analysis of BNPP hydrolysis by sAP has been carried out (see inset in Figure 1 and Table 1). It is very interesting to note that the second-

order rate constant of BNPP hydrolysis by sAP ($100 \text{ M}^{-1} \text{ s}^{-1}$ in terms of k_{cat}/K_m) under mild conditions (30 °C and pH 8.0) exceeds those of synthetic Zn^{2+} -containing chemical models (which typically lie in the range $1.3\text{--}12.7 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ at 35 °C and pH 8.6–10.5) by at least 10^6 times.^[2, 16] The specific activity towards the hydrolysis of 1 mM BNPP was also determined as $33.7 \text{ nmol min}^{-1} \text{ mg}^{-1}$. This value is higher than that for the hydrolysis of 1 mM Gly-*p*NA by sAP ($\leq 19.3 \text{ nmol min}^{-1} \text{ mg}^{-1}$, calculated from ref. [10b]), and surpasses the activities of several phosphoesterases toward the hydrolysis of 1 mM BNPP. For example, the specific activities of the alkaline phosphatase from calf intestine, chicken intestine, and *Escherichia coli* are 41.5, 16.5, and $11.1 \text{ nmol min}^{-1} \text{ mg}^{-1}$, respectively, and of wheat germ acid phosphatase $1.9 \text{ nmol min}^{-1} \text{ mg}^{-1}$.^[12] The activities of 5'-nucleotide phosphodiesterase from bovine intestine and snake venom, 3'-nucleotide phosphodiesterase from bovine spleen, and cAMP phosphodiesterase from bovine heart are 2450, 82.3, 0.8, and $0.3 \text{ nmol min}^{-1} \text{ mg}^{-1}$, respectively.^[12]

Despite the fact that the phosphodiesterase substrate BNPP is highly activated by the *p*-nitro group toward hydrolysis, its auto-hydrolytic rate is still extremely slow, with a first-order rate constant of $3 \times 10^{-10} \text{ s}^{-1}$ at pH 7.0 and 50 °C,^[2b] and $6.3 \times 10^{-8} \text{ s}^{-1}$ at pH 10.0 and 100 °C.^[17] The pseudo-first-order rate constant of BNPP hydrolysis by sAP can be extrapolated from the Michaelis–Menten kinetics at low substrate concentrations, the conditions used in many chemical modeling studies.^[1–3] The value of 1.0 s^{-1} obtained at pH 8 and 30 °C is about 10^{10} times larger than the first-order rate constant of the auto-hydrolysis of this substrate under similar conditions. This rate enhancement is quite significant when we take into account that this phosphodiester is a transition-state analogue in peptide/ester hydrolysis,^[6] and is not supposedly hydrolyzed by peptidases. Moreover, the rate of uncatalyzed phosphodiester hydrolysis is generally lower than that of peptides by a factor of about 10^4 .^[18] The much smaller k_{cat}/K_m value for the hydrolysis of BNPP than for the hydrolysis of the best peptide substrate Leu-*p*NA by sAP can thus be reasonably expected (Table 1). The slower rate of phosphodiester hydrolysis is attributed to kinetic inertness^[19] since the nucleophilic attack by hydroxide ions on the negatively charged phosphate group is not favorable as a result of charge repulsion. Nevertheless, a dinuclear center such as in sAP can neutralize the charge on the phosphate moiety quite effectively.

The mechanism for BNPP hydrolysis by sAP can be postulated (Figure 2) from the X-ray crystal structure of sAP,^[20] and the inhibitor-bound complexes of bovine lens leucine aminopeptidase in which the amino group is coordinated to one zinc center and one *gem*-diolate-like C–O[−] group bridges the two zinc ions.^[7a, 9, 21] Since BNPP and Leu-pNA bind to sAP competitively, they may bind to the active

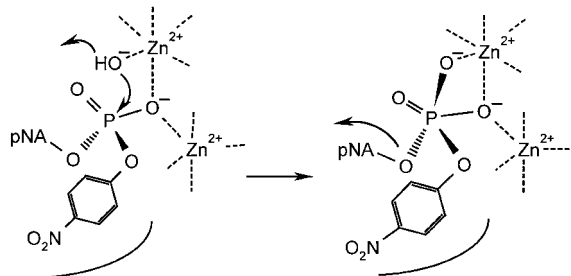


Figure 2. A plausible mechanism for the hydrolysis of BNPP by dinuclear *Streptomyces* aminopeptidase, in which the bridging P–O[−] unit mimics the bridging carbonyl group of a peptide substrate while the amino group of the peptide substrates is missing in BNPP. Presumably one coordinated hydroxide ion on one Zn²⁺ center attacks the phosphorus center at the position *trans* to the leaving group. An alternative binding mode might be that the P=O moiety mimics the amino group of peptide substrates that bind to one Zn²⁺ ion.

site in a similar manner despite the absence of the amino group in BNPP. In this model the phosphorus center of BNPP is accessible to nucleophilic attack by a coordinated water molecule.

We have described here a unique and unprecedented case that a transition-state analogue phosphodiester is indeed a substrate for a dizinc aminopeptidase, and is hydrolyzed with an enormous rate acceleration of approximately 10¹⁰ times. Dinuclear mechanisms have also been proposed in several other hydrolytic multinuclear enzymes, including urease, nucleases, and ribozymes.^[4a, 22] This dinuclear metalloprotease sAP, which exhibits this unique alternative catalysis, can thus serve as a dinuclear model system for the further investigation of dinuclear hydrolysis of both peptides and phosphodiesters.

Received: January 18

Revised version: April 15, 1999 [Z.12922IE]

German version: *Angew. Chem.* **1999**, *111*, 3097–3100

Keywords: coordination chemistry • enzyme catalysis • hydrolyses • metalloproteins

- [1] a) E. Kimura, *Prog. Inorg. Chem.* **1994**, *41*, 443–491; b) E. Kimura, T. Koike, *Adv. Inorg. Chem.* **1997**, *44*, 229–261.
- [2] a) C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, C. Giorgi, P. Paoletti, B. Valtancoli, D. Zanchi, *Inorg. Chem.* **1997**, *36*, 2784–2790; b) J. Chin, M. Banaszczuk, V. Jubian, X. Zou, *J. Am. Chem. Soc.* **1989**, *111*, 186–190; c) M. J. Young, J. Chin, *J. Am. Chem. Soc.* **1995**, *117*, 10577–10578.
- [3] a) E. Kimura, H. Hashimoto, T. Koike, *J. Am. Chem. Soc.* **1996**, *118*, 10963–10970; b) E. L. Hegg, J. N. Burstyn, *Inorg. Chem.* **1996**, *35*, 7474–7481; c) J. N. Burstyn, K. A. Deal, *Inorg. Chem.* **1993**, *32*, 3585–3586; d) E. L. Hegg, J. N. Burstyn, *J. Am. Chem. Soc.* **1995**, *117*, 7015–7016; d) A. Tsubouchi, T. C. Bruice, *J. Am. Chem. Soc.* **1994**, *116*, 11614–11618.

- [4] a) N. Sträter, W. N. Lipscomb, T. Klabunde, B. Krebs, *Angew. Chem.* **1996**, *108*, 2158–2191; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2024–2055; b) W. N. Lipscomb, N. Sträter, *Chem. Rev.* **1996**, *96*, 2375–2433; c) D. Gani, J. Wilkie, *Chem. Soc. Rev.* **1995**, *55*, 55–63; d) C. B. Black, H.-W. Huang, J. A. Cowan, *Coord. Chem. Rev.* **1994**, *135/136*, 165–202; e) M. Fothergill, M. F. Goodman, J. Petruska, A. Warshel, *J. Am. Chem. Soc.* **1995**, *117*, 11619–11627; f) H. Kim, W. N. Lipscomb, *Biochemistry* **1993**, *32*, 8465–8478; g) E. E. Kim, H. W. Wyckoff, *J. Mol. Biol.* **1991**, *218*, 449–464; h) D. W. Christianson, W. N. Lipscomb, *Acc. Chem. Res.* **1989**, *22*, 62–69; i) B. W. Matthews, *Acc. Chem. Res.* **1988**, *21*, 333–340.
- [5] a) L. Pauling, *Am. Sci.* **1948**, *36*, 51–58; b) C. Walsh, *Enzymatic Reaction Mechanisms*, Freeman, New York, **1979**.
- [6] a) K. Nishida, Y. Ohta, M. Ito, Y. Nagamura, S. Kitahara, K. Fujii, I. Ishiguro, *Biochim. Biophys. Acta* **1996**, *1313*, 47–53; b) C. V. Preuss, C. K. Svensson, *Biochem. Pharmacol.* **1996**, *51*, 1661–1668; c) L. Luan, T. Sugiyama, S. Takai, Y. Usami, T. Adachi, Y. Katagiri, K. Hirano, *Biol. Pharmacol. Bull.* **1997**, *20*, 71–75.
- [7] a) N. Sträter, W. N. Lipscomb, *Biochemistry* **1995**, *34*, 9200–9210; b) B. Lejczak, P. Kafarski, J. Zygmunt, *Biochemistry* **1989**, *28*, 3549–3555.
- [8] D. E. Tronrud, H. M. Holden, B. W. Matthews, *Eur. J. Biochem.* **1986**, *157*, 261.
- [9] N. Sträter, W. N. Lipscomb, *Biochemistry* **1995**, *34*, 14792–14800.
- [10] a) A. Spungin, S. Blumberg, *Eur. J. Biochem.* **1989**, *183*, 471–477; b) D. Ben-Meir, A. Spungin, R. Ashkenazi, S. Blumberg, *Eur. J. Biochem.* **1993**, *212*, 107–112.
- [11] L.-Y. Lin, H. I. Park, L.-J. Ming, *J. Biol. Inorg. Chem.* **1997**, *2*, 744–749.
- [12] a) J. S. Kelly, D. E. Dardinger, L. G. Butler, *Biochemistry* **1975**, *14*, 4983–4988; b) J. S. Kelly, L. G. Burtler, *Biochem. Biophys. Res. Commun.* **1975**, *66*, 316–321.
- [13] The crude enzyme mixture exhibits significant activities (nmol min^{−1} mg^{−1}) toward several substrates of aminopeptidase and phosphoesterase: 1 mM Leu-pNA, 9300; 2.5 mM Lys-pNA, 57; 5 mM *p*-nitrophenylphosphate, 5.2; and 5 mM BNPP, 4.8. After incubation of the mixture for 7 h at 69 °C the hydrolysis toward 10 mM *p*-nitrophenylphosphate was not detectable; Leu-pNA (1 mM), 67% retained; Lys-pNA (10 mM), 28%; Ala-pNA (10 mM), 49%; BNPP (10 mM), 42%. During the chromatographic steps (gel filtration and DEAE ion exchange) the phosphodiesterase activity is parallel to the aminopeptidase activity. These procedures afford a pure aminopeptidase whose activity can be eliminated by demetalation, and re-activated to different extents by several different metal ions.
- [14] a) H. Umezawa, T. Aoyagi, H. Suda, M. Hamada, T. Takeuchi, *J. Antibiotics* **1976**, *29*, 97–99; b) S. H. Wilkes, J. M. Prescott, *J. Biol. Chem.* **1985**, *260*, 13154–13162; c) S. K. Burley, P. R. David, R. M. Sweet, A. Taylor, W. N. Lipscomb, *J. Mol. Biol.* **1992**, *224*, 113–140.
- [15] a) B. Chevrier, H. D'Orchymont, C. Schalk, C. Tarnus, D. Moras, *Eur. J. Biochem.* **1996**, *237*, 393–398; b) S. H. Wilkes, J. M. Prescott, *J. Biol. Chem.* **1983**, *256*, 13517–13521.
- [16] T. Koike, E. Kimura, *J. Am. Chem. Soc.* **1991**, *113*, 8935–8941.
- [17] A. J. Kirby, M. Younas, *J. Chem. Soc. B* **1970**, 510–513.
- [18] A. Radzicka, R. Wolfenden, *Science* **1995**, *267*, 90–93.
- [19] a) F. H. Westheimer, *Science* **1987**, *235*, 1173–1178; b) D. Kahne, W. C. Still, *J. Am. Chem. Soc.* **1988**, *110*, 7529–7534.
- [20] H. M. Greenbalt, O. Almog, B. Maras, B. Spungin-Bialik, D. Barra, S. Blumberg, G. Shoham, *J. Mol. Biol.* **1997**, *265*, 620–636.
- [21] a) S. K. Burly, P. R. David, W. N. Lipscomb, *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 6916–6920; b) H. Kim, W. N. Lipscomb, *Biochemistry* **1993**, *32*, 8465–8478.
- [22] For a review, see D. E. Wilcox, *Chem. Rev.* **1996**, *96*, 2435–2458.

[*n*]-Polyurethanes: Synthesis and Characterization**

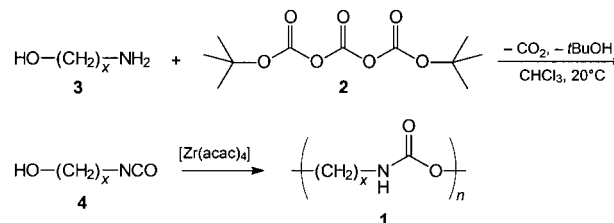
Ron M. Versteegen, Rint P. Sijbesma, and
E. W. Meijer*

Polyurethanes are a versatile class of polymers that are used in a broad range of applications.^[1] In most, if not all, cases of linear polyurethanes, the macromolecular structure is based on the reaction of dihydroxy compounds with diisocyanates, yielding A₂B₂ polymers or the [*m,n*]-polyurethanes. A comprehensive study of the parent aliphatic [*m,n*]-polyurethanes was reported by Otto Bayer in *Angewandte Chemie* in 1947.^[2] These, at that time, novel structures were compared and proposed to compete with the two series of aliphatic polyamides, the [*n*]- and [*m,n*]-nylons. Whereas the disclosure of the [*n*]-nylons quickly followed Carothers' first description of the [*m,n*]-nylons, the general class of linear aliphatic [*n*]-polyurethanes is notably absent in the impressive list of linear macromolecules, despite its structural simplicity. Here, we report on a general and convenient route to aliphatic α,ω -isocyanato alcohols and their in situ polymerization into the corresponding [*n*]-polyurethanes **1** of respectable molecular weight.

Why is it that these aliphatic [*n*]-polyurethanes have not been prepared before despite their simple structure? Obviously, this is due to the unavailability of the appropriate monomers; both the α,ω -isocyanato alcohols and the cyclic carbamates were not known and there was hitherto no general route to these classes of substances. As a result the aliphatic series is limited to a few specific structures, which were prepared using ring-opening polymerization of trimethylene urethane,^[3] while some oligomers were synthesized by a stepwise sequence.^[4] The poly(1,4-phenylene urethane) was prepared by the Curtius rearrangement of hydroxy benzoyl azide, as was reported by Kinstle and Sepulveda, and by several others.^[5] The much higher nucleophilicity of alcohols over phenols requires, however, a much milder conversion of the amino group of the easily accessible α,ω -amino alcohol into an α,ω -isocyanato alcohol, followed by a controlled polymerization. Unfortunately, most of the methods known to transform amines into isocyanates are not mild enough and furnish undefined products as the result of uncontrolled side reactions. Recently, we reported on using di-*tert*-butyltricarboxylate **2** as a versatile and mild reagent for the synthesis of unusual mono- and multi-isocyanates within minutes at room temperature.^[6] The high selectivity and reactivity of reagent **2**

is used here to synthesize α,ω -isocyanato alcohols. The latter are easily polymerized in high yields to obtain [*n*]-polyurethanes **1**.

The general reaction sequence to prepare the series of [*n*]-polyurethanes **1** with *x* = 4–12 is given in Scheme 1. The starting α,ω -amino alcohols **3** are either commercially available or were prepared by standard procedures.^[7] The synthesis of di-*tert*-butyltricarboxylate **2** has been optimized and



Scheme 1. Synthesis of [*n*]-polyurethanes (*x* = 4–12).

described in detail.^[8] This reagent is the key element for the selective formation of the intermediate α,ω -isocyanato alcohols **4**. Reaction of a small excess of **2** with **3** in chloroform at room temperature gives within 10 min the isocyanato alcohol monomer **4**. This reaction is accompanied by the formation of two equivalents of carbon dioxide and *tert*-butyl alcohol. The former escapes from the solution, while the latter stays in the reaction mixture. Under the condition employed here, *tert*-butyl alcohol is unreactive to the isocyanate, hence, it is harmless. The amino alcohol solution was added by injecting it under the surface of the di-*tert*-butyltricarboxylate solution, in order to avoid turbidity of the reaction mixture, due to the formation of carbamic acid by reaction of escaping carbon dioxide and the amino alcohol. After decomposition of the unstable carbamic acid into the initial amino alcohol, the latter reacts with already formed isocyanate, resulting in urea derivatives. This side reaction distorts the perfect stoichiometry of the AB-type polymerization, and consequently, limits the molecular weight of the polymer.

The formation of the α,ω -isocyanato alcohols has been confirmed by IR and ¹H NMR spectroscopy. In the IR spectrum, a strong absorption of the N=C=O stretch at 2274 cm⁻¹ is observed for solutions of **4** in chloroform. Figure 1b shows the ¹H NMR spectrum of 5-isocyanato-1-pentanol after reaction of 5-amino-1-pentanol (spectrum in Figure 1a) with di-*tert*-butyltricarboxylate **2**. Figure 1b reveals the absence of any side products, and also proves the relative stability of **4** in solution, however, evaporation to dryness furnished undefined products.

The polymerization of **4** is performed in situ by addition of a catalytic amount of zirconium(IV) acetylacetonate or dibutyltin dilaurate. For the short isocyanato alcohols with *x* = 2 or 3, the polymerization procedure failed and resulted in the formation of cyclic urethanes, with five- and six-membered rings, respectively. For the longer isocyanato alcohols, the precipitation of polymer **4** was observed after a few hours. The polymer was isolated by filtration in a yield of about 60%. Since the polymerization was performed in solution, a relatively large amount of soluble, cyclic oligomers was formed. Electrospray mass spectra of the filtrate showed the presence of cyclic dimers up to cyclic hexamers. The polymers

[*] Prof. Dr. E. W. Meijer, R. M. Versteegen, Dr. R. P. Sijbesma
Laboratory of Macromolecular and Organic Chemistry
Eindhoven University of Technology
P.O. Box 513, NL-5600 MB Eindhoven (The Netherlands)
Fax: (+31)40-2451036
E-mail: e.w.meijer@tue.nl

[**] We acknowledge J. L. J. van Dongen and H. W. I. Peerlings for their experimental help and stimulating discussions. Support from the Council for Chemical Sciences of the Netherlands Organization for Scientific Research (CW-NWO) with financial aid from the Netherlands Technology Foundation (STW) is gratefully acknowledged.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

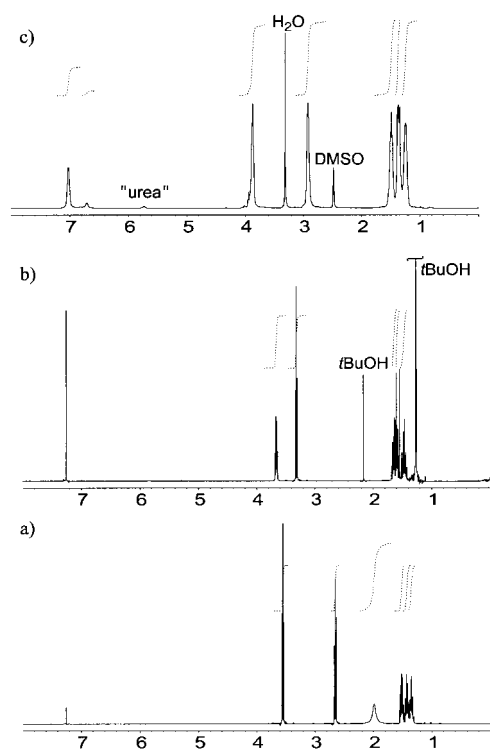


Figure 1. ^1H NMR spectra of a) 5-aminopentanol, b) 5-isocyanato-1-pentanol, c) [6]-polyurethane.

were characterized by NMR and FT-IR spectroscopy, elemental analysis, size exclusion chromatography (SEC), viscometry, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). According to NMR and FT-IR spectroscopy and elemental analyses, all polymers possess a very uniform microstructure; the results are in agreement with the assigned structures. Detailed analyses by ^1H NMR spectroscopy (Figure 1 c) showed that the polymers contain a very small amount (less than 2 %) of urea linkages, and both the *cis* and *trans* carbamate conformations are observed.

Table 1 shows the yields of the $[n]$ -polyurethanes and some of their characteristics. The molecular weights of the polymers are fairly high to respectable, despite the precipitation of the polymers from the poor solvent during preparation. The data obtained with SEC correlates nicely with the values found by viscometry using the Mark–Houwink parameters of the known $[m,n]$ -polyurethanes.^[1] Performing the polymerization

Table 1. Characteristics of $[n]$ -polyurethanes 4.

x	Yield [%]	M_w [kg mol ⁻¹] ^[a]	M_w/M_n ^[a]	$[\eta]$ [dL g ⁻¹]	M_w [kg mol ⁻¹] ^[b]	T_m [°C] ^[c]
4	61	18.9	1.4	0.16	16	194
5	63	22.3	1.5	0.17	18	127
6	65	34.4	1.4	0.22	25	157
7	56	26.5	1.5	0.24	29	114
8	55	30.5	1.6	0.24	29	146
9	61	67.4	1.6	0.43	64	116
10	57	32.6	1.7	0.30	39	148
11	63	20.3	1.5	0.18	19	119
12	59	21.4	1.6	0.26	32	141
5-co-6	48	22.7	1.4			–

[a] Measured by SEC, with NMP as solvent, relative to polystyrene standards. [b] Calculated from intrinsic viscosity in *m*-cresol at 25 °C; $K = 1.34 \times 10^4$, $a = 0.73$. [c] Measured by DSC at a heating rate of 10 K min⁻¹.

in THF, DMSO, or *N*-methylpyrrolidine (NMP), or at reflux temperature in chloroform, does not significantly change the molecular weight of the polymer, as investigated for the [6]-polyurethane.

The thermal properties of the polymers were studied by DSC, which indicated that all polymers are highly crystalline. Melting points of the polymers are given in Table 1, and plotted in Figure 2. They are much lower than the melting

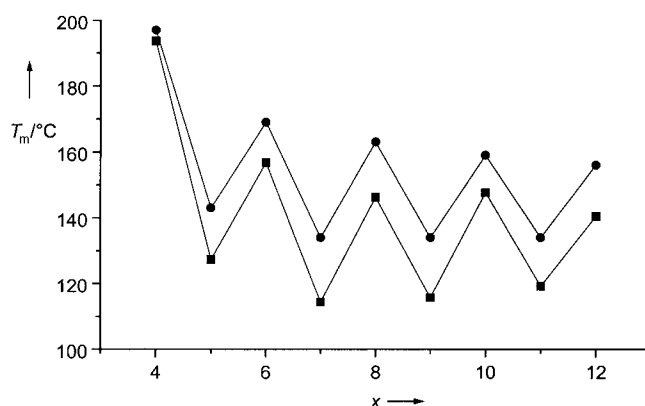


Figure 2. Melting points T_m of $[n]$ -polyurethanes; (■): experimental, (●): calculated.

points of the $[n]$ -nylons, as is also observed for $[m,n]$ -polyurethanes compared to $[m,n]$ -nylons. It is evident from Figure 2 that these $[n]$ -polyurethanes display a strong odd–even effect in their melting points. As with other polymers, for example $[n]$ -nylons,^[9] the $[n]$ -polyurethanes with an odd number of methylene units in the monomeric main chain melt at lower temperatures than the $[n]$ -polyurethanes with an even number of methylene units.^[10] The observed melting points are 10 to 20 °C lower than those predicted by the additive group theory as developed by van Krevelen.^[11] Noteworthy is that the melting points can be raised by approximately 5 °C by extensive Soxhlet extraction of the lower molecular weight fractions with hot methanol.

A random copolymer derived from 5-isocyanatopentanol and 6-isocyanatohexanol in a 1:1 molar ratio was prepared in the same way as the homopolymers. In contrast to the homopolymers, the random copolymer is soluble in chloroform, and is completely amorphous with a glass transition temperature of 8 °C according to DSC. According to TGA, all polymers are stable up to 200 °C, after which they decompose due to the reversibility of the urethane entities.

The facile synthesis of the aliphatic $[n]$ -polyurethanes by using di-*tert*-butyltricarboxylate to prepare the appropriate monomers has yielded a general class of polymers. These structures are especially interesting for biodegradable polymers, since the synthetic procedure is applicable to all amino alcohols with a spacer of at least four carbon atoms between both functionalities. Finally, this study shows that the use of new synthetic methodologies from organic chemistry is highly favorable for the area of polymer synthesis as well.

Experimental Section

The synthesis of [6]-polyurethane is given as a typical example: A solution of 5-amino-1-pentanol (9.69 mmol, 1.00 g) in chloroform (2 mL) was injected by a syringe under the surface of a stirred solution of di-*tert*-butyltricarboxylate (10.66 mmol, 2.80 g) in chloroform (30 mL). The solution was stirred for 10 min at room temperature under an argon atmosphere. ¹H NMR (400 MHz, CDCl₃, 20 °C, TMS): δ = 3.67 (q, ³J = 6.0 Hz, 2H; CH₂OH), 3.32 (t, ³J = 6.6 Hz, 2H; CH₂NCO), 1.55 (br. m; 4H; CH₂CH₂OH + CH₂CH₂NCO), 1.40 (m, ³J = 6.7 Hz, 2H; CH₂CH₂CH₂CH₂CH₂); IR (CHCl₃): $\tilde{\nu}$ = 3396 (br. s), 2971 (m), 2274 (s) cm⁻¹.

Zirconium(IV) acetylacetonate (0.1 mol%) was added, and the polymerization was carried out for 20 h with continuous stirring under argon at room temperature. The turbid reaction mixture was precipitated in diethyl ether (150 mL), and the polymeric product was collected by suction filtration in a yield of 0.81 g (63 %). M.p. 127 °C; decomposition at 200 °C; ¹H NMR (400 MHz, [D₆]DMSO, 20 °C, TMS): δ = 7.04 (br. t, 0.9H; NH *trans* conformer), 6.72 (br. m, 0.1H; NH *cis* conformer), 3.89 (t, ³J = 6.2 Hz, 2H; CH₂O), 2.95 (q, ³J = 6.0 Hz, 2H; CH₂N), 1.50 (m, ³J = 7.2 Hz, 2H; CH₂CH₂O), 1.40 (m, ³J = 7.7 Hz, 2H; CH₂CH₂N), 1.28 (m, ³J = 6.6 Hz, 2H; CH₂CH₂CH₂CH₂CH₂); ¹³C NMR (100 MHz, [D₆]DMSO, 100 °C, TMS): δ = 156.4 (C=O), 63.5 (CH₂O), 40.1 (CH₂N), 29.4 (CH₂CH₂O), 28.7 (CH₂CH₂N), 26.0 (CH₂CH₂CH₂CH₂CH₂); IR (KBr): $\tilde{\nu}$ = 3318 (br. s), 2944 (m), 2870 (w), 1684 (s), 1535 (s), 1263 (s) cm⁻¹; elemental analysis (%) for (C₆H₁₁NO₂)_n calcd: C 55.80, H 8.58, N 10.85; found: C 55.46, H 8.67, N 10.55.

Received: May 10, 1999 [Z 13388 IE]

German version: *Angew. Chem.* **1999**, *111*, 3095–3097

Keywords: amino alcohols • isocyanates • polymerizations • polyurethanes • synthetic methods

- [1] Z. Wirpsza, *Polyurethanes: Chemistry, Technology and Applications*, Ellis Horwood, London, **1993**.
- [2] O. Bayer, *Angew. Chem. A* **1947**, *59*, 257–272.
- [3] a) J. R. Schaefgen, F. H. Koontz, R. F. Tietz, *J. Polym. Sci.* **1959**, *40*, 377–387; b) Y. Iwakura, *Kobunshi Kagaku* **1945**, *2*, 305 [*Chem. Abstr.* **1950**, *44*, 5103]; c) S. Neffgen, H. Keul, H. Höcker, *Macromolecules* **1997**, *30*, 1289–1297; d) F. Bachman, J. Reimer, M. Ruppenstein, J. Thiem, *Makromol. Rapid Commun.* **1998**, *19*, 21–26.
- [4] a) Y. Iwakura, K. Hayashi, K. Iwata, *Makromol. Chem.* **1965**, *89*, 214–227; b) C. Y. Cho, E. J. Moran, S. R. Cherry, J. C. Stephans, P. A. Fodor, C. L. Adams, A. Sundaram, J. W. Jacobs, P. G. Schultz, *Science* **1993**, *261*, 1303–1305; c) A. Masuyama, K. Tsuchiya, M. Okahara, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2855–2859.
- [5] a) J. F. Kinstle, L. E. Sepulveda, *J. Polym. Sci. Polym. Lett. Ed.* **1977**, *15*, 467–469; b) K. Kurita, S. Matsuda, Y. Iwakura, *Makromol. Chem. Rapid Commun.* **1980**, *1*, 211–214; c) N. D. Ghadge, J. Y. Jadhav, *J. Polym. Sci.* **1983**, *21*, 1941–1950.
- [6] H. W. I. Peerlings, E. W. Meijer, *Tetrahedron Lett.* **1999**, *40*, 1021–1024.
- [7] Amino alcohols with *x* = 7, 9, and 10 were prepared by the hydrazine deprotection of α,ω -phthalimide alcohols, which were made from α,ω -bromo alcohols. Amino alcohols with *x* = 8, 11, and 12 were prepared by the reduction of amino ethyl esters, which were derived from lactams.
- [8] B. M. Pope, Y. Yamamoto, D. S. Tarbell, *Org. Synth.* **1978**, *57*, 45.
- [9] S. M. Aharoni, *n-Nylons: Their Synthesis, Structure and Properties*, Wiley, Chichester, **1997**, p. 60.
- [10] At first glance it is surprising that it is not the number of main chain atoms between the hydrogen bonding units that determines the odd–even effect. However, many examples are known in which the number of methylene units determines this effect.^[11] A general explanation is not known, as far as we are aware of, and needs further research.
- [11] D. W. van Krevelen, *Properties of polymers*, Elsevier, Amsterdam, **1997**, p. 151–163.

Isoporphycene: The Fourth Constitutional Isomer of Porphyrin with an N₄ Core—Occurrence of *E/Z* Isomerism**

Emanuel Vogel,* Peter Scholz, Ralf Demuth, Christoph Erben, Martin Bröring, Hans Schmickler, Johann Lex, Georg Hohlneicher,* Dominik Bremm, and Yun-Dong Wu*

Dedicated to Professor Satoru Masamune on the occasion of his 70th birthday

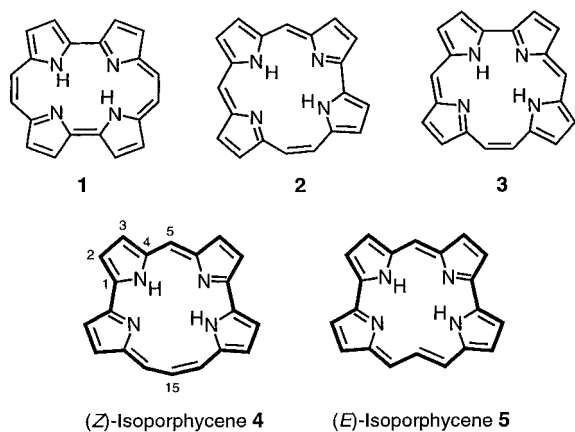
The synthesis of porphycene (**1**) in 1986^[1] led to the realization that, in principle, no less than seven constitutional isomers of porphyrin with an N₄ core are possible.^[2] Unlike porphyrin, its constitutional isomers contain one or two formal double bonds and may therefore give rise to *E/Z* isomerism. After **1** was shown to match porphyrin in many of its properties, it was clear that the isomers open a promising new chapter of porphyrin chemistry.^[3] If a further incentive for the synthesis of the isomers was needed, this was provided by the inverted porphyrins discovered simultaneously by a Japanese and a Polish group.^[4]

Porphycene (**1**), which is approximately 2 kcal mol⁻¹ more stable than porphyrin according to ab initio calculations (BLYP/6-31G** method), has meanwhile been joined by hemiporphycene (**2**)^[6] and corphycene (**3**; each as octaalkyl derivatives).^[7] Compounds **2** and **3** follow **1** on the stability scale of the constitutional isomers and are 5 and 12 kcal mol⁻¹, respectively, higher in energy than porphyrin.^[5] Similar to porphyrin, **1–3** (see Scheme 1) are excellent complexing agents; this could not be predicted with certainty as the N₄ core of the three isomers covers a smaller area and deviates more or less strongly from the square shape. Thus, a multitude of comparative investigations of the metal complexes of the isomers and the corresponding metalloporphyrins suggested itself.

The isoporphycenes [porphyrins-(3.0.1.0)] **4** and **5** (Scheme 1), in fourth place on the stability scale of the isomers,^[5] are not only interesting as complexing agents and for other porphyrin-relevant properties, but also demand attention under the aspect of stereoisomerism. Other than in the case of the constitutional isomers **1–3**, for which the *Z* isomer is strongly favored energetically over the *E* isomer, the two isoporphycene isomers only differ slightly (PM3) or

- [*] Prof. Dr. E. Vogel, Dr. P. Scholz, Dr. R. Demuth, Dr. C. Erben, Dr. M. Bröring, Dr. H. Schmickler, Dr. J. Lex
Institut für Organische Chemie der Universität
Greinstrasse 4, D-50939 Köln (Germany)
Fax: (+49) 221-470-5057
E-mail: emanuel.vogel@uni-koeln.de
- Prof. Dr. G. Hohlneicher, D. Bremm
Institut für Physikalische Chemie der Universität
Luxemburger Strasse 116, D-50939 Köln (Germany)
Fax: (+49) 221-470-5144
- Prof. Dr. Y.-D. Wu
Department of Chemistry
The Hong Kong University of Science & Technology
Clear Water Bay, Kowloon, Hong Kong (China)

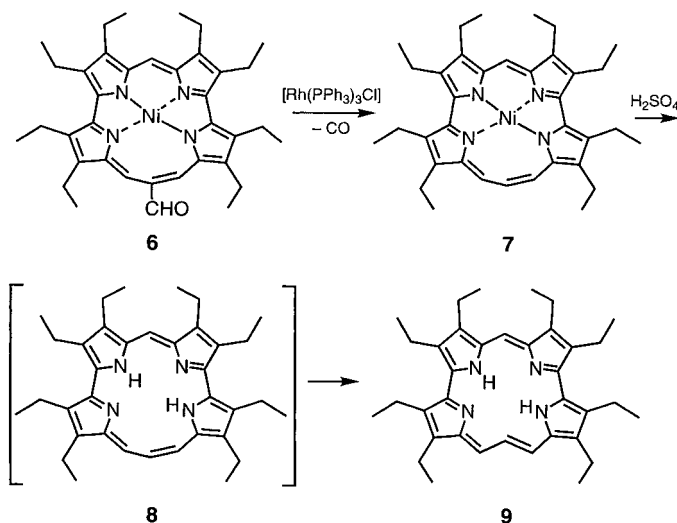
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.



PM3	23.6	24.9
BLYP/6-31G**//3-21G	19.0	26.2

Scheme 1. The known constitutional isomers of porphyrin with an N_4 core (1–3) and the fourth isomer whose synthesis appears feasible, (Z)/(E)-isoporphycene (4/5). The relative energies [kcal mol⁻¹], with respect to porphyrin, according to the PM3 and the BLYP/6-31G**//3-21G methods^[5] for the stereoisomers 4 and 5 are given.

moderately (BLYP/6-31G**) in their energy, so that their parallel existence seemed possible. However, it was uncertain whether 4 and 5 are sufficiently stable to be isolated in substance owing to their already considerable relative energy (with respect to porphyrin). Access to the stereoisomeric isoporphycenes—in the form of the octaethyl compounds 8 and 9 for reasons of solubility—was promised by the



demetalation of the metalloisoporphycenes recently obtained by template synthesis.^[8] We can now report that the octaethyl isoporphycene ligand was liberated from the nickel complex 7, isolated, and characterized.

A number of metal complexes of 15-formyl-(Z)-octaethylisoporphycene, especially the nickel complex 6, are accessible from 1,17-diformyl-2,3,6,7,11,12,15,16-octaethyl-*a,c*-bisenor-*b*-bilene by a reaction cascade initiated by template formation with suitable metal ions.^[8] When 6 was heated with tris(triphenylphosphane)rhodium(I) chloride (Wilkinson's catalyst) in benzonitrile under reflux (2 h), smooth decarbonylation

took place to provide complex 7, which was obtained as black needles with metallic sheen (m.p. 145–146°C, yield 60%) after chromatography on silica gel with dichloromethane/*n*-hexane (1/1) and crystallization from 2-propanol. It follows from the ¹H NMR spectrum that the isoporphycene ligand in 7 has the *Z* configuration, as the signals for H15 can be found similarly far downfield ($\delta = 9–10$) as those for the neighboring protons H14 and H16.

Complex 7 was characterized by X-ray crystallographic analysis. Two independent molecules are found in the elementary cell which have an approximately saddle-shaped (slightly differing) appearance due to a contraction of the ligand caused by the nickel ion. Further information on the structure of 7 will be given in a comparison with the molecular structures of the nickel complexes of octaethylporphyrin, octaethylporphycene, octaethylhemiporphycene, and octaethylcorphycene.^[9]

To liberate the ligand, 7 was treated with concentrated sulfuric acid at room temperature, the reaction mixture was poured on ice after 15 h, and sodium hydroxide (slightly less than the amount of sulfuric acid used) and then potassium carbonate were added at 0°C (color change from green to red). After conventional workup, chromatography of the product on silica gel with dichloromethane/ethyl acetate (6/1) yielded two fractions, of which the first (brown) contained the starting material and the second (dark red) the free ligand. The ligand was obtained as rhombic, violet crystals (m.p. 129°C, yield 23%) from a small amount of *n*-hexane after storing of the solution at –20°C and was identified as (E)-octaethylisoporphycene (9). As expected, 9, which is stable in the crystalline state, is chemically much more reactive than its analogues 1–3.

The surprising formation of 9, combined with a change in configuration, on demetalation of the nickel complex 7 is verified by the ¹H NMR spectrum (Figure 1, Table 1), recorded at low temperature in order to freeze out dynamic

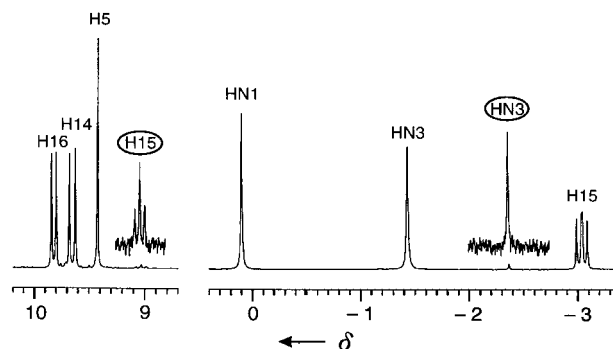


Figure 1. ¹H NMR spectrum of 9/8 (300 MHz, CD₂Cl₂/CF₃Br₂/Al₂O₃, 205 K). The encircled protons belong to (Z)-isoporphycene (8); further signals for 8 were assigned by two-dimensional experiments.

processes. The most striking feature of the spectrum is the upfield position of the H15 signals; proton H15 must therefore be located in the shielding area of the diamagnetic ring current assumed to be present in 9. This unambiguously proves the *E* configuration of 9. The porphyrinoid aromatic nature of the new constitutional isomer of porphyrin, which is already indicated by the chemical shift of H15, is supported by

Table 1. Selected physical data for the compounds **7** and **9–13** (^1H NMR: 300 MHz; ^{13}C NMR: 75.5 MHz; IR: CsI; UV/Vis: CH_2Cl_2); correct elementary analyses for **7**, **9**, and **11**.

7: M.p. 145–146 °C (from 2-propanol); ^1H NMR (CDCl_3): δ = 9.67 (d, 2H; H14,16), 9.42 (s, 1H; H5), 8.98 (t, 1H; H15), 4.03 (q, 4H; H11a,19a), 3.95 (q, 4H; H12a,18a), 3.90 (q, 4H; H2a,8a), 3.84 (q, 4H; H3a,7a), 1.79 (t, 6H; H3b,7b), 1.76 (t, 6H; H12b,18b), 1.69 (t, 6H; H11b,19b), 1.68 (t, 6H; H2b,8b); ^{13}C NMR (CDCl_3): δ = 146.03, 145.81, 144.94, 142.54, 136.89, 135.24, 135.15, 112.01, 110.22, 101.07, 20.97, 20.68, 20.55, 19.68, 18.78, 18.59, 18.51, 18.38; IR: $\tilde{\nu}$ = 2964, 2930, 2869, 1591, 1465, 1446, 1372, 1218, 1165, 1144, 1121, 1053, 1021, 956 cm^{-1} ; UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 284 (17800), 340 (12600), 403 (106600), 489 (13600), 534 (8500), 616 (7000), 662 nm (3100); MS (FAB): m/z (%): 590 (100) [M^+]

9: M.p. 129 °C (from *n*-hexane at –20 °C); ^1H NMR ($\text{CD}_2\text{Cl}_2/\text{CF}_3\text{Br}_2/\text{Al}_2\text{O}_3$, 205 K): δ = 9.82 (d, 1H; H16), 9.65 (d, 1H; H14), 9.42 (s, 1H; H5), 3.90 (q, 2H; H2a), 3.88 (q, 2H; H3a), 3.84 (q, 2H; H11a), 3.76 (q, 2H; H8a), 3.73 (q, 2H; H7a), 3.72 (q, 2H; H12a), 3.68 (q, 2H; H19a), 3.56 (q, 2H; H18a), 1.73 (t, 9H; H2b,3b,7b), 1.72 (t, 3H; H8b), 1.70 (t, 3H; H12b), 1.66 (t, 3H; H18b), 1.59 (t, 3H; H11b), 1.52 (t, 3H; H19b), 0.10 (brs, 1H; HN1), –1.43 (brs, 1H; HN3), –3.04 (dd, 1H; H15); ^{13}C NMR ($\text{CD}_2\text{Cl}_2/\text{CF}_2\text{Br}_2$, 205 K): δ = 154.05, 149.17, 148.79, 146.68, 145.70, 144.81, 140.93, 140.01, 137.41, 135.57, 133.43, 133.28, 132.06, 131.68, 129.33, 127.77, 127.06, 124.22, 115.70, 104.71, 20.23, 20.11, 20.02, 19.92, 19.29, 19.12 (2 $\times$), 18.99, 18.99, 18.69 (3 $\times$), 18.37 (3 $\times$), 18.18; IR: $\tilde{\nu}$ = 3398, 3357, 2964, 2930, 2868, 1579, 1551, 1488, 1463, 1315, 1284, 1173, 1144, 1123, 1061, 1054, 1014, 1000, 990, 950, 858, 851, 740 cm^{-1} ; UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 354 (21800), 434 (117200), 558 (5700), 615 (4700), 672 nm (6550); MS (FAB): m/z (%): 535 (100) [$(M+1)^+$], 534 (24) [M^+]

10 ($=(\text{H}_2\text{-9})^{2+}$): ^1H NMR ($\text{CDCl}_3/\text{CF}_3\text{COOH}$): δ = 10.54 (d, 2H; H14,16), 10.32 (s, 1H; H5), 4.04 (q, 4H; H2a,8a), 3.99 (q, 4H; H3a,7a), 3.91 (q, 4H; H11a,19a), 3.78 (q, 4H; H12a,18a), 1.76 (t, 6H; H12b,18b), 1.75 (t, 6H; H2b,8b), 1.73 (t, 6H; H3b,7b), 1.64 (t, 6H; H11b,19b), –0.87 (brs, 2H; HN3,4), –1.69 (brs, 2H; HN1,2), –5.80 (t, 1H; H15); ^{13}C NMR ($\text{CDCl}_3/\text{CF}_3\text{COOH}$): δ = 146.01, 143.90, 142.03, 137.93, 137.75, 135.95, 135.77,

133.55, 131.56, 126.80, 106.86, 20.69 (2 $\times$), 20.19, 19.88, 17.58, 17.17, 16.82, 16.71; UV/Vis ($\text{CH}_2\text{Cl}_2/\text{CF}_3\text{COOH}$): λ_{max} (ϵ) = 311 (11800), 365 (17700), 408 sh (63100), 428 (228500), 506 (5300), 549 (9200), 597 (7800), 652 nm (14200)^[a]

11 ($=\text{Cu}(\text{-9}-2\text{H})$): M.p. 164–165 °C (from $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$); IR: $\tilde{\nu}$ = 2963, 2929, 2868, 1578, 1522, 1477, 1457, 1449, 1406, 1372, 1314, 1265, 1214, 1168, 1143, 1121, 1053, 1021, 1005, 954 cm^{-1} ; UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 334 (17600), 374 (34800), 438 (57400), 456 (115400), 562 (8000), 584 nm (8600); MS (FAB): m/z (%): 595 (100) [M^+]

12/13: M.p. (*E/Z* mixture) 234–236 °C (from $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$); *E* isomer: ^1H NMR (CDCl_3): δ = 9.53 (d, 2H; H14,16), 9.41 (s, 1H; H5), 6.44 (m, 1H; *p*-H (pyridine)), 5.63 (m, 2H; *m*-H (pyridine)), 3.93 (q, 4H; H11a,19a), 3.89 (q, 4H; H2a,8a), 3.79 (q, 4H; H3a,7a), 3.67 (q, 4H; H12a,18a), 3.04 (br. m, 2H; *o*-H (pyridine)), 1.74 (t, 6H; H3b,7b), 1.71 (t, 6H; H11b,19b), 1.69 (t, 6H; H2b,8b), 1.67 (t, 6H; H12b,18b), –2.47 (t, 1H; H15); ^{13}C NMR (CDCl_3): δ = 146.77, 144.90, 144.58, 144.20, 142.68, 141.80, 140.93, 138.02, 135.81, 133.39, 128.72, 124.60, 122.34, 106.60, 20.76, 20.26, 19.70, 19.34, 19.34, 19.13, 18.76, 18.63; *Z* isomer: ^1H NMR (CDCl_3): δ = 9.67 (d, 2H; H14,16), 9.66 (s, 1H; H5), 8.92 (t, 1H; H15), 6.44 (m, 1H; *p*-H (pyridine)), 5.63 (m, 2H; *m*-H (pyridine)), 4.06 (q, 4H; H11a,19a), 3.94 (q, 4H; H12a,18a), 3.92 (q, 4H; H2a,8a), 3.86 (q, 4H; H3a,7a), 3.04 (br. m, 2H; *o*-H (pyridine)), 1.77 (t, 6H; H3b,7b), 1.74 (t, 6H; H11b,19b), 1.71 (t, 6H; H12b,18b), 1.62 (t, 6H; H2b,8b); ^{13}C NMR (CDCl_3): δ = 148.06, 145.33, 144.52, 144.34, 144.20, 141.90, 139.62, 135.81, 135.59, 133.87, 122.34, 114.64, 107.79, 106.21, 20.76, 20.62, 19.90, 19.77, 18.87, 18.87, 18.71, 18.63; IR: $\tilde{\nu}$ = 2964, 2929, 2868, 1602, 1564, 1446, 1485, 1464, 1400, 1373, 1311, 1216, 1154, 1140, 1122, 1061, 1039, 1017, 953, 861, 695, 632 cm^{-1} ; UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 449 (142800), 460 sh (82000), 557 (10000), 597 (9900), 667 nm (5800); MS (FAB): m/z (%): 596 (40) [$(M-\text{py})^+$], 536 (100) [(octaethylisoporphycene) $^+$]; high-resolution MS (EI) calcd for $\text{C}_{41}\text{H}_{49}\text{N}_3\text{Zn}$: 596.284, found: 596.282

[a] The molar extinction coefficients given are valid under the assumption that **9** is protonated quantitatively. Attempts to obtain salts of **9** in substance through the use of various acids always led to decomposition products.

the observation that the signals of the remaining vinylic protons (H14, H16, and H5) appear relatively far downfield, whereas those of the N-bound protons are relatively far upfield. It follows from the determination of remote couplings that **9**, as is shown in the formula drawing, is present in the tautomeric form with the protons localized at N1 and N3. This is the most stable of the four possible NH tautomers according to calculations.^[5] Because of the relatively strong N1–H $\cdots$ N2 hydrogen bond, the downfield NH signal is assigned to the proton at N1.

When the measuring temperature is raised above 298 K, a spectrum develops which corresponds to an (*E*)-octaethylisoporphycene with effective C_{2v} , C_s , or C_2 molecular symmetry (formal identity of the two halves of the molecule), depending on whether the ring skeleton of **9** is planar, concave, or twisted. According to this finding, **9** undergoes rapid (on the NMR time scale), isodynamic NH tautomerism at room temperature. From the coalescence temperature for the doublets of H14 and H16 (253 K), a Gibbs activation energy $\Delta G^\ddagger$ of 13.5 kcal mol^{-1} was determined for the NH tautomerism. This value is approximately 5 kcal mol^{-1} higher than that of octaethylisoporphycene (likewise with a trapezoidal N_4 core),^[7a] which should be due to a larger N3 $\cdots$ N4 distance and a certain steric hindrance caused by H15 of the, probably rate-determining, proton transfer between N3 and N4.

Additionally occurring signals of very low intensity at δ = 9.03 (H15) and –2.36 (HN3) in the ^1H NMR spectrum (300 MHz, 205 K) were a first indication that **9** is accompa-

nied by approximately 2 % of the *Z* isomer **8** (Figure 1). The presence of **8** became certain when 2D ROESY experiments allowed also the signals for H5, H14, and H16 of this isomer to be detected. As all attempts to separate **9** and **8** by recrystallization or with chromatographic methods (two-dimensional TLC and HPLC; also carried out under absence of light) remained unsuccessful, it is probable that the two compounds are in an extremely rapidly established acid-catalyzed equilibrium. An argument for the equilibrium hypothesis is not least the smooth reformation of **7** upon complexation of **9** with nickel ions.

In the presence of such an equilibrium, the observed quantity ratio of **9** and **8** (98:2) means that the difference in Gibbs energies ΔG^0 of the two isomers amounts to 2.5 kcal mol^{-1} , the *E* isomer being energetically favored. This result was the reason for the inclusion of the octaethyl derivatives **8** and **9** into the quantum chemical calculations, in order to take into account the steric interactions of the ethyl groups. Geometrical optimizations for the ethyl groups according to the PM3 method and for the isoporphycene skeleton according to the BLYP/3-21G** method led to the surprising result that the *E* isomer **9**—in reversal of the stability relations of **4** and **5**—is approximately 3.4 kcal mol^{-1} more stable than the *Z* isomer **8**. This is qualitatively in accordance with the experimental findings. A geometry optimization including all eight ethyl groups on the B3LYP/6-31G** level yielded a difference in energy of 1.1 kcal mol^{-1} in favor of **9**.^[10]

The UV/Vis spectrum of the *E* isomer **9** (bold-faced solid line in Figure 2; the influence of 2% of isomer **8** on the spectrum is negligible; see fluorescence excitational spectrum, Figure 3) contains a pronounced Soret band at 434 nm that

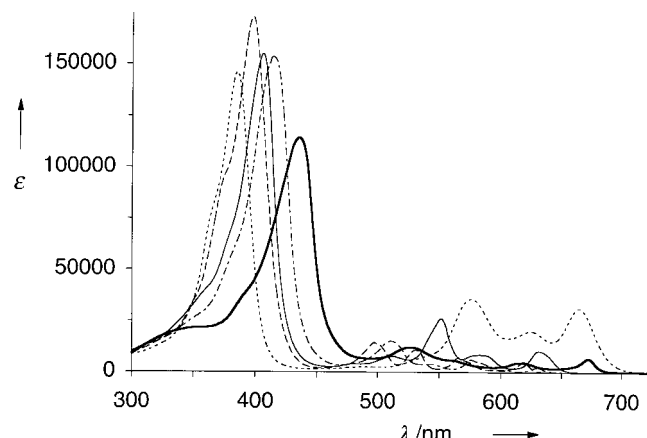


Figure 2. UV/Vis spectra (in CH_2Cl_2) of isoporphycene (**9**, —) as well as porphyrin (---), porphycene (**1**, ···), hemiporphycene (**2**, —), and corphycene (**3**, -·-·-), each as octaethyl-substituted compounds.

shows a bathochromic shift with respect to the corresponding bands of the octaethyl derivatives of porphyrin and **1–3** (also shown in Figure 2) and is distinctly less intensive. Q bands are found in the region of 558, 625, and 672 nm.

The UV/Vis spectroscopic characterization also of the *Z* isomer **8**, and thus its independent identification, was achieved with the help of low-temperature fluorescence spectroscopy (Figure 3).^[11] The fluorescence of **8** becomes visible as a well-separated band at 646 nm besides the intensive emission at 673 nm, which can be assigned unambiguously to the *E* isomer **9** upon comparison with the absorption spectrum. The intensity ratio of the two bands, which depends on the chosen excitation wavelength, is of the order expected for the 2% share of **8** determined by NMR

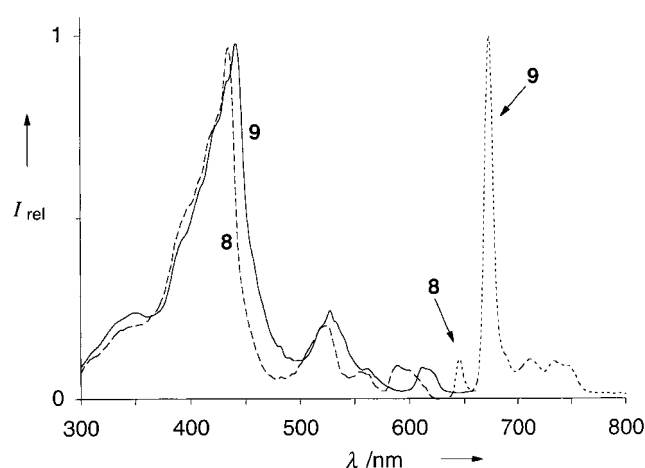


Figure 3. Fluorescence emission spectrum of **9** (containing 2% of **8**) (---) as well as fluorescence excitation spectra of **9** (—) and **8** (···). Solvent 3-methylpentane, temperature 105 K, excitation wavelength 523 nm, emission wavelengths 673 nm (**9**) and 646 nm (**8**); ordinate: relative intensity (normalized to one). In the excitation spectra the first Q band is missing as it could not be observed owing to light scattering by the sample.

spectroscopy. The excitation spectra of the isomers **8** and **9** can be obtained by detection on one of the fluorescence signals. According to Figure 3, these spectra are very similar, with the bands of the *Z* isomer being shifted by 5–12 nm to shorter wavelengths.

According to a crystal structure analysis,^[12] the ring skeleton of **9** is virtually planar (Figure 4). Only C15 protrudes slightly out of the ideal plane formed by the remaining skeleton C atoms and the N atoms (0.192 Å); this should be

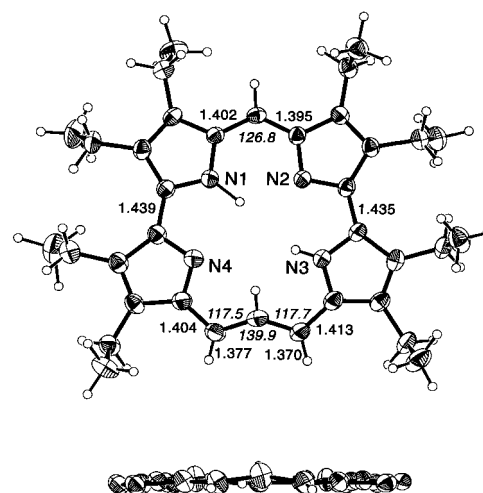


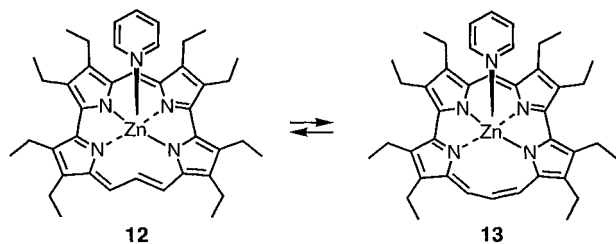
Figure 4. Structure of (*E*)-octaethylisoporphycene (**9**) in the crystal. Top: plan view; bottom: side view, without ethyl substituents. The ellipsoids correspond to the 40% probability level. Selected bond lengths [Å] and angles [°] are shown (standard deviations approximately 0.006 Å and 0.4°); further distances: N1–N2 2.826, N1–N4 2.541, N2–N3 2.541, N3–N4 3.909 Å.

due to the tendency of H15 to decrease the steric interaction with the hydrogen atom at N3. Nevertheless, the distance between H15 and HN3 remains very short (1.837 Å). The N-bound hydrogen atoms, which can be definitely localized, are in accordance with the conditions in solution at N1 and N3. The fact that **9** is a porphyrinoid aromatic compound is mirrored in the C–C bond lengths, especially those in the C13 to C17 unit (1.37–1.41 Å). An indication of the steric strain in **9** apparent from the calculations is the expansion of the C14–C15–C16 angle to 140°.

The octaethylisoporphycene **9** is N-protonated smoothly by trifluoroacetic acid—under retention of configuration—to the corresponding dication **10** (Table 1), which is stable in solution but decomposes when its isolation is attempted. The diprotonation is detectable by the fact that the signals for H5, H14, and H16 are shifted downfield by approximately 1 ppm (in analogy to porphyrin and the other isomers) and that for H15 is shifted upfield in a complementary way by no less than 2.8 ppm (to $\delta = -5.8$!). Protonated **9** must therefore sustain a sizeable diamagnetic ring current, although the presence of five hydrogen atoms on the inside of the molecule should lead to considerable deformation of the ring skeleton.

The availability of the free *E* isoporphycene ligand **9** led to the expectation that the range of metalloisoporphycenes accessible by means of template synthesis—apart from the nickel complex **7**, complexes of palladium,^[8] vanadium

(VO),^[13] platinum,^[8] and copper^[14] (**11**, Table 1; the two latter complexes are formed in only very low yields)—can be extended to complexes of other important metals. In view of the chemical sensitivity of **9**, however, successful metalation could only be expected if **9** was able to incorporate the metal ions in question rapidly. Surprisingly, **9** yielded the (pyridine)zinc complex **12/13** and the known copper complex **11** spontaneously and at room temperature, thus surpassing octaethylporphyrin in its complexation tendency towards zinc and copper ions despite the pronounced trapezoidal shape of its N₄ core.^[15]



The zinc complex with an axial pyridine ligand obtained from **9** in dichloromethane/pyridine with methanolic zinc acetate solution turned out, in analogy to the palladium complex, to be a mixture of *E* and *Z* isomers (**12** and **13**, respectively), whose composition (60:40) was determined by means of the H15 NMR signals (triplet at $\delta = -2.5$ and 8.9, respectively).^[16] It could not yet be established beyond doubt whether the paramagnetic copper complex **11** is the *E* and/or the *Z* isomer. Experiments towards the systematic investigation of the formation of metal complexes with **9** and **8** are under way.

With the synthesis of isoporphycene as the *E* isomer, a molecule distinctly more reactive than **1–3**, all of the constitutional isomers of porphyrin with an N₄ core that can be made according to thermodynamic considerations should now be in our hands. The remaining three isomers (each with *Z* configuration) are assumed to be only of fleeting existence as their relative energy increases by a further 9.9, 19.7, and 51.6 kcal mol⁻¹, respectively, based on **4**.^[5] However, it cannot be ruled out completely that metal complexes of the first two of the three isomers are still stable compounds.

Received: February 4, 1999 [Z 12996 IE]

German version: *Angew. Chem.* **1999**, *111*, 3100–3105

Keywords: isomers • N ligands • porphyrinoids • zinc

- [1] E. Vogel, M. Köcher, H. Schmickler, J. Lex, *Angew. Chem.* **1986**, *98*, 262; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 257; E. Vogel, J. *Heterocycl. Chem.* **1996**, *33*, 1461; for porphycene analogues (partial or complete replacement of the four pyrrole nitrogen atoms by other heteroatoms), see E. Vogel, M. Sicken, P. Röhrig, H. Schmickler, J. Lex, O. Ermer, *Angew. Chem.* **1988**, *100*, 450; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 411; G. DeMunno, F. Lucchesini, R. Neidlein, *Tetrahedron* **1993**, *49*, 6863; T. Nussbaumer, R. Neidlein, *Abstr. Pap. ISNA-9* (Hong Kong) **1998**, PPO7; W. M. Dai, W. L. Mak, *Abstr. Pap. ISNA-9* (Hong Kong) **1998**, PP60.
- [2] J. Waluk, J. Michl, *J. Org. Chem.* **1991**, *56*, 2729.
- [3] J. L. Sessler, S. J. Weghorn, *Expanded, Contracted & Isomeric Porphyrins*, Pergamon, Oxford, **1997**, p. 127 (Tetrahedron Organic Chemistry Series, Vol. 15).
- [4] H. Furuta, T. Asano, T. Ogawa, *J. Am. Chem. Soc.* **1994**, *116*, 767; P. J. Chmielewski, L. Latos-Grażyński, K. Rachlewicz, T. Glowiak, *Angew. Chem.* **1994**, *106*, 805; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 779; P. J. Chmielewski, L. Latos-Grażyński, K. Rachlewicz, *Chem. Eur. J.* **1995**, *1*, 68; see also A. Ghosh, *Angew. Chem.* **1995**, *107*, 1117; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1028; a rational synthesis of inverted porphyrins has meanwhile been reported: B. Y. Liu, C. Brückner, D. Dolphin, *Chem. Commun.* **1996**, 2141.
- [5] Y.-D. Wu, K. W. K. Chan, C. P. Yip, E. Vogel, D. A. Plattner, K. N. Houk, *J. Org. Chem.* **1997**, *62*, 9240 (the energy values in Scheme 1 were taken from this publication); A. Ghosh, K. Jynge, *J. Phys. Chem. B* **1997**, *101*, 5459.
- [6] H. J. Callot, A. Roher, T. Tschamber, B. Metz, *New J. Chem.* **1995**, *19*, 155 (the hemiporphycene described by these authors is a triphenyl-ethoxycarbonyl derivative); E. Vogel, M. Bröring, S. J. Weghorn, P. Scholz, R. Deponte, J. Lex, H. Schmickler, K. Schaffner, S. E. Braslawsky, M. Müller, S. Pörting, C. J. Fowler, J. L. Sessler, *Angew. Chem.* **1997**, *109*, 1725; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1651.
- [7] a) J. L. Sessler, E. A. Brucker, S. J. Weghorn, M. Kisters, M. Schäfer, J. Lex, E. Vogel, *Angew. Chem.* **1994**, *106*, 2402; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2308; b) M. A. Aukauloo, R. Guillard, *New J. Chem.* **1994**, *18*, 1205; c) H. Falk, Q.-Q. Chen, *Monatsh. Chem.* **1996**, *127*, 69; d) S. Neya, K. Nishinaga, K. Ohyama, N. Funasaki, *Tetrahedron Lett.* **1998**, *39*, 5217.
- [8] E. Vogel, M. Bröring, C. Erben, R. Demuth, J. Lex, M. Nendel, K. N. Houk, *Angew. Chem.* **1997**, *109*, 363; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 353.
- [9] For theoretical studies on the nickel, copper, and zinc complexes of the porphyrin isomers **1–4/5** (determination of the relative stabilities with respect to the corresponding metalloporphyrins), see Y.-D. Wu, D.-F. Wang, *Abstr. Pap. ISNA-9* (Hong Kong) **1998**, PP127; analogous stability examinations of chosen metal complexes of **1–4/5** were reported by another group at the same time: A. Ghosh, T. Vangberg, *Inorg. Chem.* **1998**, *37*, 6276.
- [10] D. Bremm, Dissertation, Universität Köln, in preparation.
- [11] D. Bremm, G. Hohlneicher, *J. Mol. Struct.*, in press.
- [12] Crystal structure data of **9**: C₃₆H₄₆N₄, *M*_r = 534.77, crystals from *n*-hexane; crystal dimensions 0.25 × 0.15 × 0.10 mm, monoclinic, space group *P*₂₁, *a* = 8.091(2), *b* = 21.100(6), *c* = 9.629(2) Å, β = 111.16(2)°, *V* = 1533.0(7) Å³, *Z* = 2, ρ_{calc} = 1.158 g cm⁻³; *F*(000) = 580; μ_{Mo} = 0.68 cm⁻¹; of 8656 measured reflections, 3426 were classified as independent, and 2149 as observed ($F_o^2 > 2\sigma F_o^2$); θ_{max} = 26.95°; *R*1 = 0.056, *wR*2 = 0.096; Enraf-Nonius-CAD4 diffractometer (room temperature, MoK α radiation, λ = 0.71069 Å). The structure was solved by direct methods and refined against *F*² for all independent reflections (heavy atoms with anisotropic, hydrogen atoms with isotropic temperature factors); $wR2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_c^2)^2]^{1/2}$. Programs used: structure determination SHELXS-86 and refinement SHELXL-93 (G. M. Sheldrick, Universität Göttingen). Calculations were carried out on the data processing equipment of the regional computer center, Universität Köln. 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-114108. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
- [13] R. Demuth, Dissertation, Universität Köln, **1998**.
- [14] M. Bröring, Dissertation, Universität Köln, **1996**.
- [15] The incorporation of Cu^{II} and Zn^{II} ions, which is rather slow for simple porphyrins, becomes considerably faster for supramolecular complexes of *meso*-tetrakis(4-*N*-methylpyridyl)porphyrin (on polyglutamate): E. Bellacchio, S. Gurrieri, R. Lauceri, A. Magri, L. M. Scolaro, R. Purrello, A. Romeo, *Chem. Commun.* **1998**, 1333.
- [16] The (pyridine)zinc complexes of (*E*)- and (*Z*)-octaethylisoporphycene (**12** and **13**, respectively), which coexist in solution, are obtained in two crystalline forms, of which one contains the uniform complex **13** and the other an approximately 1:1 mixture of the complexes **12** and **13**. As is also the case for the corresponding palladium complexes,^[8] **12** and **13** only differ in the structural parameters of the C₃ unit.

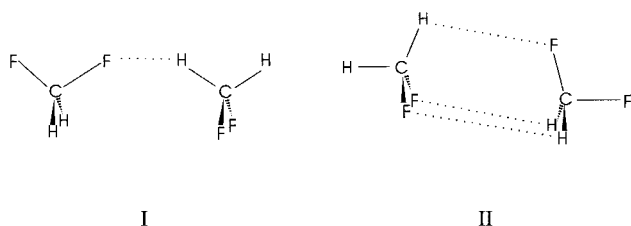
The C-F...H-C “Anti-Hydrogen Bond” in the Gas Phase: Microwave Structure of the Difluoromethane Dimer**

Walther Caminati,* Sonia Melandri, Paolo Moreschini, and Paolo G. Favero

Rotationally resolved spectroscopy combined with supersonic expansions^[1] has been very useful in obtaining detailed information on the structure, dynamics, and energetics of intermolecular hydrogen bonding.^[2] This kind of data is available for O-H...O, O-H...N, O-H...S, O-H... π , N-H...N, N-H...O, X-H...N, and X-H...O linkages (X = F, Cl, CN).^[3]

A few years ago we introduced free jet millimeter wave absorption spectroscopy for the study of molecular complexes,^[4] and obtained the first data from high-resolution spectroscopy on the solvation of ethers,^[5] cyclic amines,^[6] and diazines^[7] through the study of the 1/1 complexes with water.

Recently, while investigating the complex of difluoromethane (DFM) with water,^[8] we noticed, besides the spectrum of DFM-H₂O, a set of evenly spaced μ_a -R-branch lines. These lines were observed when either argon or neon was used as carrier gas, and persisted when water was removed from the system. Furthermore, they appeared only at backing pressures higher than 300 mbar (see Experimental Section), a feature typical for hydrogen-bonded complexes. This evidence induced us to assign the observed spectrum to the dimer of DFM, (DFM)₂, with aliphatic hydrogen atoms possibly acting as proton donors. This is unusual, but becomes plausible when electronegative substituents, such as halogen atoms, are attached to the carbon atom and the aliphatic hydrogen atoms acquire acidic character. With two hydrogen and two fluorine atoms attached to the same carbon atom, DFM can act as a double proton donor and as a double proton acceptor; in a way similar to that, for example, of water,^[9] it can form a hydrogen-bonded dimer. At the same time it is small enough to allow high level ab initio calculations. Model calculations based on the geometry of isolated DFM^[10] showed that for (DFM)₂ conformations **I** and **II** could have rotational constants in agreement with the observed band spacings.



[*] Prof. W. Caminati, Dr. S. Melandri, Dr. P. Moreschini, Prof. P. G. Favero
Dipartimento di Chimica “G. Ciamician” dell’Università
Via Selmi 2, I-40126 Bologna (Italy)
Fax: (+390)51-259456
E-mail: caminati@ciam.unibo.it

[**] We thank Mr. A. Millemaggi for technical help as well as the Ministero dell’Università e della Ricerca Scientifica e Tecnologica and the C.N.R. for financial support.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

The 37 measured rotational line frequencies (available in the Supporting Information) have been fitted within the **I** representation of Watson’s “S” reduced Hamiltonian,^[11] producing the spectroscopic constants given in Table 1. The

Table 1. Spectroscopic constants of (DFM)₂ (**I** representation, “S” reduction).^[a]

<i>A</i> [MHz]	6447.7(22) ^[b]
<i>B</i> [MHz]	1290.238(8)
<i>C</i> [MHz]	1234.614(10)
<i>D_J</i> [kHz] ^[c]	1.796(6)
<i>D_{JK}</i> [kHz]	42.6(2)
<i>H_{JK}</i> [Hz]	−0.86(18)
<i>N</i>	37
σ [MHz]	0.11
<i>P_{aa}</i> [u Å ²]	361.327
<i>P_{bb}</i> [u Å ²]	48.014 ^[d]
<i>P_{cc}</i> [u Å ²]	30.367

[a] *A*, *B*, *C*: rotational constants; *D_J*, *D_{JK}*, *H_{JK}*: centrifugal distortion constants; *N*: number of transitions in the fit; σ : standard deviation of the fit; *P_{aa}*, *P_{bb}*, *P_{cc}*: planar moments of inertia. [b] Standard errors are given in parentheses in units of the last digit. [c] The remaining quartic and sextic centrifugal distortion parameters have been set to zero because they could not be determined from the fit. [d] Corresponds to the sum of *P_{aa}* (46.037 u Å²) and *P_{cc}* (1.651 u Å²) of isolated DFM.

planar moments of inertia, which give the mass extension along the principal axes, are also reported. The *P_{bb}* value nearly coincides with the sum of *P_{aa}* and *P_{cc}* of isolated DFM. This means that the extension of the dimer along the *b* axes corresponds to the contributions of a CH₂ plus a CF₂ group and that, in agreement with either conformer **I** or **II**, the dimer has a plane of symmetry.

Assuming the geometry of DFM to remain unaltered in the dimer, we tried to obtain a plausible ground-state *r₀* structure from the experimental rotational constants. This was not possible for form **I** because an unrealistically short length for the C-H...F-C hydrogen bond (less than 1.5 Å) would have been required. In contrast, reasonable values have been obtained for the α , β , and *r* parameters of species **II** (Figure 1). They are reported in Table 2 together with the hydrogen-bond lengths.

These results have been confirmed by ab initio calculations performed at the MP2/6-31 + G(d,p) level.^[12] Only one energy minimum was

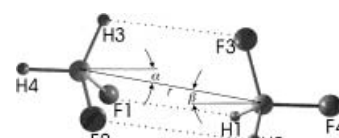


Figure 1. Schematic representation of the triply hydrogen bonded conformer **II**, the most stable, of (DFM)₂. α and β are the angles between the C-C direction and the prolongations of the H4-C and F4-C bonds, respectively.

Table 2. Hydrogen-bond parameters in (DFM)₂ (see Figure 1).

	<i>r₀</i> ^[a]	ab initio ^[b]
<i>r</i> [Å]	3.55(1)	3.524
α [°]	8.3(5)	10.6
β [°]	10.5(7)	12.4
H1-F1 [Å]	2.759	2.734 ^[c]
H3-F3 [Å]	2.628	2.588

[a] *C_s* symmetry. [b] Slightly distorted with respect to the *C_s* symmetry (C₂F₃-C₂H₃ = 2.1°). [c] Average of the slightly different H1-F1 and H2-F2 values.

Table 3. Ab initio evidence for anti-hydrogen bonding in (DFM)₂.

	shortening of C–H bond lengths ^[a]				blue shift of C–H stretches ^[a]		
	DFM	(DFM) ₂	Δl		DFM	(DFM) ₂	$\Delta \nu$
C–H ₁ [Å] ^[b]	1.0859	1.0847	– 0.0012	$\nu_{\text{symm.}}$ [cm ^{–1}]	3185	3198	+ 13
					3201	+ 16	
C–H ₃ [Å] ^[b]		1.0842	– 0.0017	$\nu_{\text{antisymm.}}$ [cm ^{–1}]	3282	3302	+ 20
					3303	+ 21	

[a] In going from DFM to (DFM)₂. [b] See Figure 1.

found, corresponding to conformer **II**. The computed structural hydrogen-bond parameters are also shown, for comparison, in Table 2.

Recently Hobza et al.^[13] observed that, while in “normal” hydrogen bonds the A–H bond length (A–H is the proton donor) increases and the $\nu_{\text{A–H}}$ band undergoes a red shift upon formation of a generic A–H...B hydrogen bond, the contrary happens in some cases, giving rise to the “anti-hydrogen bond”.^[13] In the case of (DMF)₂ ab initio calculations indicate that upon formation of the C–H...F–C bond the C–H bond lengths decrease and the C–H stretching frequencies ($\nu_{\text{C–H}}$) are blue shifted. These features, which are reported in Table 3, allow us to classify the C–H...F–C bond in (DFM)₂ as anti-hydrogen bonding.

Looking at the geometry and symmetry of the complex, it is likely that the stretching motion leading to the dissociation of the complex should almost be parallel to the *a* axis. This allows us to estimate the stretching force constant k_s by using the approximated Equation (1),^[14] where μ_D , R_{CM} , and D_J are the

$$k_s = 16\pi^4 (\mu_D R_{\text{CM}})^2 [4B_D^4 + 4C_D^4 - (B_D - C_D)^2(B_D + C_D)^2] / (h D_J) \quad (1)$$

reduced mass, the distance between the centers of mass, and the first-order centrifugal distortion constant, respectively. The value $k_s = 6.25 \text{ Nm}^{-1}$, corresponding to a harmonic stretching frequency of 64 cm^{-1} , has been obtained. The dissociation energy E_D has been evaluated to be 6.6 kJ mol^{-1} by assuming a Lennard–Jones potential function using the approximated Equation (2).^[15]

$$E_D = 1/72 k_s R_{\text{CM}}^2 \quad (2)$$

Such a dissociation energy corresponds to a binding energy of 2.2 kJ mol^{-1} for each C–H...F–C linkage. This value is much smaller than the bond energy (8.7 kJ mol^{-1}) for the O–H...F–C bond in DFM–H₂O,^[8] but the “cooperative effect” of the three weak C–H...F–C linkages makes the complex sufficiently stable for its detection with our technique.

This is, to our knowledge, the first report on such a small triply hydrogen bonded dimer and on the C–H...F–C hydrogen (or anti-hydrogen?) bond. Detailed information on the conformation, geometry, and dissociation energy have been obtained from the jet cooled rotational spectrum. Ab initio calculations showed the hydrogen bond to have anti-hydrogen bond features.

Experimental Section

The Stark and pulse modulated free jet absorption millimeter-wave spectrometer (60–78 GHz) has been described elsewhere.^[4, 16] The dimer was formed by expanding a mixture of about 5 mol% DFM in argon (or

neon) at room temperature and at a pressure of approximately 0.8 bar to about 5×10^{-3} mbar through a pulsed nozzle (repetition rate 5 Hz) with a diameter of 0.35 mm. An estimated “rotational” temperature of about 10 K was reached. All samples are commercially available and were used without further purification. The accuracy of the frequency measurements was estimated to be 0.05 MHz.

Received: March 25, 1999 [Z13211 IE]
German version: *Angew. Chem.* **1999**, *111*, 3105–3107

Keywords: hydrogen bonds • molecular dynamics • rotational spectroscopy

- [1] *Atomic and Molecular Beam Methods*, Vol. I, II (Ed.: G. Scoles), Oxford University Press, Oxford, **1988**.
- [2] T. S. Zwier, *Annu. Rev. Phys. Chem.* **1996**, *47*, 205–241.
- [3] S. Novick, “Bibliography of Rotational Spectra of Weakly Bound Complexes” available at <http://www.wesleyan.edu/chem/bios/vdw.html>, **1999**.
- [4] S. Melandri, G. Maccaferri, A. Maris, A. Millemaggi, W. Caminati, P. G. Favero, *Chem. Phys. Lett.* **1996**, *261*, 267–271.
- [5] a) W. Caminati, A. Dell’Erba, S. Melandri, P. G. Favero, *J. Am. Chem. Soc.* **1998**, *120*, 5555–5558; b) U. Spoerl, W. Stahl, W. Caminati, P. G. Favero, *Chem. Eur. J.* **1998**, *4*, 1974–1981; c) W. Caminati, P. Moreschini, I. Rossi, P. G. Favero, *J. Am. Chem. Soc.* **1998**, *120*, 11144–11148.
- [6] W. Caminati, A. Dell’Erba, G. Maccaferri, P. G. Favero, *J. Am. Chem. Soc.* **1998**, *120*, 2616–2621.
- [7] a) W. Caminati, L. B. Favero, P. G. Favero, A. Maris, S. Melandri, *Angew. Chem.* **1998**, *110*, 852–856; *Angew. Chem. Int. Ed.* **1998**, *37*, 792–795; b) W. Caminati, P. Moreschini, P. G. Favero, *J. Phys. Chem.* **1998**, *102*, 8097–8100; c) S. Melandri, M. E. Sanz, W. Caminati, P. G. Favero, Z. Kisiel, *J. Am. Chem. Soc.* **1998**, *120*, 11504–11509.
- [8] W. Caminati, S. Melandri, I. Rossi, P. G. Favero, *J. Am. Chem. Soc.* **1999**, in press.
- [9] a) T. R. Dyke, K. M. Mack, J. S. Muentner, *J. Chem. Phys.* **1977**, *66*, 498–510; b) G. T. Fraser, R. D. Suenram, L. H. Coudert, *J. Chem. Phys.* **1989**, *90*, 6077–6085.
- [10] E. Hirota, *J. Mol. Spectrosc.* **1978**, *71*, 145–159.
- [11] J. K. G. Watson in *Vibrational Spectra and Structure*, Vol. 6 (Ed.: J. R. Durig), Elsevier, New York, **1977**, pp. 1–89.
- [12] M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian 94, Revision D.3, Gaussian, Inc., Pittsburgh PA, **1995**.
- [13] P. Hobza, V. Spirko, H. L. Selzle, E. W. Schlag, *J. Phys. Chem. A* **1994**, *98*, 2501–2504; P. Hobza, V. Spirko, Z. Havlas, K. Buchhold, B. Reimann, H.-D. Barth, B. Brutschy, *Chem. Phys. Lett.* **1999**, *299*, 180–186.
- [14] a) D. J. Millen, *Can. J. Chem.* **1985**, *63*, 1477–1479; b) W. G. Read, E. J. Campbell, G. Henderson, *J. Chem. Phys.* **1983**, *78*, 3501–3508.
- [15] R. P. A. Bettens, R. M. Spycher, A. Bauder, *Mol. Phys.* **1995**, *86*, 487–511.
- [16] S. Melandri, W. Caminati, L. B. Favero, A. Millemaggi, P. G. Favero, *J. Mol. Struct.* **1995**, *352/353*, 253–258.

[Al₇{N(SiMe₃)₂}]⁻: A First Step towards Aluminum Metal Formation by Disproportionation**

Andreas Purath, Ralf Köppe, and Hansgeorg Schnöckel*

Dedicated to Professor Arndt Simon on the occasion of his 60th birthday

The formation of an Al₇₇ cluster, the largest metal atom cluster yet characterized by X-ray structure analysis, shows that metastable aluminum monohalide solutions can be the key to the synthesis of such clusters.^[1] Thus they open the way to a current area of research at the borders to nanochemistry. It is not known at this point to what extent the formation mechanism of the [Al₇₇{N(SiMe₃)₂}]₂₀ dianion is a model for the formation of the solid metal. One of our aims has therefore been to capture at low temperatures primary products of the disproportionation of AlNR₂ to Al(NR₂)₃ (R = N(SiMe₃)₂), products in which small sections of metal structure occur. The Al₇₇ compound was the only main group cluster known up to now that showed such a structure centered around a metal atom.^[2] Herein we present a further metal atom centered cluster, which as far as we are aware represents the first example of an especially small but characteristically close-packed section of metal atoms.

Co-condensation of the high-temperature molecule AlCl with a xylene/diethyl ether mixture at -196 °C and subsequent warming to -78 °C yields a metastable AlCl solution. Reaction occurs on addition of this solution to solid LiN(SiMe₃)₂ at -78 °C; subsequent slow warming to room temperature gives solid lithium chloride within one day, which is separated from the dark colored solution. After a few weeks at -30 °C, black crystals of the composition [Al₇{N(SiMe₃)₂}]⁻ [Li(OEt)₃]⁺ (**1**) precipitate from this solution; the X-ray crystal structure of **1** is shown in Figure 1.^[3]

The central Al atom in **1** is surrounded by a distorted octahedron of six further Al atoms, each of which is saturated with one NR₂ ligand. The distance from the six-coordinate central atom to its neighbors is 273 pm, a distance which is intermediate between that of typical Al–Al bonds (266 pm)^[4] and that of Al metal (286 pm). This therefore represents relatively weak Al–Al bonding, as in the [Al₄Cp₄]⁺ molecule^[5] (277 pm; Cp^{*} = C₅Me₅). On the other hand, the Al–Al bonds of the two Al₃R₃ groups are surprisingly short (254 pm), indicating that these are as strong as the “bond order 1½” Al–Al bonds of radical anions of the type R₄Al₂⁻ (253 pm).^[6]

The Al–N and N–Si distances correspond to expectations, as do the observed angles. The cation, needed for overall charge neutrality, is so far from the Al₇R₆⁻ ion that interactions having any effect on structure can be ruled out.

[*] Prof. Dr. H. Schnöckel, Dipl.-Chem. A. Purath, Dr. R. Köppe
Institut für Anorganische Chemie der Universität
Engesserstrasse Geb. Nr. 30.45, D-76128 Karlsruhe (Germany)
Fax: (+49) 721-608-4854
E-mail: hg@achpc9.chemie.uni-karlsruhe.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

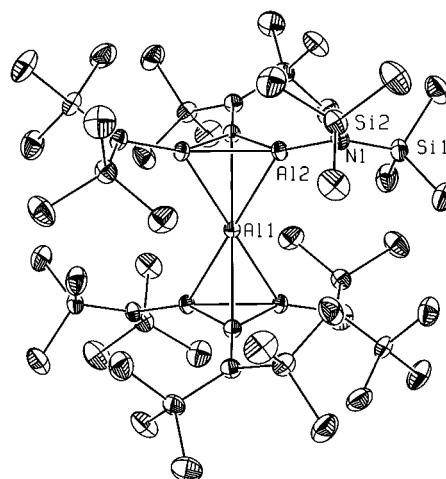


Figure 1. Structure of [Al₇{N(SiMe₃)₂}]⁻ in the crystal (ORTEP; thermal vibrational ellipsoids 50 %, H atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: Al1–Al2 2.7370(4), Al2–Al2' 2.5395(7), Al2–N1 1.8439(12), N1–Si1 1.7306(12); Al2–Al1–Al2 124.717(14), Al1–Al2–N1 138.00(4), Si1–N1–Si2 122.50(7)

The arrangement of the seven Al atoms is unusual; we are not aware of any other instance of two metal atom tetrahedra that are vertex-connected through a mutual “naked” metal atom. Such an arrangement of atoms can be viewed as a primary configuration on the way to close packing, since adding only six further Al atoms, arranged around the central atom in the plane between the three-membered rings, would give a cuboctahedral coordination sphere (Figure 2).^[7]

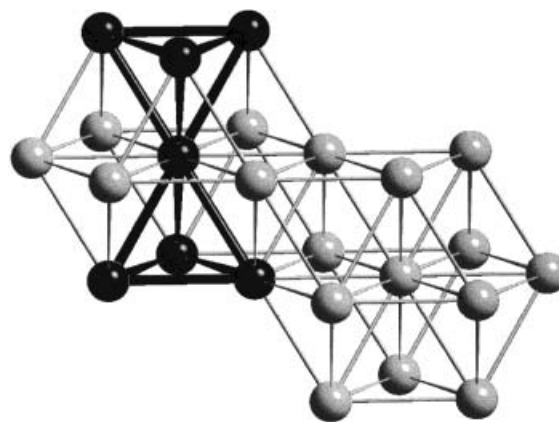


Figure 2. Section of the solid-state structure of aluminum (ccp). The Al₇ fragment is shaded darkly.

For the interpretation of bonding, it seemed reasonable to account for the conspicuously short Al–C bonds in the Al₃R₃ groups by aromatic stabilization, as formulated for Ga₃R₃²⁻ species. The same fractional bond shortening with respect to normal two-electron, two-center (2e2c) Ga–Ga bonds is observed in the latter as in **1**.^[8] This interpretation means that the Al₃R₃ groups have to be assigned a double negative charge, so that the central atom must be considered as Al³⁺, that is a comparable relationship to that in the aluminocenium cation [Cp₂⁺Al]⁺.^[9] Based on the measured and calculated high-field shifts of the ²⁷Al NMR signal of [AlCp₂]⁺, a

description of this cation as a ferrocene-like sandwich compound was justified. This interpretation could not be made to fit compound **1**, since the calculated ^{27}Al NMR signal—a measurement of the resonance was not yet possible—is not high-field shifted, but rather shifted extremely to low field.^[10] The value of $\delta = +801.6$ lies in a region reached by no other molecular Al compound until now. Since such frequencies are already halfway to the shift of aluminum metal ($\delta = +1640$ ^[11]), it is plausible to consider the central Al atom, with its special coordination sphere, to be of similar character to atoms in solid aluminum. A comparison with small anionic Al clusters (e.g. an Al_{13}^- species^[12a]), in which high-field shifts are calculated to be $\delta = -195.2$, is not fruitful. Such clusters present no contradiction to the above hypothesis, since the potential at the central Al atom is obviously completely different to that of the central atom in the Al_7R_6^- group, in which the negative charge is localized primarily on the ligands and a slight positive charge on the six outer Al atoms. Evidently, in **1** the environment of the central Al atom comes closer electronically to that of the metal than in small naked Al_n clusters.^[13] It is therefore conceivable that such compounds with well-defined environments about naked Al atoms could provide models for the physical characterization of single metal atoms with the methods of nanotechnology (Figure 3). All sensational measurements of this type to date were carried out on samples in which the contact between single Al atoms and the atoms of the bulk was not precisely defined.^[14]

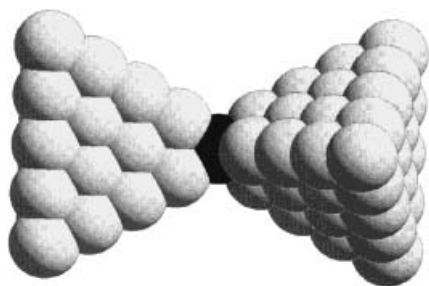


Figure 3. Model geometry for an atomic aluminum contact.^[14]

The isolation and characterization of an Al_7R_6^- cluster as the primary step towards formation of the metal provides encouragement to look for further examples of such metalloidal clusters^[15] using this reaction path, and thereby achieve better understanding of this type of complex but elementary reaction. Our chosen synthetic method—the mild disproportionation of Al^{I} compounds—shows promise in pushing back the boundaries of an area of chemistry where only a few structures have been securely characterized such as $[\text{Ga}_9\{\text{Si}(\text{SiMe}_3)_3\}_6]^-$ ^[16] or $[\text{Au}_{39}(\text{PPh}_3)_{14}\text{Cl}_6]^{2+}$.^[17]

Experimental Section

All work was carried out either in a nitrogen atmosphere on a Schlenk line or in a glove-box (MBRAUN 150) under argon with dried degassed solvents.

1: Cold AlCl_3 solution (-78°C ; 8.0 mL, 0.15 M, *m*-xylene/ Et_2O , 1.2 mmol) was added to solid $\text{LiN}(\text{SiMe}_3)_2$ (200 mg, 1.2 mmol) at -78°C . The reaction mixture was allowed to warm slowly to 20°C (several hours). After 24 h at

$+20^\circ\text{C}$ the LiCl precipitate was separated and the dark solution was stored at -30°C . After several weeks at -30°C black crystals of **1** formed in an oily precipitate. Compound **1** is insoluble in pentane and benzene and decomposed in THF. Yield in crystalline form: ca. 10 mg (4%), X-ray structure analysis: see Figure 1.

Received: May 19, 1999 [Z13441 IE]

German version: *Angew. Chem.* **1999**, *111*, 3114–3116

Keywords: ab initio calculations • aluminum • cluster compounds • metal–metal interactions • structure elucidation

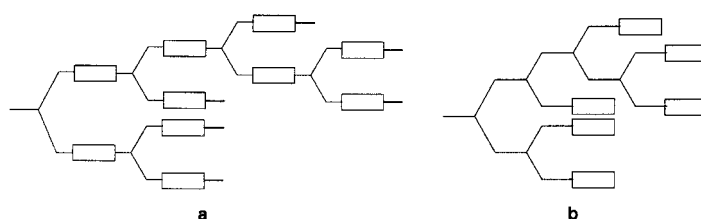
- [1] A. Ecker, E. Weckert, H. Schnöckel, *Nature* **1997**, *387*, 379.
- [2] The In_{12} compound of a recent publication likewise represents a section of close-packed In atoms: N. Wiberg, T. Blank, H. Nöth, W. Ponikvar, *Angew. Chem.* **1999**, *111*, 887; *Angew. Chem. Int. Ed.* **1999**, *38*, 839.
- [3] Crystal structure analysis of **1**: STOE IPDS diffractometer, $\text{Mo}_{\text{K}\alpha}$ radiation, measurement temperature 200(2) K, crystal mounted in perfluoropolyether, crystal dimensions: $0.5 \times 0.4 \times 0.2 \text{ mm}^3$, hexagonal, space group $R\bar{3}$, $a = b = 20.6709(15)$, $c = 17.9876(14) \text{ \AA}$, $V = 6656.1(9) \text{ \AA}^3$, $Z = 3$, $\rho = 1.033 \text{ g cm}^{-3}$, $\mu(\text{Mo}_{\text{K}\alpha}) = 0.28 \text{ mm}^{-1}$, $5.06 \leq 2\theta \leq 51.78$ in $-25 \leq h \leq 25$, $-25 \leq k \leq 25$, $-22 \leq l \leq 22$, measured reflections 21 826, 2870 independent, $2484 > 2\sigma(I)$, 138 parameters, numerical absorption correction ($T_{\text{max}} = 0.8396$, $T_{\text{min}} = 0.9122$), $R1 = 0.0351$, $wR2 = 0.0939$ (all data), $\text{GOOF} = 1.171$, 0 “restraints”, residual electron density: max./min. $0.425/-0.256 \text{ e \AA}^{-3}$. The structure was solved with direct methods and refined against F^2 for all observed reflections. Software used: SHELXS 94, SHELXL 93 (G. M. Sheldrick, Universität Göttingen). 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-120842. 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).
- [4] W. Uhl, *Z. Naturforsch. B* **1988**, *43*, 1113.
- [5] a) C. Dohmeier, C. Robl, M. Tacke, H. Schnöckel, *Angew. Chem.* **1991**, *103*, 594; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 564; b) Q. Yu, A. Purath, A. Donchev, H. Schnöckel, *J. Organomet. Chem.* **1999**, *584*, 94.
- [6] C. Pluta, K. R. Pörschke, C. Krüger, K. Hildenbrand, *Angew. Chem.* **1993**, *105*, 451; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 388.
- [7] This substance, a metastable intermediate on the path towards larger aggregates (e.g. Al_{77} cluster) or even aluminum metal, could not yet be isolated, because the synthesis of, for example, Al_{77} involves work at room temperature and briefly at higher temperatures.
- [8] Whereas Ga–Ga distances of 251.5 pm are found in neutral digallanes $[(\text{iPr}_3\text{C}_6\text{H}_2)\text{Ga}]_2$,^[8a] this distance is shortened to 244 pm in the trimeric compound $\text{K}_2[\text{Mes}_2\text{C}_6\text{H}_3\text{Ga}]_3$ ($\text{Mes} = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$).^[8b] a) X. He, R. A. Bartlett, M. O. Olmstead, K. Ruhlandt-Senge, B. E. Sturgeon, P. P. Power, *Angew. Chem.* **1993**, *105*, 761; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 717; b) X. W. Li, W. T. Pennington, G. H. Robinson, *J. Am. Chem. Soc.* **1995**, *117*, 7578.
- [9] C. Dohmeier, H. Schnöckel, C. Robl, U. Schneider, R. Ahlrichs, *Angew. Chem.* **1993**, *105*, 1714; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1655.
- [10] The following programs were used for the quantum chemical calculations of the model compound $[\text{Al}_7(\text{NH}_2)_6]^-$: a) Turbomole: O. Treutler, R. Ahlrichs, *J. Chem. Phys.* **1995**, *102*, 346; b) Funktional BP86: A. D. Becke, *Phys. Rev. A* **1998**, *38*, 3098; J. P. Perdew, *Phys. Rev. B* **1996**, *33*, 8822; c) RIDFT: K. Eichhorn, O. Treutler, H. Öhm, M. Häser, R. Ahlrichs, *Chem. Phys. Lett.* **1995**, *242*, 652; K. Eichhorn, F. Weigend, O. Treutler, R. Ahlrichs, *Theor. Chem. Acc.* **1997**, *97*, 119. The ^{27}Al NMR shifts were calculated using SCF orbitals at a molecular geometry optimized with the density functional theory (DFT) method.
- [11] Measurements of nanometer Al particles (ca. 3 nm) also produced ^{27}Al NMR shifts in this region ($\delta = 1650$): S. Faber, Dissertation, Saarbrücken, **1996**.

- [12] a) The central Al atom is surrounded by an icosahedron of 12 further Al atoms: R. Ahlrichs, S. D. Elliott, *Phys. Chem. Chem. Phys.* **1999**, *1*, 12; b) calculated Mulliken charges for Al_{13}^- were $\text{Al}_{\text{central}} = -1.86$; $\text{Al}_{\text{icos}} = +0.07$.
- [13] For $[\text{Al}_7(\text{NH}_2)_6]^-$ the Mulliken charge at the central Al atom is -0.18 , at the other Al atoms $+0.11$. By contrast, all N atoms are strongly negative (-0.66) and every H atom positively ($+0.20$) polarized. The calculation was carried out in S_6 symmetry with the orientation of NH_2 groups corresponding to that in **1**. The calculated Al–Al lengths are $d(\text{Al2}–\text{Al2}') = 254.5$ pm and $d(\text{Al1}–\text{Al2}) = 275.0$ pm. The HOMO ($13a_u$)–LUMO ($25e_u$) gap is 1.64 eV.
- [14] E. Scheer, N. Agrait, J. C. Cuevas, L. A. Yeyati, B. Ludoph, A. Martin-Rodero, G. R. Bollinger, J. M. van Ruitenbeek, C. Urbina, *Nature* **1998**, *394*, 154.
- [15] The definition chosen by Cotton for a metal cluster^[18] is so general that it includes many compounds which bear little resemblance to species such as $[\text{Al}_{77}(\text{N}(\text{SiMe}_3)_2)_{20}]^{2-}$ or the subject of this paper, $[\text{Al}_7(\text{N}(\text{SiMe}_3)_2)_6]^-$. By designating these metal-rich molecular species as metalloid clusters, we would like to distinguish them from such compounds. Metalloid (metal-like) clusters should be epitomized by the property that the number of metal–metal contacts exceeds the number of metal–ligand contacts and by the presence of metal atoms which participate exclusively in metal–metal interactions.
- [16] W. Köstler, G. Linti, *Angew. Chem.* **1997**, *109*, 2758; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2644.
- [17] B. K. Teo, X. Shi, H. Zhang, *J. Am. Chem. Soc.* **1992**, *114*, 2743.
- [18] F. A. Cotton, *Q. Rev. Chem. Soc.* **1966**, 389.

Hyperbranched Polyether Polyols with Liquid Crystalline Properties

Alexander Sunder, Marie-France Quincy,
Rolf Mülhaupt, and Holger Frey*

In general, highly branched molecules do not crystallize, but in combination with mesogenic units they can exhibit liquid crystalline (LC) phases.^[1] In this context, particularly cascade-branched molecules have been investigated, that is flexible dendrimers^[2] and their structurally less perfect analogues, the hyperbranched polymers.^[3] In principle, two different strategies have been employed for the incorporation of mesogenic structural elements into cascade-branched architectures (Scheme 1). Either the mesogen can be part of each branching monomer (**a**) or it can be coupled to the end groups of the scaffold (**b**). Structures of type **a** have been prepared by Percec et al. and Ringsdorf et al. for liquid crystal dendrimers as well as hyperbranched polymers.^[4] Structures of type **b** with mesogenic end groups attached to flexible dendrimer scaffolds have been the subject of numerous recent publications both of our group as well as others. In almost all cases the formation of smectic phases was observed.^[5] To date,



Scheme 1. Structural types of branched LC architectures; rods symbolize rigid structural elements (mesogens); connecting lines indicate flexible parts of the scaffold, for example alkyl chains. **a**: Mesogens are part of every monomer unit of the scaffold, **b**: Structurally isotropic hyperbranched scaffold with mesogenic end groups.

no hyperbranched thermotropic liquid crystal polymers with mesogenic end groups are known, since a fundamental problem is the choice of a suitable flexible and well-defined hyperbranched scaffold.

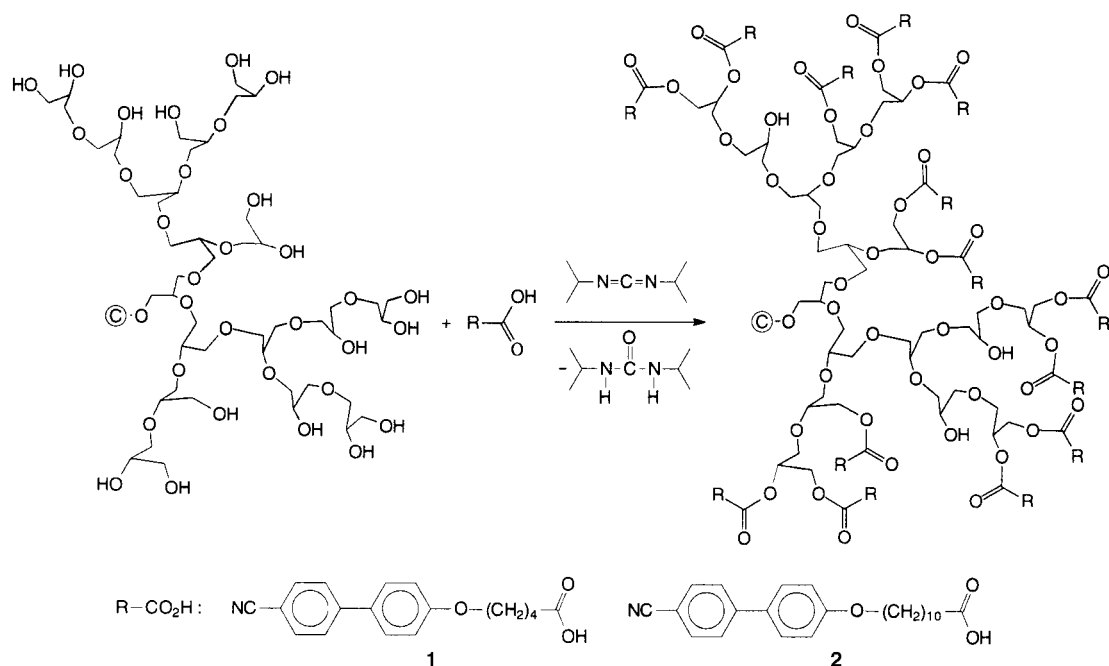
Recently, we have developed a synthetic strategy based on the ring-opening multibranching polymerization (ROMBP) of glycidol (2,3-epoxy-1-propanol), leading to hyperbranched polyglycerols with narrow polydispersity ($M_w/M_n < 1.5$, mostly < 1.3).^[6] By using this approach it was possible to achieve molecular weights of up to 8000 g mol^{-1} , that is 100 hydroxy end groups per molecule. Herein we use these highly flexible aliphatic polyether polyols ($T_g \approx -25^\circ\text{C}$) to attach mesogenic end groups in order to prepare hyperbranched LC polymers of structural type **b**.^[7] We study the effect of molecular weight of the scaffold and the influence of spacer length between mesogen and scaffold on the LC properties.

For the attachment of the mesogenic acids **1** and **2** to the OH end groups of two polyglycerol samples (**PG1**: $M_n = 1500 \text{ g mol}^{-1}$ and **PG2**: $M_n = 3500 \text{ g mol}^{-1}$)^[8] we employed a modified esterification with diisopropylcarbodiimide (Scheme 2).^[9] In order to obtain a high degree of functionalization of the polyglycerols with mesogens despite the strong difference in polarity between substrate and product, it was necessary to change the solvent in the course of the reaction. However, even after reaction times of several days it was not possible to achieve higher degrees of functionalization than 88 % of all hydroxy groups of the lower molecular weight sample **PG1** (^1H NMR, Table 1). For the higher molecular weight sample **PG2** the degree of functionalization ranged between 73 and 79 %. The incomplete reaction of the end groups is most probably explained by the bulkiness of the mesogenic units and the difference in reactivity of the primary and secondary hydroxy groups of polyglycerol.

Gel permeation chromatography (GPC) measurements showed narrow, monomodal molecular weight distributions for all three samples ($M_w/M_n < 1.2$) in agreement with the polydispersities observed for the polyglycerols used (Table 1). The apparent molecular weights determined from GPC (PS standards) correspond to the values calculated from NMR spectra in their order of magnitude.

The LC properties of the three samples prepared were investigated by differential scanning calorimetry (DSC), polarizing microscopy, and wide-angle X-ray scattering (WAXS). In general, all polyglycerols functionalized with mesogenic end groups showed similar phase behavior. In comparison with the unmodified polyglycerol samples, a

[*] Priv.-Doz. Dr. H. Frey, Dipl.-Chem. A. Sunder,
Dipl.-Chem. M.-F. Quincy, Prof. Dr. R. Mülhaupt
Institut für Makromolekulare Chemie
Hermann-Staudinger-Haus und Freiburger
Materialforschungszentrum (FMF) der Universität
Stefan-Meier-Strasse 21/31, D-79104 Freiburg (Germany)
Fax: (+49) 761-203-4709
E-mail: holfrey@mf.uni-freiburg.de



Scheme 2. Functionalization of the end groups of the hyperbranched polyglycerol with mesogenic acids **1** (C_5 spacer) and **2** (C_{11}) by coupling with diisopropylcarbodiimide (DIPC). C-OH indicates the initiator used for the anionic polymerization of glycidol (ROMBP), which has been incorporated as focal unit C .

significant increase of the glass transition temperatures (T_g) was observed in all cases. Above the glass transition broad mesophases were detected (Figure 1). Apparently, molecular weight has only a minor influence on the formation of this mesophase (Table 1, **PG1-1**, **PG2-1**). For both samples the transition enthalpy $\Delta H_{n \rightarrow i}$ of 2 J g^{-1} [10] and the threaded textures observed in the polarizing microscope (Figure 1) unambiguously indicate the presence of a nematic phase.

The phase behavior of **PG2-2** with a longer alkyl spacer between mesogen and hyperbranched scaffold is remarkably different. On the one hand the increase of the glass transition temperature compared to polyglycerol is smaller, on the other hand the temperature interval of the mesophase is broader than in the case of **PG1-1** and **PG2-1**. The transition enthalpy of about 7 J g^{-1} is significantly elevated for a nematic phase, thus indicating the presence of higher ordered smectic clusters (cybotactic structures). However, the diffraction diagrams of all investigated hyperbranched polyglycerols with mesogenic end groups (**PG1-1** as an example in Figure 2) unambiguously prove the presence of a nematic phase.

In conclusion, liquid crystalline hyperbranched polymers with narrow polydispersity, in which the LC phase is induced by mesogenic end groups, have been prepared for the first

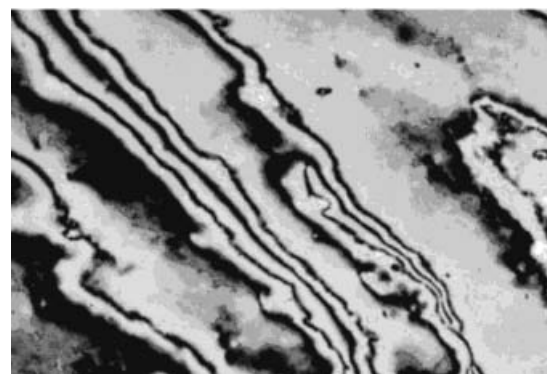
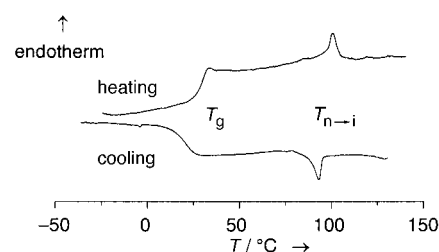


Figure 1. Top: DSC diagram of **PG1-1**. Bottom: Texture of **PG1-1** at 60°C observed with a polarizing microscope, crossed polarizers.

Table 1. Characterization of the mesogen-functionalized polyglycerols

Sample	M_n [a]	Mes. [b]	f [c] [%]	M_n [d] [g mol $^{-1}$]	M_w/M_n [d]	T_g [e] [$^\circ\text{C}$]	$T_{n \rightarrow i}$ [e] [$^\circ\text{C}$]	$\Delta H_{n \rightarrow i}$ [e] [J g $^{-1}$]	d [f]
PG1-1	1500	1	88	5300	1.16	25	97	2.15	4.4
PG2-1	3500	1	73	11000	1.13	22	97	2.23	4.4
PG2-2	3500	2	79	12800	1.15	15	129	6.77	4.4

[a] Determined by vapor pressure osmometry in methanol. [b] Coupled mesogen: length of spacers **1**: C_5 ; **2**: C_{11} . [c] Degree of functionalization f determined by NMR spectroscopy: mesogens per OH group. [d] Determined by GPC in CHCl_3 with polystyrene standards. [e] Determined by DSC. [f] Layer reflection d determined by WAXS; characteristic for mesogen–mesogen distance.

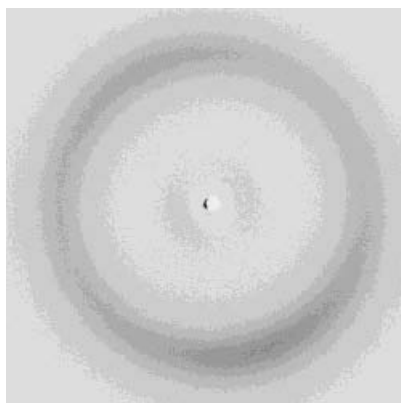


Figure 2. WAXS diagram of **PG1-1**.

time. Interestingly, in pronounced contrast to the structurally related dendrimers with mesogenic end groups^[5] broad nematic phases with low viscosities were observed. A complete functionalization of the end groups with mesogens does not seem to be a prerequisite for LC behavior. In comparison with the mesogen-substituted dendrimers, the different behavior may be explained by the spatial distribution of functionalized end groups of the polyglycerols. In contrast to the perfect dendrimer structure the end groups are not located at the same distance from the core. Specific properties of branched molecules, for example, the absence of entanglements and the high concentration of end groups, are promising for the preparation of liquid crystalline materials with low viscosity and possibly short switching times.

Received: May 3, 1999 [Z13356IE]

German version: *Angew. Chem.* **1999**, *111*, 3107–3110

Keywords: dendrimers • liquid crystals • polymers

- [1] T. J. Bunning, F.-H. Kreuzer, *Trends Polym. Sci.* **1995**, *3*, 318.
- [2] Reviews on supramolecular aspects of dendrimers: a) "Dendrimers": V. V. Narayanan, G. R. Newkome, *Top. Curr. Chem.* **1998**, *197*, 19; b) F. Zeng, S. C. Zimmerman, *Chem. Rev.* **1997**, *97*, 1681; c) H.-F. Chow, T. K.-K. Mong, M. F. Nongrum, C.-W. Wan, *Tetrahedron* **1998**, *54*, 854; d) O. A. Matthews, A. N. Shipway, J. F. Stoddart, *Prog. Polym. Sci.* **1998**, *23*, 1; e) M. Fischer, F. Vögtle, *Angew. Chem.* **1999**, *111*, 934; *Angew. Chem.* **1999**, *38*, 884.
- [3] a) B. I. Voit, *Acta Polymer.* **1995**, *46*, 87; b) Y. H. Kim, *J. Polym. Sci. Polym. Chem. Ed.* **1998**, *36*, 1685.
- [4] Hyperbranched polymers with mesogenic branching units: a) V. Percec, M. Kawasumi, *Macromolecules* **1992**, *25*, 1164; b) S. Bauer, H. Fischer, H. Ringsdorf, *Angew. Chem.* **1993**, *105*, 1658; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1589; c) V. Percec, P. W. Chu, M. Kawasumi, *Macromolecules* **1994**, *27*, 4441; d) S. W. Hanh, Y. K. Yun, J. I. Jin, O. H. Han, *Macromolecules* **1998**, *31*, 6417; e) H. R. Kricheldorf, T. Stukenbrock, C. Friedrich, *J. Polym. Sci. Polym. Chem. Ed.* **1998**, *36*, 1397; dendrimers with mesogenic branching units: f) V. Percec, P. W. Chu, G. Ungar, J. P. Zhou, *J. Am. Chem. Soc.* **1995**, *117*, 11441; g) V. Percec, *Pure Appl. Chem.* **1995**, *67*, 2031.
- [5] Flexible dendrimers with mesogenic end groups: a) H. Frey, K. Lorenz, D. Hölder, R. Mülhaupt, *Polym. Prepr. (Am. Chem. Soc. Div. Polym. Chem.)* **1996**, *37*(1), 758; b) K. Lorenz, D. Hölder, B. Stühn, H. Frey, *Adv. Mater.* **1996**, *8*, 414; c) S. A. Ponomarenko, E. A. Rebrov, N. I. Boiko, N. G. Vasilenko, A. M. Muzafarov, Y. S. Freidzon, V. P. Shibaev, *Polym. Sci. Ser. A* **1994**, *36*, 896; d) S. A. Ponomarenko, E. A. Rebrov, A. Y. Bobrovsky, A. M. Muzafarov, V. P. Shibaev, *Liq. Cryst.* **1996**, *21*, 1; e) M. Collaud Coen, K. Lorenz, J. Kressler, H. Frey, R. Mülhaupt, *Macromolecules* **1996**, *29*, 8069; f) K. Lorenz, B. Stühn, H.

- Frey, R. Mülhaupt, *Macromolecules* **1997**, *30*, 6860; g) M. W. P. L. Baars, S. H. M. Söntjens, H. M. Fischer, H. W. I. Peerlings, E. W. Meijer, *Chem. Eur. J.* **1998**, *4*, 2456; h) R. M. Richardson, S. A. Ponomarenko, N. I. Boiko, V. P. Shibaev, *Liq. Cryst.* **1999**, *26*, 101.
- [6] A. Sunder, R. Hanselmann, H. Frey, R. Mülhaupt, *Macromolecules* **1999**, *32*, 4240.
- [7] Linear polyethers with mesogenic side groups: a) D. Taton, A. Le Borgne, N. Spassky, C. Noel, *Macromol. Chem. Phys.* **1995**, *196*, 2941; b) N. Spassky, A. S. Delgado, C. Noel, *Polym. Bull.* **1997**, *38*, 157.
- [8] Absolute molecular weights of the hyperbranched polyglycerols were determined by NMR, MALDI-TOF, vapor pressure osmometry.^[6] Determination of molecular weights by GPC under standard conditions (CHCl₃, PS standards) is not possible.
- [9] Exemplified description of the synthesis of **PG2-2**: **PG2**^[6] (0.177 g, 0.51 mmol), acid **2** (1.33 g, 3.51 mmol), and *N,N*-dimethylpyridinium *p*-toluenesulfonate (1.06 g, 3.60 mmol) were placed in a 50 mL Schlenk flask and dissolved in anhydrous DMF (13 mL). DIPC (0.6 mL, 3.79 mmol) was added to the clear solution. After the mixture was stirred for five days at room temperature, the solvent was removed and additional acid **2** (0.27 g, 0.71 mmol) suspended in CH₂Cl₂ (15 mL) was added together with DIPC (0.1 mL, 0.63 mmol) (exchange of solvent). After another three days reaction time at room temperature the mixture was twice washed with saturated NaHCO₃ solution and water. After removal of the solvent, the organic residue was extracted several times with methanol, dissolved in a little CH₂Cl₂ and precipitated into methanol (crude yield 0.91 g). The crude product was precipitated three times from CH₂Cl₂ into hot ethanol. Yield: 696 mg (61 %) white solid. ¹H NMR (300 MHz, CDCl₃, 298 K): δ = 7.7–7.3 (m, 6H; NCC₆H₄), 6.85 (s, 2H; arom. H), 5.05 (d, 1H; COOCH), 4.35–4.0 (d, 1H; COOCH₂), 3.85 (s, 2H; C₆H₄OCH₂), 3.7–3.2 (m, 4H; COOCHCH₂OH, COOCHCH₂O), 2.15 (s, 2H; CH₂COO), 1.65 (s, 2H; C₆H₄OCH₂CH₂), 1.6–1.25 (m, 6H; OCOCH₂CH₂, OCO(CH₂)₆(CH₂)₂), 1.2 (s, 8H; OCO(CH₂)₂(CH₂)₄).
- [10] *Handbook of Liquid Crystals, Vol. 1* (Eds.: D. Demus, J. Goodby, G. W. Gray, H. W. Spiess, V. Vill), WILEY-VCH, Weinheim, **1998**.

Ultrastable Mesoporous Aluminosilicates by Grafting Routes**

Robert Mokaya*

There is currently great interest in the thermal and hydrothermal stability of surfactant-templated mesoporous silicas, and recent advances indicate that stable pure silica materials are obtainable.^[1–3] However, of greater importance is the stabilization of heteroatom-containing mesoporous silicates which are useful as catalysts or ion exchangers. In particular Al-containing mesoporous molecular sieves which combine stability and enhanced acidity are desirable.^[1] Despite the need for such aluminosilicates, there have been very few reports on the stabilization of Al-containing mesoporous

[*] Dr. R. Mokaya
Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge CB21EW (UK)
Fax: (+44) 1223-33-63-62
E-mail: rm140@cus.cam.ac.uk

[**] The author is grateful to the EPSRC for an Advanced Fellowship and the Royal Society for an equipment grant.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

frameworks. A significant step forward is the recent synthesis of Al-MCM-41 of excellent structural integrity and improved stability by postsynthesis grafting routes.^[4–6]

Here it is shown that extremely stable mesoporous aluminosilicates with enhanced acidity and catalytic activity can be prepared by a combination of postsynthesis grafting and hydrothermal treatment. The remarkably beneficial effects of hydrothermal treatment on the properties of Al-grafted mesoporous silicas (prepared by aqueous or nonaqueous routes in order to illustrate the versatility of the grafting procedure) are described. The high thermal and hydrothermal stability presented here has not been previously observed for Al-containing mesoporous silicas.^[7] Indeed in comparison to previously reported mesoporous aluminosilicates, the present Al-grafted materials can be described as ultrastable. Furthermore the present Al-grafted materials are also unique in that hydrothermal treatment (i.e., prolonged refluxing in distilled water), far from being detrimental, is beneficial with regard to their use as solid acid catalysts; the hydrothermally treated materials show an unusual reduction in Si/Al (the amount of Al per unit mass of material increases) accompanied by a sharp increase in acid content, which is manifested in higher catalytic activity for acid-catalyzed reactions.

The purely siliceous MCM-41 (herein designated Si-MCM) from which the Al-grafted materials were derived was prepared using normal procedures and had a surface area of 887 m² g^{−1}, a pore volume of 0.85 cm³ g^{−1}, and a pore wall thickness of 16 Å.^[8] The Al-grafted materials were prepared by two methods involving the reaction of Si-MCM with either an aqueous solution of aluminum chlorohydrate (ACH, sample CAH5) or with aluminum isopropoxide in nonaqueous media (hexane, sample CAP10). The hydrothermal stability of the Al-grafted materials was tested by subjecting the samples to refluxing in distilled water (with 1 L of water per gram of solid) for 16 to 150 h. This mode of hydrothermal treatment was selected so as to provide the sternest test of hydrothermal stability; MCM-41 materials generally exhibit greater stability to calcination in the presence of water vapor (steaming) than to boiling in water.^[9] (For example steaming at 750 °C for 4 h had little effect on the structural integrity of the parent Si-MCM; however, on refluxing in water for 16 h, Si-MCM was virtually rendered amorphous and its surface area reduced by 65 % to 325 m² g^{−1}; see Figure 1 in the Supporting Information.)

As shown in Figure 1, the X-ray powder diffraction (XRD) patterns of CAH5 and CAP10 are typical of well-ordered MCM-41. Both materials show an intense (100) diffraction peak and some well-resolved higher order (110), (200), and (210) peaks, which are an indication of good long-range hexagonal ordering. There were no significant changes in the basal spacing (d_{100}) or XRD peak intensities and linewidths resulting from refluxing of the sample for up to 48 h, and materials refluxed for 150 h were still remarkably well ordered, indicating that the pore channel system of MCM-41 remains intact during the hydrothermal treatment. The retention of structural integrity in the refluxed Al-grafted samples is confirmed by the fact that their textural properties (Table 1) remain largely unaffected. Interestingly refluxing (for 16 or 48 h) results in an uncommon increase in both the

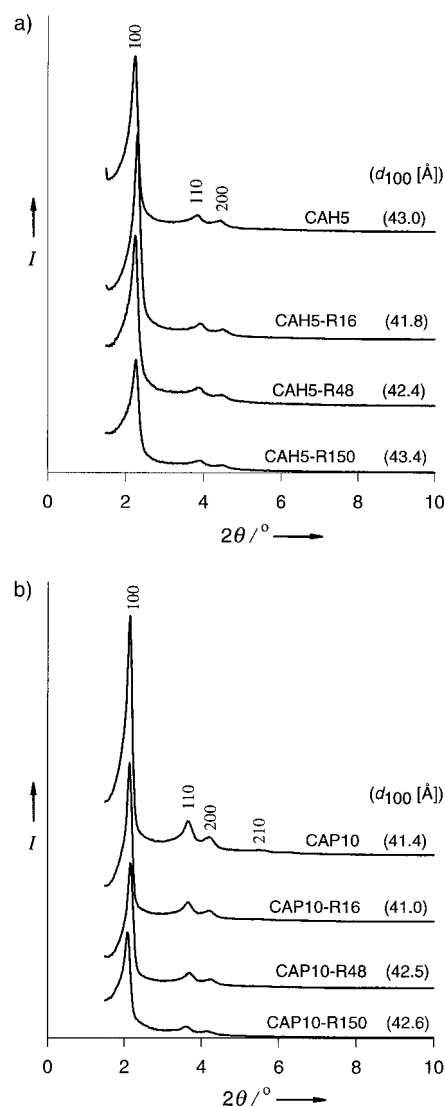


Figure 1. X-ray diffraction patterns of a) the “wet”-grafted CAH5 and b) the “dry”-grafted CAP10 mesoporous aluminosilicates before and after various hydrothermal treatments. The patterns were obtained from a Philips PW1710 diffractometer utilizing CuK α radiation ($\lambda = 1.5418$ Å) with a Ni filter for K β attenuation. I = intensity.

surface area and pore volume. (The stability observed here is brought into sharp focus when one considers that, after 16 h in boiling water, a conventional Al-MCM-41 (Si/Al = 23:1) was rendered amorphous and its surface area reduced from 667 to 285 m² g^{−1}; see Figure 2 in the Supporting Information.)

The average pore diameter and pore wall thickness of the Al-grafted materials remained largely unaffected except for materials refluxed for 150 h, which had slightly wider pores and correspondingly thinner pore walls. It is, however, worth noting that the calculation of wall thickness based on XRD and Brunauer-Joyner-Halenda (BJH) data is subject to an element of error, though this will not affect the trends observed. Pore wall thickness is considered an important factor in determining the stability of mesoporous silicas,^[2, 3] but despite having thinner pore walls, the “dry”-grafted CAP10 sample exhibits hydrothermal stability similar to that of the thicker walled “wet”-grafted CAH5. The stability of

Table 1. Elemental composition, textural properties, acidity, and catalytic activity of Al-grafted materials before and after various hydrothermal treatments.

Sample	Si/Al	Surface area [m ² g ⁻¹]	Pore volume [cm ³ g ⁻¹]	APD ^[a] [Å]	Wall thickness ^[b] [Å]	Acidity ^[c]	Cumene conversion ^[d]
CAH5	6.1:1	753	0.62	25.8	23.9	0.88	0.98
CAH5-R16	5.1:1	834	0.70	24.9	23.4	1.25	1.33
CAH5-R48	4.5:1	902	0.70	26.8	22.2	1.38	1.34
CAH5-R150	4.2:1	724	0.65	31.0	19.1	1.29	1.32
CAP10	9.8:1	850	0.76	30.9	16.9	0.63	0.64
CAP10-R16	8.1:1	894	0.81	31.0	16.3	1.18	1.29
CAP10-R48	7.1:1	864	0.80	32.5	16.6	1.28	1.32
CAP10-R150	6.5:1	810	0.77	33.7	15.5	1.30	1.36

[a] APD = Average pore diameter (determined using BJH analysis of the desorption isotherm). [b] Wall thickness = unit cell parameter (a_0) – APD, where a_0 was obtained from the XRD data using the formula $a_0 = 2d_{100}/\sqrt{3}$. [c] Given in mmoles of H⁺ per gram of sample. [d] Cumene cracking rate, in mmol per gram of catalyst per hour, after 20 min on stream. Total conversion equals a rate of 1.52. Under similar conditions the conversion rate over ultrastable Y zeolite (CBV 740, Si/Al = 21:1) and HY zeolite (Si/Al = 3.6:1) was 1.34 and 0.54, respectively.

these materials is therefore not simply due to their thicker (compared to Si-MCM) walls, but may also be related to pore wall stabilization by recrystallization involving the grafted Al.

The nature of the mesoporous structure and pore uniformity of CAH5 and CAP10 along with their refluxed analogues is illustrated by the nitrogen sorption isotherms in Figure 2. The isotherms, which all possess a steep step in the partial pressure

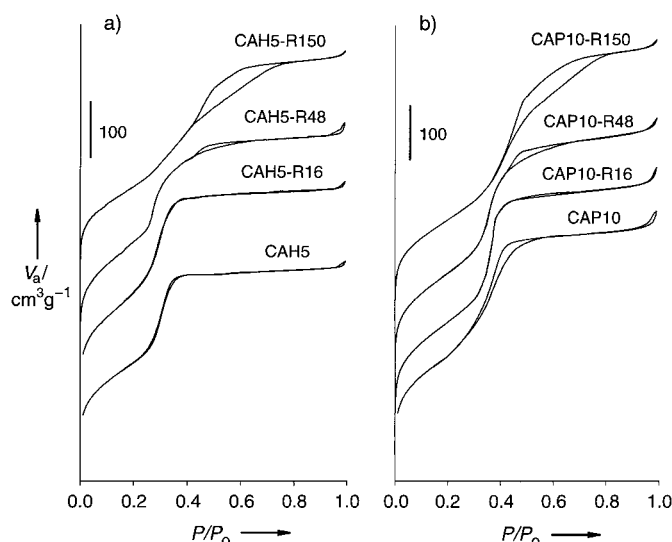


Figure 2. Nitrogen sorption isotherms for a) the “wet”-grafted CAH5 and b) the “dry”-grafted CAP10 mesoporous aluminosilicates before and after various hydrothermal treatments. P/P_0 = partial pressure as a fraction of the saturation pressure (P_0), V_a = volume of adsorbed gas.

range (P/P_0) = 0.3–0.5 are representative of materials with uniform sharply distributed pore radii. Only after refluxing for 150 h is there an increase in pore size and a broadening of the pore size distribution. The hydrothermal stability observed here is most likely due to crystallization effects (previously observed in zeolites) involving the grafted Al which act to heal defect sites in the structure of the MCM-41 materials.^[10] Such restructuring may reduce the concentration of silanols (which are the weak links in the MCM-41 framework), thus stabilizing the structure. This is likely because the Al is initially grafted onto the pure silica material

through silanol groups which are known to occur at defect sites.

The effect of refluxing on the chemical composition of the Al-grafted materials (Table 1) is unusual in that the Si/Al ratio is reduced—that is, the amount of Al per gram of material (x_{Al}) is higher for the refluxed samples and increases with the severity of the refluxing. This is in sharp contrast to the extensive dealumination observed for conventional direct mixed-gel synthesized Al-MCM-41. (For example, the Si/Al ratio of a conventional Al-MCM-41 increased from 23:1 to 370:1 when subjected to refluxing in water for 16 h.) For the present Al-grafted materials it is silica and not Al which is preferentially removed by refluxing. Since the refluxing had no significant effect on structural integrity, it is likely that the extracted silica existed as a separate (amorphous) phase which was not part of the ordered aluminosilicate framework. Indeed when analyzed by scanning electron microscopy (SEM), the refluxed samples appeared to have fewer small “fluffy” particles, which were present in larger quantities in the parent Al-grafted samples deposited on larger particle aggregates (see Figure 3a in the Supporting Information). High-resolution transmission electron microscopy (HRTEM) has shown that the small particles are largely amorphous, while the larger particle aggregates are ordered.

Based on these observations it is logical to conclude that the small particles are (nonframework) amorphous silica which is removed during refluxing (by dissolution), leaving the Al-grafted MCM-41 framework (i.e., the large particle aggregates) intact. Further evidence to support the preferential extraction of silica was obtained from X-ray photoelectron spectroscopy (XPS), which indicated that the outer surface of the refluxed samples was enriched in Al—that is, the Al concentration gradient between the surface and bulk was greater for the refluxed samples. Furthermore refluxing (for up to 48 h) did not have any significant effect on the nature and environment of the Al nuclei; the ²⁷Al MAS NMR spectra shown in Figure 3 indicate that the ratio of tetrahedrally coordinated (framework) Al ($\delta = 53$) to octahedrally coordinated (nonframework) Al ($\delta = 0$) changed little. There was, therefore, no significant extraction of Al from tetrahedral (framework) positions except for samples refluxed for 150 h, as shown for CAP10 in Figure 3b.

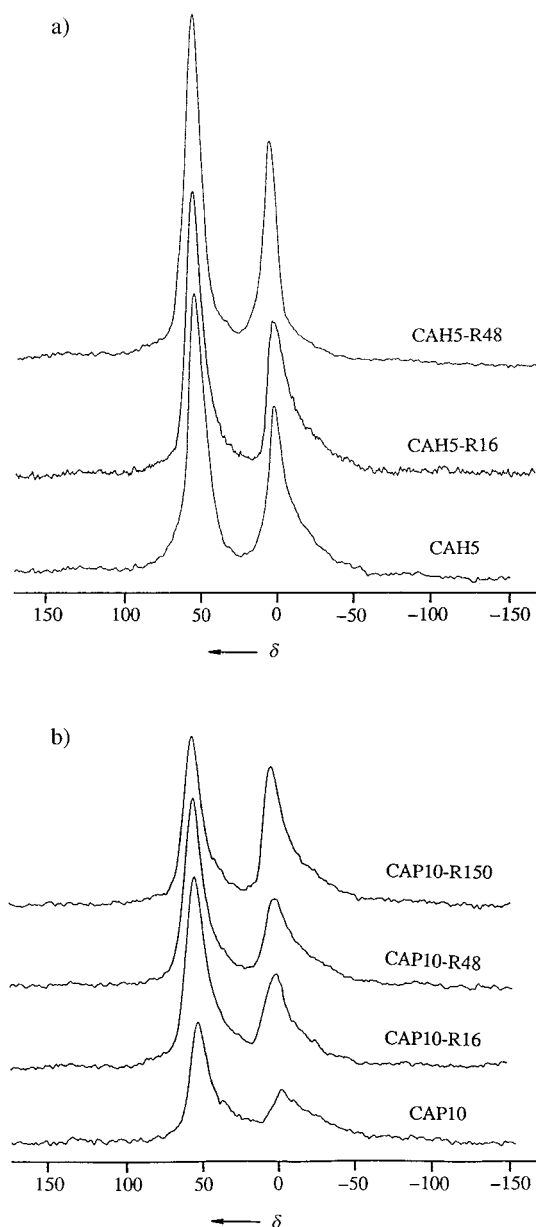


Figure 3. ^{27}Al MAS NMR spectra of a) the “wet”-grafted CAH5 and b) the “dry”-grafted CAP10 mesoporous aluminosilicates before and after various hydrothermal treatments. The spectra were recorded at 9.4 T using a Chemagnetics CMX-400 spectrometer with rotors 4 mm in diameter spun at 10 kHz. Before analysis the samples were fully hydrated.

The acid content of the Al-grafted samples and their refluxed analogues (Table 1) was determined using thermally programmed desorption of cyclohexylamine.^[11, 12] Prior to thermogravimetric analysis, the samples containing the base (cyclohexylamine) were heated at 80 °C for 2 h. The weight loss due to amine desorption from acid sites between 300 and 450 °C was used to quantify the acidity in mmol of H^+ assuming that each base molecule interacts with one Brønsted acid site. The increase in aluminum per unit mass for the refluxed samples is accompanied by an increase in acid content. However, higher aluminum content alone cannot explain the increase in acidity since the acid content of Al-grafted materials with x_{Al} similar to that of the refluxed

samples is much lower; a directly prepared ACH-grafted sample with $\text{Si}/\text{Al} = 4.2:1$ had an acid content (in millimoles of H^+ per gram of sample) of 0.89:1, compared to an acid content of 1.38 for CAH5-R48 ($\text{Si}/\text{Al} = 4.5$). It is therefore likely that refluxing has other beneficial effects. One possibility is that the “cleaning out” of some amorphous silica by desilylation improves access to the Al sites where the acid sites are located. SEM also shows that refluxing breaks up large particle aggregates into smaller ones, which may improve access to acid sites (see Figure 3b in the Supporting Information).

The conversion of cumene (which requires medium to strong acid sites) was used to illustrate the catalytic potential of the hydrothermally treated Al-grafted materials.^[4, 6] Catalytic cracking to benzene and propene was the main reaction with only trace amounts of α -methylstyrene (product of dehydrogenation over Lewis acid sites) being formed, indicating that the active sites are Brønsted acid sites.^[13] The catalytic data (Table 1) show that the grafted materials possess considerable catalytic activity which dramatically increases on refluxing (see also Figure 4 in the Supporting Information). The increase in activity is in line with the changes in acid content, which indicates that refluxing results in an increase in Brønsted rather than Lewis acid sites; this was indeed confirmed by monitoring adsorbed pyridine using Fourier transform infrared (FT-IR) spectroscopy, which can distinguish between Brønsted and Lewis acid sites.^[14]

The activity of the refluxed samples is comparable to that of USY zeolite ($\text{Si}/\text{Al} = 21:1$) and is in any case much higher than that of HY zeolite ($\text{Si}/\text{Al} = 3.6:1$) or conventional Al-MCM-41 of comparable aluminum content.^[4, 6] This enhanced solid (Brønsted) acid capability combined with a stable, well-ordered structure possessing uniform (meso) pores opens up new opportunities in the use of mesoporous aluminosilicates. Although this report has given prominence to the unusual effects of refluxing in water, it is worth noting that the Al-grafted materials are thermally stable (1000 °C for 4 h) and can also withstand prolonged steaming at 750 °C. Apart from MCM-41, other mesoporous silicas such as MCM48, MSU-*n*, and SBA-*n* have been successfully utilized to prepare ultra-stable aluminosilicates.

Experimental Section

The Al-grafted materials were prepared by an aqueous or nonaqueous method; in the aqueous (or wet) method the calcined Si-MCM (1.0 g) was added to a solution (50 mL) of ACH (0.48 mol L^{-1} with respect to Al) at 80 °C and stirred for 2 h at 80 °C. The resulting solid was obtained by filtration and thoroughly washed with distilled water (until it was free of Cl^- ions), dried at room temperature, and calcined in air at 550 °C for 4 h. The resulting Al-grafted material, designated CAH5, had a bulk Si/Al ratio of 6.1:1. In the second nonaqueous (or dry) route Si-MCM (2.0 g) was dispersed in dry hexane (50 mL) and added to 150 mL dry hexane containing the appropriate amount of aluminum isopropoxide to give a grafting gel Si/Al ratio of 10:1. The resulting mixture was stirred for 10 min and allowed to react at room temperature for 24 h. The obtained powder was filtered, washed with dry hexane, dried at room temperature, and calcined at 550 °C for 4 h. The resulting material with a bulk Si/Al ratio of 9.8:1 was designated CAP10. To assess hydrothermal stability CAH5 and CAP10 were subjected to refluxing in distilled water (with 1 L of water per gram of solid) for 16–150 h. After refluxing the samples were dried at

130 °C for 16 h. The refluxed samples were designated CAH5-RX or CAP10-RX, where X is the reflux time in hours.

Received: April 9, 1999 [Z13269IE]
German version: *Angew. Chem.* **1999**, *111*, 3079–3083

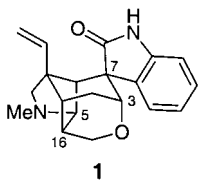
Keywords: acidity • aluminosilicates • heterogeneous catalysis • mesoporosity

- [1] A. Corma, *Chem. Rev.* **1997**, *97*, 2373.
- [2] D. Zhao, J. Feng, Q. Huo, N. Melosh, G. H. Fredrickson, B. F. Chmelka, G. D. Stucky, *Science* **1998**, *279*, 548.
- [3] S. S. Kim, W. Zhang, T. J. Pinnavaia, *Science* **1998**, *282*, 1302.
- [4] R. Mokaya, W. Jones, *Chem. Commun.* **1997**, 2185.
- [5] R. Ryoo, S. Jun, J. M. Kim, M. J. Jim, *Chem. Commun.* **1997**, 2225.
- [6] R. Mokaya, W. Jones, *Chem. Commun.* **1998**, 1839.
- [7] A. Corma, M. S. Grande, V. Gonzalez-Alfaro, A. V. Orchilles, *J. Catal.* **1996**, *159*, 375.
- [8] R. Mokaya, W. Z. Zhou, W. Jones, *Chem. Commun.* **1999**, 51.
- [9] J. M. Kim, R. Ryoo, *Bull. Korean Chem. Soc.* **1996**, *17*, 66.
- [10] D. W. Breck, *Zeolite Molecular Sieves*, R. E. Krieger Company, New York, **1974**, p. 441.
- [11] C. Breen, *Clay Miner.* **1991**, *26*, 487.
- [12] R. Mokaya, W. Jones, S. Moreno, G. Poncelet, *Catal. Lett.* **1997**, *49*, 87.
- [13] J. W. Ward, *J. Catal.* **1967**, *9*, 225.
- [14] E. R. Parry, *J. Catal.* **1963**, *2*, 371.

Total Synthesis of (±)-Gelsemine**

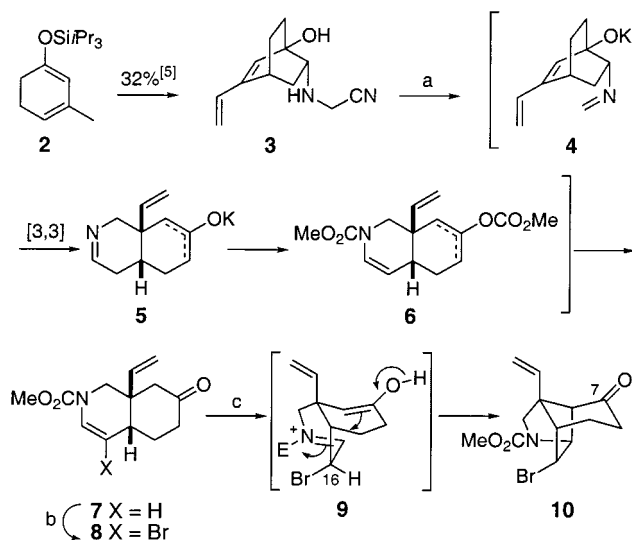
Andrew Madin, Christopher J. O'Donnell,
Taeboem Oh, David W. Old, Larry E. Overman,* and
Matthew J. Sharp

Gelsemine (**1**), the major alkaloid component of *Gelsemium sempervirens* (Carolina or yellow jasmine), was isolated in the 1870s.^[1, 2] After eighty years of extensive, and largely inconclusive degradative studies, the structure was solved in 1959 by both NMR and X-ray spectroscopic methods.^[3] The densely functionalized hexacyclic skeleton of gelsemine stimulated intensive synthetic efforts throughout the world, which resulted in four total syntheses of (±)-gelsemine.^[4] In 1988 we described the preparation of an advanced pentacyclic intermediate,^[5] which, although incorporating all the carbon atoms of gelsemine,^[5c] did not ultimately prove to



be a viable precursor to this hexacyclic alkaloid. Herein we report the total synthesis of (±)-gelsemine by a sequence whose key strategic steps are a sequential anionic aza-Cope rearrangement and Mannich cyclization, an intramolecular Heck reaction, and a complex base-promoted molecular reorganization to generate the hexacyclic ring system.

The azatricyclodecane ring system of gelsemine was assembled using a slight modification of the route we reported earlier (Scheme 1).^[5] The sequence began with 1-triisopropylsiloxy-3-methyl-1,3-cyclohexadiene (**2**),^[6] which was converted into the bicyclo[2.2.2]octene **3** in eight steps (32% overall yield).^[5] Exposure of **3** to potassium hydride and



Scheme 1. Reaction conditions: a) KH, [18]crown-6, THF, rt; ClCO₂Me, DTBMP, -78 °C → rt; KOH, MeOH, H₂O, rt, 81%; b) Br₂, 1,2,2,6,6-pentamethylpiperidine, CH₂Cl₂, -78 °C; c) TFA, reflux, 67% over 2 steps. DTBMP = 2,6-di-tert-butyl-4-methylpyridine.

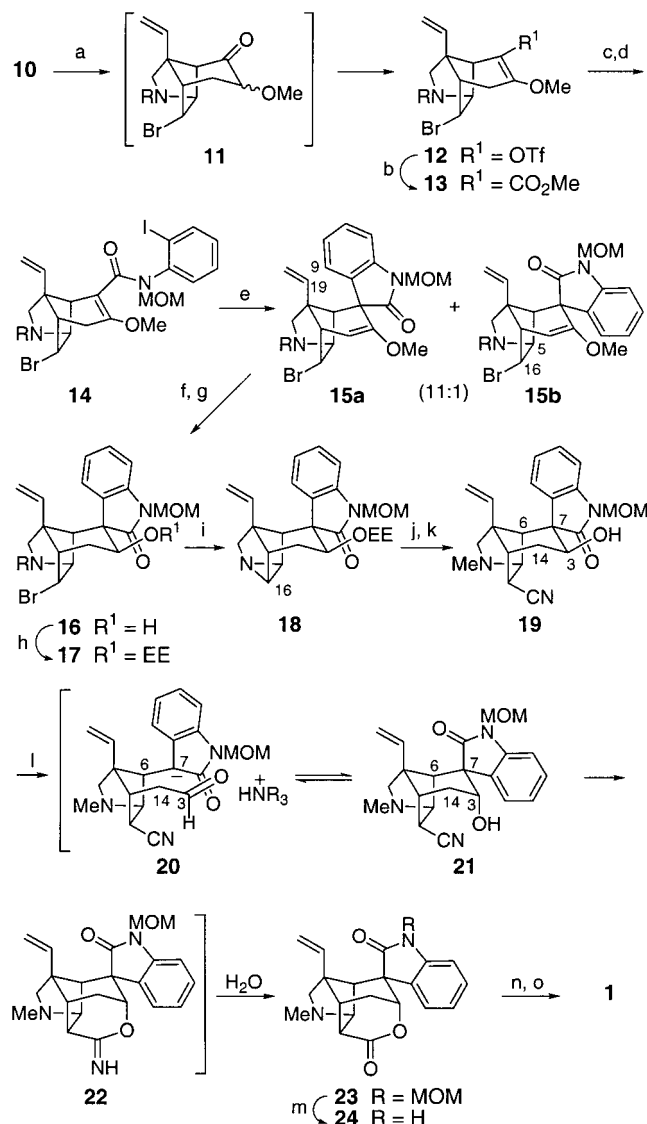
[18]crown-6 at room temperature promoted the anionic aza-Cope rearrangement of the derived formalimine alkoxide **4**.^[7] Quenching the resulting product **5** with excess methyl chloroformate, followed by selective cleavage of the carbonate functional group of **6** produced *cis*-hexahydroisoquinoline **7** in 81% yield. The enecarbamate functional group of **7** was selectively brominated and the resulting product **8** was heated at reflux in trifluoroacetic acid (TFA) to provide the azatricyclodecanone **10** as a single diastereomer in 67% yield. In this Mannich cyclization, the tetrahydropyridine ring of **8** needs to adopt a high-energy boat conformation **9** in order for the iminium ion and the enol π system to overlap. Preferential cyclization of the thermodynamically favored C16 epimer **9** of the *N*-acyliminium intermediate, delivers tricyclic product, **10** with the bromine substituent on the *exo* face. By using this extensively optimized sequence, **10** could be prepared from commercially available 3-methylanisole in 12 steps and 16% overall yield.

The next stage of the synthesis involved construction of the spirooxindole at C7 of **10** in such a way that C3 was substituted with a group containing an oxygen functionality that could be employed to form the pyran ring of gelsemine. This objective was accomplished by initially oxidizing the

[*] Prof. L. E. Overman, A. Madin, C. J. O'Donnell, T. Oh, D. W. Old, M. J. Sharp
Department of Chemistry, University of California
516 Rowland Hall, Irvine, CA 92697-2025 (USA)
Fax: (+1) 949-824-3866
E-mail: leoverma@uci.edu

[**] This work was supported by the U.S. National Institutes of Health (HL-25854). C.J.O. gratefully acknowledges the American Cancer Society for postdoctoral fellowship support (PF-98-002-01). The early stages of our gelsemine synthesis were developed by Dominique Lesuisse, William Earley, Jon Jacobsen, and Patrick Meier.

enoxytriethylsilane derivative of **10** with iodosobenzene and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in the presence of methanol to generate the corresponding α -methoxy ketone **11** as a mixture of stereoisomers (Scheme 2).^[8] Treatment of this crude intermediate with potassium hexamethyldisilazane, followed by quenching with Comins' reagent^[9] provided enol triflate **12** in 61% overall yield from **10**. Palladium-catalyzed carbonylation of **12** in the presence of methanol gave methyl ester **13** in high yield.



Scheme 2. Reaction conditions: a) KHMDs, Et_3SiCl , THF, -78°C ; $(\text{PhIO})_n$, $\text{BF}_3 \cdot \text{OEt}_2$, MeOH, CH_2Cl_2 , $-78 \rightarrow 0^\circ\text{C}$; KHMDs, Comins' reagent, THF, -78°C , 61%; b) CO (3.5 bar), $[\text{PdCl}_2(\text{dppf})_2] \cdot \text{CH}_2\text{Cl}_2$, MeOH, $(n\text{Bu})_3\text{N}$, DMF, 80°C , 94%; c) 2-iodoaniline, Me_3Al , CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{rt}$, 91%; d) NaH, MOMCl, THF, 86%; e) $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$, Ag_3PO_4 , Et_3N , THF, reflux, 61–78%; f) conc. HCl, MeOH, rt, 98%; g) $(t\text{Bu})_3\text{Al}$, PhMe, $-78^\circ\text{C} \rightarrow \text{rt}$, 71%; h) ethyl vinyl ether, pyridinium *p*-toluenesulfonate, CH_2Cl_2 , rt, 85%; i) NaCN, Me_2SO , 150°C , 99%; j) MeOTf, DTBMP, CH_2Cl_2 , 0°C ; NaCN, Me_2SO , 90°C , 85%; k) *p*-toluenesulfonic acid $\cdot \text{H}_2\text{O}$, CH_2Cl_2 , MeOH, rt, 99%; l) DBU, PhMe, reflux, 80%; m) conc. HCl, $(\text{MeOCH}_2)_2$, 55°C ; $(i\text{Pr})_2\text{NEt}$, MeOH, 55°C , 90%; n) $(t\text{Bu})_2\text{AlH}$, PhMe, $0^\circ\text{C} \rightarrow \text{rt}$; o) Et_3SiH , TFA, CH_2Cl_2 , reflux, 65% over 2 steps. HMDS = hexamethyldisilazane, Comins' reagent = 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, Tf = trifluoromethylsulfonyl, dppf = 1,1'-bis(diphenylphosphano)ferrocene, MOM = methoxymethyl, dba = dibenzylidenacetone, EE = 1-ethoxyethyl, for compounds **11** $\rightarrow$ **17**, R = CO_2Me .

This intermediate was condensed with the dimethylaluminum amide of iodoaniline^[10] and the resulting secondary amide was treated sequentially with sodium hydride and chloromethyl methyl ether to yield **14**.

The stage was set for the pivotal intramolecular Heck reaction, which we approached with some trepidation since it would require the insertion of a tetrasubstituted double bond of a vinylogous carbamate.^[11] Fortunately, the Heck cyclization was efficient under cationic Heck conditions and gave an 11:1 mixture of spirooxindole stereoisomers. The major product **15a**, isolated in 61–78% yield, was shown to have the opposite configuration of the spirooxindole as that found in gelsemine.^[12, 13]

To complete the synthesis of gelsemine we needed to epimerize the oxindole and fashion the remaining oxacyclic ring.^[14] To this end, pentacycle **15a** was hydrolyzed and the resulting ketone was reduced with triisobutylaluminum to provide equatorial alcohol **16** (71% yield) as the major product (dr = 5.6:1).^[15] Protection of this alcohol to form **17**, followed by reaction with excess sodium cyanide in dimethyl sulfoxide at 150°C delivered aziridine **18** in high yield.^[16] Methylation of **18** with methyl trifluoromethanesulfonate, followed by regioselective opening of the resulting aziridinium salt at C16 with sodium cyanide and removal of the 1-ethoxyethyl protecting group provided **19** in 85% overall yield. Finally, heating **19** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene brought about the desired molecular rearrangement to form hexacyclic lactone **23** in 80% yield after acidic workup. This complex reorganization likely occurs by a retro aldol cleavage of the C3–C7 bond which generates an intermediate such as **20**. After rotation about the C6–C7 and C3–C14 σ bonds, aldol closure affords the intermediate **21** in which both the oxindole and C3 alcohol have been epimerized. Addition of the resulting axial alcohol to the proximal nitrile to generate hexacyclic imidate **22**, followed by hydrolysis yielded **23**.

Lactone **23** was readily converted into gelsemine by initially removing the methoxymethyl protecting group to provide **24**. Reduction of this intermediate with diisobutylaluminum hydride generated a mixture of lactols, which upon further reduction with triethylsilane and trifluoroacetic acid produced ($\pm$)-gelsemine (**1**) in 59% overall yield from **23**.^[17]

The total synthesis of ($\pm$)-gelsemine (**1**) reported herein was accomplished in 1.2% overall yield by way of 26 isolated intermediates. Key steps include a sequential base-promoted aza-Cope rearrangement and Mannich cyclization, an unprecedented intramolecular Heck insertion of a tetrasubstituted vinylogous carbamate and a complex base-promoted skeletal rearrangement.

Received: April 22, 1999 [Z13304IE]
German version: *Angew. Chem.* **1999**, *111*, 3110–3112

Keywords: alkaloids • palladium • pericyclic reactions • rearrangements • total synthesis

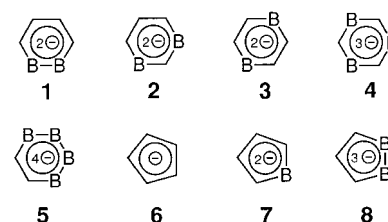
[1] For reviews, see a) Z.-J. Liu, R.-R. Lu in *The Alkaloids*, Vol. 33 (Ed.: A. Brossi), Academic Press, San Diego, **1988**, pp. 83–140, and earlier reviews in this series; b) J. E. Saxton, *Nat. Prod. Rep.* **1992**, 393–446.

- [2] F. L. Sonnenschein, *Ber. Dtsch. Chem. Ges.* **1876**, 9, 1182.
 [3] a) F. M. Lovell, R. Pepinsky, A. J. C. Wilson, *Tetrahedron Lett.* **1959**, 1;
 b) H. Conroy, J. K. Chakrabarti, *Tetrahedron Lett.* **1959**, 6.
 [4] a) Z. Sheikh, R. Steel, A. S. Tasker, A. P. Johnson, *J. Chem. Soc. Chem. Commun.* **1994**, 763; b) J. K. Dutton, R. W. Steel, A. S. Tasker, V. Popsavin, A. P. Johnson, *J. Chem. Soc. Chem. Commun.* **1994**, 765;
 c) N. J. Newcombe, F. Ya, R. J. Vijn, H. Hiemstra, W. N. Speckamp, *J. Chem. Soc. Chem. Commun.* **1994**, 767; d) D. Kuzmich, S. C. Wu, D.-C. Ha, C.-S. Lee, S. Ramesh, S. Atarashi, J.-K. Choi, D. J. Hart, *J. Am. Chem. Soc.* **1994**, 116, 6934; e) T. Fukuyama, G. Liu, *J. Am. Chem. Soc.* **1996**, 118, 7426; f) S. Atarashi, J.-K. Choi, D.-C. Ha, D. J. Hart, D. Kuzmich, C.-S. Lee, S. Ramesh, S. C. Wu, *J. Am. Chem. Soc.* **1997**, 119, 6226.
 [5] a) W. G. Earley, E. J. Jacobsen, G. P. Meier, T. Oh, L. E. Overman, *Tetrahedron Lett.* **1988**, 29, 3781; b) W. G. Earley, T. Oh, L. E. Overman, *Tetrahedron Lett.* **1988**, 29, 3785; c) M. J. Sharp, PhD thesis, University of California, Irvine (USA), **1991**.
 [6] Prepared in 92% yield from 3-methylanisole by the literature procedure: G. M. Rubottom, J. M. Gruber, *J. Org. Chem.* **1977**, 42, 1051.
 [7] a) M. Kakimoto, M. Okawara, *Chem. Lett.* **1979**, 1171; b) M. E. Okazaki, PhD thesis, University of California, Irvine (USA), **1986**.
 [8] R. M. Moriarty, O. Prakash, M. P. Duncan, R. K. Vaid, H. A. Musallam, *J. Org. Chem.* **1987**, 52, 150.
 [9] D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, 33, 6299.
 [10] M. F. Lipton, A. Basha, S. M. Weinreb, *Org. Synth.* **1980**, 59, 49.
 [11] For the first use of an intramolecular Heck reaction to form the spirooxindole functionality of gelsemine, see ref. [5b]. For recent reviews on the use of intramolecular Heck reactions in natural products total synthesis, see a) J. T. Link, L. E. Overman, *CHEM-TECH* **1998**, 28, 19; b) L. E. Overman, J. T. Link in *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), WILEY-VCH, Weinheim, **1998**, pp. 231–270.
 [12] The high selectivity for the formation of **15a** is attributed to the coordination of the angular vinyl group to the cationic palladium species during the insertion step, see A. Madin, L. E. Overman, *Tetrahedron Lett.* **1992**, 33, 4859.
 [13] The oxindole configuration was determined by nuclear overhauser enhancement (NOE) experiments. A positive NOE was observed between the hydrogen atoms on C9 and C19 of the major diastereomer **15a** while the minor diastereomer **15b** showed a positive NOE between the hydrogen atoms on C9, C5, and C16.
 [14] We anticipated that we could epimerize the oxindole based on a previous report from our laboratory, see L. E. Overman, M. J. Sharp, *J. Org. Chem.* **1992**, 57, 1035. A more direct precedent is described by Hart.^[4d]
 [15] a) J. A. Katzenellenbogen, S. B. Bowlus, *J. Org. Chem.* **1973**, 38, 627; b) G. E. Heinsohn, E. C. Ashby, *J. Org. Chem.* **1973**, 38, 4232; c) L. E. Overman, R. J. McCready, *Tetrahedron Lett.* **1982**, 23, 2355.
 [16] It has not been determined whether this unusual reaction occurs by a double displacement sequence, an S_N1 process, or by other possible mechanisms.
 [17] Synthetic ($\pm$)-gelsemine (**1**) was identical to a natural sample by TLC, ^1H NMR, ^{13}C NMR, IR, and HR-MS analysis.

A Five-Membered Ring with Three Negative Charges and Solvent-Free Lithium Counterions**

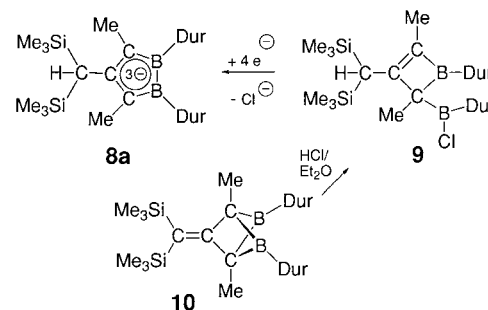
David Scheschkewitz, Matthias Menzel, Matthias Hofmann, Paul von Ragué Schleyer, Gertraud Geiseler, Werner Massa, Klaus Harms, and Armin Berndt*

Dianionic boron heterocycles like **1–3** and **7** are well characterized,^[1] whereas triply and quadruply negatively charged systems such as **4** and **5** have only been known as



ligands in transition metal triple decker complexes.^[2] The derivative of **8** described here is the first five-membered ring with three formal negative charges.^[3] Its η^5 -bound lithium counterions exhibit remarkably short distances to the ring and are free from “external” π and n ligands.

The orange-red trillithium compound **8a**·Li₃·2Et₂O (Dur = 2,3,5,6-tetramethylphenyl) with one solvent-free lithium cation is the only product (besides LiCl) from the reaction of chloroborylboretene **9** with lithium metal in Et₂O. A similar reductive ring expansion in which a B–B bond was



formed during the synthesis of a four-membered ring was reported recently.^[4] We isolated **8a**·Li₃·Et₂O with two solvent-free lithium counterions by crystallization from boiling toluene. Compound **9** is accessible from diborabicyclopentane **10**^[5] and ethereal HCl. Its constitution was secured by

[*] Prof. Dr. A. Berndt, Dr. D. Scheschkewitz, Dr. M. Menzel, G. Geiseler, Prof. Dr. W. Massa, Dr. K. Harms
 Fachbereich Chemie der Universität
 D-35032 Marburg (Germany)
 Fax: (+49) 6421-28-89-17
 E-mail: berndt@ps1515.chemie.uni-marburg.de
 Dr. M. Hofmann, Prof. Dr. P. von R. Schleyer
 Computer Chemistry Annex, Department of Chemistry
 University of Georgia, Athens, GA 30602-2525 (USA)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We are grateful to Frank Stahl for his assistance. Part of the work was carried out at the University of Erlangen-Nürnberg, Erlangen (Germany).

X-ray structure determination.^[6] Figure 1 displays the structures of **8a**·Li₃·Et₂O and **8a**·Li₃·2Et₂O in the solid state.^[7] Table 1 summarizes relevant atom distances compared to those calculated^[8] for the unsubstituted **8u**·Li₃ and for the model compound **8b**·Li₃·Me₂O (see Figure 2).

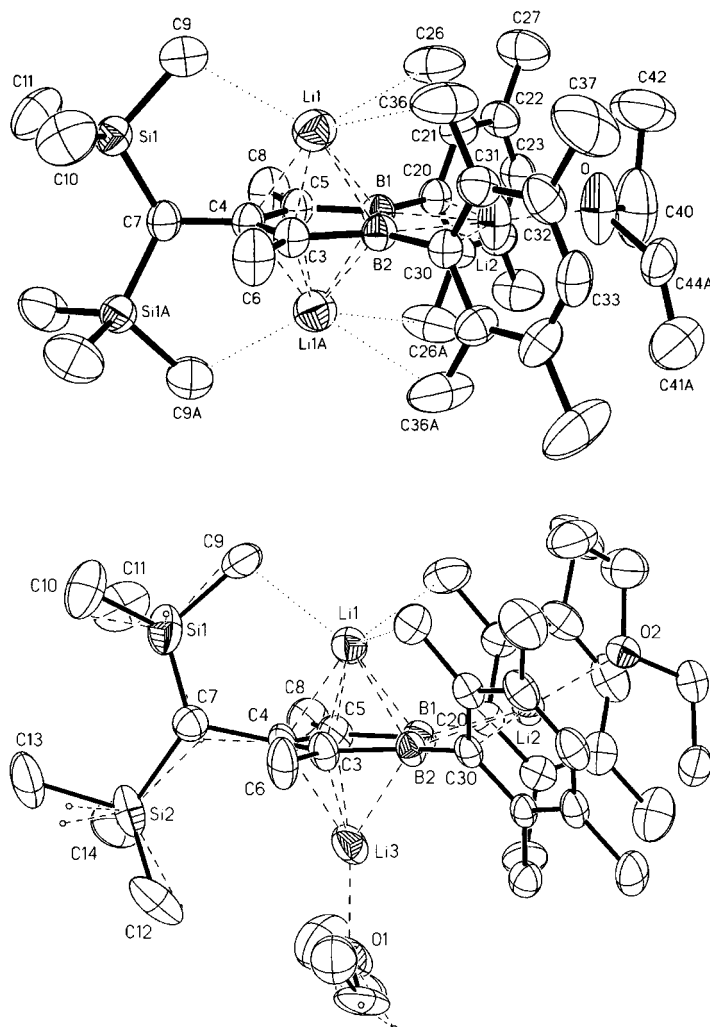


Figure 1. Structures of **8a**·Li₃·Et₂O (top) and **8a**·Li₃·2Et₂O (bottom) in the crystal; thermal ellipsoids are shown at the 30% probability level. The alternative disordered location of the CH(SiMe₃)₂ group is shown with dashed lines, and Li...methyl contacts clearly beneath the sum of the van der Waals radii ($r(\text{Me}) = 200$ pm, $r(\text{Li}) = 182$ pm) are indicated with dotted lines. Selected distances [pm]: **8a**·Li₃·Et₂O: Li1–C9 265.8(6), Li1–C26 316.2(5), Li1–C36 316.3(5); **8a**·Li₃·2Et₂O: Li1–C9/C9' 238(2)/274(2) (disorder), Li1–C29 290.6(7), Li1–C39 315.9(8).

Whereas the lithium counterions of all experimentally characterized five-membered ring anions also are coordinated by π or n ligands (aromatic ligands, ethers, or amines) from the opposite side of the ring, such ligation is completely lacking in **8a**·Li₃·Et₂O and partly lacking in **8a**·Li₃·2Et₂O. Instead, the C–H bonds of the methyl groups of the bis(trimethylsilyl)methyl substituent act as σ ligands. This is shown by the short Li1–C9 and Li1–H(C9) distances of 265.8(6) and 219(4) pm, respectively, in **8a**·Li₃·Et₂O as well as the short Li1–C9 distance of 238(2) pm in **8a**·Li₃·2Et₂O.^[9] Comparably short distances have been observed in many

Table 1. Selected bond distances [pm] of **8a**·Li₃·2Et₂O and **8a**·Li₃·Et₂O (crystal structures) as well as of **8u**·Li₃ and **8b**·Li₃·Me₂O (//B3LYP/6-31G*).

	8a ·Li ₃ ·2Et ₂ O	8a ·Li ₃ ·Et ₂ O	8u ·Li ₃	8b ·Li ₃ ·Me ₂ O
B–B	172.1(6)	169.3(4)	170.4	172.2
B–C	153.8(5) ^[a,b]	154.8(5) ^[a,b]	154.3	155.4
C–C	143.6(5) ^[a,b]	144.1(4) ^[a,b]	144.6	144.4
Li(η^2)–B	226.9(7) ^[a,c]	222.8(7) ^[a,c]	205.3	222.6
Li(η^5)–B	222.4(7) ^[a,d] 228.7(7) ^[a,c]	219.8(5) ^[a]	223.1	223.5
Li(η^5)–C(B)	209.9(7) ^[a,d] 216.6(8) ^[a,c]	208.4(5) ^[a,d]	214.7	209.2
Li(η^5)–C	207.7(7) ^[d] 212.2(8) ^[c]	205.2(5) ^[a,d]	210.8	204.2
Li(η^5)–ring	170.2(6) ^[d] 177.8(6) ^[c]	167.5(5) ^[d]	173.6	168.9

[a] Mean value. [b] In the five-membered ring. [c] For Li·Et₂O. [d] For Li without Et₂O.

solvent-free lithium compounds as a consequence of agostic interactions.^[10]

The third lithium ion (Li2) in **8a**·Li₃·Et₂O and **8a**·Li₃·2Et₂O is η^2 -coordinated to the B1–B2 σ bond.^[11] In addition Li2 is coordinated to the *ipso*-C atoms of the duryl substituents as π ligands and to one ether molecule as an n ligand.

The η^5 - π -coordinated lithium ions without external ligands display remarkably short distances to the ring C and B atoms (i.e., to the plane of the five-membered ring; see Table 1): 167.5 (5) pm (**8a**·Li₃·Et₂O) and 170.2(5) pm (Li1; **8a**·Li₃·2Et₂O). The Li3–ring distance of 177.8 (5) pm for **8a**·Li₃·2Et₂O, which is 8 pm longer than for Li1 due to the Et₂O coordination, is still among the shortest on record between five-membered rings and lithium ions.^[12] Lithium–ring distances in lithium cyclopentadienides **6**·Li vary from 178^[12a] to 201 pm,^[12b] and in the **7a**·Li₂·TMEDA dimer^[13] (**7a**: C₄H₄BNEt₂, TMEDA = *N,N,N',N'*-tetramethylethylenediamine) from 179.5 to 186.9 pm. To evaluate the influence of the magnitude of the negative charge in the unsubstituted five-membered rings on the distances to the η^5 - π -coordinated (but otherwise bare) lithium ions, we calculated the neutral series **6u**·Li, **7u**·Li₂, and **8u**·Li₃ as well as the model compound **8b**·Li₃·Me₂O (Figure 2) and also the charged “inverse sandwich” analogues D_{5h} –[C₅H₅Li₂]⁺ (i.e., [**6u**·Li₂]⁺) and C_{2v} –[C₃B₂H₅Li₂][–] (i.e., [**8u**·Li₂][–]) at the B3LYP/6-31G* level of density functional theory.^[14]

The Li–ring distance in dianionic **7u**·Li₂ (171.9 pm) is in between those in monoanionic **6u**·Li (173.0 pm) and trianionic **8u**·Li₃ (170.6 pm). The effect of increasing negative charge is also reflected by the isoelectronic series [**6u**·Li₂]⁺ (185.3 pm), **7u**·Li₂ (171.9 pm), and [**8u**·Li₂][–] (164.9 pm). The progression in the Li–ring distances within the series [**8u**·Li₂][–] (164.9 pm), **8b**·Li₃·Me₂O (168.8 pm), and **8u**·Li₃ (170.6 pm) is particularly instructive. The third lithium ion, located in the plane of the five-membered ring, increases the distances of the η^5 -coordinated lithium ions significantly, more when it is bare (in **8u**·Li₃) than when it is complexed with n and π ligands (e.g. in **8b**·Li₃·Me₂O). Hence, the short Li–ring distances found experimentally in **8a**·Li₃·Et₂O and

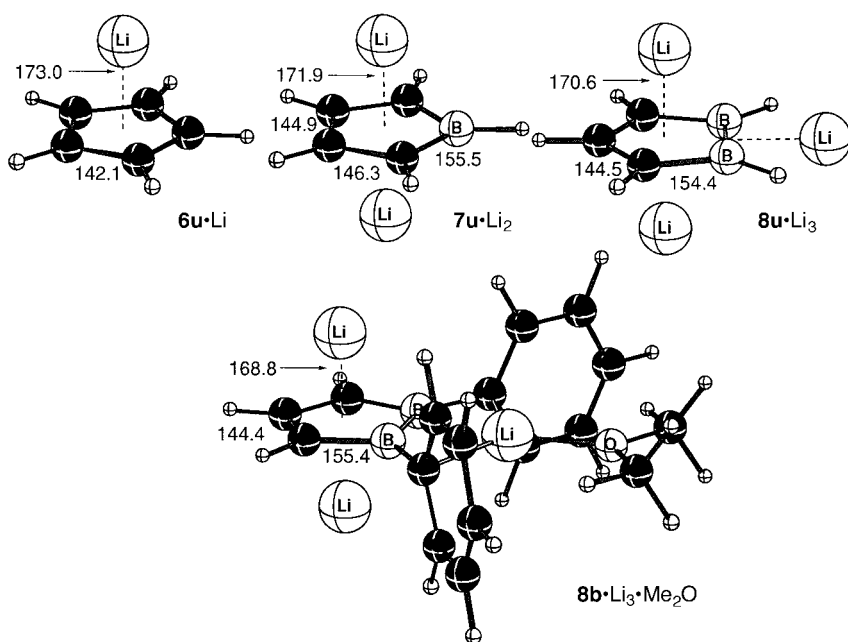


Figure 2. The B3LYP/6-31G* optimized structures of **6u**·Li, **7u**·Li₂, **8u**·Li₃, and **8b**·Li₃·Me₂O.

8a·Li₃·2Et₂O are due to the accumulation of negative charge in the five-membered ring, to the lack of external ligands at the η^5 -coordinated lithium ions, and, as the comparison with **8u**·Li₃ shows, to the σ and π coordination of the lithium ion in the ring plane.

Schnöckel et al. noted that calculated Li–C distances in substituted cyclopentadienes are shorter than in the parent molecule.^[15] This also is true for **8b**·Li₃·Me₂O and **8u**·Li₃ (Table 1). Whereas Schnöckel et al. found that Li–C distances calculated with HF/TZP are generally 2–4% longer than experimentally observed values,^[15] we determined that the Li–C and Li–B distances calculated at B3LYP/6-31G*^[14] for **8b**·Li₃·Me₂O are in very good agreement with those experimentally recorded for **8a**·Li₃·Et₂O. The B3LYP/6-31G* optimized geometry of **8u**·Li₃ has Li–C and Li–B distances that are 2–3 pm shorter than those given by MP2(fc)/6-31G* and MP2(fc)/6-31+G* calculations. The experimentally observed distances for the ring atoms were fairly well reproduced by B3LYP/6-31G*, even for the unsubstituted model **8u**·Li₃ (Table 1).

When the expected substituent effects are taken into account, the computed chemical shifts (GIAO-SCF/6-31G*//B3LYP/6-31G*^[14]) of the skeleton atoms for **8b**·Li₃·Me₂O ($\delta(^{13}\text{C}) = 105.9, 105.8, 105.9$; $\delta(^{11}\text{B}) = 20.0$) are in reasonable agreement with those measured for **8a**·Li₃·2Et₂O ($\delta(^{13}\text{C}) = 103.7, 116.2, 104.1$; $\delta(^{11}\text{B}) = 14$ and 16).^[16] The strong shielding of the η^5 - π -coordinated lithium ions ($\delta(^7\text{Li}) = -4.6$, calcd: $\delta(^7\text{Li}) = -3.2$ for **8b**·Li₃·Me₂O) is consistent with a 6- π -electron ring current in the five-membered ring.^[17, 18]

Compounds **8a**·Li₃·Et₂O and **8a**·Li₃·2Et₂O are the first with trianionic five-membered rings.^[3] The absence of external π or σ ligands at the η^5 - π -coordinated lithium counterions in **8a**·Li₃·Et₂O, as well as the highly negative charge, are responsible for the extremely short distances to the C₃B₂ ring.

Experimental Section

8a·Li₃·2Et₂O: A suspension of **9** (2.12 g, 3.8 mmol) and lithium powder (0.25 g, 45 mmol) in Et₂O (50 mL) is stirred until the ¹¹B NMR signal for **9** completely disappears (ca. 1 h). The volatile components are evaporated at 5 × 10^{−6} mbar, and the residue is then dissolved in pentane (50 mL). Excess lithium and LiCl are removed by filtration through a frit. After evaporation of the solvent **8a**·Li₃·2Et₂O (2.46 g, 95%) remains as a powdery orange-red solid in spectroscopically pure form. Red cuboid crystals (1.41 g, 57%; m.p. 183–185 °C (decomp.)) are obtained by crystallization at −30 °C from a solution of the raw product in toluene (40 mL). ¹H NMR (500 MHz, [D₈]toluene, 25 °C): $\delta = 6.65$ (s, *p*-H), 2.66 (brs, Et₂O), 2.56, 2.55 (s, duryl CH₃), 2.26 (s, CH(SiMe₃)₂), 2.18 (s, duryl CH₃), 2.03, 1.99 (s, ring CH₃), 0.60 (brs, Et₂O), 0.19 (s, SiCH₃); ¹¹B NMR (96 MHz, [D₈]toluene, 25 °C): $\delta = 15$ ($\nu_{1/2} = 190$ Hz); ⁷Li NMR (156 MHz, [D₈]toluene, 25 °C): $\delta = -0.1$ (1Li), -4.6 (2Li); ¹³C[¹¹B, ¹H] NMR (125 MHz, [D₈]toluene, 25 °C): $\delta = 155.8, 155.4$ (s, *i*-C), 137.6, 137.5, 132.0, 131.9 (s, *o*-*m*-C), 128.6, 128.5 (d, *p*-C), 116.2 (s, CCH), 104.1, 103.7 (each s, BCCH₃), 64.9 (t, Et₂O), 23.2, 23.0 (each q, *o*-CH₃), 21.6, 21.5 (each q, *m*-CH₃), 19.6 (d, CH(SiMe₃)₂), 19.1, 17.7 (each q, CH₃), 14.0 (q, Et₂O), 2.2 (q, SiCH₃).

8a·Li₃·Et₂O: ⁷Li NMR (156 MHz, [D₈]toluene, 25 °C): $\delta = 0.3$ (1Li), -3.8 (2Li); the rest of the NMR data exhibits only slight differences to that for **8a**·Li₃·2Et₂O.

9: At −110 °C, a 8 M solution of ethereal HCl (5 mL, 40 mmol) is added dropwise to **10** (7.18 g, 14.1 mmol) dissolved in Et₂O (150 mL). The mixture is warmed to −30 °C within 1 h. The volatile components are evaporated under high vacuum at −30 °C. The residue consists of **9** (7.03 g, 91%), a white, powdery, spectroscopically pure solid; m.p. 148 °C. ¹H NMR (300 MHz, CDCl₃, 25 °C): $\delta = 6.92, 6.86$ (s, *p*-H), 2.23, 2.21, 2.16, 2.08, 2.05 (s, duryl CH₃), 1.74 (s, Si₂CH), 1.66, 1.26 (s, CH₃), 0.36, 0.25 (s, SiMe₃); ¹¹B NMR (96 MHz, CDCl₃, 25 °C): $\delta = 70$ ($\nu_{1/2} = 2460$ Hz), 45 ($\nu_{1/2} = 2040$ Hz); ¹³C NMR (75 MHz, CDCl₃, 25 °C): $\delta = 162.7$ (s, =C(C)), 157.9 (s, =C(B)), 144.0, 137.2 (brs, *i*-C), 135.1, 133.3, 133.2, 132.9, 132.1 (s, *o*-*m*-C), 131.1, 131.0 (d, *p*-C), 64.7 (brs, CB₂), 25.9 (d, Si₂CH), 21.4, 19.7, 19.3, 19.1, 18.9, 18.1 (q, duryl CH₃), 18.0, 14.3 (q, CH₃), 2.8, 2.3 (q, SiMe₃).

Received: May 3, 1999 [Z13357IE]
German version: *Angew. Chem.* **1999**, *111*, 3116–3119

Keywords: ab initio calculations • boron • lithium • polyanions

- a) G. E. Herberich, B. Hessner, M. Hostalek, *Angew. Chem.* **1986**, *98*, 637; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 642; b) C. Balzereit, H.-J. Winkler, W. Massa, A. Berndt, *Angew. Chem.* **1994**, *106*, 2394; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2306; c) G. E. Herberich, B. Hessner, *Chem. Ber.* **1982**, *115*, 3115; d) G. E. Herberich, B. Buller, B. Hessner, W. Oschmann, *J. Organomet. Chem.* **1980**, *195*, 253; G. E. Herberich, H. Ohst, *Z. Naturforsch., B* **1983**, *38*, 1388.
- a) T. Deforth, H. Pritzkow, W. Siebert, *Angew. Chem.* **1995**, *107*, 748; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 681; b) K. Kawamura, M. Shang, O. Wiest, T. P. Fehlner, *Inorg. Chem.* **1998**, *37*, 608.
- The smallest trianionic ring system known up to now is an anthracene derivative: H. Bock, Z. Havlas, D. Hess, C. Näther, *Angew. Chem.* **1998**, *110*, 518; *Angew. Chem. Int. Ed.* **1998**, *37*, 502; three negative charges in a tetraanionic five-membered ring derivative are located exocyclic at atoms that each contain two silyl substituents: A. Sekiguchi, T. Matsuo, C. Kabuto, *Angew. Chem.* **1997**, *109*, 2572; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2462, and references therein.
- D. Steiner, H.-J. Winkler, C. Balzereit, T. Happel, M. Hofmann, G. Subramanian, P. von R. Schleyer, W. Massa, A. Berndt, *Angew. Chem.* **1996**, *108*, 2123; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1990.

- [5] M. Menzel, C. Wiczorek, S. Mehle, J. Allwohn, H.-J. Winkler, M. Unverzagt, M. Hofmann, P. von R. Schleyer, S. Berger, W. Massa, A. Berndt, *Angew. Chem.* **1995**, *107*, 728; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 657.
- [6] M. Menzel, H.-J. Winkler, W. Massa, K. Harms, A. Berndt, *Acta Crystallogr. Sect. C* **1999**, submitted.
- [7] Crystal structure determinations: **8a** · Li₃ · 2 Et₂O: measurements were made with a red block-shaped crystal (0.7 × 0.6 × 0.4 mm³) on a Stoe IPDS diffractometer at −80 °C using MoK_α radiation. C₄₀H₇₁B₂Li₃O₂Si₂, orthorhombic, space group *P*2₁2₁2₁, *Z* = 4, *a* = 1485.8(1), *b* = 1620.0(1), *c* = 1819.2(1) pm, *V* = 4378.8(5) × 10^{−30} m³, *ρ*_{calcd} = 1.035 g cm^{−3}; a total of 21 536 reflections were recorded in the range 1.45° < *θ* < 24.2°, resulting in 6846 independent reflections from which 3646 with *F*_o > 4σ(*F*_o) were observed. All 6846 independent reflections were used for the subsequent calculations; no absorption correction was applied (*μ* = 1.1 cm^{−1}). The structure was solved by direct methods and refined against *F*_o² with full matrix. Disorder appearing in difference Fourier syntheses were taken into account by refining split positions for the following atoms: 1) the two trimethylsilyl groups (C9, C10, C11 and C12, C13, C14) as well as C7 with site occupations of 50%; 2) the Et₂O molecule coordinated to Li1 (C42, C43) with occupations of 63(2) and 37(2)%. Non-hydrogen atoms were refined using anisotropic displacement factors. Hydrogen atoms were kept on calculated positions, and 1.2 or 1.5 times (CH₃) the equivalent isotropic *U* values of the corresponding C atom were used as displacement factors. An indicated inversion twinning could not be verified significantly. The refinement converged at *wR*₂ = 0.1060 for all reflections, corresponding to a conventional *R* = 0.0435 for the observed reflections. **8a** · Li₃ · Et₂O: measurements were made with a red block-shaped crystal (0.7 × 0.4 × 0.3 mm³) on a Stoe IPDS diffractometer at −80 °C using MoK_α radiation. C₃₆H₆₁B₂Li₃O₂Si₂, orthorhombic, space group *Pnma*, *Z* = 4, *a* = 1390.3(1), *b* = 1590.6(1), *c* = 1766.9(1) pm, *V* = 3907.2(5) × 10^{−30} m³, *ρ*_{calcd} = 1.033 g cm^{−3}; a total of 24 794 reflections were recorded in the range 2.26° < *θ* < 25.94°, resulting in 3909 independent reflections from which 2194 with *F*_o > 4σ(*F*_o) were observed. All 3909 independent reflections were used for the subsequent calculations; no absorption correction was applied (*μ* = 1.15 cm^{−1}). The solution and refinement procedure was the same as above, but the hydrogen atoms at C7–C9 were refined. The Et₂O molecule proved to be disordered over at least four positions. A residual *wR*₂ = 0.1390 was obtained for all reflections, corresponding to a conventional *R* = 0.0517 for the observed reflections. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-119471 (**8a** · Li₃ · 2 Et₂O) and CCDC-119470 (**8a** · Li₃ · Et₂O). 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).
- [8] Gaussian 94, Revision D.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1995**.
- [9] Owing to disorder, the hydrogen positions in **8a** · Li₃ · 2 Et₂O are not refined.
- [10] W. Hiller, M. Layh, W. Uhl, *Angew. Chem.* **1991**, *103*, 339; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 324; U. Siemeling, T. Redecker, B. Neumann, H.-G. Stammer, *J. Am. Chem. Soc.* **1994**, *116*, 5507; R. J. Wehmschulte, P. P. Power, *J. Am. Chem. Soc.* **1997**, *119*, 2847, and references therein.
- [11] Further examples for η²-σ coordination of lithium ions to (partial) B=B double bonds: A. A. Korkin, P. von R. Schleyer, M. L. McKee, *Inorg. Chem.* **1995**, *34*, 961, and references therein; ref. [4].
- [12] a) C. Dohmeyer, E. Baum, A. Ecker, R. Köppe, H. Schnöckel, *Organometallics* **1996**, *15*, 4702, b) D. Stalke, *Angew. Chem.* **1994**, *106*, 2256; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2168.
- [13] G. E. Herberich, M. Hostalek, R. Laven, R. Boese, *Angew. Chem.* **1990**, *102*, 330; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 317.
- [14] For terminology and methods in computational chemistry, see for example: J. B. Foresman, A. Frisch, *Exploring Chemistry with Electronic Structure Methods*, 2nd ed., Gaussian, Inc., Pittsburgh, PA, **1996**; *Encyclopedia of Computational Chemistry* (Eds.: P. von R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, H. F. Schaefer, P. R. Schreiner), Wiley, Chichester, **1998**.
- [15] See footnote 19 in ref. [12a].
- [16] The appearance of different signals in the NMR spectra at 25 °C for the boron atoms and their substituents, as well as for the boron-bound C atoms of the five-membered ring and the methyl groups attached to them, can be explained by hindered rotation of the bis(trimethylsilyl)methyl group. The rotational barrier was determined to be Δ*G*[‡] = 18.5 kcal mol^{−1}. A rotational barrier of similar magnitude (18.8 kcal mol^{−1}) was deduced for 1,1,2,2-tetrakis(trimethylsilyl)-ethane: S. Brownstein, J. Dunogues, D. Lindsay, K. U. Ingold, *J. Am. Chem. Soc.* **1977**, *99*, 2073.
- [17] a) H. Jiao, P. von R. Schleyer, *Angew. Chem.* **1993**, *105*, 1830; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1760; b) M. Bühl, W. Thiel, H. Jiao, P. von R. Schleyer, M. Saunders, A. A. L. Anet, *J. Am. Chem. Soc.* **1994**, *116*, 6005. An IGLO analysis of the individual contributions to the shielding in **8u** · Li₃ shows the influence of the ring current on the chemical shifts of the η²-bound lithium ions.
- [18] We have no explanation at present for the discrepancy between the experimental (−0.1 ppm) and the computed NMR chemical shift (3.2 ppm) of the third lithium ion in the ring plane.

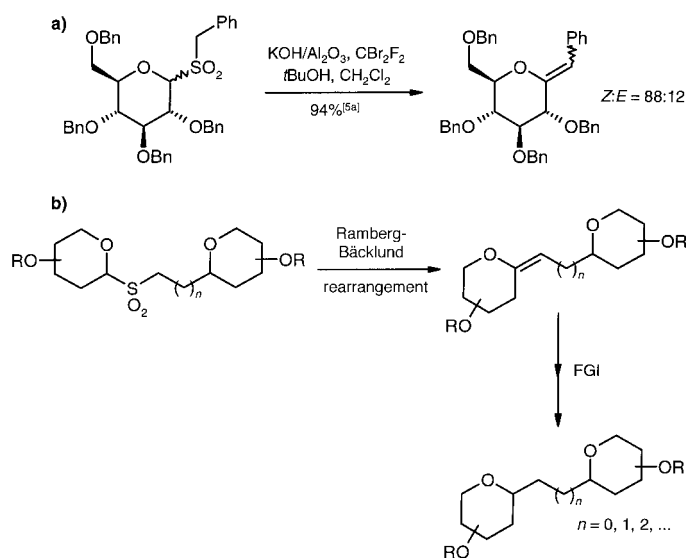
Ramberg–Bäcklund Approaches to the Synthesis of C-Linked Disaccharides**

Frank K. Griffin, Duncan E. Paterson, and Richard J. K. Taylor*

C-Disaccharides have attracted considerable interest,^[1] particularly in view of their hydrolytic stability and potential enzyme inhibitory properties. Since the first synthesis of a carba-disaccharide by Sinaÿ and Rouzaud in 1983,^[2] a number of synthetic methodologies have been developed for the preparation of this class of compounds.^[1–3] Recent work in our laboratory has focussed on the use of the Ramberg–Bäcklund rearrangement^[4] of *S*-glycoside dioxides as the key step in the formation of di-, tri-, and tetra-substituted *exo*-glycals,^[5a] which are useful intermediates for the preparation of more elaborate C-glycosides.^[5b,c] Scheme 1a illustrates this approach with a glucose-derived sulfone: The Meyers variant^[6] of the Ramberg–Bäcklund rearrangement is used to convert the sulfone directly into the corresponding *exo*-glycal without competing 1,2-glycal formation. We have now applied this methodology to the construction of C-linked disaccharides from readily prepared *S*-linked precursors. The general

[*] Prof. R. J. K. Taylor, F. K. Griffin, D. E. Paterson
Department of Chemistry
University of York
York YO10 5DD (UK)
Fax: (+44) 1904-432-516
E-mail: rjkt1@york.ac.uk

[**] We thank the Government of Papua New Guinea for an HEP Fellowship (F.K.G.) and the University of York for a studentship (D.E.P.).



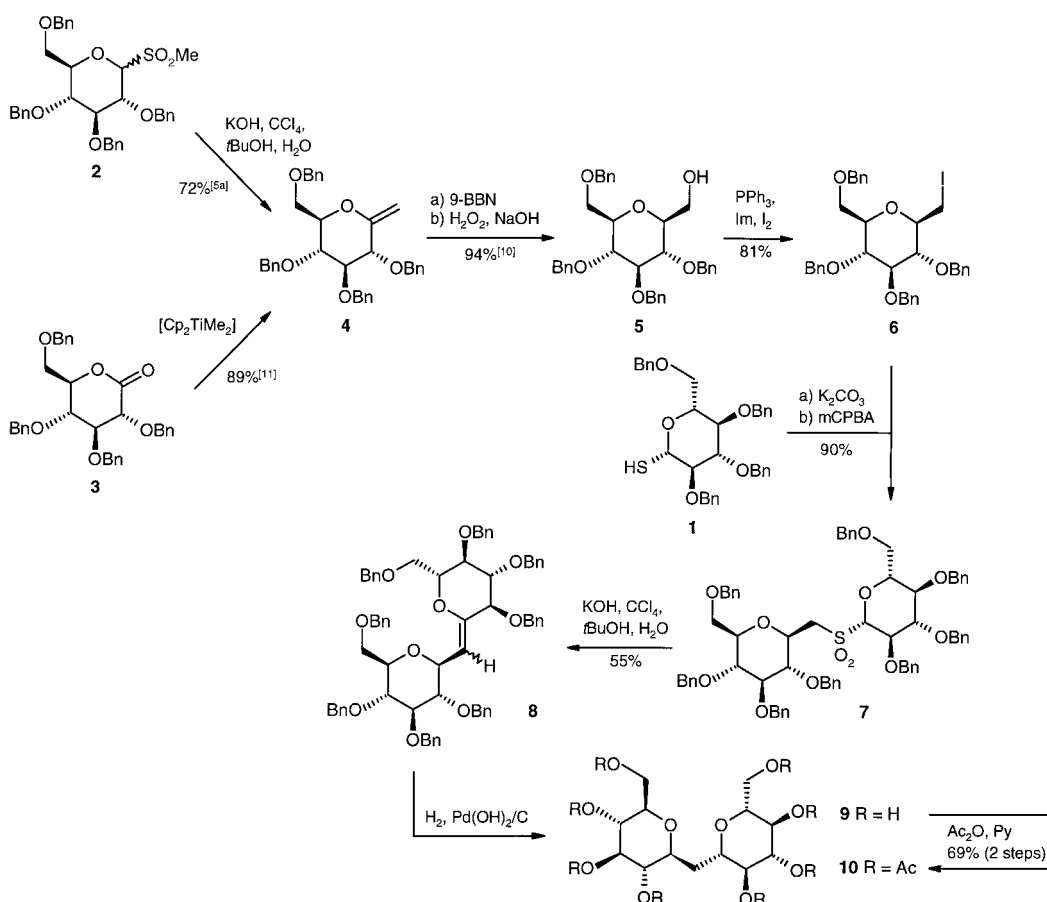
Scheme 1. The use of the Ramberg–Bäcklund rearrangement for the synthesis of an *exo*-glycal and its possible extension to C-disaccharide synthesis. Bn = benzyl, FGI = functional group interconversion.

approach is outlined in Scheme 1b: Our initial objective was to employ this methodology to prepare C-disaccharides ($n = 0$) and higher homologues. We then envisaged the extension of this chemistry to provide a more general route to a range of C-linked disaccharides. Herein we report the successful

utilization of this approach for the synthesis of C-trehalose, a higher homologue of C-trehalose, and methyl C-gentiobioside.

Our first target was a carba-analogue of trehalose, a member of a family of disaccharides in which carbohydrate residues are linked together through their anomeric centers. C-Trehaloses have been prepared by the groups of Martin^[3d] and Kishi,^[7] and recently Schmidt and Patro have reported the synthesis of novel trehalose analogues with a functionalized linking carbon atom.^[8] Our strategy (Scheme 2) required the initial preparation of sulfone **7**. This was readily obtained from the protected thioglucose **1**^[9] and iodomethyl C-glucoside **6**. Iodide **6** was prepared from the corresponding alcohol **5**, which was obtained by the stereoselective hydroboration (9-BBN) and oxidation of *exo*-glycal **4**.^[10] The *exo*-methylenic compound **4** was prepared from sulfone **2** using our Ramberg–Bäcklund procedure^[5a] or by the methylenation of tetra-*O*-benzyl-D-gluconolactone (**3**) using $[\text{Cp}_2\text{TiMe}_2]$.^[11] The two monosaccharides **1** and **6** were coupled in an efficient thioetherification process, and the resulting S-linked disaccharide was oxidized to the requisite sulfone **7** in 90% yield over the two steps.

We were delighted to find that the Ramberg–Bäcklund rearrangement of sulfone **7** proceeded under standard^[6a] Meyers conditions and that no products arising from β -elimination were observed. Enol ether **8** was obtained in a moderate, but unoptimized, 48% yield, predominantly as the



Scheme 2. Synthesis of C-trehalose. 9-BBN = 9-borabicyclo[3.3.1]nonane, Im = imidazole, mCPBA = *meta*-chloroperoxybenzoic acid, Py = pyridine.

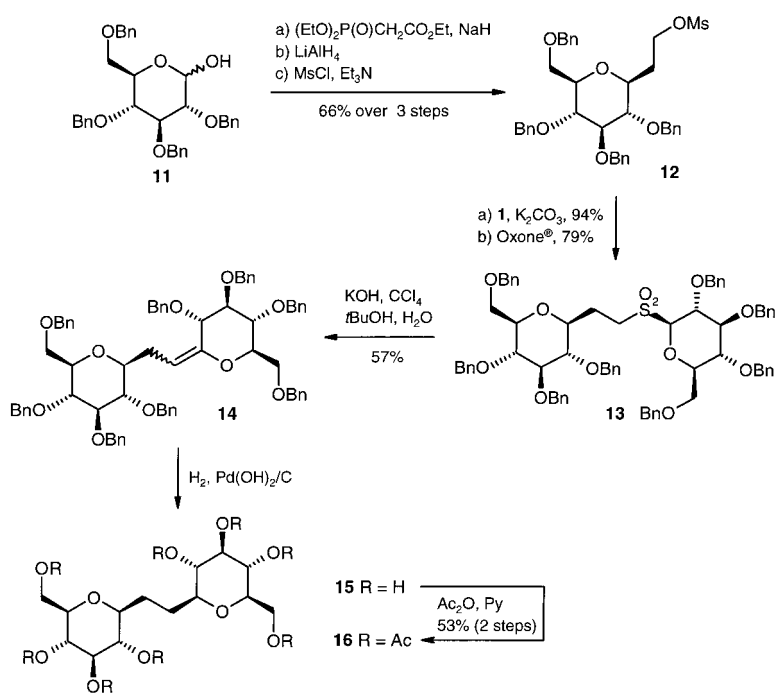
Z isomer (*Z*:*E* = 91:9). Catalytic hydrogenation of **8** achieved O-debenzylation and alkene reduction, and the product **9** was converted into octaacetate **10** to facilitate characterization. All spectroscopic data were consistent with the production of the symmetrical β,β -linked disaccharide **10**, and also agreed with published data^[3d] (e.g. ^{13}C NMR (67.9 MHz, CDCl_3): δ_{C} = 62.4, 68.9, 71.8, 73.1, 74.3, 75.9; literature values^[3d] (90 MHz, CDCl_3): δ = 62.5, 68.9, 72.0, 73.2, 74.3, 76.0).

We believe that this methodology offers a rapid, convergent, and practically simple route to β,β -(1,1')-carba-disaccharides. In addition, the intermediate enol ether **8** could be elaborated further (e.g. by hydroboration, epoxidation, or dihydroxylation)^[5b] prior to deprotection to introduce functionality to the carbon bridge.

This approach is ideally suited to analogue synthesis simply by variation of the alkylating agent. Thus, the homologated (1,1')-carba-disaccharide **15** containing a two-carbon bridge was readily prepared (Scheme 3). Lactol **11** was converted into mesylate **12** by a straightforward three-step sequence,^[12] and **12** was then employed with thiol **1** in the alkylation/oxidation sequence used earlier. This produced sulfone **13**, which underwent Ramberg–Bäcklund rearrangement to give *exo*-glycal **14** as a *Z/E* mixture (88:12) in 57% yield (unoptimized). Subsequent reduction/debenzylation produced the novel, ethylene-bridged disaccharide **15**, which was converted into octaacetate **16** ($[\alpha]_{\text{D}} = -10.9$ ($c = 0.53$, CHCl_3)) for characterization purposes. Again, the ^1H and ^{13}C NMR data were consistent with the production of the symmetrical β,β -linked disaccharide, with coincidental absorptions being observed for each sugar residue.

We next investigated the preparation of the (1,6')-carba-disaccharide, methyl *C*-gentiobioside (**21**).^[13] In view of the accessibility of the precursors, we explored the Ramberg–Bäcklund approach shown in Scheme 4. Whereas in previous examples the key Ramberg–Bäcklund rearrangement utilized an S-glycoside-derived sulfone, this alternative approach offered the opportunity to widen the scope of this synthetic route to C-linked sugars.

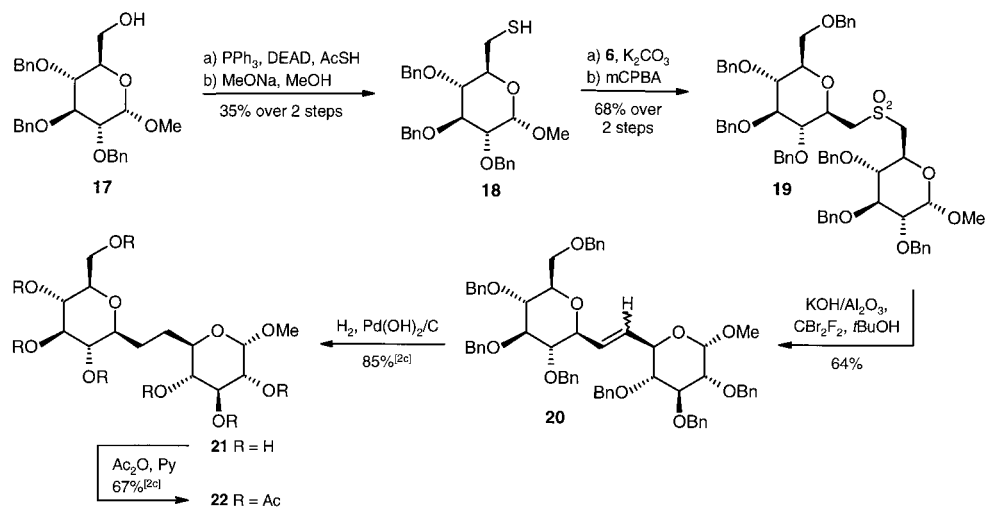
With iodide **6** (Scheme 2) in hand, we required only the complementary thiol **18**. This was obtained from alcohol **17**^[14] by Mitsunobu reaction with thiolacetic acid followed by deacetylation. Subsequent coupling of **18** with **6** followed by oxidation of the resulting sulfide gave sulfone **19** in high yield. To our delight, treatment of sulfone **19** with $\text{KOH}/\text{Al}_2\text{O}_3$ and CBr_2F_2 ^[6b] gave the desired unsaturated C-disaccharide **20**



Scheme 3. Synthesis of a higher homologue of *C*-trehalose. Ms = mesyl = methane-sulfonyl.

in 64% yield (*Z*:*E* = 70:30). This alkene has been prepared previously by Dondoni et al.^[3c] and hydrogenated to furnish methyl *C*-gentiobioside (**21**). We repeated the hydrogenation step and then prepared heptaacetate **22**, which gave consistent NMR and optical rotation data ($[\alpha]_{\text{D}} = +65$ ($c = 0.45$, CHCl_3); literature value:^[3c] $[\alpha]_{\text{D}} = +63$ ($c = 0.7$, CHCl_3)).

In summary, the Ramberg–Bäcklund rearrangement has been utilized to convert readily available sulfone-linked saccharides into C-linked disaccharides. This methodology has been employed to prepare *C*-trehalose, a higher homologue of *C*-trehalose, and methyl *C*-gentiobioside. Thus, (1,1')- and (1,6')-linked C-disaccharides have been prepared in this study: We are currently extending this methodology to prepare (1,4')-linked systems and other C-glycosides of biological interest.



Scheme 4. Synthesis of methyl *C*-gentiobioside. DEAD = diethylazodicarboxylate.

Experimental Section

All new compounds were fully characterized by high-field ^1H and ^{13}C NMR spectroscopy and by elemental analysis or high-resolution mass spectrometry.

8: To a stirred mixture of *t*BuOH (6 mL) and water (1.5 mL) at 60 °C was added powdered KOH (3 g, 53.5 mmol). After the base had dissolved, a solution of **7** (0.367 g, 0.326 mmol) in CCl_4 (6 mL) was added, and the biphasic mixture was stirred at 60 °C for 1 h. After cooling to room temperature, the pale yellow mixture was transferred to a separating funnel and the lower aqueous layer removed. The organic phase was washed with brine and dried (Na_2SO_4), and the solvent removed in vacuo. Purification by column chromatography on silica gel (light petroleum ether/EtOAc/ Et_3N 74/25/1) gave alkene **8** (0.167 g, 48 %) as a pale yellow oil. TLC: R_f = 0.36 (light petroleum ether/EtOAc 3/1); IR: $\tilde{\nu}_{\text{max}}$ (liquid film) = 1687 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3): δ = 5.11 (1 H, d, ^3J = 8.7 Hz, vinyl H); ^{13}C NMR (67.9 MHz, CDCl_3): δ = 68.7, 69.0, 72.1, 73.3, 73.5, 73.8, 74.2, 74.6, 74.9, 75.6, 77.9, 78.0, 78.2, 78.7, 83.1, 84.6, 86.7, 108.5 (C=C–O), 126.9–128.3 (aryl C), 137.8, 138.2, 138.3 ($\times 2$), 138.6, 138.7, 152.6 (C=C–O); FAB-MS: m/z : 1081 [$M+\text{Na}^+$].

Received: April 9, 1999 [Z13261 IE]

German version: *Angew. Chem.* **1999**, *111*, 3123–3125

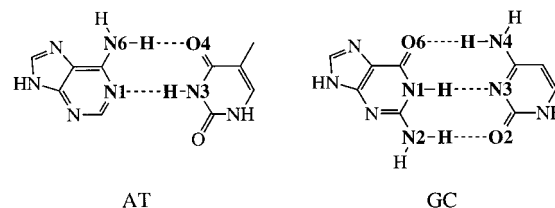
Keywords: disaccharides • glycosides • rearrangements

- [1] Reviews: D. E. Levy, C. Tang, *The Chemistry of C-Glycosides*, Pergamon, Oxford, **1995**; M. H. D. Postema, *C-Glycoside Synthesis*, CRC Press, Boca Raton, FL, **1995**; Y. Du, R. J. Linhardt, I. R. Vlahov, *Tetrahedron* **1998**, *54*, 9913–9959.
- [2] D. Rouzaud, P. Sinaÿ, *J. Chem. Soc. Chem. Commun.* **1983**, 1353–1354.
- [3] a) A. Mallet, J.-M. Mallet, P. Sinaÿ, *Tetrahedron: Asymmetry* **1994**, *12*, 2593–2608; b) T. Skrydstrup, D. Mazéas, M. Elmouchir, G. Doisneau, C. Riche, A. Chiaroni, J.-M. Beau, *Chem. Eur. J.* **1997**, *3*, 1342–1356; c) A. Dondoni, H. M. Zuurmond, A. Boscarato, *J. Org. Chem.* **1997**, *62*, 8114–8124; d) O. R. Martin, W. Lai, *J. Org. Chem.* **1993**, *58*, 176–185; e) H. Dietrich, R. R. Schmidt, *Liebigs Ann. Chem.* **1994**, 975–981; f) M. A. Leeuwenburgh, C. M. Timmers, G. A. van der Marel, J. H. van Boom, J.-M. Mallet, P. Sinaÿ, *Tetrahedron Lett.* **1997**, *38*, 6251–6254.
- [4] L. Ramberg, B. Bäcklund, *Ark. Kemi. Mineral. Geol.* **1940**, *27*, 1–50 [*Chem. Abstr.* **1940**, *34*, 4725]; for a recent review containing other key references, see R. J. K. Taylor, *Chem. Commun.* **1999**, 217–227.
- [5] a) F. K. Griffin, P. V. Murphy, D. E. Paterson, R. J. K. Taylor, *Tetrahedron Lett.* **1998**, *39*, 8179–8182; b) M.-L. Alcaraz, F. K. Griffin, D. E. Paterson, R. J. K. Taylor, *Tetrahedron Lett.* **1998**, *39*, 8183–8186; c) P. S. Belica, R. W. Franck, *Tetrahedron Lett.* **1998**, *39*, 8225–8228.
- [6] a) C. Y. Meyers, A. M. Malte, W. S. Matthews, *J. Am. Chem. Soc.* **1969**, *91*, 7510–7512; b) T.-L. Chan, S. Fong, Y. Li, T.-O. Man, C. D. Poon, *J. Chem. Soc. Chem. Commun.* **1994**, 1771–1772.
- [7] A. Wei, Y. Kishi, *J. Org. Chem.* **1994**, *59*, 88–96.
- [8] B. Patro, R. R. Schmidt, *Synthesis* **1998**, 1731–1734.
- [9] S. A. Holick, S.-H. Chiu, L. Anderson, *Carbohydr. Res.* **1976**, *50*, 215–225.
- [10] T. RajanBabu, G. S. Reddy, *J. Org. Chem.* **1986**, *51*, 5458–5461.
- [11] R. Csuk, B. I. Glänzer, *Tetrahedron* **1991**, *47*, 1655–1664.
- [12] P. Allevi, P. Ciuffreda, D. Colombo, D. Monti, G. Speranza, P. Manitto, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1281–1283; P. Allevi, M. Anastasia, P. Ciuffreda, A. Fiecchi, A. Scala, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1275–1280.
- [13] P. G. Goekjian, T.-C. Wu, H.-Y. Kang, Y. Kishi, *J. Org. Chem.* **1987**, *52*, 4823–4825; P. G. Goekjian, T.-C. Wu, H.-Y. Kang, Y. Kishi, *J. Org. Chem.* **1991**, *56*, 6422–6434.
- [14] B. Bernet, A. Vasella, *Helv. Chim. Acta* **1979**, *62*, 1990–2016.

Charge Transfer and Environment Effects Responsible for Characteristics of DNA Base Pairing**

Célia Fonseca Guerra and F. Matthias Bickelhaupt*

Although it is one of the weakest chemical interactions the hydrogen bond plays a key role in the chemistry of life, being involved, for example, in various types of self-organization and molecular recognition. A case in point is the hydrogen bonds in Watson–Crick base pairs, that is, adenine–thymine (AT) and guanine–cytosine (GC), that hold together the two helical chains of nucleotides in DNA and form the basis of the genetic code. These hydrogen bonds are commonly believed



to be predominantly electrostatic phenomena that, as suggested by Gilli et al., are substantially reinforced by resonance in the π -electron system, which makes the proton-acceptor atom more negative and the proton-donor atom more positive the so-called resonance-assisted hydrogen bonding (RAHB).^[1]

Herein we provide evidence from quantum chemical analyses that challenges this picture and emphasizes the importance of the charge-transfer nature of and environment effects on the hydrogen bonds in DNA base pairs. This has led us to the solution of a hitherto unresolved and significant discrepancy between experimental^[2] and theoretical^[3] values for distances between the proton-donor and proton-acceptor atoms in AT and GC base pairs. Our evidence is based on a thorough nonlocal density functional theoretical (DFT) investigation with the ADF program (at BP86/TZ2P) of various AT and GC model systems.^[4, 5]

Whereas our base-pairing enthalpies (298 K, BSSE corrected) of -11.8 and -23.8 kcal mol^{-1} for AT and GC, respectively, are in excellent agreement with gas-phase experimental values (-12.1 and -21.0 kcal mol^{-1}),^[6] we still arrive at the same striking discrepancies with experimental (X-ray crystal) structures^[2] that were encountered before in conventional ab initio (HF) and hybrid DFT (B3LYP) studies.^[3] As shown in Figure 1 we find N6–O4 and N1–N3

[*] Dr. F. M. Bickelhaupt
 Fachbereich Chemie
 Philipps-Universität Marburg
 Hans-Meerwein-Strasse, D-35032 Marburg (Germany)
 Fax: (+49) 6421-28-28917
 E-mail: bickel@chemie.uni-marburg.de
 Drs. C. Fonseca Guerra
 Afdeling Theoretische Chemie
 Scheikundig Laboratorium der Vrije Universiteit
 De Boelelaan 1083, NL-1081 HV Amsterdam (The Netherlands)

[**] F.M.B. thanks the Deutsche Forschungsgemeinschaft (DFG) for a habilitation fellowship and the Fonds der Chemischen Industrie (FCI) for financial support.

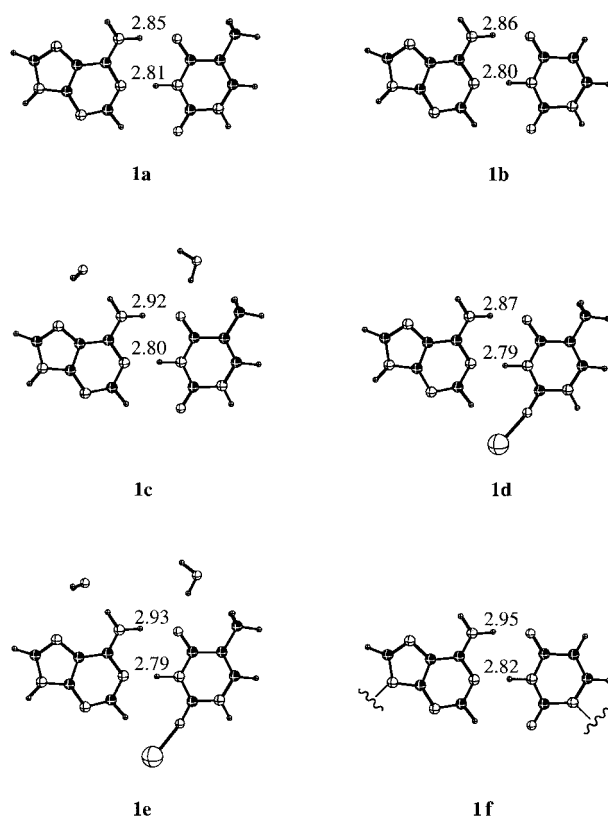


Figure 1. N6–O4 and N1–N3 distances [Å] in adenine–thymine (**1a**), adenine–uracil (**1b**), and various AT model systems containing water molecules and/or a sodium ion (**1c–e**) determined from BP86/TZ2P computations, as well as in the crystal of sodium adenyl-3',5'-uridine hexahydrate as determined from an X-ray diffraction study (**1f**).^[2b]

hydrogen-bond lengths in AT of 2.85 and 2.81 Å, respectively, (**1a**) which are essentially equal to those in AU (**1b**). These values have to be compared with 2.95 and 2.82 Å from experiment (**1f**). Even more eye-catching is the situation for the three hydrogen bonds in GC (Figure 2), namely O6–N4, N1–N3, and N2–O2, for which we find a bond length pattern that is short-long-long (2.73, 2.88, and 2.87 Å, **2a**), which is significantly different from the experimental values that are long-long-short (2.91, 2.95, and 2.86 Å, **2f**). We have verified that these inconsistencies are not induced by our neglecting the glycosidic N–C bond. Methylation of the bases at N9 (adenine or guanine) or N1 (thymine or cytosine), for example, which is a way to mimic the glycosidic N–C bond, has basically no effect on the hydrogen bonds in AT and GC base pairs: hydrogen-bond energies (zero K, no BSSE correction) differ by 0.0 and 0.3 kcal mol^{−1}, respectively, and the largest change in hydrogen-bond lengths amounts to 0.01 Å at BP86/TZ2P (not shown in the figure). Likewise, the hydrogen-bond lengths of the GC pair consisting of nucleotides (**2b**, Figure 2) differ only slightly from those in the plain GC pair (**2a**), that is, by 0.02 Å or less at BP86/DZP.

To trace the origin of the discrepancy between quantum chemical and experimental structures we have analyzed the A–T and G–C interactions of *C_s*-symmetric base pairs (whose hydrogen bonds differ by less than 0.005 Å and 0.1 kcal mol^{−1} from those of the *C_i* symmetric **1a** and **2a**) in the conceptual framework provided by the Kohn–Sham molecular orbital

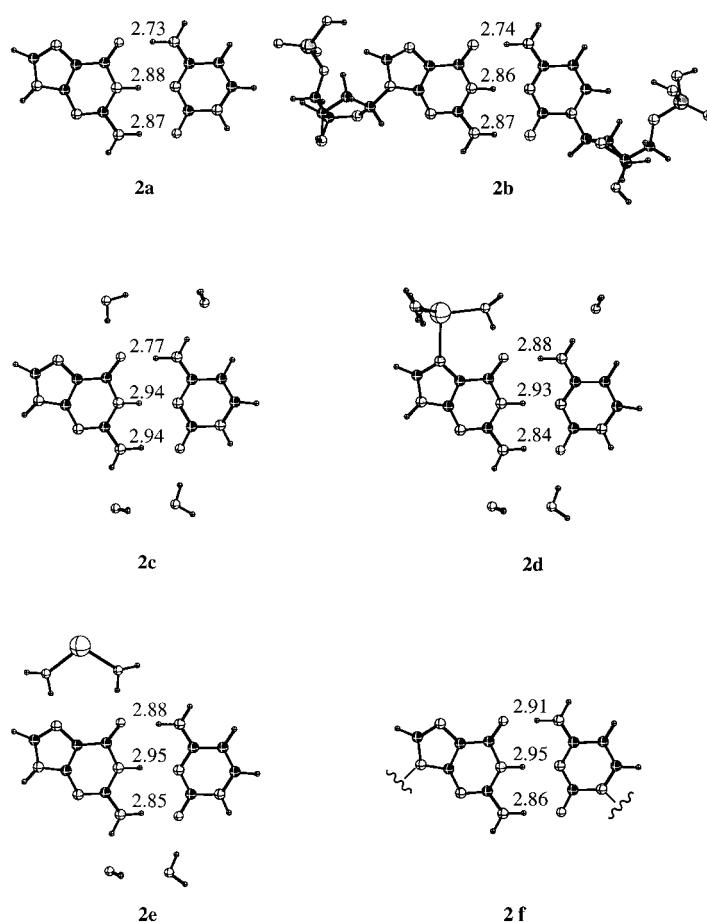


Figure 2. O6–N4, N1–N3, and N2–O2 distances [Å] in guanine–cytosine (**2a**), in the nucleotide pair dGMP–dCMP with inclusion of the backbone (**2b**), and various GC model systems containing water molecules and/or a sodium ion (**2c–e**) determined from BP86/TZ2P (**2a**, **2c–e**) and BP86/DZP (**2b**) computations, as well as in the crystal of sodium guanylyl-3',5'-cytidine nonahydrate as determined by an X-ray diffraction study (**2f**).^[2c]

(KS-MO) model through a decomposition of the actual interaction energy (ΔE_{int}) into the classical electrostatic interaction (ΔV_{elst}), the attractive orbital interactions comprising charge transfer and polarization (ΔE_{oi}), and the Pauli repulsive orbital interactions between closed shells (ΔE_{Pauli}).^[5] It appears that in both DNA base pairs, AT and GC, the bonding orbital interactions associated with hydrogen bonding are of comparable magnitude as the electrostatic attraction (for AT ΔE_{oi} and ΔV_{elst} are -22.4 and -32.1 kcal mol^{−1}, respectively, and for GC -34.1 and -48.6 kcal mol^{−1}, respectively). A more detailed examination of ΔE_{oi} and the associated changes in the wavefunction (orbital mixings) shows that the hydrogen-bonding orbital interactions are predominantly provided by charge-transfer interactions in the σ -electron system between a lone pair on a nitrogen or oxygen atom on one base and the N–H σ^* -acceptor orbitals of the other base. Figure 3 shows the relevant frontier-orbital interactions for AT that emerge from our Kohn–Sham MO analysis (a similar diagram can be drawn for GC). Indeed, we do find orbital interactions in the π -electron system that are reminiscent of the RAHB model: by polarization of the π -charge distribution within a DNA base they compensate the build-up of charge caused by charge-transfer hydrogen

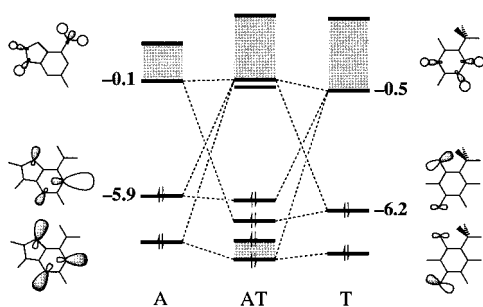


Figure 3. Frontier orbital interactions between adenine and thymine in AT (**1a**) from BP86/TZ2P Kohn–Sham DFT analyses (the base HOMO and LUMO energies of the σ -electron systems are given in eV). The group of lowest unoccupied orbitals involved is represented by a block.

bonding in the σ -electron system. The corresponding π interaction amounts to -1.7 and -4.8 kcal mol $^{-1}$ for AT and GC, respectively, that is, only 3 and 6% of the total attractive interactions $\Delta E_{\text{oi}} + \Delta V_{\text{elst}}$. In that respect π assistance is of minor importance. On the other hand the π interactions contribute 14–20% of the net bond enthalpies and, on the very shallow potential energy surface they are able to bring about a shortening of the hydrogen bonds by 0.1 Å. In this sense one may speak of a certain π assistance, despite this term being rather small compared to the charge-transfer and electrostatic interactions.

Additional support for charge transfer comes from an analysis of the deformation density $\rho_{\text{pair}}(r) - \rho_{\text{base1}}(r) - \rho_{\text{base2}}(r)$, that is, the redistribution of charge density that is caused by the formation of a DNA base pair from its constituting bases. This can be quantified by using an extension of the Voronoi deformation density (VDD) method,^[7] in which the change in atomic charges associated with base pairing ΔQ_A is defined and related to the deformation density by Equation (1), where VVA means the volume of the Voronoi cell of atom A in the base pair.

$$\Delta Q_A^{\text{VDD}} = - \int_{\text{VVA}} [\rho_{\text{pair}}(r) - \rho_{\text{base1}}(r) - \rho_{\text{base2}}(r)] dr \quad (1)$$

The interpretation of VDD atomic charges is rather straightforward. Instead of measuring the amount of charge associated with a particular atom A, they directly monitor how much charge flows, as a result of chemical interactions between DNA bases, out of ($\Delta Q_A > 0$) or into ($\Delta Q_A < 0$) the Voronoi cell of atom A, that is, the region of space that is closer to nucleus A than to any other nucleus. We have verified that all VDD values are stable with respect to variations of the basis by computing the VDD charges at BP86 with three different Slater-type basis sets, namely, DZ (unpolarized double- ζ), DZP (singly polarized double- ζ), and TZ2P (doubly polarized triple- ζ): the maximum deviation is 0.01 electrons. This affects neither the physical picture nor our conclusions. Full details of our analyses will be published elsewhere.

The donor–acceptor interaction in AT associated with the hydrogen bond N1...H–N3 (involving two donating adenine orbitals with N1 lone-pair character) leads to a net transfer of 0.05 electrons from A to T (computed with σ virtuals on T only and all other virtuals removed). This is counteracted by a transfer of 0.04 electrons back from T to A as a consequence

of the hydrogen bond N6–H...O4 (involving one donating thymine orbital with O4 lone-pair character), which leads to a slight build-up of negative charge on thymine. Likewise, for the GC pair, we find a build-up of negative charge on guanine that stems from a transfer of 0.05 electrons from G (with one lone pair donating atom, O6) to C through hydrogen bond O6...H–N4 that is outweighed by the transfer of 0.07 electrons back from C (with two donating atoms, N3 and O2) to G through the two hydrogen bonds N1–H...N3 and N2–H...O2.

The simultaneous occurrence of hydrogen bonds that donate charge in opposite directions reduces the net build-up of charge on the DNA bases, and one might thus expect that these hydrogen bonds reinforce each other. However, the corresponding analysis of the bond energy shows that there is no such synergism. The deformation density (not shown here) reveals that this is so because each hydrogen bond creates its own local charge separation that is not affected by the occurrence of another hydrogen bond.

It appears from a breakdown of the VDD charges into contributions from the σ -end π -electron system ($\Delta Q_A = \Delta Q_A^{\sigma} + \Delta Q_A^{\pi}$) that virtually all charge transfer occurs in σ symmetry. The ΔQ_A^{π} values reveal that the π system of each individual DNA base polarizes in such a way that the accumulation of positive or negative charge around the donating or accepting atoms, caused by the charge transfer in the σ -electron system, is counteracted and partly relieved. However, we do not find any synergism between ΔE_{σ} and ΔE_{π} , that is, ΔE_{σ} is not increased by the occurrence of the π -electron polarization.

The extremely shallow potential-energy surface that we find for the hydrogen bonds in DNA base pairs makes it plausible that the structure of AT and GC in the crystal or under physiological conditions is significantly influenced by interactions with the environment, such as, hydration, coordination of alkali metal ions (Na $^{+}$), and hydrogen bonding to hydroxyl groups of the sugar. Therefore, we have tried to simulate the major environmental effects that occur in the crystals used in the experimental X-ray structure determinations of AT and GC, namely, the crystal of sodium adenylyl-3',5'-uridine hexahydrate (ApU hexahydrate, **1f**)^[2b] and that of sodium guanylyl-3',5'-cytidine nonahydrate (GpC nonahydrate, **2f**).^[2c] And indeed, as can be seen from Figures 1 and 2, the addition of water molecules (simulating a part of the hydration and hydrogen bonding with ribose OH groups) and the introduction of the sodium counterions along **1a–e** and **2a–e** deforms the geometry of AT and GC in such a way that excellent agreement between our DFT model (for example, **1e**: N6–O4 and N1–N3 are 2.93 and 2.79 Å, respectively; **2e**: O6–N4, N1–N3, and N2–O2 are 2.88, 2.95, and 2.85 Å, respectively) and the experimental structures is obtained. Our results show that present-day approximate DFT not only provides a highly efficient but, if appropriate model systems are chosen, also a suitable and accurate alley towards describing and understanding hydrogen bonding in DNA base pairs.

Received: March 26

Revised version: June 2, 1999 [Z13216IE]

German version: *Angew. Chem.* **1999**, *111*, 3120–3122

Keywords: charge transfer • density functional calculations • DNA structures • hydrogen bonds • resonance assistance

- [1] a) G. Gilli, F. Bellucci, V. Ferretti, V. Bertolasi, *J. Am. Chem. Soc.* **1989**, *111*, 1023; b) H. Umeyama, K. Morokuma, *J. Am. Chem. Soc.* **1977**, *99*, 1316. See also, for example, c) G. A. Jeffrey, W. Saenger, *Hydrogen Bonding in Biological Structures*, Springer, Berlin, **1991**, p. 37; d) G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, New York, **1997**, p. 103.
- [2] a) W. Saenger, *Principles of Nucleic Acid Structure*, Springer, New York, **1984**; b) N. C. Seeman, J. M. Rosenberg, F. L. Suddath, J. J. P. Kim, A. Rich, *J. Mol. Biol.* **1976**, *104*, 109; c) J. M. Rosenberg, N. C. Seeman, R. O. Day, A. Rich, *J. Mol. Biol.* **1976**, *104*, 145.
- [3] a) J. Sponer, J. Leszczynski, P. Hobza, *J. Phys. Chem.* **1996**, *100*, 1965; b) K. Brameld, S. Dasgupta, W. A. Goddard III, *J. Phys. Chem. B* **1997**, *101*, 4851; c) J. Bertran, A. Oliva, L. Rodríguez-Santiago, M. Sodupe, *J. Am. Chem. Soc.* **1998**, *120*, 8159.
- [4] a) C. Fonseca Guerra, O. Visser, J. G. Snijders, G. te Velde, E. J. Baerends in *Methods and Techniques for Computational Chemistry* (Eds.: E. Clementi, G. Corongiu), STEF, Cagliari, **1995**, p. 305; b) A. Becke, *Phys. Rev. A* **1988**, *38*, 3098; c) J. P. Perdew, *Phys. Rev. B* **1986**, *33*, 8822 (erratum: *Phys. Rev. B* **1986**, *34*, 7406).
- [5] a) F. M. Bickelhaupt, N. M. M. Nibbering, E. M. van Wezenbeek, E. J. Baerends, *J. Phys. Chem.* **1992**, *96*, 4864; b) T. Ziegler, A. Rauk, *Theor. Chim. Acta* **1977**, *46*, 1.
- [6] Mass spectrometric data from I. K. Yanson, A. B. Teplitsky, L. F. Sukhodub, *Biopolymers* **1979**, *18*, 1149, with corrections proposed in ref. [3b].
- [7] F. M. Bickelhaupt, N. J. R. van Eikema Hommes, C. Fonseca Guerra, E. J. Baerends, *Organometallics* **1996**, *15*, 2923.

Stereoselective Synthesis of Coordination Compounds: Self-Assembly of a Polymeric Double Helix with Controlled Chirality**

Olimpia Mamula, Alex von Zelewsky,* Thomas Bark, and Gérald Bernardinelli

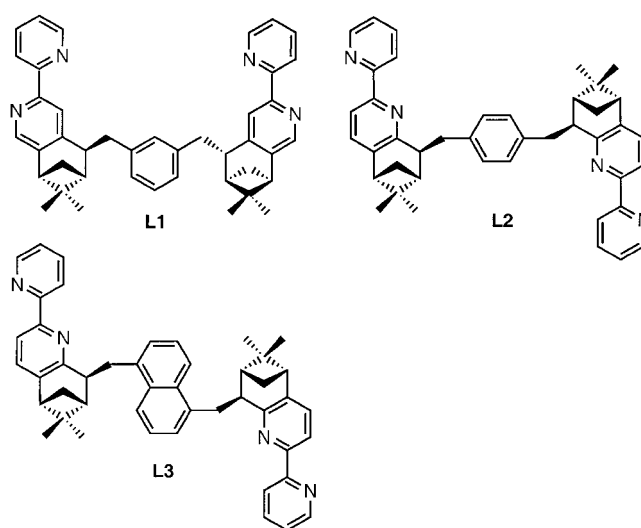
The formation of helical structures by the assembly of metal coordination species has received a great deal of attention in recent years. The field of helicates has recently been reviewed by Piguet et al.,^[1] and several observations of infinite coordination helices have been reported.^[2–13] Most of these infinite helices are formed from achiral ligands,^[2–9] consequently yielding racemates of *P* and *M* helices. In a few cases chiral predetermination is achieved by the use of enantiopure ligands.^[10–13]

[*] Prof. Dr. A. von Zelewsky, O. Mamula, T. Bark
Institute of Inorganic Chemistry
University of Fribourg
Perolles, CH-1700, Fribourg (Switzerland)
Fax: (+41) 26-300-97-38
E-mail: alexander.vonzewelsky@unifr.ch
Dr. G. Bernardinelli
Laboratory of X-Ray Crystallography
University of Geneva (Switzerland)

[**] This work was supported by the Swiss National Science Foundation. We thank M. Düggeli for preparing (–)-5,6-pinene-bpy.

Here we describe a self-assembled coordination polymer that is chirally predetermined and represents, to the best of our knowledge, the first example for intertwining of two single-stranded helicates to form an infinite, highly symmetric double helix. The two strands of this double helix are connected neither by chemical bonds nor through attractive intermolecular forces, except unspecific van der Waals interactions.

We have shown recently that CHIRAGEN-type ligands^[14] can give rise to the formation of self-assembled helicates that are predetermined in their chirality. With metals that give octahedral coordination, 4,5-CHIRAGEN[*m*-xylyl] (**L1**) yields dinuclear species of M₂L₃ stoichiometry.^[15] This 2:3 stoichiometry seems to be fairly common, since several other ligands in which two bidentate units are connected through a bridge provide such assemblies.^[1, 16–19] The use of the 5,6-CHIRAGEN **L2** containing a *para*-xylylidene bridge with



metals that form tetrahedral coordination species, such as Ag⁺ and Cu⁺, yielded highly symmetric, circular, hexanuclear single-stranded helicates; the chirality is again totally predetermined by the chiral pinene groups present in these ligands.^[20] To investigate further the influence of the ligand geometry on the molecular assembly, we varied the bridge in the 5,6-CHIRAGEN ligand. Here we report the structural properties of the species obtained with the ligand **L3**, in which the bridge has been derived from 1,5-dimethylnaphthalene.

The ligand **L3** was synthesized following the general procedure (Scheme 1) that has been applied for several other ligands of the CHIRAGEN family.^[14, 21, 22] The ligand was completely characterized, and its NMR spectra show the symmetry expected owing to the C₂ axis perpendicular to the naphthalene plane and passing through its center. As a consequence of the high stereoselectivity in its synthesis, the ligand is isomerically pure within NMR analytical accuracy. According to the NMR spectra, a self-assembled species with high symmetry is formed upon addition of Ag⁺, as in the case of **L2**.^[20] Figure 1 shows the aromatic part of the ¹H NMR spectra of the free ligand **L3** (b) and of the silver complex (a).

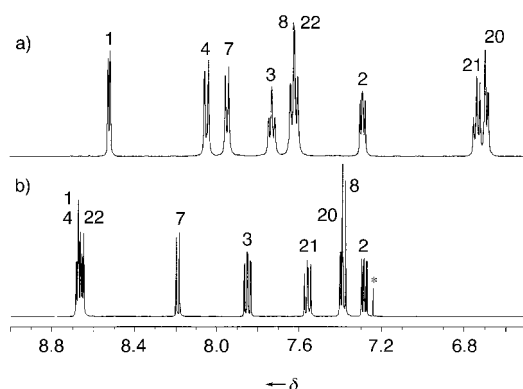
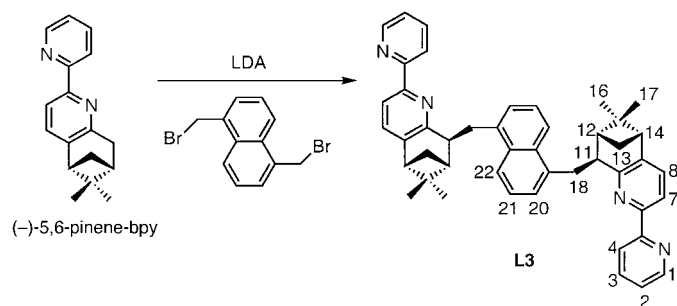


Figure 1. Aromatic part of the ^1H NMR spectra (500 MHz) of a) the Ag^+ compound in CD_3CN and b) **L3** in chloroform (*). The spectrum of **L3** in CD_3CN is almost identical, but much less intense owing to very low solubility.

The preservation of C_2 symmetry for the ligand in the complex on the NMR time scale, combined with the observation of oligonuclear species in the electrospray (ES) mass spectrum, can be explained either by the formation of circular helicates, similar to those observed with **L2**, or by rapid dynamic equilibria between fragments. Redissolution of the crystals does not result in a change in the NMR spectra, indicating a completely reversible behavior of the compound upon the solid/solution transition.

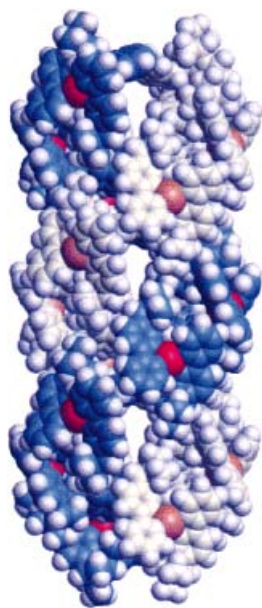


Figure 2. Side view of the cationic polymer, Figure 3 a projection in the direction of the sixfold screw axis, and Figure 4

Crystals suitable for X-ray analysis were obtained by slow diffusion of diethyl ether into a solution of the 1:1 complex, with PF_6^- as anion, in acetonitrile. The analysis of the diffraction data shows an infinite double helix. The helical pitch, given by the distance between equivalent atoms generated by one full rotation of the sixfold screw axis, is 3.417 nm (two times the crystallographic c axis).

Figure 2 presents a side view of the cationic polymer, Figure 3 a projection in the direction of the sixfold screw axis, and Figure 4

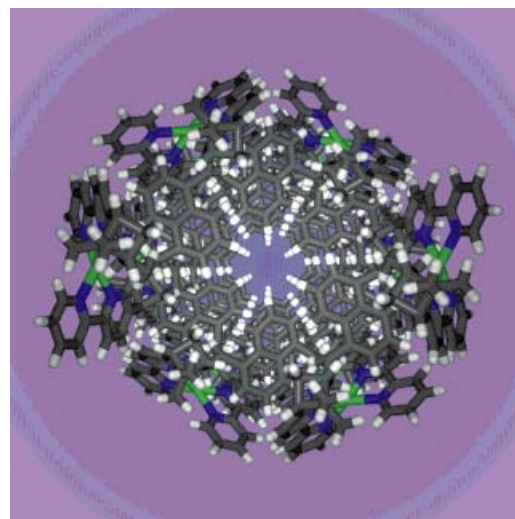


Figure 3. Perspective view of the double-stranded helix along the C_6^4 screw axis.

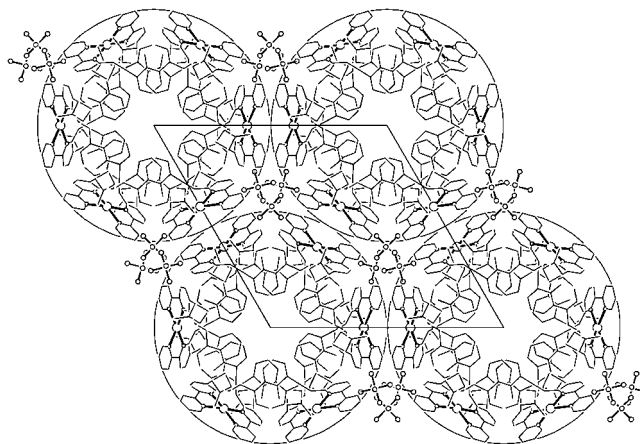


Figure 4. Molecular packing as seen along the crystallographic c axis. The PF_6^- anions occupy the channels between three adjacent double helices.

the packing as seen along the crystallographic c axis. In the following, the various, quite unusual features of this structure will be discussed. All metal centers have a strongly distorted tetrahedral coordination geometry, and their chirality is predetermined by the pinene groups in the ligands. Thus, the metal centers show homochiral coordination with absolute configuration Λ .^[23] The nitrogen–silver distance of 2.28(3) Å is quite normal. The local coordination geometry is therewith very similar in the circular helicate with **L2** and in the double-stranded helix with **L3**. The angle between the planes defined by the two N–Ag–N chelate rings at one metal center is 67.5(4)°, and the bite angle of each bipyridine unit is 71.3(9)°. The chirality of the double helix is P . P helicity combined with local Λ configuration at each tetrahedral metal center was already observed in related structures.^[20, 24]

An exceptional feature of this cationic polymer is the high degree of symmetry (D_6^4) of its double-helical arrangement. In addition to the C_6^4 axis parallel to the main direction of the helix, the Ag^+ ions and the naphthalenes are located on twofold axes. These C_2 axes are perpendicular to the direction

of the helix, and, on account of the conformation of the ligand in the helical structure, such an arrangement is in contradiction to the intrinsic molecular symmetry of the 1,5-disubstituted naphthalene moiety. Indeed, the crystal structure shows a disorder of the naphthalene bridge. This disorder has been resolved by two distinct orientations of the 1,5-disubstituted naphthalene (Figure 5 a).

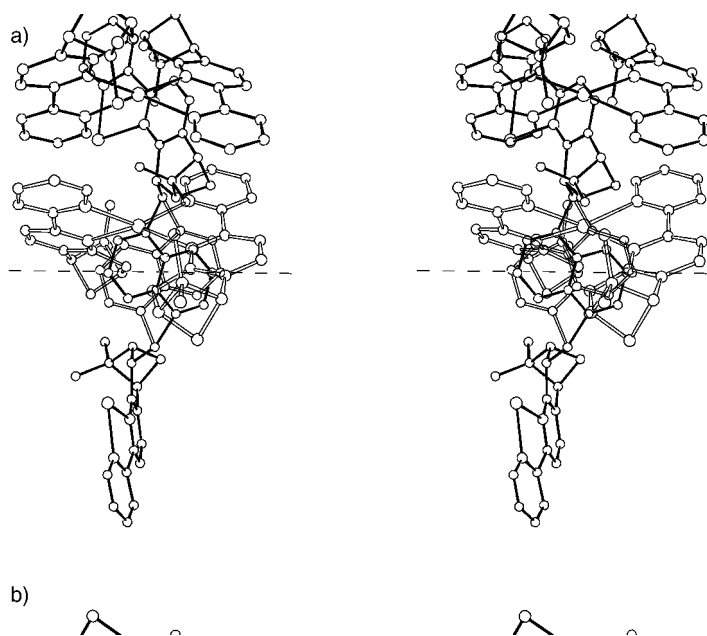


Figure 5. a) Stereoview of the two distinct orientations of the disordered naphthalene bridge. b) Stereoview emphasizing the π -stacking interactions between the bpy moieties of neighboring double helices.

If an isolated double-stranded helix is considered, no obvious reason for the intertwining can be recognized. A detailed analysis shows that there is no π stacking between the aromatic parts of the complexes. Moreover, the nature of the ligand precludes hydrogen-bond interactions between the strands, as observed in the DNA double helix. Nevertheless, the two intertwined strands are topologically inseparable (except by an “unscrewing” along the axis of the helix).

An analysis of the molecular packing reveals almost perfect π -stacking interactions involving four bipyridine moieties between neighboring double helices (parallel mean planes separated by 3.68 Å, Figure 5b). Thus, 12 π - π interactions per one full turn of the double helix, as well as the electrostatic attraction between the cationic polymer and the anions, are undoubtedly responsible for the cohesion of the crystal.

They consequently contribute to the driving force for the formation of the double helix itself. These π -stacking interactions lead to a closest approach of 4.694(4) Å for two silver centers from neighboring double helices, which is much closer than the silver-silver distances within one strand (11.003(9) Å). The channels between the infinite double helices are filled with the counterions PF_6^- , which are located on twofold crystallographic axes. The low calculated density for the crystal ($\rho_{\text{calcd}} = 1.102 \text{ g cm}^{-3}$) is significant of a loosely packed structure (probably due to the nonexistence of specific attractive interactions between the two strands), yet there are no cavities that are large enough to accommodate guest molecules. This is in agreement with the thermochemical investigations, which show no weight loss and no DSC signal (DSC = differential scanning calorimetry) for a sample up to 250 °C, and also with the fact that no solvent molecules have been detected in the crystallographic analysis.

In conclusion, the highly symmetrical solid-state structure reported here is another example for the versatility of the CHIRAGEN ligands in forming configurationally predetermined self-assembled structures. The relatively small variation of the bridging group leads from a highly fragile solid containing discrete molecular ions (**L2** as ligand) to a thermally remarkably stable crystalline material with linear double helices of nanometer-sized diameter (2.46 nm) and “infinite” length (**L3** as ligand). The absolute configuration of the natural product (–)- α -pinene used in ligand synthesis determines the chirality of the final structure. Thus, this class of ligands seems to be highly appropriate for applications in molecular and crystal engineering.^[25, 26]

Experimental Section

1,5-Bis(bromomethyl)naphthalene (BBMN) was prepared by standard methods.

Ligand **L3** was synthesized according to published procedures.^[27] Starting from (–)-5,6-pinene-bpy (1107 mg, 4.42 mmol) and BBMN (694 mg, 2.21 mmol), pure **L3** (826 mg, 1.27 mmol, yield 57 %) was obtained after column chromatography (SiO_2 ; hexanes/ $\text{Et}_2\text{O}/\text{NEt}_3$ 16/4/1) and recrystallization from hot MeCN. The product was characterized by NMR spectroscopy (the ^1H and ^{13}C signals were fully assigned), FAB-MS, UV/Vis, and elemental analysis. All data confirm the structure of the enantiomerically pure ligand **L3**.

$[\text{Ag}(\text{L3})\text{PF}_6]_{2\infty}$: Ligand **L3** (80.0 mg, 122.5 μmol) and $\text{AgOSO}_2\text{CF}_3$ (31.5 mg, 122.5 μmol) were placed in MeOH (5 mL). The mixture was stirred for 3 h, when all solids had dissolved, and then concentrated to about 2 mL. NH_4PF_6 (300 mg) in MeOH (2 mL) was then added dropwise. The precipitate obtained was filtered off and washed with MeOH and Et_2O . It was dissolved in a few milliliters of MeCN, and traces of unchanged ligand were filtered off. The solvent was removed, and the resulting yellow powder dried under high vacuum. Yield: 98 %. ^1H NMR (500 MHz, 25 °C, CDCl_3 , TMS): δ = 8.52 (dm, 2H, H(1), $^3J_{1,2}$ = 4.9 Hz), 8.04 (d, 2H, H(4), $^3J_{4,3}$ = 8.2 Hz), 7.94 (d, 2H, H(7), $^3J_{7,8}$ = 8.1 Hz), 7.73 (dd, br, 2H, H(3), $^3J_{3,4} \approx 7.5 \text{ Hz}$, $^3J_{3,2} \approx 7.2 \text{ Hz}$), 7.64–7.60 (m, 4H, H(8), H(22)), 7.29 (dd, 2H, H(2), $^3J_{2,1}$ = 5.0 Hz, $^3J_{2,3}$ = 7.1 Hz), 6.75–6.68 (m, 4H, H(20), H(21)), 4.22 (dm, 2H, H(18a), $^2J_{18a,18b}$ = 14.8 Hz), 3.47 (dm, 2H, H(11), $^3J_{11,18b}$ = 11.5 Hz), 3.23 (dd, 2H, H(18b), $^2J_{18b,18a}$ = 14.8 Hz, $^3J_{11,18b}$ = 11.4 Hz), 2.95 (dd, 2H, H(14), $^3J_{14,13a}$ = 5.6 Hz, $^4J_{14,12}$ = 5.6 Hz), 2.56 (ddd, 2H, H(13a), $^2J_{13a,13b}$ = 10.3 Hz, $^3J_{13a,14}$ = 5.6 Hz, $^3J_{13a,12}$ = 5.5 Hz), 1.83 (dd, broad, 2H, H(12)), 1.54 (d, 2H, H(13b), $^2J_{13b,13a}$ = 10.0 Hz), 1.27 (s, 6H, H(17)), 0.60 (s, 6H, H(16)); the ^{13}C NMR signals were fully assigned; elemental analysis calcd for $\text{C}_{46}\text{H}_{44}\text{AgN}_4\text{F}_6\text{P}$: C 61.00, H 4.90, N 6.19; found: C 60.57, H 4.89, N 6.51.

Crystal structure determination of $[\text{Ag}(\text{L3})](\text{PF}_6)_\infty$; $M_r = 905.7$ (for one unit of $\text{Ag}(\text{L3})\text{PF}_6$ in two asymmetric units); $\mu = 3.658 \text{ mm}^{-1}$, $F(000) = 2784$, $\rho_{\text{calc}} = 1.102 \text{ g cm}^{-3}$, hexagonal, space group $P6_222$ (no. 180), $Z = 6$, $a = 23.524(2)$, $c = 17.086(2) \text{ \AA}$, $V = 8188(2) \text{ \AA}^3$, from 25 reflections ($2\theta < 33^\circ$); colorless prism, $0.26 \times 0.34 \times 0.40 \text{ mm}$, mounted on a quartz fiber with RS3000 oil. Cell dimensions and intensities were measured at 200 K on a Stoe Stadi4 diffractometer with graphite-monochromated $\text{Cu K}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$), ω - 2θ scans, scan width $1.05^\circ + 0.35 \text{ tg } \theta$, scan speed $0.06^\circ \text{ s}^{-1}$. Two reference reflections measured every 45 min showed no variation. $-23 < h < 23$, $0 < k < 23$, $0 < l < 16$, and all antireflections of these; of 11 176 measured reflections, 2812 were unique and of these 1957 were observed ($|F_o| > 4\sigma > (F_o)$); $R_{\text{int}} = 0.17$ for 8364 equivalent reflections. Data were corrected for Lorentz and polarization effects and for absorption^[28] (min./max. absorption 2.121/3.641). The structure was solved by direct methods using MULTAN 8,^[29] and the XTAL^[30] system was used for all other calculations. The chirality of the structure was refined, and the Flack parameter^[31] converged to $x = 0.13(6)$. Full-matrix least-squares refinement based on F using a weighting of $1/(\sigma^2(F_o) + 0.0001(F_o^2))$ gave final values of $R = 0.095$, $wR = 0.094$, and $S = 3.14(9)$ for 255 variables and 1957 contributing reflections. Hydrogen atoms were placed in calculated positions. All atoms of the ligand, except for the methylene bridge (C18) between the disordered naphthalene and the pinene moieties, were refined with soft restraints (99) on bond lengths, bond angles, and, for the aromatic fragments, torsional angles; max./min. residual electron density $+0.74/-0.49 \text{ e \AA}^{-3}$. The Ag and P atoms are located on special positions 6h and 6j, respectively, and the two positions of the disordered naphthalene unit are related by the symmetry operation $x, x - y - 1, 4/3 - z$ (around the C_2 axis in the special position 6i). A majority of the crystals showed significant disorders or cleavages, leading to poor diffraction, very large overall displacement parameters, and enlarged or split diffraction profiles. A refinement of the structure in the less symmetric space group $P6_2$ (loss of the twofold axes perpendicular to the c axis) leads to the observation of the same disorder and suggests the presence of C_2 (pseudo)merohedral twinning. The quality of the data does not allow a differentiation between a twinned crystal in $P6_2$ and a disordered structure in $P6_222$, but the overall results could be considered as identical. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-119096. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+49)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Received: April 30, 1999 [Z13348IE]

German version: *Angew. Chem.* **1999**, *111*, 3129–3133

- [10] D. A. Evans, K. A. Woerpel, M. J. Scott, *Angew. Chem.* **1992**, *104*, 439–441; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 430–432.
- [11] R. W. Saalfrank, M. Decker, F. Hampel, K. Peters, H. G. von Schnering, *Chem. Ber.* **1997**, *130*, 1309–1313.
- [12] P. K. Bowyer, K. A. Porter, A. D. Rae, A. C. Willis, S. B. Wild, *Chem. Commun.* **1998**, 1153–1154.
- [13] J. F. Modder, G. van Koten, K. Vrieze, A. L. Spek, *Angew. Chem.* **1989**, *101*, 1723–1725; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1698–1700.
- [14] P. Hayoz, A. von Zelewsky, H. Stoeckli-Evans, *J. Am. Chem. Soc.* **1993**, *115*, 5111–5114.
- [15] H. Muerner, A. von Zelewsky, G. Hopfgartner, *Inorg. Chim. Acta* **1998**, *271*, 36–39.
- [16] J.-M. Lehn, *Supramolecular Chemistry—Concepts and Perspectives*, VCH, Weinheim, **1995**.
- [17] M. Albrecht, *Chem. Soc. Rev.* **1998**, *27*, 281–287.
- [18] D. L. Caulder, K. N. Raymond, *Angew. Chem.* **1997**, *109*, 1508–1510; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1439–1442.
- [19] P. Baret, D. Gaude, G. Gellon, J.-L. Pierre, *New J. Chem.* **1997**, *21*, 1255–1257.
- [20] O. Mamula, A. von Zelewsky, G. Bernadinelli, *Angew. Chem.* **1998**, *110*, 301–305; *Angew. Chem. Int. Ed.* **1998**, *37*, 289–293.
- [21] P. Hayoz, A. von Zelewsky, *Tetrahedron Lett.* **1992**, *33*, 5165–5168.
- [22] H. Muerner, A. von Zelewsky, H. Stoeckli-Evans, *Inorg. Chem.* **1996**, *35*, 3931–3935.
- [23] A. von Zelewsky, *Stereochemistry of Coordination Compounds*, Wiley, Chichester, **1996**.
- [24] G. Baum, E. C. Constable, D. Fenske, T. Kulke, *Chem. Commun.* **1997**, 2043–2044.
- [25] M. J. Zaworotko, *Angew. Chem.* **1998**, *110*, 1269–1271; *Angew. Chem. Int. Ed.* **1998**, *37*, 1211–1212.
- [26] A. J. Blake, N. R. Champness, P. Hubberstey, W.-S. Li, M. A. Withersby, M. Schröder, *Coord. Chem. Rev.* **1999**, *183*, 117–138.
- [27] H. Muerner, P. Belser, A. von Zelewsky, *J. Am. Chem. Soc.* **1996**, *118*, 7989–7994.
- [28] E. Blanc, D. Schwarzenbach, H. D. Flack, *J. Appl. Crystallogr.* **1991**, *24*, 1035–1041.
- [29] P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, M. M. Woolfson, *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data*, Universities of York, England, and Louvain-la-Neuve, Belgium, **1987**.
- [30] *XTAL 3.2 User's Manual* (Eds.: S. R. Hall, H. D. Flack, J. M. Stewart), Universities of Western Australia and Maryland, **1992**.
- [31] H. D. Flack, *Acta Crystallogr. Sect. A* **1983**, *39*, 879–881.

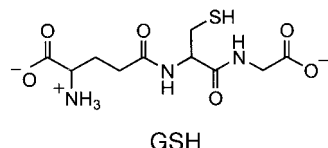
Keywords: bipyridine ligands • chirality • helical structures • silver • supramolecular chemistry

- [1] C. Piguet, G. Bernardinelli, G. Hopfgartner, *Chem. Rev.* **1997**, *97*, 2005–2062.
- [2] C. Kaes, M. W. Hosseini, C. E. F. Rickard, B. W. Skelton, A. H. White, *Angew. Chem.* **1998**, *110*, 970–973; *Angew. Chem. Int. Ed.* **1998**, *37*, 920–922.
- [3] H.-P. Wu, C. Janiak, L. Uehlin, P. Klüfers, P. Mayer, *Chem. Commun.* **1998**, 2637–2638.
- [4] O. J. Gelling, F. van Bolhuis, B. L. Feringa, *Chem. Commun.* **1991**, 917–919.
- [5] K. Biradha, C. Seward, M. J. Zaworotko, *Angew. Chem.* **1999**, *111*, 584–587; *Angew. Chem. Int. Ed.* **1999**, *38*, 492–495.
- [6] S. R. Batten, B. F. Hoskins, R. Robson, *Angew. Chem.* **1997**, *109*, 652–653; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 636–637.
- [7] M. A. Withersby, A. J. Blake, N. R. Champness, P. Hubberstey, W.-S. Li, M. Schröder, *Angew. Chem.* **1997**, *109*, 2421–2423; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2327–2329.
- [8] K. A. Hirsch, S. R. Wilson, J. S. Moore, *Chem. Commun.* **1998**, 13–14.
- [9] N. Masciocchi, G. A. Ardizzoia, G. LaMonica, A. Maspero, A. Sironi, *Angew. Chem.* **1998**, *110*, 3561–3564; *Angew. Chem. Int. Ed.* **1998**, *37*, 3366–3369.

A Novel Dinuclear Diaminoplatinum(II) Glutathione Macrochelate**

Piedad del Socorro Murdoch, Nicole A. Kratochwil, John A. Parkinson, Marina Patriarca, and Peter J. Sadler*

How do platinum anticancer drugs reach their DNA target sites in cells despite the presence of millimolar concentrations of the thiol tripeptide glutathione^[1] (γ -L-Glu-L-Cys-Gly, GSH)? This is a long-standing puzzle, for which there is



currently no answer.^[2] Reactions of platinum drugs with GSH in cells^[3] are thought to be deactivating. Cisplatin-resistant tumor cells often contain elevated GSH levels, and transport of Pt out of cells is facilitated by GS-X pumps.^[4] However, coadministration of cisplatin with GSH as a chemoprotectant does not appear to diminish the activity of cisplatin.^[5] The major product from reaction of cysteine derivatives with *cis*-diam(m)inoplatinum(II) complexes is thought to be the bridged dimer $[(\text{am})_2\text{Pt}(\mu_2\text{-SR})_2\text{Pt}(\text{am})_2]$, where am is am(m)ine or one-half of a diamine.^[6–8] These bridged complexes are unlikely to be reactive towards DNA bases, although the ammine complexes can slowly release ammonia. There is now much interest in other types of adducts of GSH with *cis*-diamine complexes,^[6, 9] which might be more reactive.

In this work we have isolated and characterized a new product formed by reactions of either GSH or glutathione disulfide (GSSG) with the anticancer complex $[\text{Pt}(\text{en})\text{Cl}_2]$ (**1**, en = ethylenediamine) under physiologically relevant conditions: an unusual glutathione-bridged diplatinum(II) macrochelate. Although stable, it is potentially reactive, and such species could play an important role in the mechanism of action of platinum anticancer complexes.

We first studied reactions between **1** (100 μM) and GSSG or GSH (1:2 molar ratio, pH 7, 310 K) by HPLC. Representative chromatograms for the GSSG reaction are given in the Supporting Information (Figure S1, UV detection). Five new peaks appeared within the first few hours. One peak (C) was an intermediate, and after 24 h two peaks (D and E)

predominated. The time course for this reaction, as determined by on-line HPLC-ICP-MS measurements of Pt concentrations, is shown in Figure 1b. Chromatograms for the GSH reaction were similar, although the reaction was slightly faster than that with GSSG (Figure 1; $t_{1/2} = 0.9$ h (GSH) and 1.3 h (GSSG)) and the ratio E:D was higher for the GSSG reaction.

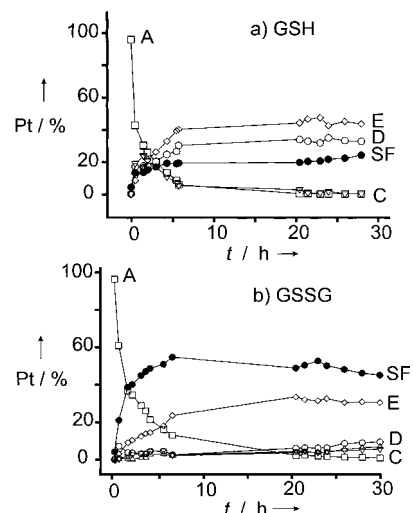
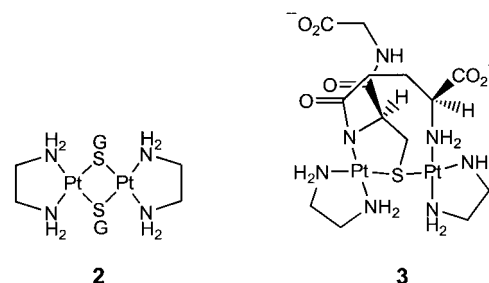


Figure 1. Time courses of the reactions of $[\text{Pt}(\text{en})\text{Cl}_2]$ (**1**) with a) GSH and b) GSSG, as determined by measurements of Pt concentrations using HPLC-ICP-MS. Peak assignments: A: **1**; C: unknown; D: **2**; E: **3**; SF = solvent front (contains Pt species not retained by the column; for GSSG includes a Pt–GSSG adduct). See also Figure S1 in the Supporting Information.

The HPLC-ESI-MS experiments on reaction mixtures after 24 h showed that the two major species corresponding to peaks D and E were identical for GSSG and GSH reactions. Both gave a cluster of ions related to the isotopic distribution of Pt and N, with the species for peak D having its most abundant peak $[M^+]$ at m/z 1121 corresponding to $\text{Pt}_2\text{S}_2\text{C}_{24}\text{N}_{10}\text{O}_{12}\text{H}_{48}$ (calcd 1122; complex **2**), and that for peak E $[M^+ + \text{H}]$ at m/z 814 corresponding to $\text{Pt}_2\text{S}_2\text{C}_{14}\text{N}_7\text{O}_6\text{H}_{30}$ (calcd 814; complex **3**). A peak in the solvent front at m/z 866, corresponding to the isotopic distribution characteristic of $\text{Pt}_2\text{S}_2\text{C}_{22}\text{N}_8\text{O}_{12}\text{H}_{40}$ ($[\text{Pt}(\text{en})(\text{GSSG})]$), was detected for the GSSG but not the GSH reaction.



The courses of the reactions of **1** with GSSG and GSH were also followed by 2D ^1H , ^{15}N HSQC NMR spectroscopy using ^{15}N -**1**. After 24 h both reactions gave rise to the same set of nine major 2D NMR $^1\text{H}/^{15}\text{N}$ cross-peaks. These cross-peaks corresponded to the summation of peaks obtained from the

[*] Prof. Dr. P. J. Sadler, Dr. P. del Socorro Murdoch, Dr. N. A. Kratochwil, Dr. J. A. Parkinson, Dr. M. Patriarca
Department of Chemistry
University of Edinburgh
West Mains Road, Edinburgh EH9 3JJ (UK)
Fax: (+44) 131-650-6452
E-mail: p.j.sadler@ed.ac.uk

[**] We thank the EU (Marie Curie Research Training Grant, no. ERB4001GT963865 to N.A.K. and COST Action D8), the BBSRC, and the EPSRC for their support for this work. We are grateful to Dr. A. M. Gouldsworthy and M. Scott for their advice and assistance with ESI-MS measurements, and Professor A. M. Sargeson of the Australian National University for stimulating discussion.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

separated HPLC peaks D and E. Peak D gave rise to a single $^1\text{H}/^{15}\text{N}$ cross-peak at $\delta = 5.1/-10.0$, characteristic of $\text{Pt}-^{15}\text{NH}_2$ *trans* to S.^[10] When linked with the ESI-MS data, this suggests that peak D corresponds to the symmetrical S-bridged dimer $[\{\text{Pt}(\text{en})(\mu_2\text{-SG})\}_2]$ (**2**). Peak E gave rise to eight $^1\text{H}/^{15}\text{N}$ NMR cross-peaks (Table 1), consistent with the presence of two $\{\text{Pt}([^{15}\text{N}]\text{-en})\}^{2+}$ units with two nonequivalent protons on each of the four nonequivalent ^{15}N atoms. The ^{15}N shifts suggest that two ^{15}N atoms are *trans* to S and two are *trans* to N/Cl. The ESI-MS data for peak E corresponded to a di- $\text{Pt}(\text{en})$ complex containing only one glutathione ligand. The structure of complex **3** was deduced from an extensive series of single-pulse 1D ^1H , $^1\text{H}\{^{15}\text{N}\}$, and 1D-TOCSY NMR experiments, combined with 2D homonuclear $^1\text{H}\{^1\text{H}\{^{15}\text{N}\}\}$ -DQF-COSY, TOCSY, ROESY, NOESY, and heteronuclear $[^1\text{H},^{15}\text{N}]$ HSQC, HSQC-TOCSY (Figure 2), and HSQC-NOESY NMR experiments. The important results are summarized below and in Table 1.

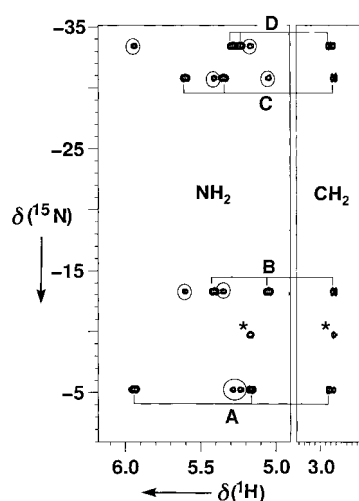


Figure 2. 2D $[^1\text{H}, ^{15}\text{N}]$ HSQC-TOCSY NMR spectrum (11.74 T, mixing time 54 ms) of the species eluted with chromatographic peak E (complex **3**). Four $\text{H}_2^{15}\text{N}\text{-CH}_2$ spin systems can be seen (A, B, C, D). Those belonging to the same $[^{15}\text{N}]\text{-en}$ ligands are apparent from the circled cross-peaks (A/D, B/C). Resonances for the species from residual chromatographic peak D (complex **2**) are indicated by *.

Specific assignments were made for all of the ^1H and ^{15}N resonances of each $\{\text{Pt}([^{15}\text{N}]\text{-en})\}^{2+}$ residue of **3**. For the coordinated glutathione, the Gly-NH resonance showed couplings to the doublet of doublets at $\delta = 4.18$ (Gly- $\text{H}\alpha^a$) and 3.61 (Gly- $\text{H}\alpha^b$). The doublet at $\delta = 5.05$ for Cys- $\text{H}\alpha$ was coupled to the Cys- $\text{H}\beta^b$ proton at $\delta = 2.76$, but not to its

geminal partner Cys- $\text{H}\beta^a$ at $\delta = 2.70$. No signal assignable to Cys-NH was observed. A spin system consisting of five protons in the region $\delta = 2.0\text{--}3.5$ was assigned to the CHCH_2CH_2 moiety of $\gamma\text{-Glu}$, and broadened resonances at $\delta = 6.20$ and 5.13 were assigned to $\gamma\text{-Glu-NH}(1)$ and $\gamma\text{-Glu-NH}(2)$, respectively. The former was a doublet consistent with a $\gamma\text{-Glu-NH}(1)$ to $\gamma\text{-Glu-H}\alpha$ torsion angle of about 90° . The latter resonance was a triplet with two large couplings, consistent with a torsion angle $\gamma\text{-Glu-NH}(2)$ to $\gamma\text{-Glu-H}\alpha$ of 180° . Broadening at the base of these resonances can be attributed to the presence of ^{195}Pt satellites (two-bond ^{195}Pt , ^1H coupling (^2J)) broadened by chemical shift anisotropy relaxation. Specific rOes were observed as follows: Gly-NH to en-NH(A), Gly-NH to Cys- $\text{H}\alpha$, Gly-NH to both Gly- $\text{H}\alpha$ protons, $\gamma\text{-Glu-NH}(1)$ to $\gamma\text{-Glu-H}\alpha$, $\gamma\text{-Glu-NH}(2)$ to $\gamma\text{-Glu-H}\alpha$, $\gamma\text{-Glu-NH}(1)$ to $\gamma\text{-Glu-H}\gamma^a$, $\gamma\text{-Glu-H}\gamma^a$ to en-NH(A'). A particularly strong rOe was also observed between Cys- $\text{H}\beta^b$ and $\gamma\text{-Glu-H}\alpha$. When a sample corresponding to chromatographic peak E was freeze-dried and redissolved in D_2O , all of the resonances assigned to NH protons disappeared except for that of $\gamma\text{-Glu-NH}(1)$. This was now a singlet and subsequently disappeared slowly over a period of 24 h, suggesting a relatively buried environment.^[11]

Figure 3 shows a model for complex **3** which is consistent with all these observations. The rOe between Gly-NH and

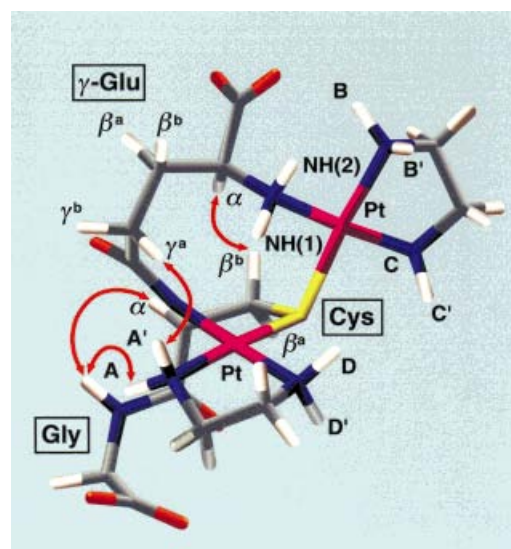


Figure 3. Structure for complex **3** (chromatographic peak E) which is consistent with observed NMR rOe (inter-residue rOes are indicated by arrows) and coupling constant data. Assignments for peaks B/B', C/C', and D/D' are nonstereospecific.

Table 1. ^1H and ^{15}N NMR resonance assignments for complex $[^{15}\text{N}]\text{-3}$ (chromatographic peak E).

	$^{15}\text{NH}_2$		CH_2		$^{15}\text{NH}_2$	
	$\delta(^{15}\text{N})$ (<i>trans</i> to)	$\delta(^1\text{H})$	$\delta(^1\text{H})$	$\delta(^1\text{H})$	$\delta(^{15}\text{N})$ (<i>trans</i> to)	$\delta(^1\text{H})$
$\{\text{Pt}([^{15}\text{N}]\text{-en})\}$	-5.50 (S) -13.37 (S)	5.95 (A), 5.18 (A') 5.41 (B), 5.05 (B')	2.84 2.75	2.70 2.74	-33.00 (N) -30.50 (N)	5.30 (D), 5.24 (D') 5.60 (C), 5.35 (C')
$\text{H}_2\text{-SG}$	$\delta(\text{NH})$	$\delta(\text{H}\alpha)$	$\delta(\text{H}\beta^a)$	$\delta(\text{H}\beta^b)$	$\delta(\text{H}\gamma^a)$	$\delta(\text{H}\gamma^b)$
Gly	7.86	4.18, 3.61				
Cys	-	5.05	2.70 ^[a]	2.76 ^[b]		
$\gamma\text{-Glu}$	6.20 (NH1), ^[c] 5.13 (NH2)	3.20	2.00	2.35	3.25	2.55

[a] $^3J(\text{H,H}) = 0$ Hz, $^2J(\text{H,H}) = 14$ Hz. [b] $^3J(\text{H,H}) = 5.9$ Hz, $^2J(\text{H,H}) = 14$ Hz. [c] Exchanges only slowly with ^2H .

en-NH₂(A) places Gly on one side of one of the Pt^{II} coordination planes, and the rOe between γ -Glu-H γ^a and en-NH₂(A') places γ -Glu on the opposite side of the same Pt^{II} coordination plane. The large rOe between γ -Glu-H α and Cys-H β^b is consistent with the close proximity of these two atoms in the model. The structure therefore consists of two square-planar (en)Pt^{II} centers bridged by a μ_2 -thiolate S atom. One (en)Pt^{II} unit forms a five-membered ring by binding to the deprotonated amide N atom of Cys, and the other is coordinated to the γ -Glu NH₂ group, giving rise to a ten-membered macrochelate ring.

Complex **3** appears to be a novel adduct with an unprecedented structure. It is intriguing that this is a product from both GSH and GSSG reactions. Platinum(II)-induced disulfide bond cleavage has been reported previously, although the reactions studied were quite slow.^[12–15]

Our preliminary HPLC and NMR studies show that **3** (but not **2**) reacts with the nucleotide guanosine 5'-monophosphate at micromolar concentrations in aqueous solution at neutral pH. Several Pt complexes containing chelated diamines are currently on clinical trial, and the discovery of complex **3** may therefore have significant implications for understanding their mode of action.

Experimental Section

[Pt(en)Cl₂] (**1**) and [¹⁵N]-**1** were synthesized according to previously described procedures.^[16] Reduced glutathione (GSH) was purchased from Acros, and oxidized glutathione (GSSG) from Sigma.

The NMR data sets were acquired using Varian UNITY INOVA 600 and Bruker DMX 500 NMR spectrometers equipped with z-field gradient triple resonance NMR probes and operating at ¹H resonance frequencies of 599.841 and 500.13 MHz, respectively. Data acquisition and processing conditions have been described previously.^[17]

Analytical separations were carried out on a BioCAD SPRINT Workstation using a Nucleosil 100-5SA cation-exchange column (250 × 4.6 mm, 100 Å, 5 μ m, Hichrom) with ammonium acetate buffer (2 mM). The time courses of reactions between **1** (100 μ M, 2 mL) and GSSG or GSH (20 mM, 20 μ L) at 1:2 molar ratios were carried out at 310 K and followed chromatographically by injection of aliquots of the mixture onto the HPLC column at various time intervals after mixing, with detection at 223 nm. The pH values of GSSG and GSH solutions were adjusted to 7 before mixing with **1**.

Positive-ion electrospray mass spectrometry (ESI-MS) was performed on a Platform II mass spectrometer (Micromass, Manchester, UK). The atmospheric pressure ionization (API)-ESI ion source was interfaced to an LC Waters 2690 HPLC system using the same column and procedure as above, with a splitting ratio of 1/5. The source temperature was 413 K, and the drying gas flow rate was 450 L h⁻¹. A potential of 2.8 kV was applied to the probe tip, and a cone voltage of 50–90 V over 300–2000 Da was used. The quadrupole was scanned at 100 amu⁻¹. The mass accuracy of all measurements was within 0.1 *m/z* units.

An inductively coupled plasma mass spectrometer (ICP-MS) Plasma Quad 3 from VG Elemental (Winsford, UK) was used for Pt determinations. The ICP-MS was coupled with a Gilson 305 pump, a Gilson manometric module, and a Rheodyne sample injector through PEEK tubing connected directly to the Meinhardt concentric nebulizer. Data were acquired at mass 195, using the VG software for time-resolved analysis, with a dwell time of 300 ms. Chromatographic separations were carried out as described above at a flow rate of 0.8 mL min⁻¹, using a 20- μ L sample loop. Samples were diluted to 1:1000 before injection to give concentrations of approximately 100 nM Pt.

The pH measurements were made using a Corning 240 pH meter equipped with an Aldrich microcombination electrode standardized with buffers at pH 4, 7, and 10.

Received: May 18, 1999 [Z13435IE]

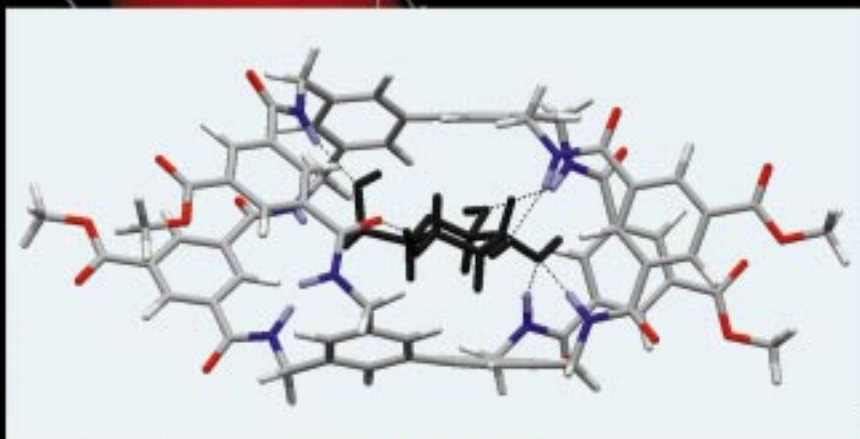
German version: *Angew. Chem.* **1999**, *111*, 3062–3065

Keywords: antitumor agents • bioinorganic chemistry • glutathione • NMR spectroscopy • platinum

- [1] A. Meister in *Glutathione. Chemical, biochemical, and medical aspects* (Eds.: D. Dolphin, O. Avramovic, R. Poulson), Wiley, New York, **1989**, pp. 1–48.
- [2] J. Reedijk, J. M. Teuben in *Cisplatin—chemistry and biochemistry of a leading anticancer drug* (Ed.: B. Lippert), WILEY-VCH, Weinheim, **1999**, pp. 339–362. See also section 3 of Z. Guo, P. J. Sadler, *Angew. Chem.* **1999**, *111*, 1610–1630; *Angew. Chem. Int. Ed.* **1999**, *38*, 1512–1531.
- [3] S. J. Berners-Price, P. W. Kuchel, *J. Inorg. Biochem.* **1990**, *38*, 327–345.
- [4] a) T. Ishikawa, C. D. Wright, H. Ishizuka, *J. Biol. Chem.* **1994**, *269*, 29085–29093; b) T. Ishikawa, J.-J. Bao, Y. Yamane, K. Akimaru, K. Frindrich, C. D. Wright, M. T. Kuo, *J. Biol. Chem.* **1996**, *271*, 14981–14988.
- [5] D. T. Dorr in *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy 2* (Eds.: H. M. Pinedo, J. H. Schornagel), Plenum Press, New York, **1996**, pp. 131–154.
- [6] T. G. Appleton, J. W. Connor, J. R. Hall, P. D. Prenzler, *Inorg. Chem.* **1989**, *28*, 2030–2037.
- [7] T. G. Appleton, *Coord. Chem. Rev.* **1997**, *166*, 313–359.
- [8] K. C. Strevler, C. M. Jensen, *Inorg. Chem.* **1993**, *32*, 2608–2609.
- [9] A. Bernareggi, L. Torti, R. M. Facino, M. Carini, G. Depta, B. Casetta, N. Farrell, S. Spadacini, R. Ceserani, S. Tognella, *J. Chromatogr.* **1995**, *669*, 247–263.
- [10] S. J. Berners-Price, P. J. Sadler, *Coord. Chem. Rev.* **1996**, *151*, 1–40.
- [11] The resonance also remained present up to pH 11.5 during the course of a pH titration of complex **3** when all other NH resonances had disappeared through fast exchange with the solvent.
- [12] A. K. Fazlur-Rahman, J. G. Verkade, *Inorg. Chem.* **1992**, *31*, 2064–2069.
- [13] E. L. M. Lempers, K. Inagaki, J. Reedijk, *Inorg. Chim. Acta* **1988**, *152*, 201–207.
- [14] N. Ohta, K. Inagaki, H. Muta, T. Yotsuyanagi, T. Matsuo, *Int. J. Pharmaceut.* **1998**, *161*, 15–21.
- [15] N. Ohta, D. Chen, S. Ito, T. Futo, T. Yotsuyanagi, K. Ikeda, *Int. J. Pharmaceut.* **1995**, *118*, 85–93.
- [16] a) E. Zang, P. J. Sadler, *Synthesis* **1997**, 410–414; b) L. T. Ellis, H. M. Er, T. W. Hambley, *Aust. J. Chem.* **1995**, *48*, 793–806.
- [17] S. J. Berners-Price, U. Frey, J. D. Ranford, P. J. Sadler, *J. Am. Chem. Soc.* **1993**, *115*, 8649–8659.

X-ray crystal structure of glucose bound to the *E. coli* galactose chemoreceptor protein (*Science* 1988, 242, 1290; see also Figure 1). Polar and apolar residues surrounding the carbohydrate are highlighted in yellow and green, respectively. Hydrogen bonds in the neighborhood of the binding site are shown as broken green lines.

Inset: A synthetic receptor designed to mimic the binding site by providing both polar and apolar interactions.



Carbohydrate Recognition through Noncovalent Interactions: A Challenge for Biomimetic and Supramolecular Chemistry

Anthony P. Davis* and Richard S. Wareham

“Nucleic acids for control, proteins for effect, lipids and carbohydrates as fuel and building materials.” As a crude summary of the natural world, this statement would have satisfied most biochemists three decades ago. However, the placing of carbohydrates at the bottom of this hierarchy was undeserved and, with hindsight, unwise. As carriers of information, oligosaccharides have far greater potential than the other two biopolymers. While three different nucleotides or amino acids can be used to create just six distinguishable molecules, over 1000 possibilities may be generated from three monosaccharides. It was unlikely that Nature would ignore this resource, and it is now quite clear that she did not. Carbohydrate recognition is known to mediate cell adhesion (and

therefore, to a large extent, the development of multicellular organisms), the infection of cells by pathogens, the distribution and reactivity of proteins within cells, and many aspects of the immune response. “Glycobiologists” studying these effects can justly claim to be working at one of the major frontiers in the biological sciences. To supramolecular chemists, carbohydrate recognition represents a challenge to architectural and synthetic talents, and an opportunity to answer fundamental questions in an important and topical area. On the one hand, carbohydrates present complex three-dimensional arrays of functionality to their surroundings, posing intriguing problems in receptor design. On the other, the principles of saccharide recognition by biomolecules are not

well understood. X-ray crystallography reveals the expected polar and hydrophobic interactions in protein–carbohydrate complexes, but does not explain the thermodynamic driving force for desolvation and complex formation. This review charts the progress of supramolecular chemistry towards truly biomimetic carbohydrate recognition. The journey is not yet complete, with the most challenging part still to come. However, the landmarks have been pleasing, often impressive, and perhaps suggestive of future success.

Keywords: bioorganic chemistry • carbohydrates • molecular recognition • receptors • supramolecular chemistry

1. Introduction

The role of oligosaccharides in biological regulation has attracted a great deal of attention in recent years.^[1] It has been realized that the information-carrying potential of oligosaccharides is far greater than that of proteins and nucleic acids of equivalent molecular weight, and that their presence on cell surfaces and on many proteins suggests an importance which was previously unrecognized. Oligosaccharides are now known to mediate cell–cell recognition, including the infection of cells by bacteria and viruses, moderate the behavior of enzymes and other proteins, and fulfil various functions in the immune response. The recognition of saccharides is also

important for carbohydrate metabolism, and for the transport of these highly polar molecules across cell membranes.

The raised profile of carbohydrates has attracted attention from the synthetic chemical community, where a renaissance in carbohydrate chemistry, especially oligosaccharide synthesis,^[2] is clearly apparent. Supramolecular chemists have likewise responded, drawn by the challenge of designing carbohydrate receptors, and also by practical and theoretical considerations. Synthetic carbohydrate receptors could be used as drugs (e.g. anti-infective agents), to target cell types (acting as “synthetic antibodies”), to transport saccharides or related pharmaceuticals across cell membranes, or in carbohydrate sensors. On the theoretical side, carbohydrate recognition by natural systems is still quite poorly understood. The X-ray crystallography of protein–carbohydrate complexes reveals, not surprisingly, that the polar groups are bound by hydrogen-bond donor and acceptor groups, or occasionally to metal ions, while the hydrophobic regions are complemented by nonpolar surfaces.^[3] However, complex formation requires

[*] Prof. A. P. Davis, Dr. R. S. Wareham
Department of Chemistry, Trinity College
Dublin 2 (Ireland)
Fax: (+353) 1-671-2826
E-mail: adavis@tcd.ie

that host and guest be desolvated. What drives the replacement of water by carbohydrate-OH in a natural binding site? This and other issues are subjects of active debate^[4] to which studies on synthetic receptors could make important contributions.

It should be said at this stage that carbohydrate recognition which is both effective and genuinely biomimetic is still a goal for the future. This review, which surveys the progress so far, is divided into two main sections. The first covers receptors which operate in organic solvents and, though effective, are not forced to select between carbohydrates and water molecules. Arguably, these are biomimetic only where they can extract carbohydrates from aqueous solution, and therefore mimic transport across cell membranes. The second covers receptors operating in water. Though biomimetic they are not yet effective, by the standards normally expected in supramolecular chemistry. The only synthetic receptors which are truly effective in water rely on boronate formation. However, these systems are neither biomimetic nor, in the strictest sense, supramolecular (given that recognition occurs through covalent bond formation). They are therefore outside the scope of this article and have, in any case, been subjects of several recent reviews.^[5]

2. Carbohydrate Recognition in Organic Media

Carbohydrates in their pyranose and furanose forms are generally characterized by a complex, divergent array of polar functional groups. Most are hydroxy groups, capable of donation and acceptance of hydrogen bonds. Perhaps the most obvious approach to carbohydrate recognition is to surround these groups with a complementary, *convergent* arrangement of H-bond donor and/or acceptor functionality. Nature provides ample encouragement for this strategy, as the X-ray crystal structures of protein–carbohydrate complexes

invariably reveal intensive hydrogen bonding between host and guest (see for example Figure 1).^[3] Hydrogen bonding is especially effective in nonpolar organic media, where solvent does not compete significantly for binding sites. In these circumstances, the preorganized deployment of polar functionality should be sufficient for success.

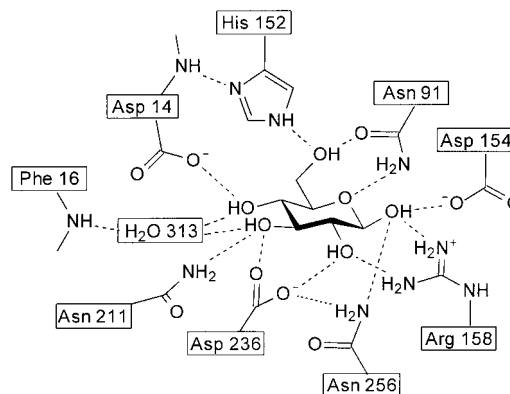


Figure 1. Intermolecular hydrogen bonds in the complex between D-glucose and “D-galactose-binding” bacterial periplasmic protein. (Adapted from reference [3a]; see also frontispiece on p. 2978.)

Although this strategy is readily conceived, its execution is complicated by the size of carbohydrates, the “three-dimensional” arrangement of their functionality (in contrast, for example, to the nucleobases) and the subtle variations in their structures. The frameworks of carbohydrate receptors must be relatively large, so that they can traverse or (ideally) encapsulate their substrates, while maintaining the rigidity necessary for preorganisation of the binding functional groups. Rigidity is also necessary to inhibit “self-quenching” of binding functionality; H-bond donor *and* acceptor sites are present in most (neutral) polar functional groups.

Tony Davis was born in Watford, Hertfordshire, England in 1954. He received a B.A. in Chemistry from Oxford University in 1977, then stayed on for a D.Phil. under Dr. G. H. Whitham and two years postdoctoral work with Prof. J. E. Baldwin. In 1981 he moved to the ETH Zürich as a Royal Society European Exchange Fellow working with Prof. A. Eschenmoser, then in 1982 was appointed as a Lecturer in Organic Chemistry at Trinity College, Dublin. In 1995 he was promoted to Associate Professor. His research interests include the application of organosilicon reagents to organic synthesis, and various aspects of supramolecular chemistry. He is presently coordinator of an EU-funded Training and Mobility of Researchers (TMR) Network entitled “Towards an Understanding of Carbohydrate Recognition in Aqueous Solution”, which includes several of the groups whose work is mentioned in this article.

Richard Wareham was born in Hemel Hempstead, Hertfordshire, England in 1970. In 1991 he received a B.Sc. in Chemistry from Lancaster University before undertaking his Ph.D. with Jeremy Kilburn at the University of Southampton. From 1995 to 1998 he held a Postdoctoral Fellowship in Trinity College, Dublin, working on the design and synthesis of carbohydrate receptors. He is currently employed by Newport Synthesis Ltd. in Baldoye, Co. Dublin.



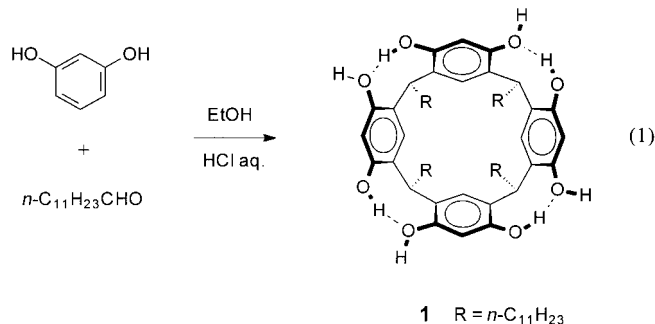
A. P. Davis



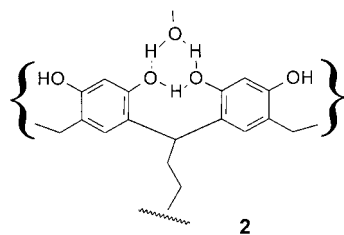
R. S. Wareham

2.1. "Face-to-Face" Recognition

Given the challenge of fully encapsulating a carbohydrate, it is unsurprising that the first successful carbohydrate receptor employed a "face-to-face" binding geometry. The octahydroxy calix[4]arene **1**, first reported by Aoyama et al. in 1988, could be obtained in a single step from resorcinol and dodecanal [Eq. (1)].^[6] The bowl-shaped framework of **1**



cannot encompass a furanose or pyranose, but possesses a preorganized array of binding sites which can span the face of a carbohydrate nucleus. Assuming the illustrated pattern of intramolecular hydrogen bonding, each site can in principle form cooperative hydrogen bonds to a hydroxy group as shown in **2**. Accordingly, **1** was capable of extracting four



equivalents of water into solution in CCl_4 .^[6,7] When the water was replaced by concentrated (1–5.5 M) aqueous solutions of certain carbohydrates, these also were extracted. The best studied was D-ribose (**3**), shown to form a complex of stoichiometry $1 \cdot 3 \cdot 2\text{H}_2\text{O}$. The sugar was found to be in its α -pyranose form **3p α** , despite the predominance of **3p β** in aqueous solution (Figure 2). Similarly extracted were D-

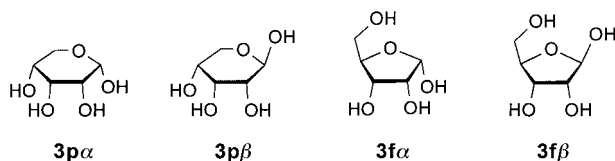
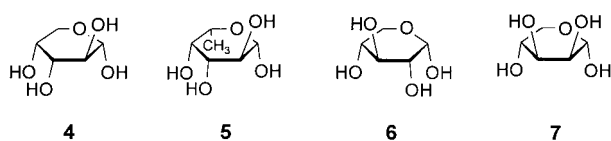


Figure 2. Cyclic forms of D-ribose (**3**). **p** = pyranose, **f** = furanose.

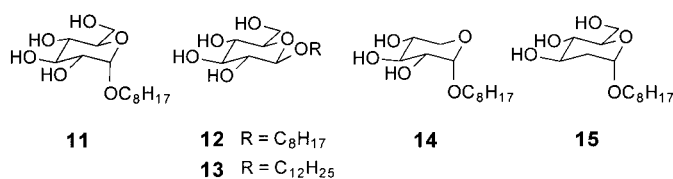
arabinose (**4**) and L-fucose (**5**), but not D-xylose (**6**) or D-lyxose (**7**).^[8] These and other experiments^[9] suggested that the carbohydrates bound to **1** through a ditopic interaction



involving the C(1) and C(4) hydroxy groups in a *cis* arrangement (see structure **8**), promoted (through an uncertain mechanism) by a third *cis*-hydroxy group at C(3).

No fully-oxygenated aldohexose was extracted by **1**, presumably because of the hydrophilic terminal CH_2OH group possessed by all these molecules in their pyranose forms. However, it was shown that the ketohexose fructose **9**^[8] was successfully extracted by **1** and, to a marginally greater extent, by a trimeric analogue of the receptor.^[10] Success was also met with methyl β -D-glucoside (**10**), although the observed stoichiometry of **10**:**1**:2 implied a new complex geometry in this case.^[11] The glucoside was presumed to be sandwiched between two molecules of **1** (Figure 3). Methyl α -D-glucoside was not extracted, possibly because steric hindrance from the axial methoxy group would prevent association with the second molecule of receptor.

The carbohydrates discussed thus far were necessarily studied by extraction because of their insolubility in nonpolar organic solvents. By contrast, certain long-chain alkyl glycosides are freely soluble in, for example, CDCl_3 , and are therefore useful for studies in homogeneous solution.^[12] Octyl glucosides **11** and **12** were both investigated as substrates for receptor **1**.^[11] Complexation could be detected by NMR spectroscopy



(separate signals for free and bound receptor, indicating slow exchange on the NMR time scale), and also by circular dichroism induced in the achiral receptor by the chiral substrates.^[13] Interestingly, the measurements implied substrate:receptor stoichiometries of 4:1, with high degrees of cooperativity. The proposed binding model involved a glucoside at each $\text{OH} \cdots \text{OH}$ site of the receptor, with reinforcement from inter-saccharide hydrogen bonds. The less oxygenated substrates **14** and **15**, unable to make these latter bonds, were not substantially bound by the receptor.

Receptor **1** was found to have one further property of interest, the ability to control the reactivity of one of its

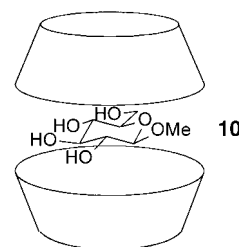
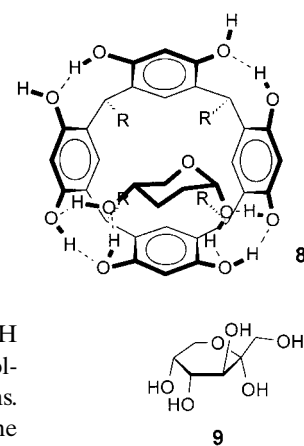
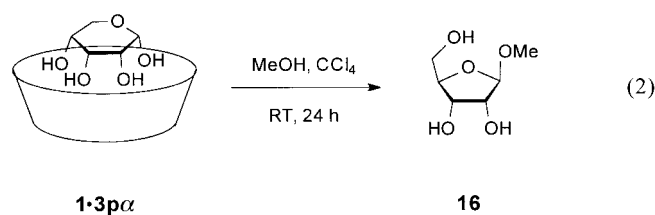


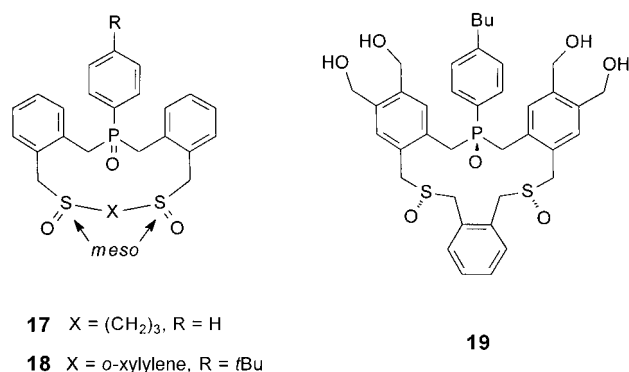
Figure 3. Proposed 2:1 "sandwich" complex between **1** and methyl β -D-glucoside (**10**). Molecules of **1** are represented as truncated cones.

substrates. The complex between **1** and ribose (**3**) in CCl_4 reacted with methanol to give almost exclusively the β -furanoside **16** [Eq. (2)].^[14] This result is somewhat mysterious,



as the ribose is supposed to be bound in the pyranose form **3pa**. However, the selectivity is impressive, as conventional methods generally give a mixture of isomers.

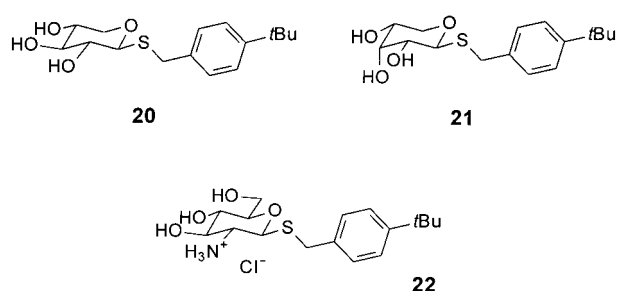
The “face-to-face” binding geometry is also exploited by receptors **17–19**, investigated by Gellman and co-workers. Recognition by **17** and **18** was initially studied by HPLC on



xylose- and ribose-functionalized silica; **17** was more strongly retained by the former, and **18** by the latter. However, NMR binding studies in CD_2Cl_2 , with xyloside **20** and riboside **21** as substrates, yielded rather low association constants ($30\text{--}40\text{ M}^{-1}$) and could not confirm the selectivity.^[15] Having established that the triad of oxygens in **17** and **18** are more suitable for binding alkylammonium ions,^[16] the investigators added peripheral hydroxy groups (giving **19**) and studied binding to hexoseammonium salts such as **22**.^[17] Despite the use of a hydroxylic medium ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 9:1) their results suggested a significant role for $\text{OH}\cdots\text{OH}$ interactions within the complexes.

2.2. Encapsulation by Steroid-Based Receptors: The Cholaphanes

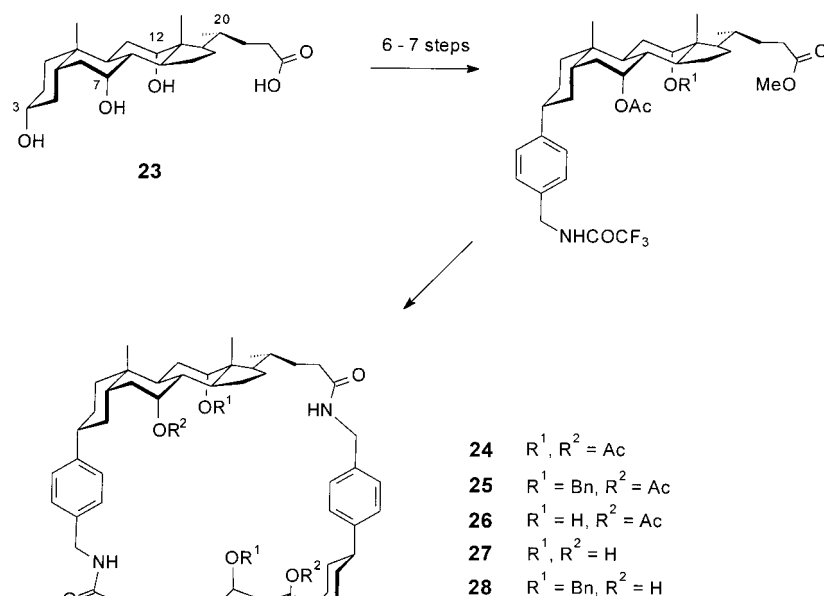
Although well-spaced, the binding sites in the above receptors are *co-directed*, rather than *convergent*. While this arrangement is suitable for certain carbohydrates, it predisposes the system to self-association and to



the complex stoichiometries observed with certain substrates. It also limits versatility, precluding the simultaneous recognition of all groups in all possible carbohydrates. Progress towards carbohydrate receptors with fully tunable recognition properties required frameworks able to fully encapsulate a monosaccharide nucleus, surrounding it with various patterns of preorganized, inward-directed functionality. Seeking large, rigid and functionalized units as building blocks for such frameworks, several groups have exploited the inexpensive steroid cholic acid (**23**).^[18]

The potential of this starting material was demonstrated with the synthesis of the first “cholaphanes”, reported in 1989.^[19] As shown in Scheme 1, these macrocycles **24–28** were prepared from **23** through conversion of the steroidal $3\alpha\text{-OH}$ to a *p*-aminomethylphenyl spacer, followed by cyclodimerization. Two series were synthesized, one in which the steroidal 7- and 12-positions carried the same functional groups (**24**, **27**) and one in which they were differentiated (**25**, **26**, **28**). Although the framework in **24–28** is not entirely rigid,^[20] it is conformationally restricted by the extended polycyclic/aromatic segments stretching from C20 of the steroids to the benzylic methylene carbon atoms. In open conformations it surrounds a substantial cavity bounded by the annular amides and the inward-directed functional groups at C7 and C12.

In initial tests, the cholaphanes were exposed to dodecyl β -D-glucopyranoside (**13**) in CDCl_3 .^[21] For both **27** and **28**,



Scheme 1. Synthesis of “cholaphanes” **24–28** from cholic acid (**23**).

complex formation was clearly indicated by ^1H NMR spectroscopy. Substantial downfield motions were observed for the amide NH signals, strongly suggesting that they were acting as H-bond donors, and other movements pointed to significant changes in the conformations of the macrocycles. The pattern of shifts was consistent with 1:1 stoichiometry, analysis yielding binding constants (K_a) of 1740 and 700 M^{-1} for **27** and **28**, respectively. Although it could not be proven beyond doubt that the carbohydrate entered the cavities of the macrocycles, the sizes of the binding constants, the number of affected proton signals, and molecular modeling studies (Figure 4) all supported this hypothesis.

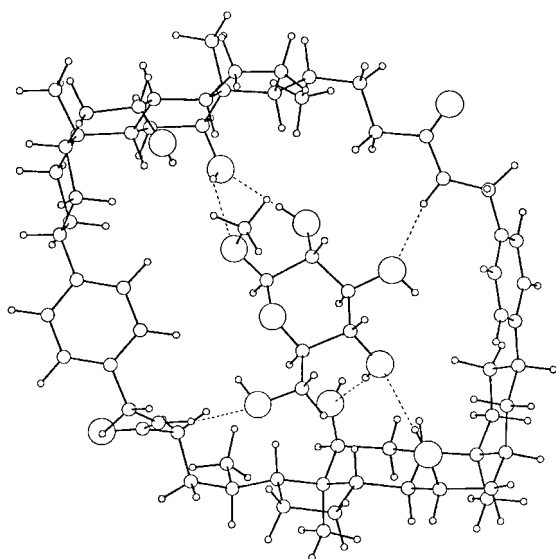
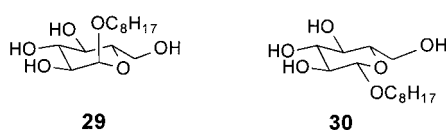


Figure 4. A possible conformation for **27** and methyl β -D-glucoside (employed as a model for **13**) revealed by molecular modeling. Dotted lines represent intermolecular hydrogen bonds, ranging in length from 2.06 to 2.32 Å.

The chirality of the cholaphane framework raised the possibility of enantioselective, as well as diastereoselective, carbohydrate recognition. This was investigated in a series of experiments employing cholaphane **27**, the octyl D-glucosides **11** and **12** and the corresponding L-enantiomers **29** and **30**.^[22]



The results, presented in Table 1, revealed significant diastereoselectivity between **11** and **12** (factor of 5.5) and enantioselectivity between **12** and **30** (factor of 3). The enantioselectivity

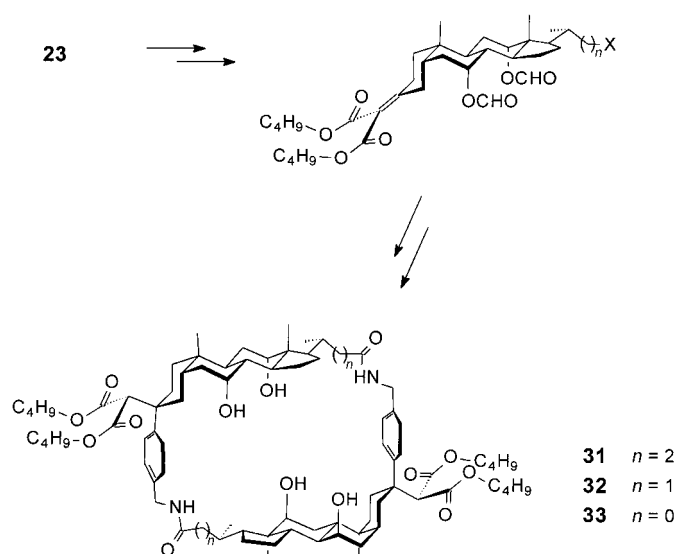
Table 1. Association constants K_a in CDCl_3 between tetrahydrocholaphane **27** and the isomeric octyl glucopyranosides **11**, **12**, **29**, and **30**.^[a]

Glucoside	K_a [M^{-1}]
11 (α -D)	545 ($\pm 4\%$)
12 (β -D)	3100 ($\pm 14\%$)
29 (α -L)	1030 ($\pm 10\%$)
30 (β -L)	1000 ($\pm 14\%$)

[a] Determined by ^1H NMR titration at 298 K.

lectivity is perhaps especially significant as it cannot be ascribed to a difference in carbohydrate solvation energies, or intramolecular hydrogen bonding patterns (see Section 2.3). All such factors are, of course, identical for the two enantiomers.

For a second generation of cholaphanes, improvements were sought in two respects. First, control of framework flexibility should promote enhanced preorganization of binding groups, greater selectivity, and higher binding constants for well-matched substrates. Second, externally directed alkyl chains would guard against insolubility in nonpolar solvents (the solubility of **27** in CDCl_3 had been barely sufficient for the complexation studies). The structural objectives were met with the series of macrocycles **31–33** (Scheme 2), in which



Scheme 2. Synthesis of cholaphanes **31–33** from cholic acid (**23**). X = protected or masked carboxy group.

sequential shortening of the steroidal side-chain culminates in a receptor (**33**) with very little conformational freedom.^[23] Investigations failed to uncover the “well-matched substrate” for **33** (unless it is the cluster of water molecules revealed in the crystal structure; Figure 5), but titrations against glucoside **12** in CDCl_3 confirmed that **31–33** are all competent as

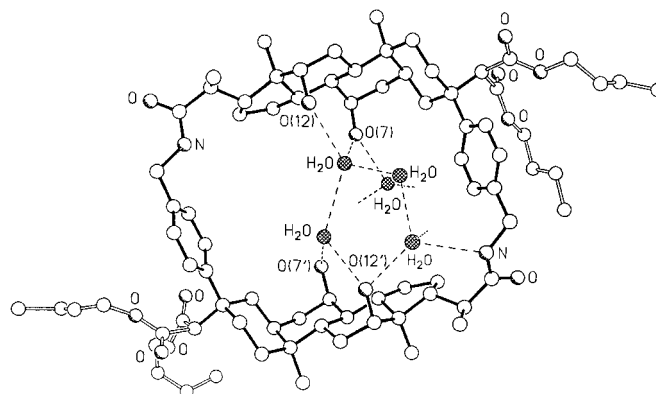
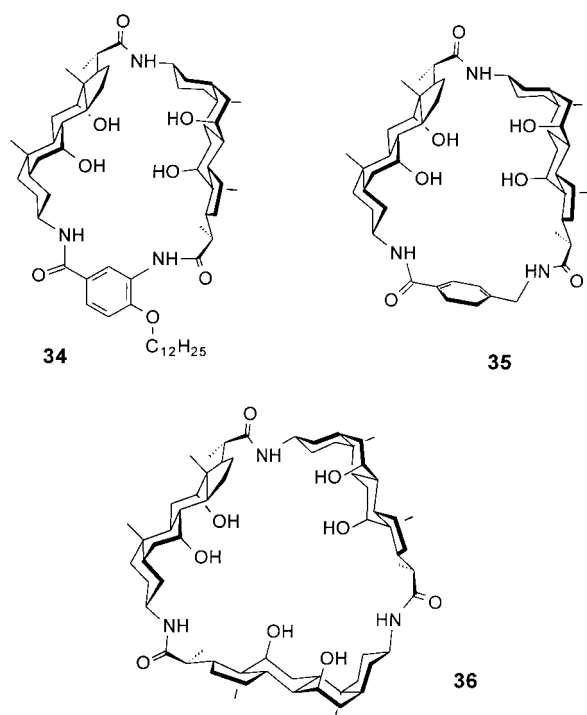


Figure 5. X-ray structure of **33** crystallized from $\text{CHCl}_3/\text{MeOH}$, showing five included molecules of water per formula unit.

carbohydrate receptors ($K_a = 1305$, 600 , and 1560 M^{-1} , respectively). Receptor **33** was able to extract methyl β -D-glucoside (**10**) from aqueous solutions ($1\text{--}2.5 \text{ M}$) into CHCl_3 , significantly outperforming **31** and (surprisingly) **27** in this respect.

2.3. Alternative Frameworks Based on Cholic Acid

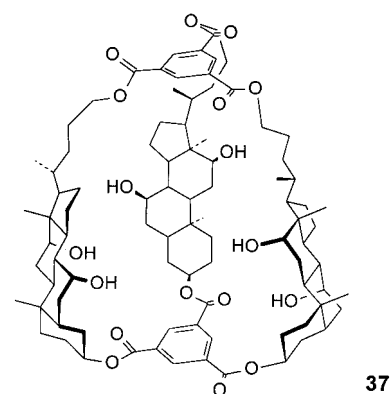
The “bis-nor” cholic acid unit used in **33** was also employed in the design of “cyclocholamides” such as **34–36**.^[24] Truncation of the steroidal side chain results again in frameworks with, at most, very limited conformational mobility. A useful feature of this architecture is the tuning of cavity size possible through variation of the third component of the cyclotrimer.



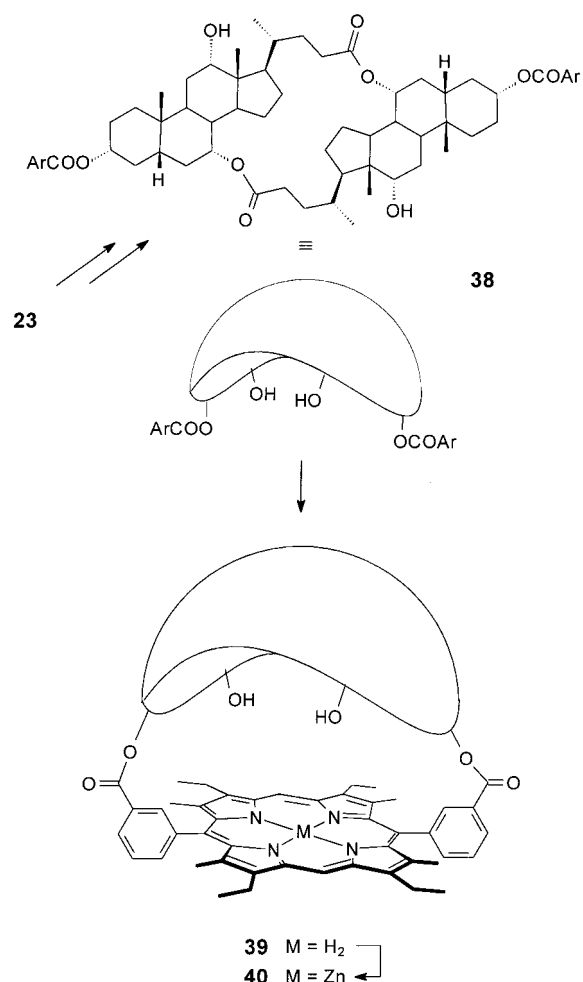
While **35** and **36** both showed evidence of binding to glucoside **12** in CDCl_3 (K_a for **12** + **35** = 750 M^{-1} ; K_a for **12** + **36** not determined due to multiple stoichiometries^[25]) the smaller cavity of **34** proved unable to accept the carbohydrate.

Three molecules of **23** were used, by Kohmoto and co-workers, to construct the “triply bridged cyclophane” **37**.^[26] This macrobicyclic hexaol was tested in CDCl_3 against glucosides **11** and **12**, yielding significant but modest binding constants of 293 and 245 M^{-1} , respectively. Further work is needed to establish the potential of this novel but rather flexible architecture.

Cholic acid was exploited again in the receptors **38–40**, synthesized^[27] (Scheme 3) and investigated^[28] by Bonar-Law and Sanders. This study was useful in that binding constants were measured for a range of organic-soluble glycosides under several sets of conditions. Some of the results are collected in Table 2. The “cyclocholate” **38**, with just two hydroxy groups, was moderately effective in CDCl_3 . Addition of the porphyrin spacer (in **39**) produced a general improve-



ment, apparently without direct involvement of the NH groups in binding. Transferring the binding studies to CH_2Cl_2 lowered the binding constants, presumably because of improved solvation of host and/or guest. Introduction of the metal ion (in **40**) caused changes in the geometries of the



Scheme 3. Preparation of receptors **38–40**. Ar = 3-formylphenyl.

complexes, consistent with additional $\text{Zn} \cdots \text{O}$ interactions, but, rather surprisingly, did not produce substantial increases in K_a . This result was taken to indicate poor complementarity between host and guests, inhibiting the cooperation of all three binding sites. Interestingly, addition of small quantities

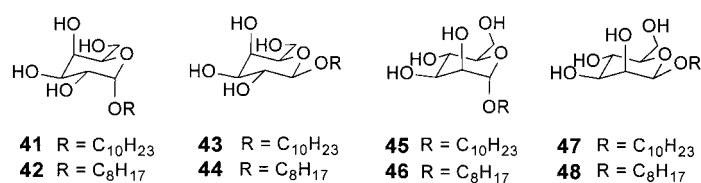


Table 2. Association constants K_a [M⁻¹] between receptors **38–40** and organic-soluble glycosides (solvents as indicated).^[a]

	38	39		40	
	(CDCl ₃)	(CHCl ₃)	(CH ₂ Cl ₂)	(CH ₂ Cl ₂)	(CH ₂ Cl ₂ + H ₂ O) ^[b]
α -D-galactoside 41	39			490	
β -D-galactoside 43				200	
α -D-glucoside 11	450	1740	370	910	
α -L-glucoside 29				260	
β -D-glucoside 12	680	3900	770	1480	6700
α -D-mannoside 45	2300	30 000	7900	7000	12 300
β -D-mannoside 47				5200	18 500

[a] Determined by UV and/or ¹H NMR titration at 295 K. [b] Approximately 0.09 mol L⁻¹ water added to titration solvent.

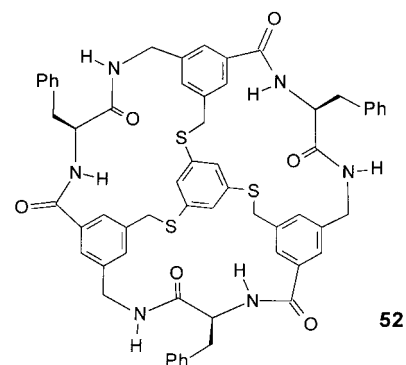
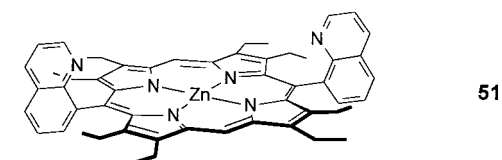
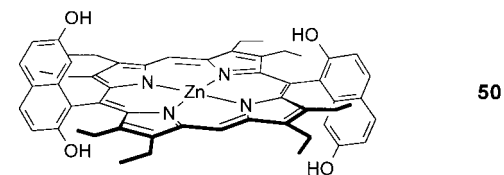
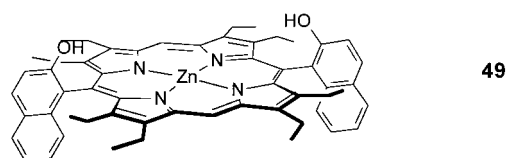
of water or methanol raised the binding constants, presumably by “plugging the gap” between host and guest (a strategy quite widely used by Nature; see Figure 1).

As shown in Table 2, the substrates employed with **38–40** included the glucosides **11**, **12**, and **29**, the galactosides **41** and **43**, and the mannosides **45** and **47**. Although the diastereoselectivities are impressive (e.g. a factor of ca. 60 between mannoside and galactoside binding to **38**), the authors point out that the inherent “stickiness” of some carbohydrates may be greater than others. In particular, intramolecular hydrogen bonding might be especially favorable in some cases, reducing the potential for intermolecular H-bond formation. Indeed, control experiments showed the aggregation tendencies of the glycosides to decrease in the order α -mannoside > β -glucoside > α -galactoside; thus the best substrates were also the best able to self-associate. Having said this, the ability of **40** to discriminate between enantiomers **11** and **29** (factor of 3.5) is unquestionably a specific effect.

2.4. Valleys, Bowls, Rings, and Cages: Further Architectures with Convergent Functionality

The Zn-porphyrin unit in **40** may be seen as a model for the metal centers (Ca²⁺, Mn²⁺ or Mg²⁺) found in certain carbohydrate binding proteins.^[3c] This motif was combined again with H-bonding sites in the “U-shaped” receptors **49–51**, by Mizutani, Ogoshi et al. With octyl β -D-glucoside (**12**) in CHCl₃, these molecules were able to form complexes with K_a = 180, 2090, and 41 400 M⁻¹, respectively.^[29] Receptor **50** (but not **51**) once more increased in potency on addition of a small quantity of hydroxylic solvent.

The macrotricyclic “bowl” **52**, designed by Still and co-workers, provides another means of surrounding small polar molecules with preorganized hydrogen-bonding functionality. Although used mainly for the recognition of peptides and amino acid derivatives,^[30] this receptor is also capable of accepting saccharide substrates.^[31] The macrocycle **52** has



been tested against a range of glycosides in CDCl₃, as illustrated in Table 3.^[32] Judgements on the diastereoselectivity must be tempered by the considerations discussed above. Indeed, it is notable that the general pattern of affinities found

Table 3. Association constants K_a measured in CDCl₃ between receptor **52** and octyl pyranosides.^[a]

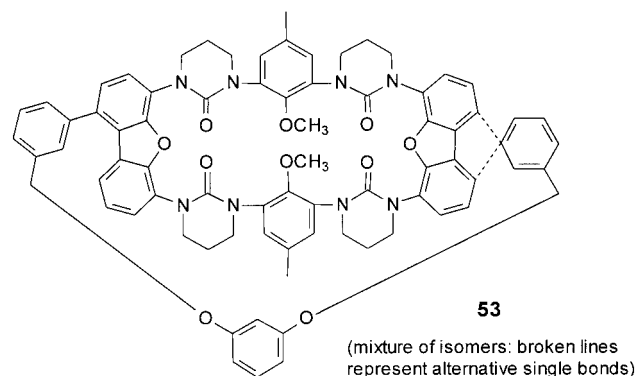
Pyranoside	K_a [M ⁻¹]	Pyranoside	K_a [M ⁻¹]
α -D-galactoside 42	270	β -D-galactoside 44	640
α -D-glucoside 11	380	α -L-glucoside 29	160
β -D-glucoside 12	1770	β -L-glucoside 30	450
α -D-mannoside 46	5800	β -D-mannoside 48	230

[a] Determined by ¹H NMR titration at 296 K.

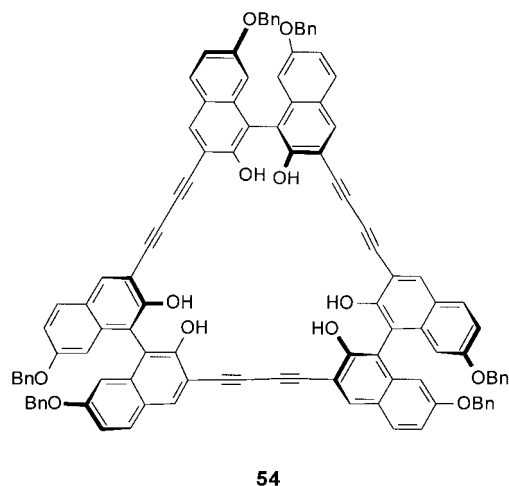
for **38–40** (mannoside > glucoside > galactoside) is repeated with this very different receptor. Nonetheless the enantioselectivity shown for **12** versus **30** (factor of 3.9), and the selectivity between mannoside anomers **46** and **48** (factor of 25) are undoubtedly impressive.

An alternative bowl (or, perhaps more accurately, “basket”) was employed in early work by the group of D. J. Cram.^[33] Receptor **53** (studied as a mixture) possesses a cavity fringed with potent H-bond acceptor groups. They were unable to extract methyl α - or β -D-glucoside from aqueous solution into CDCl₃ (perhaps a reflection of their lack of

H-bond *donor* capability), but significantly promoted the lipophilization of these substrates from the solid state.



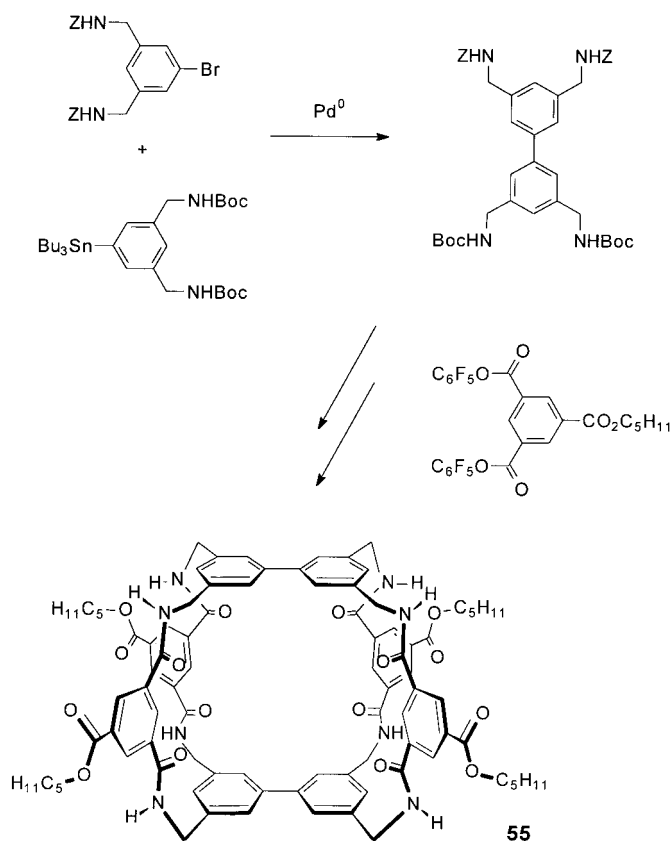
The macrocycle **54** can surround a monosaccharide with six phenolic hydroxy groups.^[34] Though competent as a carbohydrate receptor ($K_a = 370$, 195, and 90 M^{-1} in CDCl_3 with **12**, **11**, and **29**, respectively), it is somewhat overshadowed by its anionic relatives discussed in Section 2.6.



A recent development from the authors' laboratory is the octa-amide **55**.^[35] This new architecture, constructed as shown in Scheme 4, was designed to provide both apolar and polar contacts to a monosaccharide such as glucose (Figure 6). As shown in Table 4, it is capable of binding octyl β -D-glucoside (**12**) with $K_a \approx 1000\text{ M}^{-1}$ in the quite competitive medium of $\text{CDCl}_3/\text{CD}_3\text{OH}$ (92:8), and with $K_a = 300\,000\text{ M}^{-1}$ in pure CHCl_3 . Also notable are its selectivity for β vs. α glucoside (factor of 50 in the former medium), and its ability to dissolve glucose in CHCl_3 . The degree of complementarity between host and guest raises the hope that this system might also succeed in water when the esters are hydrolyzed to carboxylates. However, at time of writing this possibility remains to be tested.

2.5. Specific Motifs for Carbohydrate Recognition: 2-Aminopyridines and Related Substructures

In all the receptors described thus far, designs have focussed on the *disposition* of binding functionality rather



Scheme 4. Synthetic route to octaamide **55**. Boc = *tert*-butoxycarbonyl.

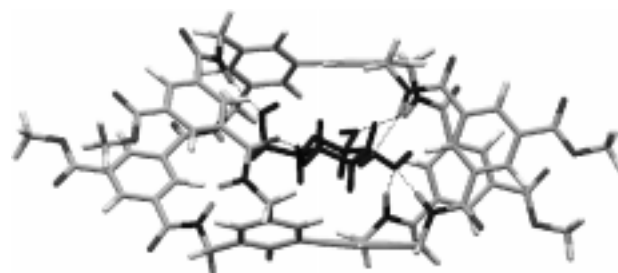


Figure 6. Possible conformation for **55**, modeled as the analogous tetramethyl ester, plus β -D-glucopyranose. Six intermolecular hydrogen bonds are present, shown as broken lines. Hydrogens on carbon atoms 1–3 of the carbohydrate are positioned to form close CH- π interactions with the host.

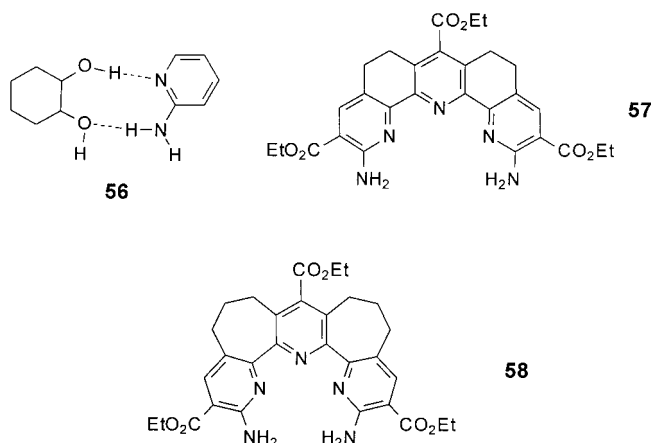
Table 4. Association constants $K_a[\text{M}^{-1}]$ between receptor **55** and organic-soluble glycosides (solvents as indicated).

	$\text{CDCl}_3/\text{CD}_3\text{OH}$ (92:8) ^[a]	CHCl_3 ^[b]
β -D-glucoside 12	980 ($\pm 2\%$)	300 000 ($\pm 6\%$)
α -D-glucoside 11	20 ($\pm 23\%$)	13 000 ($\pm 8\%$)
β -D-galactoside 44	220 ($\pm 5\%$)	110 000 ($\pm 12\%$)

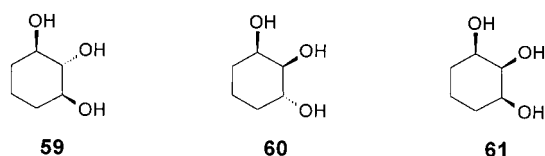
[a] Determined by ^1H NMR titration at 303 K. [b] Determined by fluorescence titration.

than its precise nature. An alternative approach is to seek recognition motifs likely to be specifically effective for carbohydrates and then, as a second step, incorporate them in more elaborate frameworks. The X-ray crystallography of protein-carbohydrate complexes provides the obvious starting point for such a search. Arguably it is only moderately

helpful, in that most conceivable hydrogen-bonding patterns seem to contribute to natural carbohydrate recognition (see Figure 1).^[36] However, several groups have noted the potential of doubly hydrogen-bonding groups for binding vicinal diols, and have discerned a predominance of such groups (primary amides, carboxylates, and guanidiniums) in natural carbohydrate binding sites. Anslyn and co-workers have exploited the 2-aminopyridine unit as a heterocyclic analogue of the asparagine/glutamine primary amide side chain. In principle it can bind a diol as in **56**, and can be incorporated in rigid, preorganized structures such as **57** and **58**.^[37] The latter

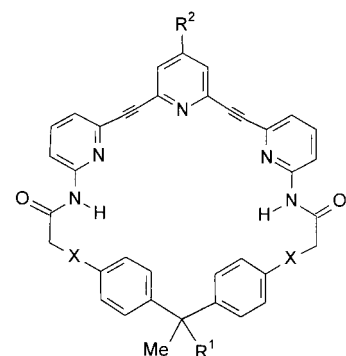
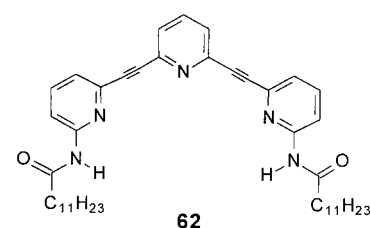


receptors were tested in CDCl_3 against *cis*- and *trans*-1,2-cyclohexane diols ($K_a = 5\text{--}17\text{ M}^{-1}$), and the triols **59**–**61** ($K_a = 35\text{--}110\text{ M}^{-1}$). It is notable that, of the triols, the all-*trans*



isomer **59** was bound more than twice as strongly as **60** and **61**. Given that *trans* 1,2-diols exhibit weaker intramolecular hydrogen bonding than their *cis* isomers,^[38] this result provided early evidence for a linkage between strong intramolecular hydrogen bonding and reduced “stickiness” in carbohydrate derivatives (see Section 2.3). The study included just one actual carbohydrate derivative, the glucoside **13**, which was shown to bind to receptor **58** with $K_a = 190\text{ M}^{-1}$.

The pattern of H-bonding “valencies” in **57** and **58** is repeated, with rather broader spacing, in the receptors **62**–**65**. Developed by Inoue et al. to target β -ribofuranosides, they were found to bind the methyl furanoside **16** in CDCl_3 with $K_a = 30, 2400, 5200$, and 50 M^{-1} , respectively.^[39] This sequence reflects the a) value of macrocyclization in preorganising binding functionality, b) the potential for tuning H-bonding power through changes in the basicity (or acidity) of functional groups (in this case by addition of the alkoxy group to the central pyridine ring), and c) the damage which can be caused by intramolecular hydrogen bonding within a receptor (in this case a pair of $\text{NH}\cdots\text{O}$ bonds in receptor **65**). The binding geometry proposed for the complex between **16** and **63** is illustrated in Figure 7. Macrocycle **64** was able to



63 $R^1 = \text{Me}$, $R^2 = \text{H}$, $X = \text{CH}_2$

64 $R^1 = i\text{Bu}$, $R^2 = \text{OnBu}$, $X = \text{CH}_2$

65 $R^1 = \text{Me}$, $R^2 = \text{H}$, $X = \text{O}$

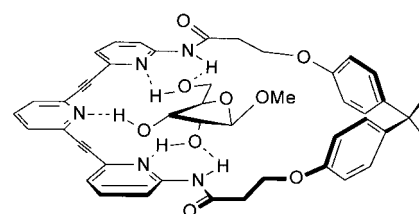
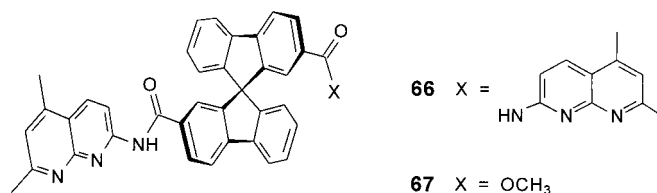


Figure 7. Receptor **63** complexed to ribofuranoside **16** in the geometry hypothesized by Inouye et al.

solubilize the pentoses ribose (**3**), deoxyribose, arabinose (**4**), xylose (**6**), and lyxose (**7**) in CDCl_3 , as well as the ketohexose fructose (**9**). The aldohexoses glucose, mannose, and galactose were, however, unaffected.

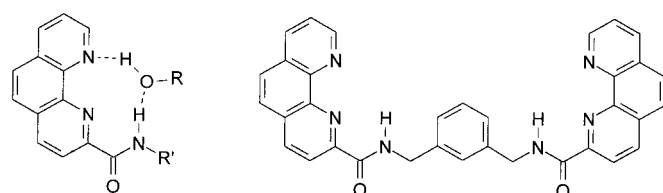
An “extended analogue” of the 2-aminopyridine unit was employed by Diederich and co-workers in receptors **66** and **67**.^[40] These “chiral clefts” were prepared in both enantio-



meric forms and shown to bind the octyl glucosides **11** and **12**, and mannoside **46**, in CDCl_3 . Binding constants ranged between 180 and 1270 M^{-1} , in the now-familiar sequence α -glucoside $<$ β -glucoside $<$ α -mannoside (cf. Tables 2 and 3). Perhaps surprisingly receptor **67**, with only one naphthyridine,

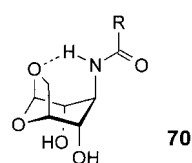
proved essentially as potent as **66**. However, while **66** showed significant enantioselectivity (e.g. factor of 2 for the α -glucosides), **67** was ineffective in this respect.

Two-point binding of a single hydroxy group is proposed for phenanthroline carboxamides **68**.^[41] This motif has not yet been employed to bind carbohydrates, but has been incorporated in receptors such as **69** targeted at cyclohexanediols. Receptor **69** is complementary to *cis*-1,3-cyclohexanediol,



68-ROH

69

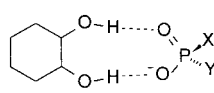


70

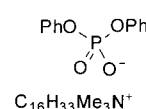
binding this substrate with $K_a = 1150 \text{ M}^{-1}$ in CDCl_3 [cf. 13 M^{-1} for cyclohexanol + **68** ($R' = \text{CH}_2\text{Ph}$)]. The conformationally restricted diol **70** is also under development as an “interaction unit” for OH recognition.^[42]

2.6. Recognition by Anionic Centers: The Phosphate-Diol Motif

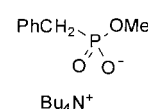
Arrays of ionic centers have certain advantages in receptor design. Assuming they are of the same charge, the centers cannot be self-complementary. Rather, they should repel each other and thus help to maintain a well-defined cleft or cavity. Moreover, they often form exceptionally strong hydrogen bonds due to their acidity (if cationic) or basicity (if anionic). Several groups have explored the potential of anionic centers for carbohydrate recognition.^[34, 43, 45–47] Particular attention has been paid to phosphates and phosphonates, which can participate in receptor frameworks while providing two H-bond acceptor sites capable, in principle, of binding diol units as in **71**.^[44] As illustrated in Table 5, the simple mono-phosph(on)ate receptors **72–75** have been tested against alkyl β -D-glucosides and, in the case of **72** and **73**, several other alcohols and polyols. Phosphonates **73** and **74**, due to Das and Hamilton,^[45, 46] are seen to be remarkably potent,



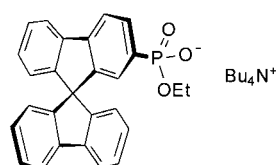
71 X, Y = O, C



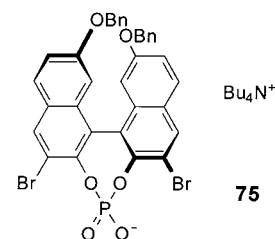
72



73



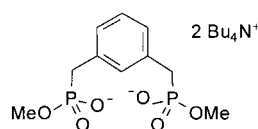
74



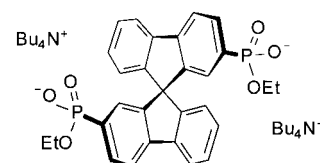
75

especially considering the competitive nature of the CD_3CN solvent. Comparisons between the different substrates reveal a strong enhancement of K_a on moving from alcohol to vicinal diol, and a further substantial increase between diol and carbohydrate.^[43, 45]

Receptors **73–75** have been “extended” to give the polytopic analogues **76–79**. The second phosphonate group in **76** was found to raise binding constants by factors of 4–9



76



77

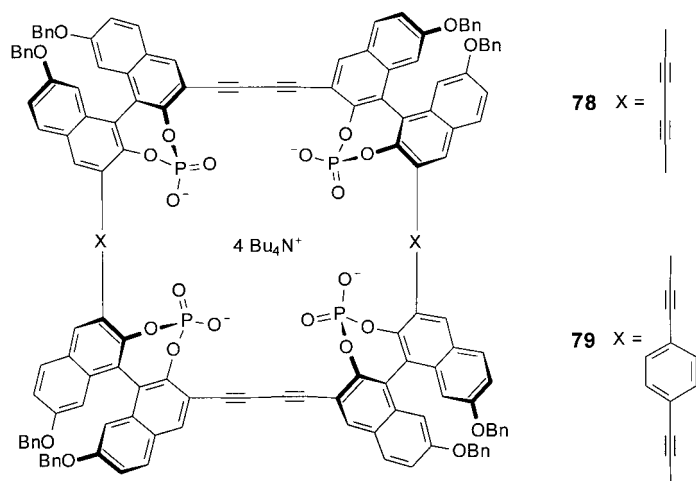
with octyl pyranosides as substrates.^[45] Larger increments (factors of 9–17) were observed for the more rigid spirobi-fluorene framework (**74** vs. **77**).^[46] Although the chiral **77** was studied as a racemic mixture, analysis of the data allowed enantioselectivities to be estimated. The ratio of 5.1 for the K_a values with glucoside **12** is the highest yet reported for a biomimetic carbohydrate receptor.

Studies by the Diederich group on tetraphosphate **78** were complicated by higher stoichiometries, but allowed an estimate of 15000 M^{-1} for the binding constant to glucoside **12** in $\text{CD}_3\text{CN}/\text{CD}_3\text{OD}$ (98:2).^[34] It is notable that monomer **75** showed no detectable binding to **12** after addition of the hydroxylic cosolvent. The larger macrocycle **79** was inves-

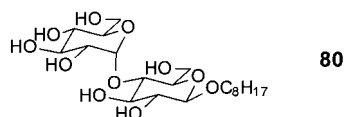
Table 5. Association constants K_a between phosph(on)ates **72–75** and hydroxy compounds.^[a]

Receptor	Solvent	T [K]	Substrate	K_a [M^{-1}]	Ref.
72	CDCl_3 ^[b]	298	cyclohexanol	0.9	[43]
72	CDCl_3 ^[b]	298	<i>trans</i> -cyclohexane-1,2-diol	13–19 ^[c]	„
72	CDCl_3 ^[b]	298	dodecyl β -D-glucoside 13	470–900 ^[c]	„
73	CD_3CN	293	cyclohexanol	11	[45]
73	CD_3CN	293	<i>trans</i> -cyclohexane-1,2-diol	330	„
73	CD_3CN	293	octyl β -D-glucoside 12	4400	„
74	CD_3CN	293	octyl β -D-glucoside 12	3220	[46]
75	CD_3CN	300	octyl β -D-glucoside 12	170	[34]

[a] Determined by ^1H NMR titration. [b] Containing water at concentrations of 2.5–3 mM. [c] Estimates of K_a varied depending on choice of NMR signal to be analyzed.

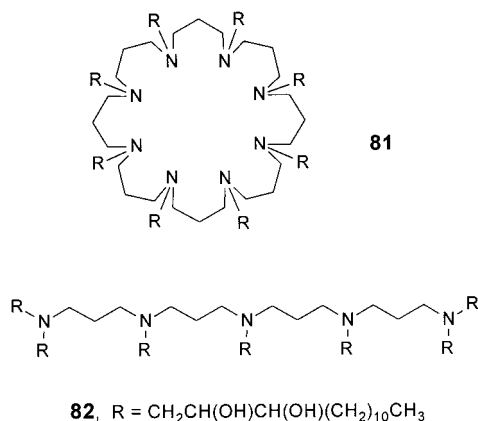


tigated in $\text{CD}_3\text{CN}/\text{CD}_3\text{OD}$ (88:12), a still more polar solvent system. Binding to monosaccharide **12** was suppressed in this medium, but disaccharides such as **80** formed 1:1 complexes with K_a values between 10750 and 12500 M^{-1} .^[47]



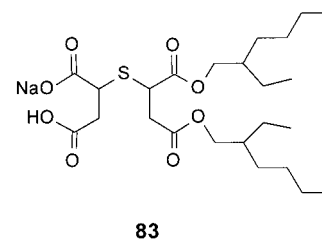
2.7. "Recognition" without Preorganization: Receptors Lacking Well-Defined Binding Sites

There remain a few systems which bind carbohydrates in organic media by multiple interactions, but do not provide geometrically defined clefts or cavities for their substrates. For example the flexible octa-amine **81** was found by Aoyama and co-workers to extract ribose, fructose, and glucose from 3 M aqueous solutions into CCl_4 .^[48] The glucose complex exhib-



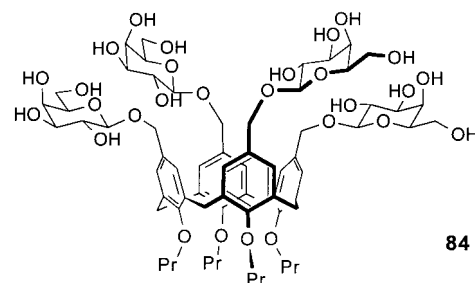
ited 1:1 host-guest stoichiometry, and did not contain significant coextracted water (in the absence of carbohydrate, ca. 40 equivalents of water were solubilized in the organic medium). The acyclic analogue **82** was also effective to some degree. In a study by Greenspoon and Wachtel, reverse

micelles composed of surfactant **83** were also shown to solubilize glucose, in this case by dissolving the monohydrate in CDCl_3 .^[49] For the molecular architect, it is sobering to

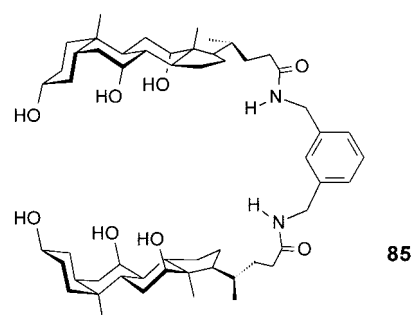


consider that, until the advent of **55**, these were the *only* reports of biomimetic "recognition" of this especially challenging and hydrophilic substrate.

The tetragalactosylcalixarene **84** of Dondoni et al. probably also belongs in this section, possessing a rigid core but rather flexible polar extensions. NMR studies in CD_3OD and



$(\text{CD}_3)_2\text{SO}$ produced no evidence of binding to neutral carbohydrates, but a positive (though unquantified) result for D-glucosamine hydrochloride.^[50] Finally, cholic acid reappears in the flexible "tweezer" **85**, from the group of Burrows. Using variable-temperature NMR this molecule was shown to bind pentyl β -D-glucoside in CDCl_3 ,^[51] foreshadowing the studies on steroid-derived macrocycles discussed in Section 2.2.



3. Carbohydrate Recognition in Aqueous Solution

If carbohydrate recognition is nontrivial in apolar media, it presents an exceptional challenge in water. In aqueous media, a carbohydrate receptor must expel a cluster of water molecules from its binding site before it accepts its substrate.

Yet the typical carbohydrate largely resembles a water cluster, differing only in the precise positioning of hydroxy groups and the presence of small patches of hydrophobic surface. As discussed below, the fact of natural carbohydrate recognition illustrates the effectiveness of preorganization and probably also the subtle, still mysterious nature of water as a solvent. However, with binding constants for protein-monosaccharide complexes apparently limited to about 10^7 M^{-1} ,^[52] even Nature finds carbohydrate recognition difficult.

3.1. The Biological Background; Carbohydrate Recognition in Nature

Natural carbohydrate recognition is mediated by various classes of protein. Leaving aside the enzymes whose function is to both bind and transform carbohydrate substrates, important categories are; a) antibodies, of which over 70% (when induced by whole cells) are normally directed towards oligosaccharide epitopes,^[53] b) the lectins, which are used by animals, plants, bacteria and viruses for the recognition of cell-surface oligosaccharides, and c) the bacterial periplasmic proteins which are involved in carbohydrate transport and chemotaxis in Gram-negative organisms. The most intensively studied are the lectins, because of their controlling influence in many biological processes.^[1c-e, 3b,c] Lectins were originally isolated from plants, and exploited for their ability to agglutinate certain types of cell (dependent on the cell-surface carbohydrates present) and also to induce mitosis. Well-studied examples are concanavalin A, from the legume *Canavalia ensiformis*, and "GS-IV" from *Griffonia simplicifolia*.^[4a,c] Paradoxically, their precise role in plants is still somewhat mysterious.^[1d, 3c] However, it has become clear that lectins are ubiquitous in the natural world, and are widely employed for cell recognition and adhesion. Medicinally important examples are the bacterial and viral lectins which initiate the infection of target cells (e.g. influenza haemagglutinin), the collectins, such as "mannose-binding protein", which bind to oligosaccharides on certain invading organisms as part of an antibody-independent immune response,^[1e] and the selectins which mediate the recruitment of leukocytes into inflammatory tissue sites.^[1c] Although of less general relevance, the bacterial periplasmic proteins are significant because of their high binding constants to monosaccharides (see below), and their suitability for X-ray crystallography.^[3a]

Carbohydrate recognition by all three classes of protein has been investigated in the solid state by crystallography, and in solution by various techniques including, in particular, microcalorimetry. Structural studies on the lectins reveal shallow binding sites, consistent with their need to recognize sugar residues protruding from cell surfaces.^[3c] Binding to monosaccharides is usually weak (in biological terms), with K_a values typically in the region 10^3 – 10^4 M^{-1} .^[1c, 4b] However, extended binding regions lead to much stronger attachment to oligosaccharides in some cases,^[54] while in others the provision of multiple binding sites and/or the tendency of lectins to aggregate^[55] results in high affinities for multivalent substrates ("glycoside cluster effect").^[1e] The limited structural data on

antibody-carbohydrate complexes again shows the carbohydrates in clefts at the protein surface.^[56] By contrast, the bacterial periplasmic proteins can fully surround their monosaccharide substrates and are correspondingly more potent, with K_a generally between 10^6 and 10^7 M^{-1} .^[3a]

Protein-carbohydrate recognition is generally established through networks of hydrogen bonds and complementary contacts between nonpolar surfaces. Interestingly, the non-polar residues on the protein are almost always aromatic, suggesting a role for specific CH- π interactions.^[57] For the lectins and periplasmic binding proteins, most of the hydrogen bonds involve planar, multivalent side chain groups (Asn, Asp, Glu, Gln, Arg, His; cf. Figure 1).^[3a,c] In contrast, it seems that antibodies make greater use of main chain amides for hydrogen bonding.^[56] The most general H-bonding motif appears to be $\text{NH}\cdots\text{OH}\cdots\text{O}=\text{C}$. Although this subsumes many possibilities, it usefully highlights the importance of cooperative hydrogen bonding by the sugar hydroxy groups. While side chain hydroxy groups are rare in carbohydrate binding sites, it is very common to find water molecules in specific bridging positions between protein and substrate. Metal ions such as Ca^{2+} are required for full activity of many lectins (including concanavalin A), but only for the "C-type lectins" (e.g. mannose-binding protein) have direct metal-carbohydrate interactions been observed.

Calorimetric studies have shown that protein-carbohydrate complexation provides an excellent example of "enthalpy-entropy compensation".^[4d, 58] In data tabulated by Toone,^[4b] binding enthalpies vary from -2.0 to $-22 \text{ kcal mol}^{-1}$, while free energies range between -2.8 and $-8.5 \text{ kcal mol}^{-1}$. The spread of binding free energies is reduced by entropies which decrease in step with the enthalpies. Thus, a plot of $-\Delta H^\circ$ versus $-T\Delta S^\circ$ reveals points scattered fairly closely about a line of gradient 1.05 (Figure 8). At one end of

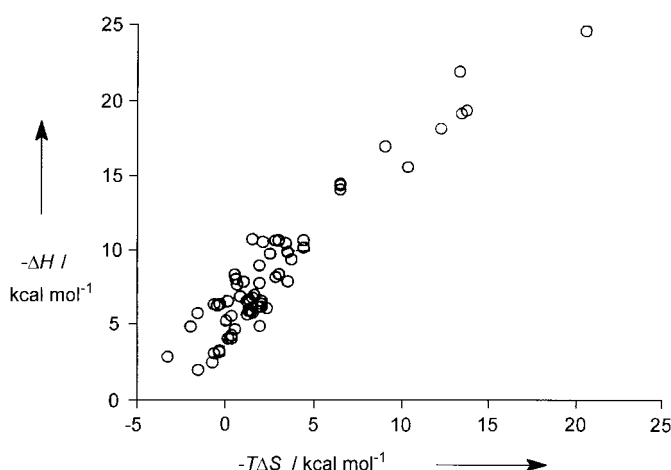
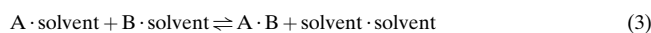


Figure 8. Enthalpy-entropy compensation plot for antibody/lectin-carbohydrate interactions. The slope of the plot is 1.05, with a correlation coefficient of 0.95. (Adapted from ref. [4b].)

the scale ($-\Delta H^\circ$ = small), ΔS° is just positive (favouring binding). However, for most of the range ΔS° is negative and opposes complexation.

3.2. The Driving Force for Natural Carbohydrate Recognition

Despite the wealth of structural data on carbohydrate–protein complexes, the driving force for their formation is still uncertain. The issue relates to wider debates on the nature of the hydrophobic effect, and the effectiveness of hydrogen bonding for molecular recognition in aqueous solution. In somewhat simplistic terms, the central question may be expressed as follows.^[59] The formation of a 1:1 complex can be represented by the equilibrium in Equation (3). If all



depicted interactions are similar in strength, equilibrium lies well to the left because of the large excess of solvent. If reaction in the forward direction is to be favored, it must generally be driven *either* by an especially *strong* interaction between A and B (intrinsic binding) *or* by especially *poor* interactions between A and/or B and solvent, compared to the interactions between the solvent molecules themselves (solvophobic binding).

For the recognition of polar molecules in nonpolar solvents, it is usually clear that intrinsic binding is dominant. For the recognition of nonpolar molecules in water, it is equally clear that binding is essentially solvo(hydro)phobic. However, for the recognition of carbohydrates in water it is a) remarkable (at first sight) that Nature succeeds at all, and b) uncertain whether intrinsic or hydrophobic binding is more important. On the one hand, the similarity between the carbohydrate hydroxy groups and the competing water molecules underlay an early suggestion (later modified) that hydrophobic interactions between nonpolar patches on host and guest provided the major driving force.^[4c] On the other hand, the H-bond networks observed by crystallography focussed attention on intrinsic binding.^[3a] It should be noted, however, that crystallography by itself cannot easily distinguish between the options. Complex formation must inevitably be favoured by complementarity between receptor and substrate, whatever the source of the overall binding free energy.^[4b]

The most prudent assumption must be that both intrinsic and hydrophobic binding contribute significantly to biological carbohydrate recognition. It is undoubtedly credible that the preorganized polar groups within a binding site could make exceptionally favorable contacts with a carbohydrate substrate. Equally, as argued persuasively by Lemieux et al.,^[4a,c, 60] the arrangement of polar and nonpolar groups at a “poly-amphiphilic surface” (such as a carbohydrate or its binding site) is not necessarily compatible with effective hydration. While polar groups may be strongly bound to water molecules, there may be no efficient way to interconnect the first hydration shell. Displacement of these water molecules could provide an important driving force for complex formation. The negative enthalpies and entropies of formation of most protein–carbohydrate complexes might be thought to preclude dependence on the hydrophobic effect (which is generally understood to promote association through an *increase* in entropy).^[61, 62] However studies in supramolecular chemistry and biochemistry have revealed examples of

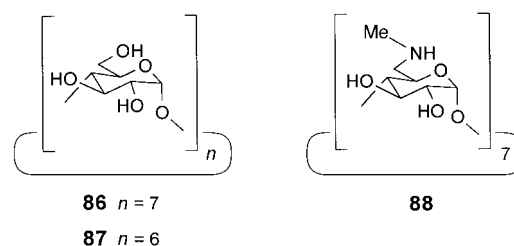
complexation in water which are clearly driven by solvation differences, yet show strongly negative ΔH° and $T\Delta S^\circ$.^[63, 59] Moreover, Chervenak and Toone have used calorimetric data for several lectin carbohydrate interactions in H₂O versus D₂O to infer directly that solvent reorganization provides an *enthalpic* driving force for binding.^[64]

3.3. Recognition in Model Systems

3.3.1. Pentoses, Hexoses, and Methyl Glycosides

As emphasized above, the biomimetic recognition of carbohydrates presents exceptional challenges which remain to be overcome. To date, most studies in water have taken one of two approaches. On the one hand they have considered substrates for which the challenge is minimized, for example oligosaccharides with extended hydrophobic surfaces, or monosaccharides with hydrophobic appendages. On the other they have employed “difficult” monosaccharide substrates while adopting methods capable of detecting very small binding constants. Work in the latter category is described in this section, while the remainder is covered later.

Several groups have investigated the binding of monosaccharides to β -cyclodextrin (**86**).^[65–69] This host is sufficiently large to encapsulate a sugar molecule, and appears to possess the necessary amphiphilicity. Unfortunately its spectroscopic



properties give little help to studies of carbohydrate recognition, which have therefore employed calorimetry or indirect methods involving displacement of fluorescent dyes. There are inconsistencies in the reported data,^[68] but the majority view is that the binding of hexoses is undetectable^[65, 66] or extremely weak^[68] (e.g. $K_a = 0.6 \text{ M}^{-1}$ for D-glucose),^[70] while that of pentoses is slightly stronger (e.g. $K_a = 5.3 \text{ M}^{-1}$ for D-ribose,^[65] estimates of $1^{[65]}$ and $17^{[66]}$ M^{-1} for D-xylose). The hepta(methylamino) analogue **88** was also shown to bind D-ribose, with $K_a = 26 \text{ M}^{-1}$.^[71]

α -cyclodextrin (**87**) possesses a smaller cavity which can only partially accept a pyranose nucleus. Nonetheless, a calorimetric study on this host, performed by Danil de Namor and co-workers, revealed quite significant binding constants to hexoses as well as pentoses.^[66] As shown in Table 6, binding was found to be entropy-driven, with extremely small negative enthalpies (through which complex formation was detected). It is interesting to note a) that the balance between ΔH° and ΔS° concurs with the entropy–enthalpy plot in Figure 8, and b) that the general “order of stickiness” mannose > glucose > galactose proposed for organic media

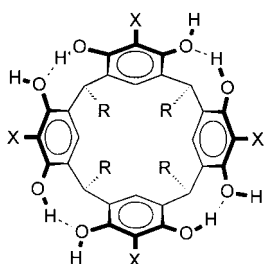
Table 6. Association constants K_a and thermodynamic parameters, determined by microcalorimetry, for binding of monosaccharides to α -cyclodextrin (**87**) at 298.15 K in aqueous solution.^[a]

Monosaccharide	K_a [M ⁻¹]	ΔG° [kJ mol ⁻¹]	ΔH° [kJ mol ⁻¹]	ΔS° [J K ⁻¹ mol ⁻¹]
D-glucose	36	-8.9	-0.14	29.4
D-fructose	52	-9.8	-0.05	32.8
D-mannose	59	-10.1	-0.11	33.5
D-galactose	15	-6.8	-0.32	21.7
D-xylose	37	-8.9	-0.09	29.8
L-xylose	117	-11.8	-0.12	39.2

[a] Errors in ΔH° estimated at ± 10 –20%. K_a values uncertain by factors of 1.3–2.0.

(see Section 2.3) is repeated here for a study in water. The enantioselectivity recorded for xylose is also of interest. These results are remarkable in that they represent the only examples to date of significant noncovalent binding of the common hexoses to a model system in water. Thus far the measurements have been made by just one technique operating at the limit of its sensitivity. Further studies using other methods could be illuminating, and should be encouraged.

Following their success with **1** in organic media, the group of Aoyama investigated the calixarenes **89**–**91** in water.^[72, 73] Though ineffective for most pentoses and hexoses, prototype



89 X = H R = CH₂CH₂SO₃Na

90 X = CH₃

91 X = OH

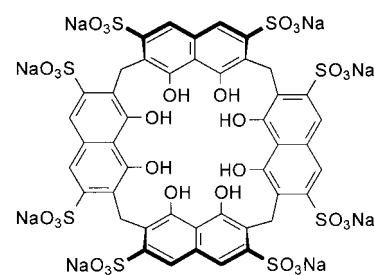
89 showed significant affinities for certain alcohols, and to some extent for the more lipophilic monosaccharides.^[72] As shown in Table 7, substitution with methyl or hydroxy groups improved potency,^[72] as did the removal of two or four protons.^[73] This and other data was used to argue the case for a specific CH- π interaction between host and guest.

“Cyclotetrachromotropylenes” (**92**), studied by Poh and Tan, is an interesting variation on the calixarene theme. An extended hydrophobic surface is combined with 16 water-solubilizing functional groups. Its cleft-shaped inner surface

 Table 7. Selected association constants K_a for binding of monosaccharides to water-soluble calixarenes **89**–**91**.^[a]

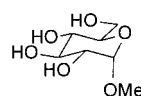
	89	90	91	89 ²⁻	89 ⁴⁻
D-arabinose	0.85	2.1	2.5		
D-2-deoxyribose	1.2	4.9	3.9		
D-fucose	1.8	6.0	8.4	16	26

[a] Determined by ¹H NMR titration at 298 K.

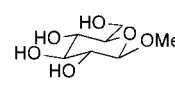


92

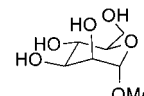
appears better suited to linear, as opposed to cyclic, alcohols, as evidenced by K_a values of 3000 M⁻¹ to butanol, 2500 M⁻¹ to hexanol, and 700 M⁻¹ to cyclohexanol. However, while showing no ability to bind xylose, glucose, or mannose, it gave significant binding constants of 28, 6, and 75 M⁻¹ to methyl α -D-glucoside (**93**), β -D-glucoside (**10**), and α -D-mannoside (**94**), respectively.^[74]



93



10

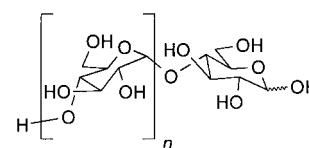


94

3.3.2. Oligosaccharides

Though structurally complex, oligosaccharides are generally easier to bind than monosaccharides because of their extended surface areas. Indeed, both amyloses^[75] and, especially, cycloamyloses (cyclodextrins)^[69] associate (as hosts) with a range of molecules in aqueous solution. While all these phenomena are relevant to carbohydrate recognition, we focus here on cases where the oligosaccharides may be seen as “targets”.

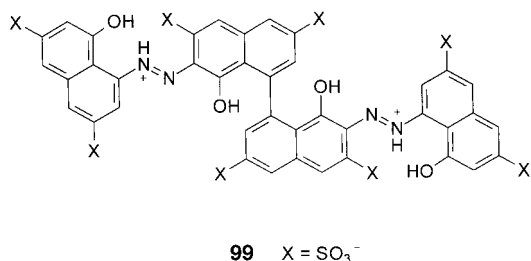
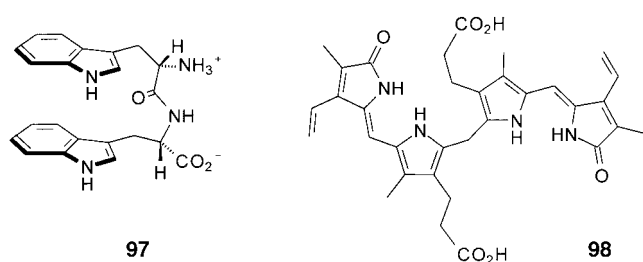
Use of maltose (**95**) and maltotriose (**96**) as substrates allows detectable binding to acyclic, relatively non-preorganized hosts. Both caused fluorescence enhancement in L-tryptophanyl-L-tryptophan (**97**), an interesting (if primitive) model for the apolar motifs found in many natural carbohydrate binding sites. Titration data was consistent with 1:1 binding, but with K_a values of just 1 M⁻¹ for **95** and 8 M⁻¹ for **96**.^[76] A study employing CD spectroscopy revealed that bilirubin (**98**) can also associate with **95** and **96**, as well as other di- and oligo-saccharides (but not glucose).^[77]



95 n = 1

96 n = 2

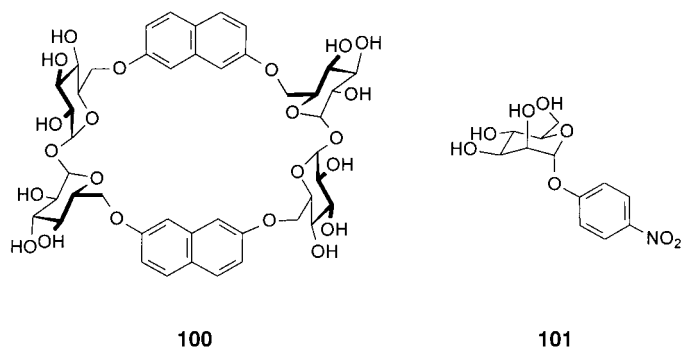
Cyclotetrachromotropylene (**92**) has been found to bind cyclodextrins, with K_a = 85–140 M⁻¹.^[78] Arguments based both on NMR spectroscopy and molecular models suggest that **92** acts as the host, providing a groove-shaped binding site which can accept the exterior of a cyclodextrin ring. Its linear relative “calchichrome” (**99**) is even more effective (K_a =



$380\text{--}570\text{ M}^{-1}$),^[79] although in this case the mode of complexation is perhaps less certain.

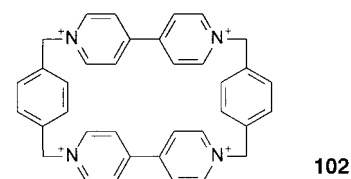
3.3.3. Weak Interactions Probed through “Enforced Proximity”

Weak interactions, such as those involved in carbohydrate recognition, may be detected as modulations of stronger binding forces. If aryl glycosides are used as substrates, the aryl units may be paired with hydrophobic cavities to give reliable binding motifs which can position the carbohydrate close to receptor functionality. This approach has been adopted, in particular, by the group of Penadés, who have studied the binding of *p*-nitrophenyl glycosides to α -cyclodextrin (**87**) and the “glycophane” **100**.^[80] In the case of α -cyclodextrin, the carbohydrate moieties generally lowered complexation relative to *p*-nitrophenol (PNP). By contrast, the PNP glycosides bound more strongly to **102** than did PNP or 1-(*p*-nitrophenyl)glycerol. The additional binding energy (relative to PNP) was in the range $4.6\text{--}7.5\text{ kJ mol}^{-1}$, and was greatest for axial glycosides such as α -mannoside **101**.

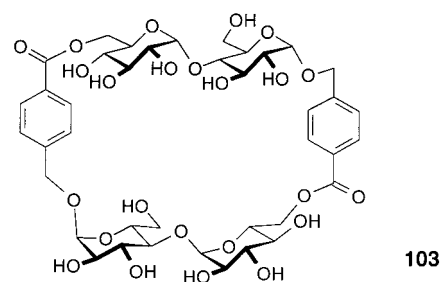


Intermolecular NOEs between carbohydrate residues in **100** and **101** supported the notion that carbohydrate–carbohydrate interactions were responsible for the higher affinities. In

related work the binding of phenyl glycosides to cyclophane **102** was studied by Smith and Stanley.^[81] In this case the equatorial glycosides were more strongly bound, probably for steric reasons.^[82]



Alternatively, weak interactions can sometimes be studied *within* molecules, taking advantage of covalent bonding to enforce proximity. The glycophane **103** has been thus used, in a demonstration of carbohydrate–arene stacking. NMR spec-



tra in D_2O revealed significant upfield displacements of certain carbohydrate signals, consistent with a closed conformation placing one of the pyranose rings in contact with the aromatic spacer. The shifts were not observed in $[\text{D}_6]\text{DMSO}$ or CD_3OD , confirming the hydrophobic nature of the interaction.^[83]

3.4. Carbohydrate Recognition at Surfaces

Finally, it should not be forgotten that natural carbohydrate recognition often takes place at cell surfaces.^[54b] It is well-accepted that water molecules behave atypically in the vicinity of an interface, with significant consequences for noncovalent interactions. In particular, it seems that hydrogen bonding may be far stronger at a hydrated surface than in bulk water.^[84] Kunitake et al. have studied the binding of carbohydrates from aqueous solution to monolayers of **104–106**, as well as Aoyama’s calixarene **1** (Figure 9).^[85] Their modified electrodes responded to the presence of carbohydrates at remarkably low concentrations (Table 8). Although receptor **1** showed no substantial advantage over **104** and **106**, the differing selectivities strongly suggest a role for specific recognition through non-covalent interactions.

Even more remarkable was the behavior of hydrophobic pockets created on gold surfaces, by the Fuhrhop group, through treatment with a steroidal thiol followed by octadecanethiol (Figure 10).^[86] The ion permeabilities of these surfaces were studied by cyclic voltammetry with $[\text{Fe}(\text{CN})_6]^{3-}$ as the redox probe. The moderate currents observed initially could be partially blocked by monosaccharides, including

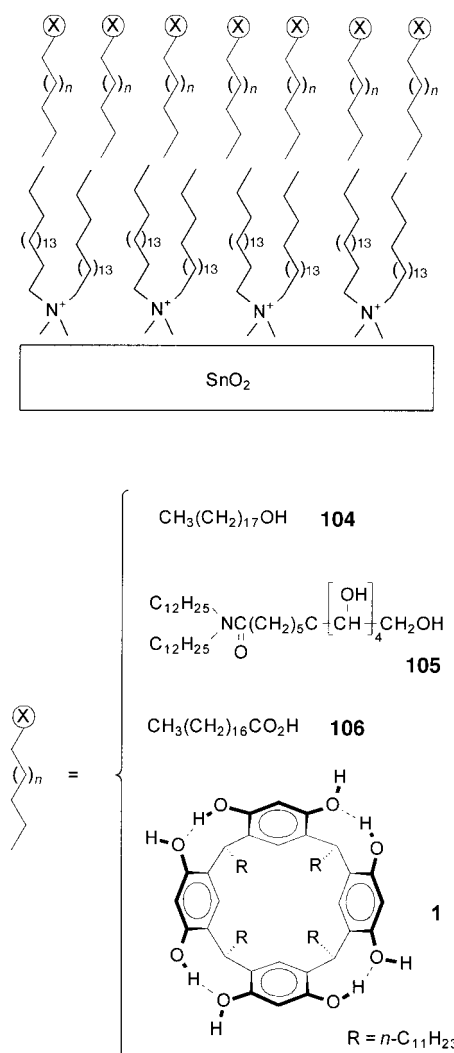


Figure 9. Schematic view of modified electrodes used to detect carbohydrate recognition at monolayer surfaces. Langmuir–Blodgett (LB) deposition is used to coat SnO_2 glass, first with bis(octadecyl)dimethylammonium bromide (to create a hydrophobic surface) and then with amphiphiles **104**–**106** or **1**. The potential of the electrode is monitored against Ag/AgCl in the presence of increasing concentrations of carbohydrates.

Table 8. Threshold concentrations for potentiometric detection of carbohydrates by electrodes modified with **105–107** or **1**, as shown in Figure 9.

	Threshold concentrations [10^{-4} M]			
	104	105	106	1
ribose	1.7	4.8	1.0	0.42
xylose	1.8	4.6	0.6	2.2
glucose	8.4	17	0.4	6.0
sucrose	14	25	3.6	8.7

glucose. The effects were slow to build up and difficult to reverse,^[87] but did not seem to involve covalent bond formation.

Carbohydrate-binding properties have also been shown for a silica surface under aqueous conditions. In this case the effect relied on “sugar clustering”; the octagalactosyl calixarene **107** was strongly bound while galactose itself showed no affinity.^[88]

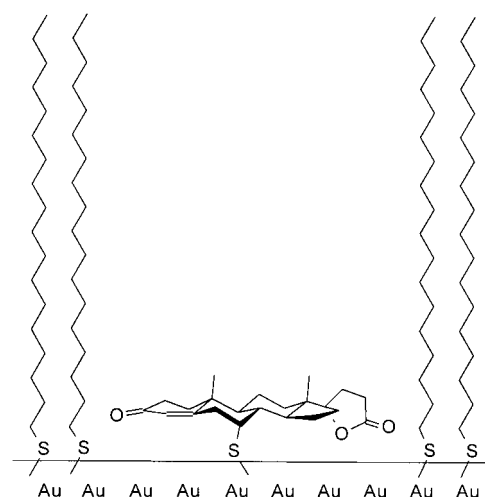
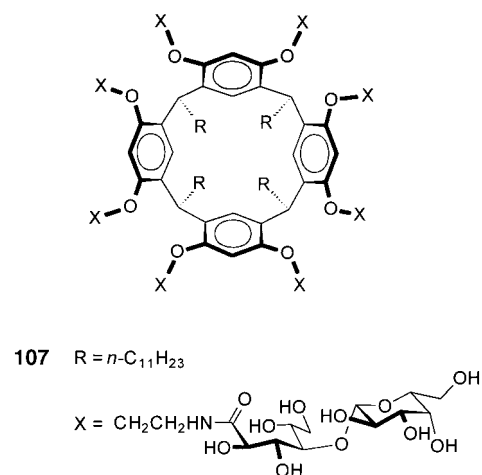


Figure 10. Hydrophobic pocket formed on gold by chemisorption of a steroidal thiol, followed by coverage of the remaining surface with an octadecanethiol self-assembled monolayer.



4. Conclusion

The quest for biomimetic carbohydrate recognition has produced much of interest over the past few years. Strong binding has been achieved in organic media, and apparently also at aqueous interfaces. Studies in aqueous solution have set the stage for future efforts. However, there is still no designed, monomeric receptor which can compete effectively with bulk water for low concentrations of monosaccharide substrates. This applies both in homogeneous media and in two-phase (aqueous-organic) systems, where extractions have invariably employed $\approx 1\text{M}$ solutions of substrate.^[89] The combination of potency with designed specificity is still further away, perhaps inaccessible without radically new approaches. The challenge remains, and should yield insight and enjoyment for some years to come.

A.P.D. must thank a series of co-workers whose efforts have contributed to work discussed in this article, notably Richard Bonar-Law, Brian Murray, John Walsh, and Khadga Bhattarai. Our research has received financial support from Enterprise Ireland, the Irish Science and Technology Agency, and from

the EU "Human Capital and Mobility" and "Training and Mobility for Researchers" programs. Collaborations with David Williams (Imperial College, London) and Peter Ashton (University of Birmingham) have been vital to our progress, as has the generous supply of cholic acid provided by Freedom Chemical Diamalt GmbH.

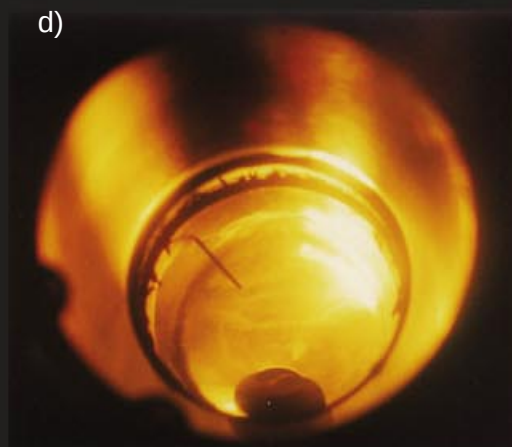
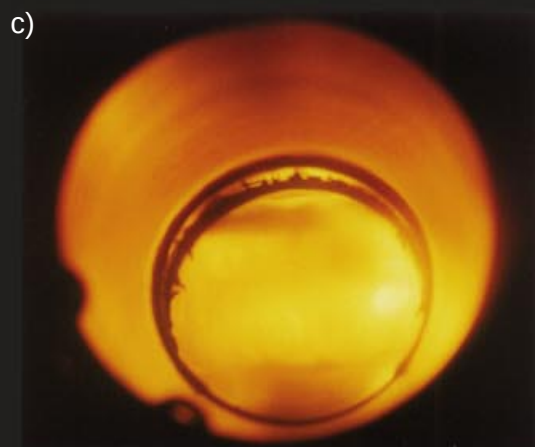
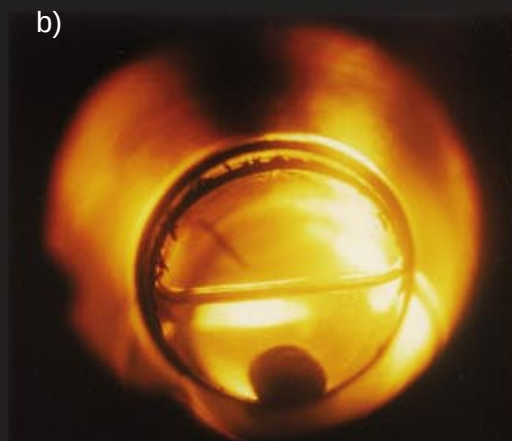
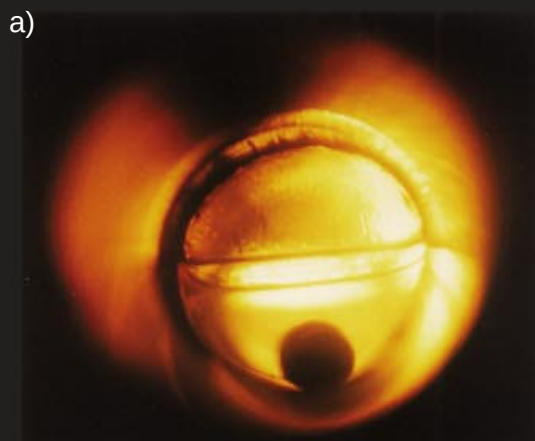
Received: September 3, 1998 [A2991E]

German version: *Angew. Chem.* **1999**, *111*, 3160–3179

- [1] See for example: a) N. Sharon, H. Lis, *Chem. Br.* **1990**, 26, 679; b) S. Hakomori, *Pure Appl. Chem.* **1991**, 63, 473; c) S. D. Rosen, C. R. Bertozzi, *Curr. Opin. Cell Biol.* **1994**, 6, 663; d) N. Sharon, H. Lis, *Essays Biochem.* **1995**, 30, 59; e) Y. C. Lee, R. T. Lee, *Acc. Chem. Res.* **1995**, 28, 321; f) R. A. Dwek, *Chem. Rev.* **1996**, 96, 683.
- [2] Recent reviews: C. H. Wong, R. L. Halcomb, Y. Ichikawa, T. Kajimoto, *Angew. Chem.* **1995**, 107, 435; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 412; C. H. Wong, R. L. Halcomb, Y. Ichikawa, T. Kajimoto, *Angew. Chem.* **1995**, 107, 559; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 521; S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem.* **1996**, 108, 1482; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1380; K. C. Nicolaou, B. M. Smith, J. Pastor, Y. Watanabe, D. S. Weinstein, *Synlett* **1997**, 401; P. Arya, R. N. Ben, *Angew. Chem.* **1997**, 109, 1280; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1280. See also articles in: *Glycoscience Synthesis of Oligosaccharides and Glycoconjugates* (Eds.: H. Driguez, J. Thiem), Springer, Berlin, **1997**; *Preparative Carbohydrate Chemistry* (Ed.: S. Hanessian), Marcel Dekker, New York, **1997**; *Modern Methods in Carbohydrate Synthesis* (Eds.: S. H. Khan, R. A. O'Neill), Harwood Academic, Chur, Switzerland, **1996**.
- [3] a) F. A. Quiocho, *Pure Appl. Chem.* **1989**, 61, 1293; b) N. Sharon, *Trends Biol. Sci.* **1993**, 18, 221; c) W. I. Weis, K. Drickhamer, *Ann. Rev. Biochem.* **1996**, 65, 441.
- [4] a) R. U. Lemieux in *Carbohydrate Antigens* (Eds.: P. J. Garegg, A. A. Lindberg), American Chemical Society, **1993**, pp. 5–18; b) E. J. Toone, *Curr. Opin. Struct. Biol.* **1994**, 4, 719; c) R. U. Lemieux, *Acc. Chem. Res.* **1996**, 29, 373; d) J. P. Carver, *Pure Appl. Chem.* **1993**, 65, 763.
- [5] T. D. James, P. Linnane, S. Shinkai, *Chem. Commun.* **1996**, 281; T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Angew. Chem.* **1996**, 108, 2038; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1911; B. D. Smith, *Supramol. Chem.* **1996**, 7, 55; K. R. A. S. Sandanayake, T. D. James, S. Shinkai, *Pure Appl. Chem.* **1996**, 68, 1207.
- [6] Y. Aoyama, Y. Tanaka, H. Toi, H. Ogoshi, *J. Am. Chem. Soc.* **1988**, 110, 634.
- [7] Y. Aoyama, Y. Tanaka, S. Sugahara, *J. Am. Chem. Soc.* **1989**, 111, 5397.
- [8] Although shown here as α -pyranose structures, it was not proven that **4**, **5**, and **9** were extracted in these forms.
- [9] Y. Kikuchi, Y. Kato, Y. Tanaka, H. Toi, Y. Aoyama, *J. Am. Chem. Soc.* **1991**, 113, 1349.
- [10] Y. Tanaka, Y. Ubukata, Y. Aoyama, *Chem. Lett.* **1989**, 1905.
- [11] Y. Kikuchi, Y. Tanaka, S. Sutarō, K. Kobayashi, H. Toi, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, 114, 10302.
- [12] The self-association of these amphiphilic molecules is a potential complicating factor which gives cause for concern. However, measurements in CHCl_3 have suggested that, for most cases, the problem is not serious for concentrations below 5 mM in this solvent. See references [11] and [28].
- [13] Y. Kikuchi, K. Kobayashi, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, 114, 1351.
- [14] Y. Tanaka, C. Khare, M. Yonezawa, Y. Aoyama, *Tetrahedron Lett.* **1990**, 31, 6193.
- [15] P. B. Savage, S. K. Holmgren, J. M. Desper, S. H. Gellman, *Pure Appl. Chem.* **1993**, 65, 461.
- [16] P. B. Savage, S. K. Holmgren, S. H. Gellman, *J. Am. Chem. Soc.* **1993**, 115, 7900.
- [17] P. B. Savage, S. H. Gellman, *J. Am. Chem. Soc.* **1993**, 115, 10448.
- [18] For reviews discussing cholic acid and other steroids as building blocks in supramolecular chemistry, see: a) A. P. Davis, *Chem. Soc. Rev.* **1993**, 22, 243; b) A. P. Davis, R. P. Bonar-Law, J. K. M. Sanders in *Comprehensive Supramolecular Chemistry*, Vol. 4 (Ed.: Y. Murakami), Pergamon, Oxford **1996**, pp. 257–286; c) Y. X. Li, J. R. Dias, *Chem. Rev.* **1997**, 97, 283; d) P. Walliman, T. Marti, A. Fürer, F. Diederich, *Chem. Rev.* **1997**, 97, 1567.
- [19] R. P. Bonar-Law, A. P. Davis, *J. Chem. Soc. Chem. Commun.* **1989**, 1050; see also: R. P. Bonar-Law, A. P. Davis, *Tetrahedron* **1993**, 49, 9829; R. P. Bonar-Law, A. P. Davis, B. J. Dorgan, *Tetrahedron* **1993**, 49, 9855.
- [20] R. P. Bonar-Law, A. P. Davis, *Tetrahedron* **1993**, 49, 9845.
- [21] R. P. Bonar-Law, A. P. Davis, B. A. Murray, *Angew. Chem.* **1990**, 102, 1497; *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 1407.
- [22] K. M. Bhattacharai, R. P. Bonar-Law, A. P. Davis, B. A. Murray, *J. Chem. Soc. Chem. Commun.* **1992**, 752.
- [23] K. M. Bhattacharai, A. P. Davis, J. J. Perry, C. J. Walter, S. Menzer, D. J. Williams, *J. Org. Chem.* **1997**, 62, 8463.
- [24] a) A. P. Davis, J. J. Walsh, *Chem. Commun.* **1996**, 449; b) A. P. Davis, S. Menzer, J. J. Walsh, D. J. Williams, *Chem. Commun.* **1996**, 453.
- [25] A. P. Davis, R. S. Wareham, unpublished results.
- [26] S. Kohmoto, D. Fukui, T. Nagashima, K. Kishikawa, M. Yamamoto, K. Yamada, *Chem. Commun.* **1996**, 1869.
- [27] R. P. Bonar-Law, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 1* **1995**, 3085.
- [28] R. P. Bonar-Law, J. K. M. Sanders, *J. Am. Chem. Soc.* **1995**, 117, 259.
- [29] T. Mizutani, T. Murakami, N. Matsumi, T. Kurahashi, H. Ogoshi, *J. Chem. Soc. Chem. Commun.* **1995**, 1257; T. Mizutani, T. Kurahashi, T. Murakami, N. Matsumi, H. Ogoshi, *J. Am. Chem. Soc.* **1997**, 119, 8991.
- [30] J.-I. Hong, S. K. Namgoong, A. Bernardi, W. C. Still, *J. Am. Chem. Soc.* **1991**, 113, 5111; W. C. Still, *Acc. Chem. Res.* **1996**, 29, 155.
- [31] Molecular modeling in our own laboratory suggests that roughly half of a pyranoside nucleus can enter the cavity of **52**.
- [32] R. Liu, W. C. Still, *Tetrahedron Lett.* **1993**, 34, 2573.
- [33] J. W. Canary, Ph.D. dissertation, UCLA, **1988**. We are grateful to Prof. Canary for details of this unpublished work.
- [34] S. Anderson, U. Neidlein, V. Gramlich, F. Diederich, *Angew. Chem.* **1995**, 107, 1722; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1596.
- [35] A. P. Davis, R. Wareham, *Angew. Chem.*, in press.
- [36] It should, however, be noted that the involvement of serine, tyrosine and threonine hydroxy groups is relatively uncommon. See for example reference [3c].
- [37] C.-Y. Huang, L. A. Cabell, V. Lynch, E. V. Anslyn, *J. Am. Chem. Soc.* **1992**, 114, 1900; C.-Y. Huang, L. A. Cabell, E. V. Anslyn, *J. Am. Chem. Soc.* **1994**, 116, 2778.
- [38] L. P. Kuhn, *J. Am. Chem. Soc.* **1954**, 76, 4323.
- [39] M. Inouye, T. Miyake, M. Furusyo, H. Nakazumi, *J. Am. Chem. Soc.* **1995**, 117, 12416.
- [40] J. Cuntze, L. Owens, V. Alcazar, P. Seiler, F. Diederich, *Helv. Chim. Acta* **1995**, 78, 367.
- [41] D. A. Bell, S. G. Diaz, V. M. Lynch, E. V. Anslyn, *Tetrahedron Lett.* **1995**, 36, 4155.
- [42] M. López de la Paz, G. Ellis, S. Penadés, C. Vicent, *Tetrahedron Lett.* **1997**, 38, 1659.
- [43] J. M. Coterón, F. Hackett, H. J. Schneider, *J. Org. Chem.* **1996**, 61, 1429.
- [44] Other bonding patterns are of course possible; see for example reference [46].
- [45] G. Das, A. D. Hamilton, *J. Am. Chem. Soc.* **1994**, 116, 11139.
- [46] G. Das, A. D. Hamilton, *Tetrahedron Lett.* **1997**, 38, 3675.
- [47] U. Neidlein, F. Diederich, *Chem. Commun.* **1996**, 1493.
- [48] K. Kobayashi, F. Ikeuchi, S. Inaba, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, 114, 1105.
- [49] N. Greenspoon, E. Wachtel, *J. Am. Chem. Soc.* **1991**, 113, 7233.
- [50] A. Dondoni, A. Marra, M. C. Scherrmann, A. Casnati, F. Sansone, R. Ungaro, *Chem. Eur. J.* **1997**, 3, 1774.
- [51] J. F. Kinneary, T. M. Roy, J. S. Albert, H. Yoon, T. R. Wagler, L. Shen, C. J. Burrows, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989**, 7, 155. For design work related to **85**, see also: S. M. Evans, C. J. Burrows, C. A. Venanzi, *J. Mol. Struct.* **1994**, 308, 159; S. M. Evans, C. J. Burrows, C. A. Venanzi, *J. Mol. Struct.* **1995**, 334, 193.
- [52] This figure should be compared to that of 10^6 , normally considered the lower limit of "tight" binding in biochemical circles, and 10^{15} for the biotin-avidin complex.
- [53] R. U. Lemieux, *Chem. Soc. Rev.* **1989**, 19, 347.

- [54] a) See for example: J. H. Naismith, R. A. Field, *J. Biol. Chem.* **1996**, 271, 972; L. Delbaere, M. Vandonselaar, L. Prasad, J. W. Quail, K. S. Wilson, D. Zbigniew, *J. Mol. Biol.* **1993**, 230, 950; b) for a review on polyvalent interactions in biological systems see: M. Mammen, S.-K. Choi, G. M. Whitesides, *Angew. Chem.* **1998**, 110, 2908; *Angew. Chem. Int. Ed.* **1998**, 37, 2754.
- [55] This tendency also explains the ability of lectins to cause cells to agglutinate. For example concanavalin A consists of four subunits, each with a carbohydrate binding site, and can therefore act as a “biological glue” between cell surfaces.
- [56] M. Cygler, D. R. Rose, D. R. Bundle, *Science* **1991**, 253, 442; A. Zdanov, Y. Li, D. R. Bundle, S. J. Deng, C. R. MacKenzie, S. A. Narang, N. M. Young, M. Cygler, *Proc. Natl. Acad. Sci. USA* **1994**, 91, 6423.
- [57] M. Nishio, Y. Umezawa, M. Hirota, Y. Takeuchi, *Tetrahedron* **1995**, 51, 8665.
- [58] J. D. Dunitz, *Chem. Biol.* **1995**, 2, 709.
- [59] For a more rigorous discussion, see: F. N. Diederich, *Cyclophanes*, Royal Society of Chemistry, Cambridge, **1991**, pp. 246–263.
- [60] R. U. Lemieux, L. T. J. Delbaere, H. Beierbeck, U. Spohr, in *Host-Guest Molecular Interactions: From Chemistry to Biology* (Ed.: I. O. Sutherland), Wiley, Chichester, **1991**, p. 231 (*CIBA Foundation Symposium* 158).
- [61] W. Blokzijl, J. B. F. N. Engberts, *Angew. Chem.* **1993**, 105, 1610; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1545.
- [62] This conflict with the conventional view of the hydrophobic effect has led Lemieux to propose the term “hydrphobic” for effects deriving from the hydration of amphiphilic surfaces. See reference [4c].
- [63] Leading references: S. B. Ferguson, E. M. Seward, F. Diederich, E. M. Sanford, A. Chou, P. Inocencio-Szweda, C. B. Knobler, *J. Org. Chem.* **1988**, 53, 5593; D. B. Smithrud, T. B. Wymans, F. Diederich, *J. Am. Chem. Soc.* **1991**, 113, 5420.
- [64] M. C. Chervenak, E. J. Toone, *J. Am. Chem. Soc.* **1994**, 116, 10533.
- [65] Y. Aoyama, Y. Nagai, J. Otsuki, K. Kobayashi, H. Toi, *Angew. Chem.* **1992**, 104, 785; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 745.
- [66] A. F. Danil de Namor, P. M. Blackett, M. C. Cabaleiro, J. M. A. Al Rawi, *J. Chem. Soc. Faraday Trans.* **1994**, 90, 845.
- [67] W. Hirsch, T. Muller, R. Pizer, P. J. Ricatto, *Can. J. Chem.* **1995**, 73, 12.
- [68] F. Hackett, J. M. Coterón, H. J. Schneider, V. P. Kazachenko, *Can. J. Chem.* **1997**, 75, 52.
- [69] For leading references to cyclodextrins in general, see: “Cyclodextrins”: *Comprehensive Supramolecular Chemistry*, Vol. 3 (Eds.: J. Szejtli, T. Osa), Pergamon, Oxford, **1996**; A. Harada, in *Large Ring Molecules* (Ed.: J. A. Semlyen), Wiley, Chichester, **1996**, pp. 407–432; C. J. Easton, S. F. Lincoln, *Chem. Soc. Rev.* **1996**, 25, 163.
- [70] The minority^[67] claims $K_a = 420 \text{ M}^{-1}$ for D-glucose + **86**. However, the reliance of these workers on a medical “glucose meter” to detect unbound glucose is suspect. The test is based on oxidation of the glucose by glucose oxidase, and could not distinguish between bound and unbound carbohydrate unless exchange kinetics were unrealistically slow.
- [71] A. V. Eliseev, H.-J. Schneider, *J. Am. Chem. Soc.* **1994**, 116, 6081.
- [72] K. Kobayashi, Y. Asakawa, Y. Kato, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, 114, 10307.
- [73] R. Yanagihara, Y. Aoyama, *Tetrahedron Lett.* **1994**, 35, 9725.
- [74] B.-L. Poh, C. M. Tan, *Tetrahedron* **1993**, 49, 9581.
- [75] Leading reference: T. Oguchi, H. Yamasato, S. Limmatvapirat, E. Yonemochi, K. Yamamoto, *J. Chem. Soc. Faraday Trans.* **1998**, 94, 923. See also: Y. Aoyama, J. Otsuki, Y. Nagai, K. Kobayashi, H. Toi, *Tetrahedron Lett.* **1992**, 33, 3775.
- [76] J. Otsuki, K. Kobayashi, H. Toi, Y. Aoyama, *Tetrahedron Lett.* **1993**, 34, 1945.
- [77] K. Kano, K. Yoshiyasu, S. Hasimoto, *J. Chem. Soc. Chem. Commun.* **1988**, 801.
- [78] B.-L. Poh, C. M. Tan, *Tetrahedron Lett.* **1994**, 35, 6387.
- [79] B. L. Poh, *Tetrahedron* **1996**, 52, 10979.
- [80] J. M. Coterón, C. Vicent, C. Bosso, S. Penadés, *J. Am. Chem. Soc.* **1993**, 115, 10066; J. Jiménez-Barbero, E. Junquera, M. Martinpastor, S. Sharma, C. Vicent, S. Penadés, *J. Am. Chem. Soc.* **1995**, 117, 11198; E. Junquera, J. Laynez, M. Menéndez, S. Sharma, S. Penadés, *J. Org. Chem.* **1996**, 61, 6790.
- [81] S. A. Staley, B. D. Smith, *Tetrahedron Lett.* **1996**, 37, 283.
- [82] M. A. Lipton, *Tetrahedron Lett.* **1996**, 37, 287.
- [83] J. C. Morales, S. Penadés, *Angew. Chem.* **1998**, 110, 673; *Angew. Chem. Int. Ed.* **1998**, 37, 654.
- [84] K. Ariga, T. Kunitake, *Acc. Chem. Res.* **1998**, 31, 371.
- [85] K. Kurihara, K. Ohto, Y. Tanaka, Y. Aoyama, T. Kunitake, *J. Am. Chem. Soc.* **1991**, 113, 444.
- [86] J.-H. Fuhrhop, T. Bedurke, M. Gnade, J. Schneider, K. Doblhofer, *Langmuir* **1997**, 13, 455.
- [87] Washing with water was ineffective. Dilute hydrochloric acid was required to regenerate the initial state.
- [88] T. Fujimoto, C. Shimizu, O. Hayashida, Y. Aoyama, *J. Am. Chem. Soc.* **1997**, 119, 6676.
- [89] The (non-biomimetic) boronate systems discussed in reference [5] are, of course, excluded from these comments.

The disappearance of phase boundaries in the water/cyclohexane system (80/20 wt %): a) 25 °C, b) 250 °C, c) at the critical point, d) above the critical point. See also explanations in the review.



Chemistry in Supercritical Water

Dirk Bröll,* Claudia Kaul, Alexander Krämer, Petra Krammer, Thomas Richter,
Matthias Jung, Herbert Vogel,* and Peter Zehner

Dedicated to Professor Hans-Jürgen Quadbeck-Seeger on the occasion of his 60th birthday

Growing research activity in the field of supercritical fluids as a reaction medium has been observed since the end of the 1980s. In more recent times attention has been increasingly devoted to supercritical water. As a ubiquitous reaction medium it not only affords advantages from the points of view of ecology, economics, and safety, but it is also of particular interest on account of its solvent parameters (ionic product and dielectric constant), which can be adjusted over a range by means of pressure and temperature. For improving production, purely physical parameters (pressure and temperature) can be altered without the need for a change in solvent, which would be tantamount to a redesign of the entire plant. However, high temperatures and high pressures—the critical parameters for

water being 374.2 °C and 22.1 MPa—entail high specific investments. Furthermore, upon use of conventional reactor materials high levels of corrosion occur, so that the search for corrosion-resistant reactor materials and also catalysts is an important research task. Moreover, in the supercritical range of pressures and temperatures there is a shortfall of thermodynamic data for aqueous multicomponent systems, which are indispensable for the correct kinetic description of a reaction. To explore the potential of supercritical water for synthesis, it is therefore essential to devote equal attention to corrosion, thermodynamics, and chemical kinetics. Classes of reactions for which supercritical water is particularly suitable as reaction medium are hydrolyses, hydrations, dehydrations,

and oxidations. The potential of supercritical water for syntheses involving these classes of reactions was investigated by means of pilot experiments on model substances. The reactions considered in some detail are the hydrolysis of ethyl acetate, reactions of acetonitrile and acetamide as well as the dehydration of 1,4-butanediol. Studies of the kinetics of the reactions were supplemented by measurements of corrosion and determinations of density and phase boundary lines in subcritical and supercritical aqueous solutions.

Keywords: corrosion • hydrolyses • kinetics • oxidations • supercritical fluids

1. Introduction

The trend towards using supercritical fluids in chemical practice intensified only at the beginning of the 1980s. Technical processes with carbon dioxide as supercritical medium were developed (decaffeination and hop extraction); initial approaches for this purpose were already in existence in

the 1950s.^[1] Furthermore, owing primarily to the special solvent properties of supercritical fluids, supercritical fluid chromatography (SFC) and the dissolution and subsequent precipitation of particles having adjustable particle size distributions (RESS, SAS)^[2] now form part of industrial practice.^[1, 3]

Supercritical water (SCW^[**]) has been growing in importance as a medium for chemical reactions for about ten years.^[4] This is attributable primarily to relatively recent targets set in waste water treatment, namely, the elimination of poorly biodegradable substances. It is possible to convert these substances into less toxic and more readily degradable compounds.^[5] In that time there has been a marked rise in general interest in the use of the special *pVT*-dependent

[*] Dipl.-Ing. D. Bröll, Prof. Dr.-Ing. H. Vogel, Dipl.-Ing. C. Kaul, Dipl.-Ing. A. Krämer, Dr.-Ing. P. Krammer, Dipl.-Ing. T. Richter, Dipl.-Ing. M. Jung
Fachbereich Chemie der Technischen Universität
Institut für Chemische Technologie
Petersenstrasse 20, D-64287 Darmstadt (Germany)
Fax: (+49) 61-51-16-34-65
E-mail: hervogel@hrz1.hrz.tu-darmstadt.de
Dr.-Ing. P. Zehner
BASF AG
ZAV/A-M 300
D-67056 Ludwigshafen (Germany)

[**] The abbreviation SCW designates in particular water in the supercritical state, that is, $T > T_c$ (374.2 °C) and $p > p_c$ (22.1 MPa). The term has been extended in this review to cover the subcritical region, that is, $250\text{ °C} \leq T \leq 450\text{ °C}$ and $p > p_c$.

physical properties of SCW. Further, it is only very recently that the potential for synthesis which SCW chemistry affords has caught the eye of chemists.

Many technically important syntheses are afflicted by the selectivity–conversion problem; that is, starting from the reactants and products there are also reaction pathways which lead to unwanted byproducts (reaction networks). Reactions proceeding with nearly 100% yield are rare. Important items in the chemist's toolkit for optimizing these reaction networks with respect to the desired product are usually catalysts, in

addition to the classical process parameters of temperature, pressure, and concentration. An additional fine-tuning knob which every synthetic chemist loves to twiddle is the choice of reaction medium, that is, the solvent. However, for the industrial chemist a change in solvent in process development is associated with very high expense, since the entire work-up procedure must be altered.

A key advantage of chemistry in SCW is the possibility of varying the properties of the reaction medium over a wide range solely by changing the pressure and temperature and

Dirk Bröll, born in 1972 in Darmstadt, Germany, studied chemistry at the Darmstadt University of Technology. He obtained his Diplom in 1996 under the supervision of Professor Vogel with a thesis on the extractive purification of process waste water containing carboxylic acids. Since the end of 1996, in the course of work for a doctorate, he has been studying heterogeneously catalyzed partial oxidation reactions in supercritical water.



D. Bröll



H. Vogel



P. Zehner

Herbert Vogel was born in 1951 in Nauheim, Germany. Following an apprenticeship and high school studies he studied chemistry at the Technische Hochschule Darmstadt. In the course of his dissertation under the supervision of Professor Alarich Weiss he worked on the transport properties of liquids. After 12 years in industry at BASF AG in Ludwigshafen he went back to the Darmstadt University of Technology in 1993, where he is at present Professor of Chemistry at the Institute for Chemical Technology. His research work is concerned with heterogeneous catalysis, chemistry in supercritical fluids and renewable raw materials.

Peter Zehner was born in 1942 in Mannheim, Germany. Following an apprenticeship and high school studies he studied process technology at the Technical University of Karlsruhe. In the course of his dissertation under the supervision of Prof. E.-U. Schlünder he worked on the energy transport in gas flow processes with fixed particles at high temperatures. At BASF AG, Ludwigshafen, he worked on mixing and reaction technology for more than 20 years. In 1987 he gained his habilitation at the University of Kaiserslautern in the field of multiphase flow processes. He has been working on process development on fine chemicals and intermediates for the past three years.

***Claudia Kaul**, born in 1970 in Idar-Oberstein, Germany, studied chemistry at the Darmstadt University of Technology. In 1995 under the supervision of Professor Vogel she prepared her Diplom thesis on the corrosion behavior of steels in supercritical aqueous solutions. Building on this she started her doctoral work at the beginning of 1996 on the behavior of inorganic materials in supercritical aqueous solutions. – **Alexander Krämer**, born in 1969 in Lampertheim, Germany, studied chemistry at the Darmstadt University of Technology, where in 1996 he completed his Diplom thesis under the supervision of Professor Vogel. He investigated phase equilibria and densities of aqueous solutions at high pressures and temperatures. In the course of his work towards a doctorate he has been studying heterogeneously catalyzed partial oxidation reactions in supercritical water since the end of 1996. – **Petra Krammer**, born in 1969 in Heidelberg, Germany, studied chemistry at the Darmstadt University of Technology. In 1993 under the supervision of Professor G. Luft she completed her Diplom thesis on the degradation by chemical oxidation of para-toluenesulfonic acid using hydrogen peroxide. She obtained her doctorate in 1998 under the supervision of Professor Vogel in the field of chemistry under supercritical conditions. Since the end of 1998 she has been working in the Paint Shop Process Department at Adam Opel AG in Rüsselsheim, Germany. – **Thomas Richter**, born in 1972 in Rüdesheim, Germany, studied chemistry at the Darmstadt University of Technology. In 1998 he completed his Diplom thesis on dehydration and partial oxidation reactions in supercritical water under the guidance of Professor Vogel. Since the middle of 1998 he has been working for a doctorate on heterogeneously catalyzed partial oxidation reactions in supercritical water. – **Matthias Jung**, born in 1966 in Darmstadt, studied chemistry at the Darmstadt University of Technology, where in 1997 he completed his Diplom thesis on the reactive extraction of acid-laden aqueous solutions under the supervision of Professor Vogel. Since the end of 1997 he has been working on a doctoral dissertation on hydration and dehydration equilibria in subcritical and supercritical water.*

thus optimizing the reaction without changing solvent. This can be seen particularly clearly in the variation of the relative static dielectric constant ϵ and the pK_w value as a function of temperature and pressure (see Table 1), two physical properties which have a decisive effect on polarity and acid/base-catalytic properties. Furthermore, the reaction kinetics can be strongly affected in the supercritical region by varying the pressure (kinetic pressure effect). In addition, many nonpolar organic substances (e.g. cyclohexane) and gases (e.g. oxygen) are highly soluble in SCW so that restrictions in mass transfer due to phase boundaries do not apply.

The possibilities described are based in the final analysis on the ability of water to can give rise to unique spatial structures through hydrogen bonding. Changes in these structures result in significant modifications in physicochemical properties.^[6–8]

In summary, SCW has great potential with regard to the optimization of chemical syntheses. There are, however, drawbacks arising from working at high pressures (high investment costs), the problem of corrosion (expensive materials), and the lack of kinetic and thermodynamic data. For these reasons applied research in the field of chemistry in SCW must not remain confined to synthetic chemistry, but rather also address the issues concerning materials and thermodynamics.

2. Water in the Supercritical State

Important physicochemical properties of water are presented in Table 1 as a function of pressure and temperature.^[9, 10] The density ρ of SCW can be changed continuously from high (liquidlike) to low (gaslike) values without phase transition by varying the pressure and temperature.

The high relative static dielectric constant ϵ of 78.5 at 25 °C drops to a value of about 6 at the critical point, thus clarifying the difference in the solution properties of SCW by comparison with normal water. The reasons for the relatively low value of the dielectric constant are found in the reduced number of hydrogen bonds^[11, 12] brought about by the density and temperature. At high pressure (i.e. high density) substances with ionic bonds (e.g. KCl, Na₂SO₄, NaOH) can be dissolved, and at low density nonpolar organic substances (e.g. cyclohexane) and gases (e.g. oxygen) can be dissolved. In the latter case SCW behaves almost like a nonaqueous solvent. According to quantum-mechanical calculations the molecules of supercritical water take part in the breakage and formation of chemical bonds by significantly lowering the activation energy.^[13]

In the supercritical region supercritical water exhibits very high specific heat capacities c_p (e.g. 29.2 kJ kg^{−1} K^{−1} at 400 °C and 29 MPa),^[10] so that c_p can vary continuously over a wide range depending on the pressure and temperature. In highly exothermic reactions, such as partial oxidations in SCW, this could diminish the problem of hot spots.

The ionic product of water K_w is heavily dependent on density and temperature, so that this property can be used for optimizing acid/base-catalyzed reactions. At $pK_w \leq 14$ water is more suitable as a medium for heterolytic reactions, and at $pK_w \geq 14$ it is more suitable for homolytic reactions.^[14] However, the transition from heterolytic to homolytic is fluid and not sharply demarcated.

The dynamic viscosity η decreases with temperature at high density (collisional transfer of momentum) and increases with temperature at low density (translational transfer of momentum). At moderate supercritical temperatures and high densities η is only a tenth to a twentieth of its value under normal conditions.^[13] This leads to the expectation of advantages with regard to selectivity and space-time yield, especially in the case of heterogeneously catalyzed reactions, in which the overall reaction rate is often limited by mass transfer to and from the active centers.

The attribution of a physical effect as the cause for the course of a particular chemical reaction in SCW is complicated since all the physical properties are highly dependent on temperature and pressure. Moreover, water can appear as a reactive component as well as a catalyst.^[15–17] Thermodynamic data for pure water are available over a wide range of pressures and temperatures.^[10, 18] However, apart from a few binary systems which have been investigated corresponding data for aqueous multicomponent systems are often lacking (see Section 4). In these cases the lack of data on pressure- and temperature-dependent specific volumes especially needs to be emphasized. These allow the exact determination of residence times in continuously operated reactors. Such data can be determined only by means of many experiments.

3. Reaction Kinetics in Supercritical Fluids

On account of the high compressibility of supercritical fluids special importance is attached to pressure when carrying out chemical reactions in these media. Apart from the process parameters of temperature and concentration the rate constant k_x of a reaction can be greatly affected by the pressure. The relationship given in Equation (1) applies,^[19, 20]

Table 1. Physicochemical properties of water as a function of temperature and pressure.^[9, 10]

	"Normal" water	Subcritical water	Supercritical water		Superheated steam
T [°C]	25	250	400	400	400
p [MPa]	0.1	5	25	50	0.1
ρ [g cm ^{−3}]	0.997	0.80	0.17	0.58	0.0003
ϵ	78.5	27.1	5.9	10.5	1
pK_w	14.0	11.2	19.4	11.9	–
c_p [kJ kg ^{−1} K ^{−1}]	4.22	4.86	13	6.8	2.1
η [mPas]	0.89	0.11	0.03	0.07	0.02
λ [mW m ^{−1} K ^{−1}]	608	620	160	438	55

$$\left(\frac{\partial \ln k_x}{\partial p}\right)_{T, x_i} = \frac{-\Delta V^\ddagger}{RT} \quad (1)$$

where $\Delta V^\ddagger$ is the molar volume of activation, which is often interpreted as the change in molar volume in going from the reactants to the transition state. However, this physicochemical interpretation of the volume of activation has to be treated with caution, especially in more complex reactions; in such cases $\Delta V^\ddagger$ should be considered as only a purely formal fitting parameter for the quantitative description of the dependence on pressure. Since in the case of supercritical reactions the absolute value of the volume of activation $\Delta V^\ddagger$ is often high, substantial variations in rate constants can be achieved here.

The volume of activation is usually split into two terms [Eq. (2)].^[13] The first term is an expression of the difference in molecular size between the reactants and the transition state

$$\Delta V^\ddagger = \Delta V_1^\ddagger + \Delta V_2^\ddagger \quad (2)$$

(intrinsic or reaction-specific term). The second term provides information about the interactions between reactants and solvent molecules (extrinsic or solvent-specific term). In supercritical fluids the latter usually predominates and hence determines the pressure dependence of the kinetics. Reactions in supercritical fluids are decisively influenced by these solvent-specific interactions and their unusual solution properties.

As in normal fluids the physical properties in the neighborhood of a dissolved particle are also fundamentally different from the average value for the solution; this is described as a “clustering” or “cage” effect. This cluster formation, which occurs more intensely in supercritical fluids, means that there is a local increase in density, and the molecules involved in the cluster are in dynamic equilibrium with the solvent molecules. A local diminution in density around dissolved particles is also possible.^[21] This behavior can become apparent in different ways in terms of reaction kinetics, and each case has to be considered separately on the basis of the theory of collisions in solution.^[22] In reactions controlled by diffusion, the rate of reaction can be increased in the fluid phase by a reduction in viscosity and the increased diffusion of the reactants associated with this. On the other hand, however, barriers to diffusion can also be erected by the cage effect.^[23]

The rate of a reaction is also controlled by the probability of decomposition of the activated complex (energy transfer from the activated complex to the reaction medium). Supercritical fluids are characterized by particles possessing high mobility (high reaction rate) and simultaneously high density so that this energy transfer is favored.^[24] Furthermore, the model of unimolecular reactions postulated by Lindemann applies, making it possible to draw up a detailed reaction mechanism in accordance with the RRKM theory with incorporation of partition functions on the basis of statistical mechanics.^[22] For example, a detailed reaction mechanism with a total of 184 elementary reactions is given for the oxidation of methanol and hydrogen in SCW.^[25]

Of interest with regard to exercising influence on chemical reactions in SCW is the mode of action of a cosolvent. With a cosolvent the solubility of a substance can be increased

considerably, especially when strong hydrogen-bonding or Lewis acid–base interactions occur between the solvent molecules. The solubility of the solute can be augmented by a factor of 10 to 100 owing to the increase in molecular interactions between the solvent and dissolved particles.^[21]

4. Mixed-Phase Thermodynamics of Supercritical Fluids

The phase diagram of a pure substance is simple and easy to comprehend. The substance is in the supercritical state when its temperature and pressure are higher than their critical values (Figure 1 a). In the case of binary mixtures the phase

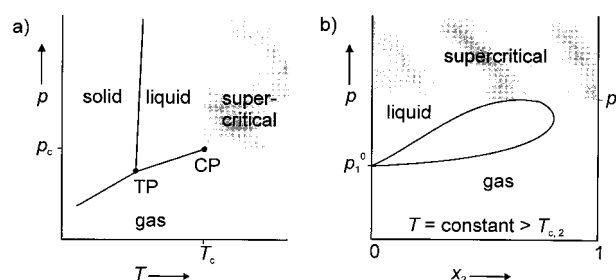


Figure 1. Phase diagrams (schematic).^[26] a) Supercritical region of a pure substance. TP: triple point, CP: critical point, p_c : critical pressure, T_c : critical temperature. b) Supercritical region of a simple binary mixture with a supercritical component 2. p_1^0 : vapor pressure of component 1, x_2 : mole fraction of component 2, $T_{c,2}$: critical temperature of component 2.

diagram is extended by one degree of freedom, the concentration. A simple binary mixture (continuous critical curve) at constant temperature with one supercritical component is supercritical at all pressures higher than the critical pressure of the mixture. Accordingly, the critical pressure here is the upper boundary of the two-phase region (Figure 1 b).^[26]

The phase diagrams can be classified into six main types in accordance with Van Konynenburg and Scott.^[27] For mixtures with yet more components—as is the case for even the simplest of chemical reactions—the phase diagrams are so complex that they cannot be determined with finite effort. Attempts have already been made to carry out calculations for such complex mixtures with the aid of equations of state.^[28, 29] There is, however, an added difficulty in that these are reacting systems whose composition changes over time. The mixed-phase thermodynamic description of these reacting supercritical systems is an unsolved problem. This may be one reason among many others for the technical application of supercritical fluids having mainly been limited in the past to thermal separation processes (e.g. fluid/solid and fluid/liquid extraction processes). In these processes no chemical changes take place. The phase diagrams are thus accessible by experiment and hence capable of mathematical description, which makes reliable scale-up from the laboratory to the industrial scale possible.

Since SCW has so far played a secondary role as a solvent and reaction medium, there are only a few systematic studies of the phase behavior and the densities of mixtures with organic substances.^[30, 31] These data, however, are indispen-

sable for studying reaction kinetics and designing industrial plants. The determination of phase boundary lines is presented below for the water/cyclohexane system by way of example. Cyclohexane is a potential reactant for partial oxidations (oxidation of cyclohexane to cyclohexanol/cyclohexanone) as well as a possible cosolvent with water (see Section 3).

There are no generally applicable mathematical models for calculating the densities of complex mixtures in the subcritical and supercritical regions. Although various general equations describing the density of liquids under high pressures^[32, 33] became established as early as the beginning of the 20th century, their validity is mainly limited to pure substances and to low temperatures. The differences in density relative to pure water which occur may be explained with the example of the water/methanol system.

4.1. Experimental Section

All measurements were carried out in a 30-mL cylindrical optical cell made of Inconel 625 (Figure 2). Two oppositely placed, graphite-sealed sapphire windows allow the visual



Figure 2. Optical cell with seals and sapphire windows for the measurement of phase boundary lines and densities in SCW. See text for details.

observation of the whole of the interior.^[34] To ensure thorough mixing a magnetic rod made of an aluminum-nickel-cobalt alloy, and encased in Inconel 625 to protect it against corrosion, is used. A permanent magnet rotating outside the cell causes the magnetic rod to rotate. The temperature of the viewing cell is controlled by means of cartridge heaters distributed over the circumference. The temperature is measured by means of a thermocouple in the interior. Two screw presses serve to convey the components into the previously evacuated viewing cell and to generate pressure afterwards.

4.2. Phase Boundary Lines for the Water/Cyclohexane System

In the determination of the phase boundary lines the industrially relevant range of 200 to 400 °C and 20 to 36 MPa was investigated.^[35, 36] Phase boundary lines for the two-phase (liquid/gaseous) and the single-phase (fluid) states were recorded. Defined quantities of the two components were metered into the cold viewing cell using the screw presses. The pressure is brought up to the saturated vapor pressure by subsequent heating. The phase transition is identified visually. By varying the pressure and determining the corresponding temperature it was possible to obtain several phase transitions for a mixture and thus establish the course of the phase boundary line. Such isopleths were determined for mixtures of different composition so that it was possible to establish the phase boundary surface and the course of the critical curve in the region studied. The results of these measurements are presented in Figure 3.

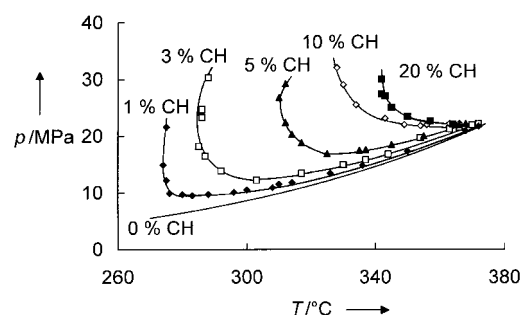


Figure 3. Isopleths of the water/cyclohexane (CH) system.

The phase boundary curves of the mixtures exhibit a minimum and rise steeply as the pressure is increased. This indicates a type 3 phase diagram according to the classification of Van Konynenburg and Scott.^[27] This is in agreement with the results of Schneider et al., who studied the water/cyclohexane system at higher concentrations of cyclohexane.^[36] Studies on the water/*n*-hexane system also revealed similar behavior.^[31] As the concentration of the organic component decreases the single-phase region is shifted to lower temperatures and pressures.

The frontispiece (p. 2998) shows the disappearance of the phase boundaries with rising pressure and temperature. At 25 °C and corresponding vapor pressure three phases are discernible: water phase, cyclohexane phase, and gas phase (a). Above 250 °C the two liquid phases merge (b). At the critical point some clouding and in some cases complete blackout occurs (c). In the supercritical region only a homogeneous fluid phase remains (d).

4.3. Determination of the Densities of Water/Methanol Mixtures

To be able to determine the reaction kinetics for the partial oxidation of methane (see Section 6.5.2) in supercritical water the density of the reaction mixture is needed. To obtain the density defined quantities of a mixture of water and methanol

are metered by means of the screw presses into the heated viewing cell. Since the volume of the viewing cell is known the density of the mixture can be calculated. By adding further material in this way at constant temperature different pressures can be established and the associated densities determined. By way of example in Figure 4 the densities of a

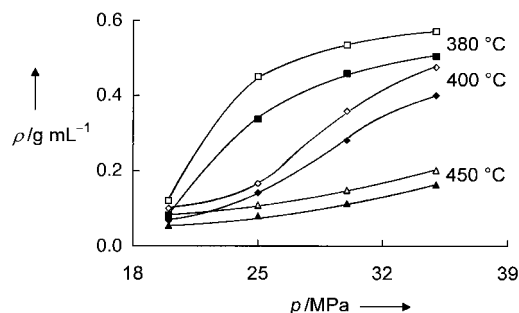


Figure 4. Density of a water/methanol mixture with 5 wt % methanol (filled symbols) and of pure water (open symbols) at three different temperatures as a function of pressure.

mixture containing 5 wt % of methanol as a function of pressure and temperature are compared with that of pure water. The difference in density between the mixture and pure water becomes smaller as the temperature rises.

5. Corrosion of Metallic Materials in Supercritical Aqueous Solutions

There is so far no universally applicable material which can withstand the reaction conditions in aqueous supercritical fluids. In the presence of acids, oxygen, and halogen and sulfur compounds supercritical water has a corrosive action on reactor materials and fittings. Accordingly, the materials must simultaneously be resistant to temperature and pressure up to approximately 500 °C and 50 MPa and also be resistant to corrosion by the substances employed.

Extensive investigations have shown that none of the metallic materials commercially available at present fulfills all these requirements at the same time.^[37–42] For example the material Ducrolloy manufactured by powder metallurgy exhibits outstanding resistance to corrosion in supercritical solutions,^[43] but it is not suitable as a reactor material on account of its low tensile strength and expansion characteristics. The problem can be solved in part through structural measures by carrying out the reaction in a corrosion-resistant inner tube which is fitted in a pressure-bearing container. The requirements for reactor fittings and packings such as heterogeneous catalysts, support materials, and linings then reduces to resistance to temperature and corrosion. Another approach to a solution consists of coating the materials.

The specific rate of change in mass of nickel alloys in SCW is particularly high at high pressures, in correlation with the ionic product of water.^[38–42] In the presence of phosphoric acid, however, marked pitting occurs even at low pressures. It is postulated that the cause of this is the formation of low-melting nickel(III) phosphates.^[42] Kriksunov and MacDon-

ald^[44] developed a model in which the specific rate of change in mass can be calculated as a function of density, H^+ concentration, and oxygen concentration. In summary, there is still a high need for research in this field since the underlying corrosion mechanisms are still not adequately understood.

5.1. Experimental Section

In this section by way of example the behavior of copper and silver as potential oxidation catalysts together with iridium as reactor coating material under the influence of supercritical aqueous solutions will be described as a function of temperature, pressure, and chemical composition. The corrosive media employed were pure water, aqueous acetic acid (as a model substance for the carboxylic acids produced in partial oxidations), and aqueous solutions containing oxygen (hydrogen peroxide served as the source of oxygen).

The experiments were carried out in continuous high-pressure equipment the central component of which is a 250-mL autoclave made of the nickel-based alloy Inconel 625 (wall thickness 25 mm, metallic sealing). Inconel 625 has proved to be effective in SCW both under acid as well as oxygenated conditions and has exhibited adequate stability. The aqueous solutions were conveyed through an electric preheater made of Inconel 625 and through the autoclave with the aid of a high-pressure diaphragm pump. The material leaving the reactor was cooled and decompressed in two stages.

The corrosion studies were carried out at temperatures of 330 to 410 °C and pressures of 25 to 35 MPa since the physical properties of the aqueous media employed vary particularly markedly in this range. Before and after treatment the samples were characterized by gravimetry, optical microscopy, scanning electron microscopy, energy-dispersive X-ray analysis, and X-ray diffraction. The metal ion concentrations in the aqueous solutions from the reactor were analyzed with the aid of atomic absorption spectroscopy.

The test materials were available in the form of metal plates (10 × 10 × 1 mm) and powders. Compacts (diameter 9 mm, thickness 1 mm) were prepared from the metal powders using a hydraulic press, and these were sintered at suitable temperatures in an atmosphere of nitrogen. By appropriate choice of the compacting pressure and sintering conditions (temperature, heating rate, heating time) surfaces of the order of 1 m² g^{−1} (in accordance with Brunauer, Emmett and Teller) were produced.

5.2. Corrosion Behavior in Water

The materials investigated were resistant in pure SCW; changes in mass for copper, silver, and iridium were below the limit of detection. Surface changes were not discernible under the scanning electron microscope.

5.3. Corrosion Behavior in Water/Acetic Acid

The results of the action of aqueous acetic acid on the test materials at 25 MPa are presented by way of example in Figure 5. The specific rate of change in mass χ for copper is

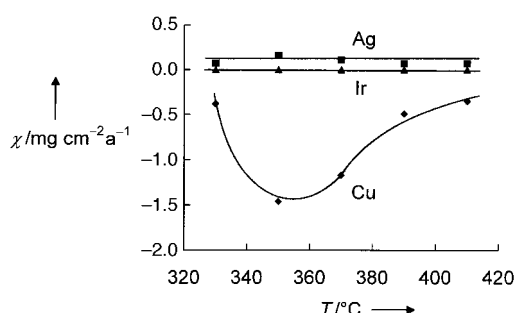


Figure 5. Specific rate of change in mass χ ($a = \text{year}$) for silver, iridium, and copper in an aqueous solution of acetic acid (3 wt %) as a function of temperature at 25 MPa.

greatest just below the supercritical region. This may be explained by the relatively high dissociation constants of water and acetic acid in this subcritical region (Table 1). When the temperature is increased further and the supercritical region attained χ falls distinctly once more. However, even in the least favorable case of $\chi = -1.46 \text{ mg cm}^{-2} \text{a}^{-1}$ the values for copper are still very low. By varying the pH value through the addition of acetic acid the effect of acid concentration on the corrosive attack of copper was also examined.^[45] In the subcritical region χ increases distinctly on addition of acetic acid. Here water and acetic acid are present in more highly dissociated form than in the supercritical region.^[44] The increased number of ions favors electrochemical and acid-induced corrosion. Increasing the acid concentration from 1.5 to 6 wt % causes the χ values to be trebled. In the supercritical region increasing the acid concentration has no effect since here the aqueous acetic acid solution is present in a substantially less highly dissociated form.

Silver exhibits no variations in the specific rate of change of mass as a function of temperature. Oxide layers, which could be postulated to explain the slight increase in mass found, are not discernible. Energy-dispersive X-ray analysis and X-ray diffraction studies after the experiments demonstrated only the presence of pure silver. One possible explanation for the increase in mass is the intercalation of oxygen, which was present in the water used at a concentration of 8 mg L^{-1} . It is known that silver can absorb considerable amounts of oxygen in its lattice.^[46, 47]

Iridium, the potential reactor coating material, is inert to supercritical acetic acid solutions. No changes in mass or to the surface are observed.

5.4. Corrosion Behavior in Water/Oxygen

Figure 6 illustrates the effects of oxygenated aqueous solutions on the test materials. Adherent oxide layers are formed on the surface of copper (375 °C, 25 MPa). X-ray

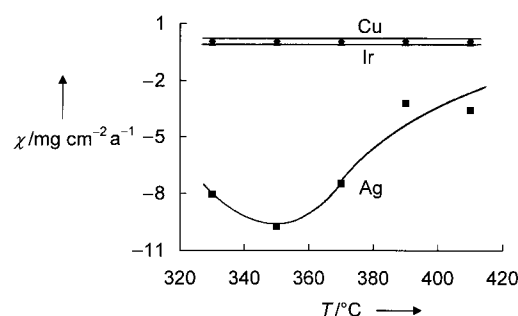


Figure 6. Specific rate of change in mass χ for copper, iridium, and silver in an aqueous solution containing oxygen (1.4 wt %) as a function of temperature at 25 MPa.

diffraction analyses demonstrated that these are copper(I) and copper(II) oxide layers.^[45] They passivate the metal to further attack. The formation of the oxide layer has already gone to completion after 20 h, and the rate of formation of the oxide layer is largely independent of temperature in the range under study.

In oxygen-containing aqueous solution silver exhibits high specific rates of change in mass, the maximum value being almost $\chi = -10 \text{ mg cm}^{-2} \text{a}^{-1}$. This is attributed to the instability of silver oxides under these conditions.^[48] The effect is most pronounced in the subcritical region, due once more to the high ionic product. Long-term tests showed that this is a uniform general attack.

The potential reactor coating material, iridium, is stable in oxygenated solutions (no changes in mass or to the surface). More extensive tests with chlorine-containing additives at 300 to 400 °C and 25 MPa demonstrated that iridium is a very stable material even under these conditions. However, its poor workability caused by its high melting point of 2410 °C is a problem.

6. Potential for Syntheses

Water in its supercritical state is a very reactive substance, permitting chemical reactions without the addition of strong acids or bases. Such reactions can be used for synthesis, recycling of waste, and refining of biomass. Some examples are shown below.

Studies by Korzenski and Kolis^[49] show that Diels–Alder reactions can be carried out in SCW. For example, in the reaction of 2,3-dimethyl-1,3-butadiene with acrylonitrile at 293 °C and with a residence time of 25 min, 3,4-dimethylcyclohex-3-enyl cyanide was obtained in 100% yield. In comparative reactions of different dienes with electron-deficient dienophiles in SCW it was possible to demonstrate higher yields and purer products than under conventional conditions. The occurrence of polymerization products in anhydrous reactions was markedly suppressed.

Organometallic reactions have so far been carried out mainly in supercritical carbon dioxide and will not be considered further here. Very few reactions in SCW are described, but among them is the successful cyclotrimerization of acetylene under CpCo catalysis.^[50]

Organic geochemical processes proceeding under hydrothermal conditions such as the formation of petroleum are of great interest. To arrive at a better understanding of these processes various groups have been studying reactions of model constituents under hydrothermal conditions. Klein et al.^[51, 52] employed the compounds PhCH_2XPh ($\text{X} = \text{CH}_2\text{O}$, O , NH , S) and PhCH_2XYPh ($\text{XY} = \text{CH}_2\text{CH}_2$, OCH_2 , CH_2O).

Apart from the total oxidation of organic compounds (SCWOs) partial oxidation reactions in SCW have also been studied. In the oxidation of methane at 380 °C and a pressure of 30 to 60 MPa 15 to 20% of the carbon consumed appeared in the form of methanol.^[53]

A further interesting field of application of supercritical water is the degradation of biomass, the fluidization of wood, and the degradation of lignocellulose material. Since the biomass contains 40–50 wt% of cellulose, D-glucose is suitable as a model substance. Following its degradation in SCW it was possible to detect inter alia 5-hydroxymethylfurfural in relatively large concentrations.^[54] Antal et al.^[55] carried out acid-catalyzed dehydration reactions on various low molecular weight alcohols, such as ethanol and propanol, in order to obtain more detailed information about the OH functionality in the cellulose polymer and its reactivity under subcritical and supercritical conditions. Useful surveys may be found from Savage et al.^[23] and Subramaniam and McHugh.^[56]

6.1. Experimental Section

To explore the synthetic potential of SCW, hydrolysis, hydration, dehydration, and partial oxidation reactions as well as other reactions of various model substances were carried out in the subcritical and supercritical regions without the addition of mineral acids and bases. An attempt was thus made to overcome the disadvantages of classical reaction methods (inter alia catalyst and neutralization costs, production of salt and low space–time yields). Most investigations in SCW have so far taken place either in batch vessels or small reactors, so that wall effects arising from the corresponding reactor material could not always be excluded. For this reason a continuous system was constructed with which throughputs of 4 L h^{-1} are possible. The maximum operating conditions were chosen to be 50 MPa and 500 °C, which may be regarded as realistic upper limiting values for industrial applications. The centerpiece of this system (Figure 7) is a tubular reactor ① made of Inconel 625 (having an internal volume of 10 or

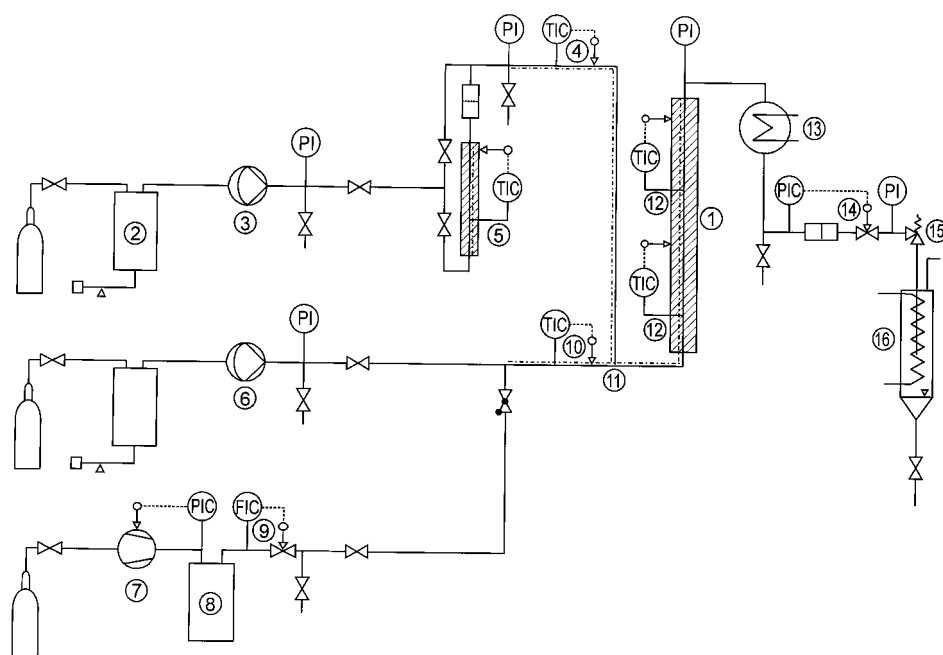


Figure 7. Flow diagram of the high-pressure installation for reactions in SCW. See text for explanations. FIC = flow indication and control, PI = pressure indication, PIC = pressure indication and control, TIC = temperature indication and control.

50 mL depending on the thickness of tube used), with which residence times of between 5 and 400 s may be achieved.

From a supply vessel ② under nitrogen pressure water is metered in through a weigh-controlled diaphragm pump ③ and brought up to reaction temperature by means of a resistance heater ④. A reactor ⑤ capable of being heated can optionally be connected in series ahead of this in order to introduce molecular oxygen into the reactor from the silver-catalyzed decomposition of hydrogen peroxide. The organic component is conveyed in the same manner through a second diaphragm pump ⑥. Organic gases such as methane are first transported by a diaphragm compressor ⑦ into a pressurized storage tank ⑧, from which a stream is withdrawn at a steady rate with a mass flowmeter ⑨ and fed to the reactor through an electric preheater ⑩.

The streams are combined in a mixing head ⑪ and conducted into the reactor. The nickel-based alloy used, Inconel 625, has proved to be effective in corrosion tests (see Section 5) carried out in SCW and exhibited adequate stability. The tubular reactor used is maintained at the required operating temperature with the aid of an electrically heated two-zone tubular furnace ⑫. The hot discharge from the reaction traverses a cooling section ⑬ and a filtering unit, and after this it is decompressed to ambient pressure through a control valve ⑭ constructed in two stages and an overflow valve ⑮ in order to avoid cavitation damage to the valve seats.

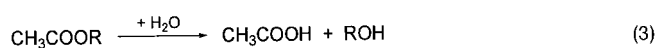
The material discharged from the reactor is separated into a liquid and a gas phase in a cooled phase separator ⑯. The liquid components are analyzed by GC-MS (qualitative) as well as by GC-FID and HPLC (quantitative). In the case of the hydrolysis of poly(tetrahydrofuran diacetate) and poly(tetrahydrofuran) (see Sections 6.2.3 and 6.2.4) the products discharged from the reactor were analyzed by means of SFC/

CI-MS. Gaseous components were quantified by GC-TCD (TCD = thermal conductivity detector). The gas chromatographs have an external preevaporation device based on that developed by Deans^[57] with a coupled gas metering system. If not stated otherwise the experiments were carried out at 250 to 450 °C and 23 to 35 MPa using a mean residence time of 2 min and a reactor admission concentration of 5 wt % for the organic substance.

6.2. Hydrolyses

6.2.1. Simple Carboxylic Acid Esters

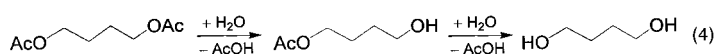
The hydrolysis of ethyl acetate proceeds selectively to form acetic acid and ethanol [Eq. (3), R = Et]. Only above 350 °C are small quantities of ethylene, CO, and CO₂ found in the gas



phase. At a reaction temperature of 350 °C and with residence times of 150 s or more almost complete conversion was achieved (see Section 7.1). To investigate the effect of the ester group the hydrolysis of methyl, *n*-butyl, and benzyl acetate was carried out. The rate of hydrolysis rises in the sequence benzyl > methyl > ethyl > *n*-butyl. The equilibrium conversion ratios achieved are 88 % for methyl acetate, 98 % for ethyl acetate, 60 % for *n*-butyl acetate, and 44 % for benzyl acetate.

6.2.2. 1,4-Butanediol Diacetate

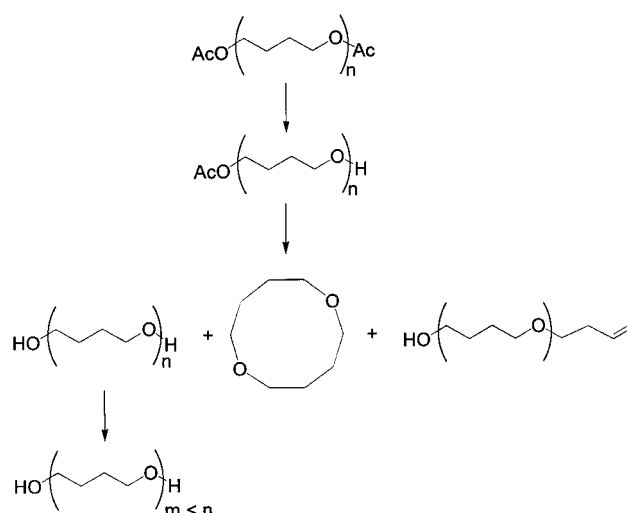
1,4-Butanediol diacetate served as a model substance for the hydrolysis of poly(tetrahydrofuran diacetate), an intermediate in the synthesis of poly(tetrahydrofuran). The reaction proceeds in a manner comparable to the hydrolysis of ethyl acetate [Eq. (4)]. In the subcritical region the



conversion rises from 39 % at 250 °C to nearly 100 % at 350 °C. On passing through the critical point it first falls slightly and then rises again to 97 % when the temperature is raised further to 400 °C. In addition to 1,4-butanediol, tetrahydrofuran (THF) is also formed at temperatures above 350 °C.

6.2.3. Poly(tetrahydrofuran diacetate)

On account of the saponification of 1,4-butanediol diacetate described in Section 6.2.2, the hydrolysis of poly(tetrahydrofuran diacetate) was also investigated (Scheme 1). At 250 °C the products have only one acetyl group. At temperatures ranging from 350 to 400 °C poly(tetrahydrofuran diacetate) is completely converted. In addition to poly(tetrahydrofuran), cyclic and olefin species appear.



Scheme 1. Hydrolysis of poly(tetrahydrofuran diacetate) in SCW.

6.2.4. Poly(tetrahydrofuran)

As the temperature is raised poly(tetrahydrofuran) is broken down increasingly rapidly to form small chains having relative molar masses in the range of 200 to 500 (Scheme 1, bottom).

6.2.5. Acetamide and Benzamide

The hydrolysis of acetamide to form acetic acid proceeds almost quantitatively. Acetonitrile is formed only in small quantities (see Section 7.2). The hydrolysis of benzamide proceeds selectively with formation of benzoic acid. In the temperature range of 300 to 400 °C benzamide undergoes hydrolysis more slowly than acetamide, while the reaction is faster than that of acetamide at temperatures above 400 °C.

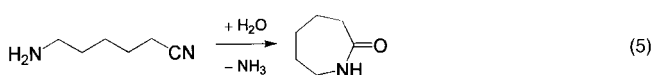
6.3. Hydration Reactions

6.3.1. Acetonitrile and Benzonitrile

On hydration of acetonitrile the only products detected in the liquid phase were acetamide and acetic acid. The ammonia produced is bound in the form of ammonium acetate (see Section 7.2). Benzonitrile reacts to form benzamide and then benzoic acid in accordance with pseudo-first-order kinetics. At 380 °C and 25 MPa the half-life is approximately 8 min. At all the temperatures studied benzonitrile is hydrated to the amide more rapidly than acetonitrile.

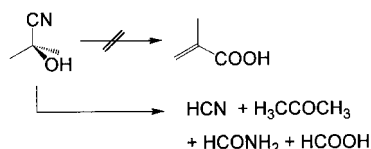
6.3.2. ϵ -Aminocapronitrile

ϵ -Aminocapronitrile is an intermediate in the production of ϵ -caprolactam from butadiene. Up to a temperature of 380 °C ϵ -caprolactam is formed as a stable end product via the intermediate ϵ -aminocaproamide [Eq. (5), overall selectivity approximately 80 %].



6.3.3. Acetone Cyanohydrin

Acetone cyanohydrin is an intermediate in the production of methyl methacrylate by the ACH process. In subcritical and supercritical water decomposition results in the formation of acetone, prussic acid, formamide, and formic acid. Methacrylic acid was not detected (Scheme 2).



Scheme 2. Decomposition of acetone cyanohydrin in SCW.

6.4. Dehydration Reactions

Numerous studies of the dehydration of alcohols in supercritical water have already been carried out. Most of these, however, have involved primary monoalcohols such as ethanol^[14, 55, 58] or propanol^[59, 60] and more rarely diols such as ethylene glycol^[58] or 1,3-butanediol.^[61] Olefins were often found as reaction products.

6.4.1. Ethanol

Ethanol proved to be kinetically stable in SCW. Dehydration to form ethylene occurs at a significant rate only at elevated temperatures.^[55]

6.4.2. Cyclohexanol

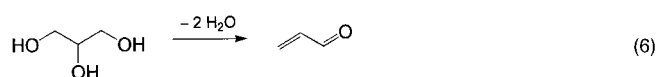
The dehydration of cyclohexanol was investigated under batch conditions at 395 °C and 30 MPa using an initial concentration of 10 wt% and a residence time of 3 h. A batch autoclave made of Inconel 625 having a volume of 1 L was employed for this purpose. Water was put into the reaction vessel first, and the organic substance was added through a screw press after the heating phase until a mass fraction of 10 wt% was attained. In doing so the pressure assumes a level in keeping with the temperature and the quantity of added substance. After the reaction the product is almost exclusively cyclohexene. Thus, despite the excess water the equilibrium lies on the side of the alkene.

6.4.3. 1,4-Butanediol

In the subcritical and supercritical region 1,4-butanediol is selectively dehydrated to form THF. THF is stable under the chosen reaction conditions. No further decomposition products were found (see Section 7.3).

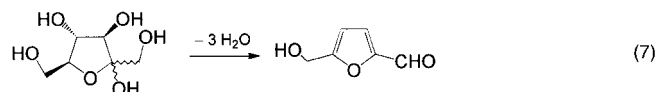
6.4.4. Glycerin

The dehydration of glycerin, a potentially renewable raw material, to form acrolein [Eq. (6)] does not set in to any notable extent until the temperature reaches 350 °C.



6.4.5. Fructose

The industrial production of 5-hydroxymethylfurfural (5-HMF) is particularly interesting since it can readily be converted into furandicarboxylic acid, which is a polymer component similar to terephthalic acid.^[54] A simple pathway to 5-HMF is a prerequisite for the production of new polymers based on renewable raw materials. D-Fructose was successfully dehydrated to 5-HMF [Eq. (7)] in the temperature range

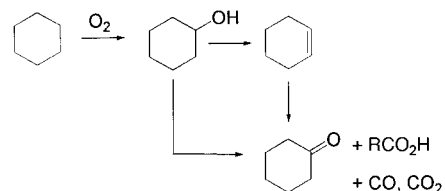


of 250 to 350 °C and 250 bar with a selectivity of approximately 30% and with a conversion ratio of approximately 60%.

6.5. Partial Oxidation Reactions

6.5.1. Cyclohexane

The oxidation of cyclohexane was investigated at a molar ratio of cyclohexane to oxygen of two to one. In pure SCW cyclohexane is stable over the specified ranges of residence times and temperatures. The products identified on addition of oxygen were cyclohexene, cyclohexanol, cyclohexanone, and carboxylic acids together with carbon monoxide and carbon dioxide (Scheme 3). As the temperature goes up from

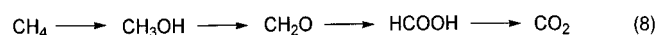


Scheme 3. Partial oxidation of cyclohexane in SCW.

350 to 400 °C the selectivity in favor of the useful products (-ene, -ol, -one) rises to values of 30% with complete reaction of the oxygen.

6.5.2. Methane

In the studies, the molar ratio of methane to oxygen was ten to one. Methane is stable in SCW up to a temperature of 450 °C.^[62] The extent to which the methane reacts rises with increasing temperature and pressure. In agreement with the literature^[62–64] the products of methane oxidation found were carbon monoxide, carbon dioxide, methanol, and small quantities of formaldehyde and formic acid [Eq. (8)]. The



highest selectivity achieved in favor of methanol was 39 % at 420 °C and 35 MPa with a residence time of 23 s. The associated consumption of oxygen was 13 %.

6.6. Other Reactions

6.6.1. Formaldehyde

Formaldehyde is not stable in SCW, and its decomposition is highly dependent on temperature. At temperatures above the critical temperature formaldehyde reacts to completion to form methanol, formic acid, carbon monoxide, and carbon dioxide. Carbon monoxide is the main product at higher reaction temperatures and methanol at lower reaction temperatures (Figure 8). This conversion of formaldehyde by a

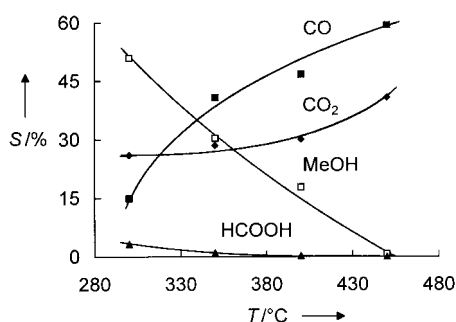


Figure 8. Selectivity S with respect to the products CO, CO₂, methanol, and formic acid in the decomposition of formaldehyde as a function of temperature at 30 MPa and with a residence time of 2 min.

Cannizzaro reaction into methanol and carbon monoxide (formic acid) affords the possibility of transforming dilute formaldehyde waste water into easily separable methanol (integrated environmental protection).

6.6.2. Formic Acid

At low temperatures (300 °C) formic acid decomposes preferentially into carbon monoxide and water. At higher temperatures (> 380 °C) the reaction pathway switches to the production of hydrogen and carbon dioxide (Figure 9).^[55, 65]

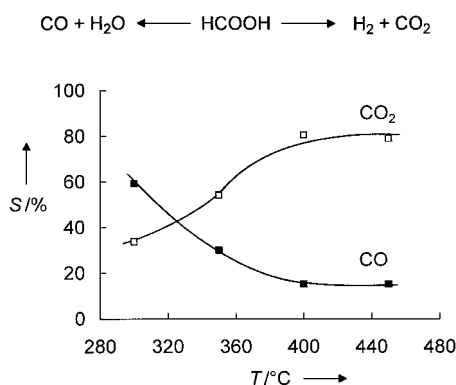


Figure 9. The two decomposition pathways of formic acid and the selectivity S with respect to the products CO and CO₂ as a function of temperature at 30 MPa and with a residence time of 2 min.

6.6.3. Acetic Acid

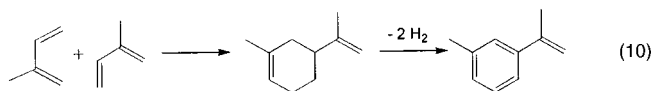
Up to temperatures of 400 °C acetic acid does not decompose. At temperatures above 400 °C limited reaction to the extent of 2% was found. According to Meyer et al.^[66] the decomposition of acetic acid in the temperature range of 475 to 600 °C and at 24.6 MPa results principally in methane and carbon dioxide [Eq. (9)]. Accordingly, the decomposition of



acetic acid does not occur to any significant extent until temperatures above 450 °C are reached.

6.6.4. Isoprene

The reaction of isoprene in SCW was conducted in batch mode (see Section 6.4.2) in the temperature range of 300 to 410 °C at 25 MPa and with an initial concentration of 8 wt %. The residence time was 1 h. The main products were Diels–Alder adducts such as dipentene and some terpenes [Eq. (10)]. No hydration products could be detected.



7. Kinetic Studies

In Section 6 preliminary studies on the potential of SCW for synthesis were presented. More precise kinetic studies will now be presented with reference to the hydrolysis of ethyl acetate, hydration of acetonitrile, hydrolysis of acetamide, and dehydration of 1,4-butanediol.

7.1. Hydrolysis of Ethyl Acetate

The hydrolysis of ethyl acetate was carried out in the tubular reactor (see Section 6.1) under the following conditions: 23 to 30 MPa, 250 to 450 °C, and a residence time of 5 to 230 s. The concentration–time curves established are shown in Figure 10 for 350 and 380 °C and 25 MPa by way of

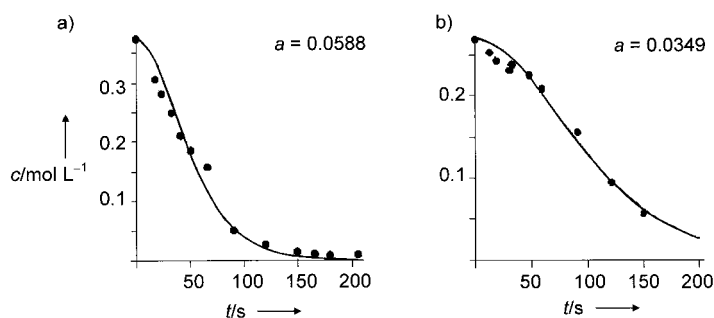


Figure 10. Comparison of the calculated (line) and experimental variation in concentration (dots) in the hydrolysis of ethyl acetate at a) 350 °C, 25 MPa and b) 380 °C, 25 MPa. The parameter a is defined in Equation (13).

example, and they exhibit an S-shaped pattern such as can be expected for an autocatalytic reaction.

The dependence of the conversion on time and temperature, however, was surprising (Figure 11). The highest conversion levels were found at approximately 350 °C; any

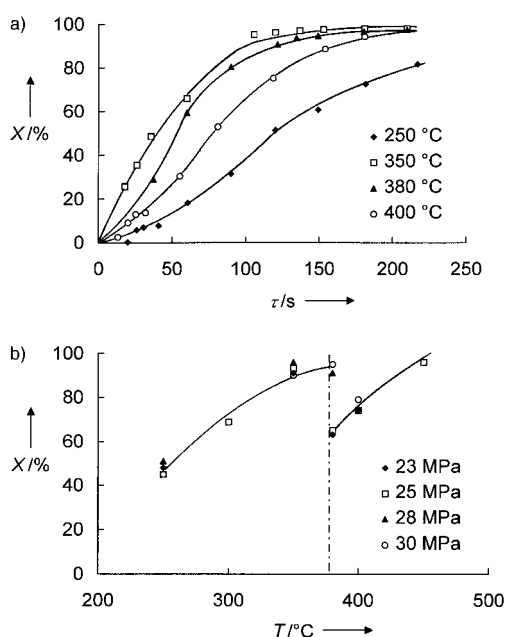


Figure 11. Conversion X in the hydrolysis of ethyl acetate as a function of residence time τ at 28 MPa for four temperatures (a) and as a function of temperature for a mean residence time of 2 min for four pressures (b).

further rise in temperature led in the supercritical region to a decline in conversion. Both the addition of acetic acid as well as that of sodium sulfate result in accelerated saponification (Figure 12).

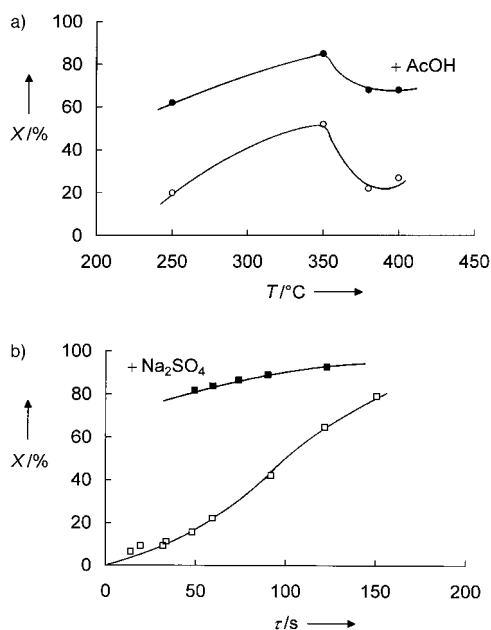
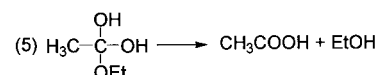
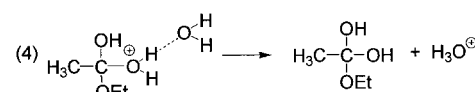
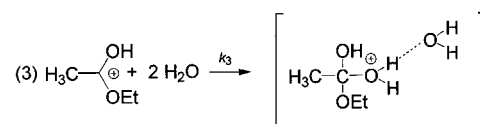
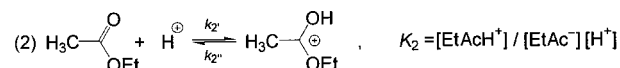
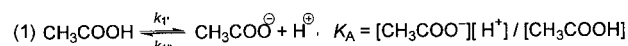


Figure 12. Plot of the conversion X in the hydrolysis of ethyl acetate at 25 MPa a) with a residence time of 60 s with (10 wt %) and without addition of acetic acid as a function of temperature; and b) at 25 MPa and 380 °C with (1 wt %) and without sodium sulfate as a function of residence time.

A number of mechanisms (e.g. A_{AC1} , A_{AC2} , A_{A11} , A_{A12}) are known for the acid-catalyzed hydrolysis of esters.^[67] The A_{AC2} mechanism^[68] (Scheme 4, top) occurs most frequently, as has



assumptions and boundary conditions:

$[\text{H}_2\text{O}]$ is a function of T and p

$[\text{AcOH}] = [\text{EtAc}]_0 - [\text{EtAc}]$

$[\text{AcO}^-] = [\text{H}^+]$

$[\text{H}^+] = (K_A [\text{AcOH}])^{1/2}$

$[\text{EtAcH}^+] = K_2 [\text{EtAc}][\text{H}^+]$

Scheme 4. Top: A_{AC2} mechanism for the hydrolysis of ethyl acetate.^[68] Bottom: assumptions and boundary conditions for analyzing the kinetics of this hydrolysis.

been shown by numerous kinetic studies.^[69, 70] This involves specific acid catalysis. Based on the assumptions and boundary conditions presented in the bottom of Scheme 4, the reaction scheme gives rise to the differential equation (11), which is completely soluble with Equation (12); a is defined in Equation (13). The kinetics of the hydrolysis of ethyl acetate

$$\frac{d[\text{EtAc}]}{dt} = -k_3 K_2 [\text{H}_2\text{O}]^2 \sqrt{K_A} [\text{EtAc}] \sqrt{[\text{EtAc}]_0 - [\text{EtAc}]} \quad (11)$$

$$[\text{EtAc}] = [\text{EtAc}]_0 \left[1 - \tanh \left\{ \frac{a \sqrt{[\text{EtAc}]_0} t}{2} \right\}^2 \right] \quad (12)$$

$$a = k_3 K_2 [\text{H}_2\text{O}]^2 \sqrt{K_A} \quad (13)$$

can be very well described (see Figure 10) by mathematical fitting of the model parameter a to the results of the measurement. In addition to the rate constant k_3 the parameter a also incorporates the equilibrium constant K_2 , the K_A value for the acetic acid, and the water concentration.

The water concentration^[10] together with the K_A values for acetic acid^[71] under the reaction conditions can be obtained from the literature, so that the product of the rate constant k_3 and the equilibrium constant K_2 can be calculated from the parameter a as a function of pressure and temperature. On the assumption that the temperature dependence of k_3 can be

approximated by an Arrhenius expression (activation energy E_a) and K_2 by a van't Hoff expression (enthalpy of reaction $\Delta_R H$), the temperature dependence of the product ($k_3 K_2$) is given by Equation (14). Figure 13 shows the form of $\ln(k_3 K_2)$

$$\ln(k_3 K_2) = -\frac{(\Delta_R H + E_a)}{RT} + \text{const} \quad (14)$$

as a function of the reciprocal temperature at four different pressures. The curves exhibit a kink above 350 °C at the transition from the subcritical to the supercritical region,

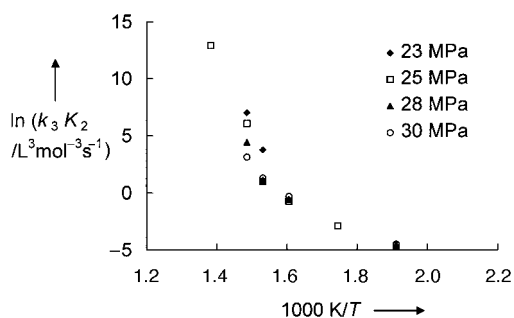
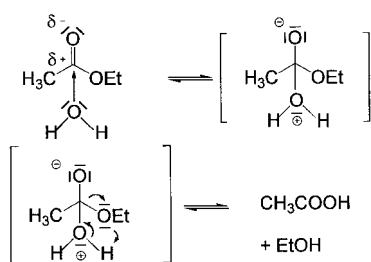


Figure 13. Modified Arrhenius plot of the hydrolysis of ethyl acetate at four pressures.

which can be interpreted as an indication of a change in the reaction mechanism (see also Figure 11b).^[72] The variation of the activation volume^[71] can also be evaluated as a further indication of a change in reaction mechanism on passing from the subcritical region ($\Delta V^\ddagger = -100 \text{ cm}^3 \text{ mol}^{-1}$) to the supercritical region ($\Delta V^\ddagger = +3000 \text{ cm}^3 \text{ mol}^{-1}$).

It is known that apart from an acid-catalyzed mechanism, ester hydrolysis in a neutral medium is also possible (Scheme 5).^[73] In the first rate-determining step a water



Scheme 5. Postulated mechanism for the uncatalyzed hydrolysis of ethyl acetate.^[73]

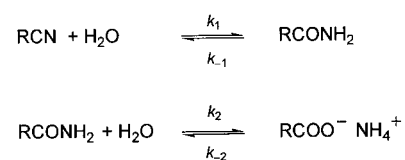
molecule makes a nucleophilic attack on the carbon atom of the carbonyl group of the ester, and then the hydrolysis is concluded by proton transfer with formation of carboxylic acid and alcohol.

The experimental results described above permit the conclusion that in the subcritical region (250 to 350 °C) ester hydrolysis proceeds preferably by an $A_{AC}2$ mechanism, since here the pK_w value of the water is distinctly lower than 14. In the supercritical region with pK_w values of 19 to 20 a nucleophilic, non-proton-catalyzed mechanism is probably dominant.

7.2. Hydration of Acetonitrile and Hydrolysis of Acetamide

The potential of SCW for syntheses involving the hydration of nitriles was investigated using acetonitrile as model substance (300 to 450 °C and 23 to 32 MPa). The residence time was 10 to 250 s. Reactions of acetamide,^[74] isobutyronitrile,^[52, 75, 76] benzonitrile,^[75, 76] benzamide,^[77] and butyronitrile^[78] in the subcritical region have already been described.

The reaction of acetonitrile in SCW ensues selectively via the amide to form the carboxylic acid (Scheme 6, Table 2).



Scheme 6. Mechanism for the hydrolysis of nitriles in SCW. R = Me, Ph.

Table 2. Rate constants k_i [s^{-1}] at 400 °C and 25 MPa as well as activation energies E_a [kJ mol^{-1}] at 25 MPa for the hydrolysis of acetonitrile and benzonitrile in SCW.

	Acetonitrile	Benzonitrile
k_1	4.5×10^{-3}	4.9×10^{-3}
k_{-1}	6.0×10^{-3}	≈ 0
k_2	1.3×10^{-2}	6.8×10^{-3}
k_{-2}	1.0×10^{-8}	≈ 0
E_a	92 ^[a]	109 ^[b]

[a] The value for acetamide is 47 kJ mol^{-1} . [b] The value for benzamide is 111 kJ mol^{-1} .

Under normal conditions the nitrile reacts in a finite time only on addition of strong acids or bases. In contrast, when subcritical or supercritical water is used as solvent and coreactant no additives are needed. As a result, no mineral acids are used, and the subsequent problem of waste water disposal does not arise.

The hydrolysis of acetamide as a successor reaction in the hydration of acetonitrile was investigated separately from the latter under the same reaction conditions. Acetamide does not react exclusively to form the acid, but rather in an equilibrium reaction small quantities of acetonitrile are formed as well as acetic acid.

The measured changes in concentration in the reaction of acetonitrile to form the amide and the carboxylic acid are well described using a pseudo-first-order kinetic model. Figure 14

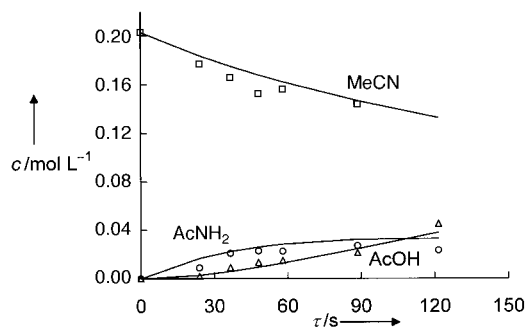


Figure 14. Modeled variation of concentration in the reaction of acetonitrile with water in comparison with values measured at 25 MPa and 400 °C.

shows the simulated changes in concentration in comparison with the measured values. Only when the reaction proceeds beyond 30 %, which in these experiments only occurred above 450 °C, is there any significant difference between the model and experiment. Autocatalytic effects due to the acetic acid formed and/or the ammonium acetate formed from it are a possible cause of this. It was possible to obtain support for this assumption by means of experiments in which the products of the reaction were added in advance. Both the addition of acetic acid and ammonium acetate had a marked impact on the extent of reaction. These effects were not taken into account in the kinetic model. The hydrolysis of acetamide proceeds much faster than the hydration of acetonitrile (see Table 2).

Comparison with benzonitrile as a model substance for aromatic nitriles shows that the reaction rates and activation energies are of the same order of magnitude as for acetonitrile (Table 2). By comparison with the hydrolysis of benzamide (model substance for aromatic amides) the hydrolysis of acetamide exhibits lower dependence on temperature, and this is reflected in the activation energies.

7.3. Dehydration of 1,4-Butanediol

The dehydration of 1,4-butanediol to form THF is carried out on an industrial scale today in the liquid phase at elevated temperatures in the presence of a catalyst for the elimination of water, such as sulfuric or phosphoric acid,^[79–81] acid salts,^[82] or acid ion exchangers. Corrosion and waste disposal problems are the disadvantages associated with this.

The kinetic studies were performed under the following reaction conditions: 5 wt % butanediol in the starting solution, 23 to 35 MPa, 300 to 400 °C, 15 to 165 s residence time. 1,4-Butanediol eliminates water in SCW with a selectivity of almost 100 % to form THF, which proved to be stable under the reaction conditions. The measurements may be described by a pseudo-first-order kinetic equation (Figure 15).

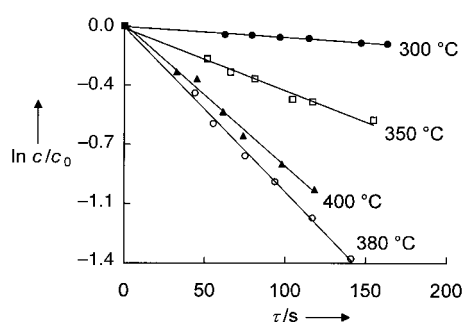


Figure 15. Logarithmic plot of 1,4-butanediol concentrations at a pressure of 30 MPa and four temperatures as a function of residence time τ (initial concentration 5 wt % butanediol).

An increase in temperature in the range of 300 to 380 °C results at all pressures in an increase in conversion, that is, the space–time yield. A further increase in temperature to 400 °C causes the values to fall again. Addition of 1 wt % acetic acid resulted in a marked rise in conversion ratios (Figure 16). The

activation energies according to Arrhenius were determined from the temperature dependence of the reaction. They range from 88 to 116 kJ mol^{−1} and tend to rise with pressure.

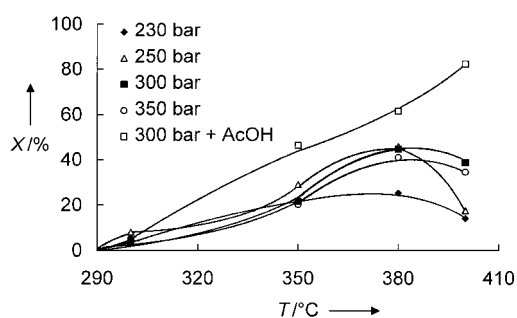


Figure 16. Conversion X in the dehydration of 1,4-butanediol using a mean residence time of 60 s and at four pressures as a function of temperature. The addition of acetic acid accelerates the reaction significantly (compare the filled and open squares).

The dependence of the rate constants on pressure is shown at various temperatures in Figure 17. As expected this is not very marked in the subcritical region. The activation volumes

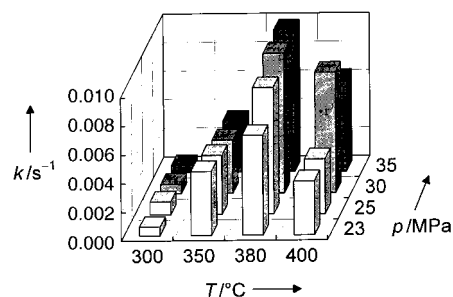
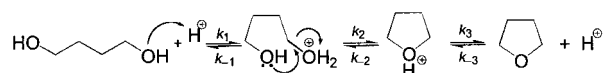


Figure 17. Experimental rate constants for the dehydration of 1,4-butanediol to form THF as a function of pressure and temperature.

determined from this on the basis of Equation (1) assume positive values (141 cm³ mol^{−1} at 300 °C and 94 cm³ mol^{−1} at 350 °C) in the subcritical region and negative values (−134 cm³ mol^{−1} at 380 °C and −320 cm³ mol^{−1} at 400 °C) in the supercritical region. This means that when the pressure is increased the reaction can be retarded in the subcritical region and accelerated in the supercritical region.

The mechanism under conventional conditions has been adequately elucidated (Scheme 7).^[83–85] As a result of this ionic mechanism the dissociation constant of the water



Scheme 7. Reaction mechanism for the dehydration of 1,4-butanediol to form THF.^[83–85]

exercises a powerful effect on the kinetics. In the vicinity of the critical point the pK_w value becomes steadily higher as the density decreases, and so the dissociation of the water steadily declines. As a result, the conversion rates or rate constants fall again when the temperature is increased to 400 °C. In Figure 18 the extent of reaction at 25 MPa is shown as a function of temperature in comparison with the dissociation constant of water.

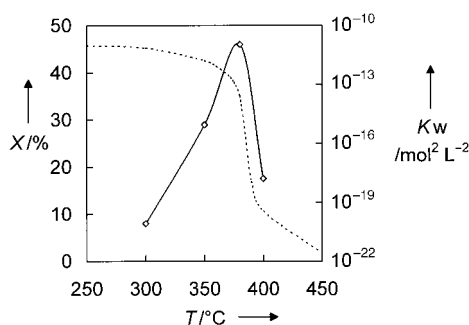


Figure 18. Conversion X in the dehydration of 1,4-butanediol to form THF at 25 MPa with a mean residence time of 60 s as a function of temperature (solid line) in comparison with the K_w value of the water (dashed line, log plot).

8. Summary and Outlook

Supercritical water not only affords great advantages by comparison with conventional solvents from the points of view of ecology, economics, and safety, but it is also a suitable reaction medium particularly on account of its solvent parameters (ionic product and dielectric constant), which can be varied by adjusting the pressure and temperature. Apart from the supercritical wet oxidation already used in practice, chemical syntheses such as hydrolysis, hydration, dehydration, addition and partial oxidation reactions can also be carried out in SCW.

In the subcritical region, where the ionic product of water is relatively high, it was possible to carry out reactions with very high selectivity without the use of a catalyst. Under normal conditions such reactions proceed only with a mineral acid catalyst. Addition of acetic acid in catalytic quantities resulted in acceleration of the reaction for the hydrolysis of ethyl acetate and the dehydration of 1,4-butanediol. In the saponification of ethyl acetate in SCW reaction proceeds preferably by an ionic or nonionic mechanism depending on the conditions. In the supercritical region where the ionic product is relatively low, nonionic mechanisms are evidently preferred. In this region water acts as if it were a nonaqueous solvent.

Studies of corrosion in SCW have shown that specifically in the transition region from subcritical to supercritical the highest specific rates of change in mass occur, this being brought about by the sharp change in the dissociation of water. Despite detectable corrosion silver and copper appear to be suitable as catalysts for partial oxidation reactions in SCW. In corrosion tests using oxygenated aqueous solutions stable oxide layers form on the surface of copper, while in the case of silver removal of material was found due to the instability of the silver oxides formed.

Knowledge of the precise position of the supercritical region is of great interest since here there are no longer any limits to mass transfer. The determination of phase boundary lines for systems of industrial interest, shown here with the example of the water/cyclohexane system, provides accurate information about the phase behavior of the system as a function of the process parameters. Furthermore precise details of densities are needed in order to determine the

kinetics of reaction. Calculations carried out on the basis of the density of pure water possibly give rise to incorrect results.

Research in the field of the heterogeneous catalysis of reactions in the moderately supercritical region of fluid water appear highly promising, since practically all the partial steps such as external and internal mass transfer as well as the chemical reaction processes on the surface of the catalyst are positively affected. Future studies in the field of SCW chemistry should also extend to the degradation of biopolymers, especially carbohydrates, since this may well open up a route in which degradation more or less in situ to form monosaccharides with simultaneous change in functionality could be achieved. To carry out precise kinetic measurements on heterogeneously catalyzed reactions, further studies in a continuously operated gradient-free differential loop-type reactor are planned, the focus being on heterogeneously catalyzed partial oxidation reactions.

Despite all the advances there are still unsolved problems such as the identification of suitable reactor and catalyst materials, which in particular must possess outstanding resistance to corrosion in order to open up further types of reactions in chemistry in SCW and to optimize fields which have already been opened up. Applied research in the field of SCW chemistry must not be restricted to synthetic chemistry alone; problems of materials and thermodynamic issues also have to be taken into consideration.

The authors express their thanks to the BASF AG, Ludwigshafen, the Deutsche Forschungsgemeinschaft (DFG), the Federal Ministry for Education, Science, Research and Technology (BMBF), and the Max-Buchner-Forschungstiftung for financial support.

Received: November 30, 1998 [A315IE]
German version: *Angew. Chem.* **1999**, *111*, 3180–3196

- [1] V. Krukoniš, G. Brunner, M. Perrut in *Proceedings of the 3rd International Symposium on Supercritical Fluids, Vol. 1* (Strasbourg, France) **1994**, pp. 1–22.
- [2] RESS = rapid expansion of supercritical solutions, SAS = supercritical antisolvent process.
- [3] P. G. Debenedetti, *AIChE J.* **1990**, *36*, 1289–1298.
- [4] W. Schilling, E. U. Franck, *Ber. Bunsen-Ges. Phys. Chem.* **1988**, *92*, 631–636.
- [5] T. Hirth, E. U. Franck, *Chem. Ing. Tech.* **1994**, *66*, 1355–1358.
- [6] M. Klose, J. I. Naberuchin, *Wasser – Struktur und Dynamik*, 1st ed., Akademie-Verlag, Berlin, **1986**.
- [7] H. Weingärtner, E. U. Franck, G. Wiegand, N. Dahmen, G. Schwedt, F. H. Frimmel, B. C. Gordalla, K. Johannsen, R. S. Summers, W. Höll, M. Jekel, R. Gimbel, R. Rautenbach, W. H. Glaze in *Ullmann's Encyclopedia of Industrial Chemistry, Vol. A28* (Eds.: B. Elvers, S. Hawkins), 5th ed., VCH, Weinheim, **1996**.
- [8] H. Ohtaki, T. Radnai, T. Yamaguchi, *Chem. Soc. Rev.* **1997**, 41–51.
- [9] K. Tödheide in *Water—a Comprehensive Treatise, Vol. 1* (Ed.: F. Franks), 1st ed., Plenum, New York, **1972**, p. 514.
- [10] L. Haar, J. S. Gallagher, G. S. Kell, *NBS/NRC Wasserdampfafeln*, 1st ed., Springer, Heidelberg, **1988**, pp. 19–214.
- [11] K. P. Johnston, C. Haynes, *AIChE J.* **1987**, *33*, 2017–2026.
- [12] H. D. Cochran, P. T. Cummings, S. Karaboni, *Fluid Phase Equilib.* **1992**, *71*, 1–16.
- [13] R. W. Shaw, T. B. Brill, A. A. Clifford, C. A. Eckert, E. U. Franck, *Chem. Eng. News* **1991**, 69(51), 26–39.

- [14] X. Xu, C. De Almeida, M. J. Antal, Jr., *J. Supercrit. Fluids* **1990**, *3*, 228–232.
- [15] J. M. L. Penninger, *Fuel* **1988**, *67*, 490–496.
- [16] T. J. Houser, C.-C. Tsao, J. E. Dyla, M. K. Van Atten, M. E. McCarville, *Fuel* **1989**, *68*, 323–327.
- [17] T. D. Thornton, P. E. Savage, *J. Supercrit. Fluids* **1990**, *3*, 240–248.
- [18] W. Wagner, A. Kruse, *Zustandsgrößen von Wasser und Wasserdampf*, 1st ed., Springer, Berlin, **1998**.
- [19] G. Luft, *Kinetics of high pressure chemical reactions*, EEC Socrates Intensive Course, Erlangen, **1997**, p. 5.
- [20] H. Tiltcher, H. Hofmann, *Chem. Eng. Sci.* **1987**, *42*, 959–977.
- [21] P. G. Debenedetti, *Chem. Eng. Sci.* **1987**, *42*, 2203–2212.
- [22] K. J. Laidler, *Chemical Kinetics*, 1st ed., Harper & Row, New York, **1987**.
- [23] P. E. Savage, S. Gopalan, T. I. Mizan, C. J. Martino, E. E. Brock, *AIChE J.* **1995**, *41*, 1723–1778.
- [24] S. W. Benson, *Thermochemical Kinetics*, 1st ed., Wiley, New York, **1976**.
- [25] M. K. Alkam, V. M. Pai, P. B. Butler, W. J. Pitz, *Combust. Flame* **1996**, *106*, 110–130.
- [26] “Gas Extraction”: G. Brunner, *Top. Phys. Chem.* **1994**, *4*.
- [27] P. H. Van Konynenburg, R. L. Scott, *Philos. Trans. R. Soc. London A* **1980**, *298*, 495–540.
- [28] R. Dohrn, *Berechnung von Phasengleichgewichten*, 1st ed., Vieweg, Braunschweig, **1994**.
- [29] R. J. Sadus, *AIChE J.* **1994**, *40*, 1376–1403.
- [30] M. Neichel, E. U. Franck, *J. Supercrit. Fluids* **1996**, *9*, 69–74.
- [31] E. Brunner, *J. Chem. Thermodynam.* **1990**, *22*, 335–353.
- [32] M. Jakubith, *Chemische Verfahrenstechnik*, 1st ed. VCH, Weinheim, **1991**.
- [33] A. Wohl, *Z. Phys. Chem.* **1921**, *99*, 234–241.
- [34] E. Brunner, *J. Chem. Thermodynam.* **1990**, *22*, 335–353.
- [35] A. Krämer, Diplomarbeit, Technische Hochschule Darmstadt, **1996**.
- [36] K. Bröllos, K. Peters, G. M. Schneider, *Ber. Bunsen-Ges. Phys. Chem.* **1970**, *74*, 682–686.
- [37] C. Fill, H. Tiltcher in *DECHEMA-Jahrestagung*, Vol. 3, Dechema e.V., Frankfurt, **1995**, pp. 259–261.
- [38] D. B. Mitton, P. A. Marrone, R. M. Latanision, *J. Electrochem. Soc.* **1996**, *143*, 59–61.
- [39] A. J. Thomas, E. F. Gloyna, *Tech. Rep. Univ. Tex. Austin, Cent. Res. Water Resour.* **1991**, 229, 1–50.
- [40] P. Kritzer, N. Boukis, E. Dinjus, *Mater. Corros. (Weinheim, Ger.)* **1997**, *48*, 799–805.
- [41] P. Kritzer, N. Boukis, E. Dinjus, *Corrosion* **1998**, *54*, 689–699.
- [42] P. Kritzer, N. Boukis, E. Dinjus, *Mater. Corros.* **1998**, *49*, 1–16.
- [43] S. Fodi, Dissertation, Universität Karlsruhe, **1998**.
- [44] L. B. Kriksunov, D. D. MacDonald, *J. Electrochem. Soc.* **1995**, *142*, 4069–4073.
- [45] C. Kaul, Diplomarbeit, Technische Hochschule Darmstadt, **1995**.
- [46] L. M. Zoss, S. N. Suci, W. L. Sibitt, *Trans. Am. Soc. Mech. Eng.* **1954**, *69*–71.
- [47] X. Bao, M. Muhler, B. Pettinger, Y. Uchida, G. Lehmppfuhl, R. Schlögl, G. Ertl, *Catal. Lett.* **1995**, *32*, 171–183.
- [48] G. Schikorr, *Die Zersetzungserscheinungen der Metalle*, 1st ed., Verlag J. A. Barth, Leipzig, **1943**.
- [49] M. B. Korzenski, J. W. Kolis, *Tetrahedron Lett.* **1997**, *38*, 5611–5614.
- [50] H. Borwieck, O. Walter, E. Dinjus, J. Rebizant, *J. Organomet. Chem.* **1998**, *570*, 121–127.
- [51] M. T. Klein, Y. G. Menta, L. A. Torry, *Ind. Eng. Chem. Res.* **1992**, *31*, 182–187.
- [52] M. T. Klein, L. A. Torry, B. C. Wu, S. H. Townsend, *J. Supercrit. Fluids* **1990**, *3*, 222–227.
- [53] E. U. Franck in *Proceedings of the 2nd International Symposium on Supercritical Fluids*, Vol. A (Boston, USA) **1991**, pp. 91–95.
- [54] M. J. Antal, Jr., W. S. L. Mok, *Carbohydr. Res.* **1990**, *199*, 91–109.
- [55] “Supercritical Fluids”: M. J. Antal, A. Brittain, C. DeAlmeida, S. Ramayya, J. C. Roy, *ACS Symp. Ser.* **1987**, *329*, 77–86.
- [56] B. Subramaniam, M. A. McHugh, *Ind. Eng. Chem. Process Des. Dev.* **1986**, *25*, 1–12.
- [57] W. David, *LABO* **1994**, *7–8*, 62–68.
- [58] S. Ramayya, A. Brittain, C. DeAlmeida, W. Mok, M. J. Antal, *Fuel* **1987**, *66*, 1364–1371.
- [59] “Supercritical Fluid Sciences and Technology”: R. Narayan, M. J. Antal, *ACS Symp. Ser.* **1989**, *406*, 226–241.
- [60] R. Narayan, M. J. Antal, *J. Am. Chem. Soc.* **1990**, *112*, 1927–1931.
- [61] M. A. B. West, M. R. Gray, *Can. J. Chem. Eng.* **1987**, *65*, 645–650.
- [62] J. H. Lee, N. R. Foster, *J. Supercrit. Fluids* **1996**, *9*, 99–105.
- [63] T. Hirth, R. Schweppe, S. Jähne, G. Bunte, N. Eisenreich, H. Krause, *High Pressure Chem. Eng.* **1996**, *163*–168.
- [64] P. E. Savage, R. Li, J. T. Santini, *J. Supercrit. Fluids* **1994**, *7*, 135–144.
- [65] N. Akiya, P. E. Savage, *AIChE J.* **1998**, *44*, 405–415.
- [66] J. C. Meyer, P. A. Marrone, J. W. Tester, *AIChE J.* **1995**, *41*, 2108–2121.
- [67] E. S. Gould, *Mechanismus und Struktur in der organischen Chemie*, 2nd ed., Verlag Chemie, Weinheim, **1971**.
- [68] K. Yates, R. A. McClelland, *J. Am. Chem. Soc.* **1967**, *89*, 2686–2692.
- [69] A. A. Frost, R. G. Pearson, *Kinetik und Mechanismen homogener chemischer Reaktionen*, 1st ed., Verlag Chemie, Weinheim, **1964**.
- [70] K. A. Connors, *Chemical Kinetics—The Study of Reaction Rates in Solution*, 1st ed., VCH, Weinheim, **1990**.
- [71] P. Krammer, Dissertation, Technische Universität Darmstadt, **1998**.
- [72] O. Levenspiel, *Chemical Reaction Engineering*, 2. Aufl., Wiley, New York, **1972**.
- [73] G. M. Barrow, *Physikalische Chemie Teil III*, 5th ed., Bohmann/Vieweg, Wien/Braunschweig, **1984**, p. 98.
- [74] D. S. Lee, E. F. Gloyna, *Environ. Sci. Technol.* **1992**, *26*, 1587–1593.
- [75] M. T. Klein, C. L. Harrell, B. Izzo, T. Adschiri in *Proceedings of the 4th International Symposium on Supercritical Fluids*, Vol. B (Sendai, Japan), **1997**, 535–538.
- [76] M. T. Klein, B. Izzo, C. L. Harrell, T. Adschiri in *Proceedings of the 4th International Symposium on Supercritical Fluids*, Vol. B (Sendai, Japan), **1997**, 543–546.
- [77] C. C. Tsao, Y. Zhou, X. Liu, T. J. Houser, *J. Supercrit. Fluids* **1992**, *5*, 107–113.
- [78] S. D. Iyer, M. T. Klein, *J. Supercrit. Fluids* **1997**, *10*, 191–200.
- [79] J. Schneiders (BASF AG), DE-B 1043342, **1957** [*Chem. Abstr.* **1961**, *55*, 2686a].
- [80] W. Reppe, O. Hecht, A. Steinhöfer (I.G. Farbenindustrie AG), DRP 696779, **1937** [*Chem. Abstr.* **1941**, *35*, 59154].
- [81] W. Reppe (Gen. Aniline & Film Corporation), US-A 2251292, **1938** [*Chem. Abstr.* **1941**, *35*, 69828].
- [82] W. Reppe, H.-G. Trieschmann (I.G. Farbenindustrie AG), DRP 713565, **1939** [*Chem. Abstr.* **1944**, *38*, 15337].
- [83] B. G. Hudson, R. Barker, *J. Org. Chem.* **1967**, *32*, 3650–3658.
- [84] A. Streitwieser, C. H. Heathcock, *Organische Chemie*, 1st corrected ed., VCH, Weinheim, **1986**, p. 801.
- [85] A. Molnar, M. Bartok, *Helv. Chim. Acta* **1981**, *64*, 389–398.

Milestones in the Biochemistry of Silicon: From Basic Research to Biotechnological Applications

Reinhold Tacke*

Dedicated to Professor Klaus Rühlmann on the occasion of his 70th birthday

About two decades ago the first comprehensive books dealing with biological aspects of silicon chemistry were published.^[1–4] Since that time it has been generally accepted that silicon is an essential element for many biological systems, being required for the production of structural materials and/or for metabolic processes. However, unlike the well established biochemistry and pharmacology of a great number of unnatural organosilicon compounds (compounds containing at least one Si–C bond),^[5, 6] little is known at the molecular level about how cells transport, process, and use silicon. For many other essential elements specific binding sites (for example in enzymes), through which they exert their biological effects, are well established,^[7] but this is not yet the case for silicon. This, together with the lack of evidence for biologically generated Si–C bonds and the kinetic instability of Si–OC bonds under physiological conditions has prompted the development of alternative ideas for the mode of action of silicon. These (very controversial) concepts include the proposal that the essentiality of silicon may not be a result of the direct action of silicon (in whichever chemical form) on biological functions, but rather may be related to its ability to limit the bioavailability of other elements, such as aluminum, calcium, and iron.^[8, 9] Bearing this dilemma in mind, the results of some very recent studies in marine silicon biochemistry make one sit up: biochemists and molecular biologists working with marine organisms that produce large quantities of silicified structures (biosilicification) are now starting to identify the proteins, genes, and molecular mechanisms that control the formation of these structures. These investigations, which are the main subject of this article, can be regarded as milestones in the development of silicon biochemistry.

Dissolved silicon in seawater occurs mostly as the undissociated orthosilicic acid, $\text{Si}(\text{OH})_4$, whose total content in the world's oceans amounts to about 10^{17} mol (ca. 9.6 teratonnes (Tt); $T \triangleq 10^{12}$), and whose concentration averages about

$70 \mu\text{M}$.^[10] A variety of marine organisms, such as diatoms, silicoflagellates, radiolarians, and sponges, contain silica skeletons ($\text{SiO}_2 \cdot n\text{H}_2\text{O}$) that are built up by taking up orthosilicic acid from seawater. The gross production of biogenic silica in surface waters was estimated to amount to 240 ± 40 Tmol of silicon per year. This means, marine biological systems process the gigantic amount of about 6.7 gigatonnes (Gt; $G \triangleq 10^9$) of silicon annually.^[10] The genetically controlled biosynthesis of silica is accomplished under mild physiological conditions,^[3] whereas the geochemical and industrial syntheses of silica typically require extreme conditions of temperature, pH, and/or pressure.

Diatoms constitute the largest class (more than 10000 recent species) of protists living in seawater, brackish water, and freshwater. Of the oceanic planktonic organisms for which silica is an important structural component, diatoms are the dominant source of biogenic silica in the surface layers of the world's oceans. These organisms produce shape-controlled silica structures of breathtaking beauty (Figure 1). The intriguing species-specific design and ornamentation of the cell wall's silica is the basis for diatom systematics and clearly indicates a genetic determination.

The diatom cell wall (frustulum) is made of nanostructured amorphous silica that is associated with polysaccharides and proteins.^[3] The frustulum consists of two parts, the epitheca and hypotheca, each being composed of a valve and several silica strips (girdle bands). It is the girdle band region in which epitheca and hypotheca overlap. New cell walls are produced in a specialized vesicle (silica deposition vesicle, SDV): soluble silicon is taken up from the environment and concentrated in the SDV, and here the insoluble silica is formed and subsequently secreted. Recently, the first data were reported that correlate distinct silica elements with specific proteins within the diatom cell wall.^[12–14] A new family of calcium-binding glycoproteins, the EDTA-extractable so-called frustulins, were identified as constituents of the cell wall of the marine diatom *Cylindrotheca fusiformis* (EDTA = ethylenediamine tetraacetate).^[12, 13] In addition, there is another family of glycoproteins in the cell wall that are resistant to EDTA treatment and therefore appear to be more tightly associated with the silica scaffold.^[14] These proteins can be isolated after complete dissolution of the cell wall with

[*] Prof. Dr. R. Tacke
Institut für Anorganische Chemie der Universität
Am Hubland, D-97074 Würzburg (Germany)
Fax: (+49) 931-888-4609
E-mail: r.tacke@mail.uni-wuerzburg.de

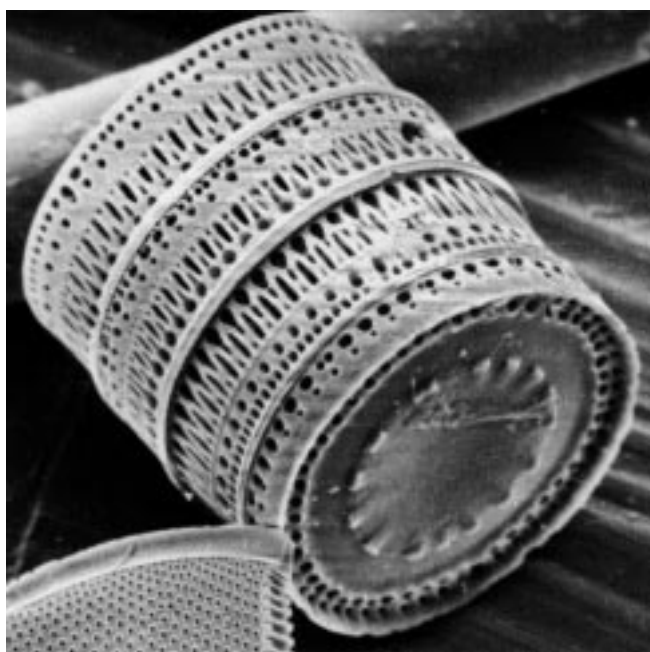
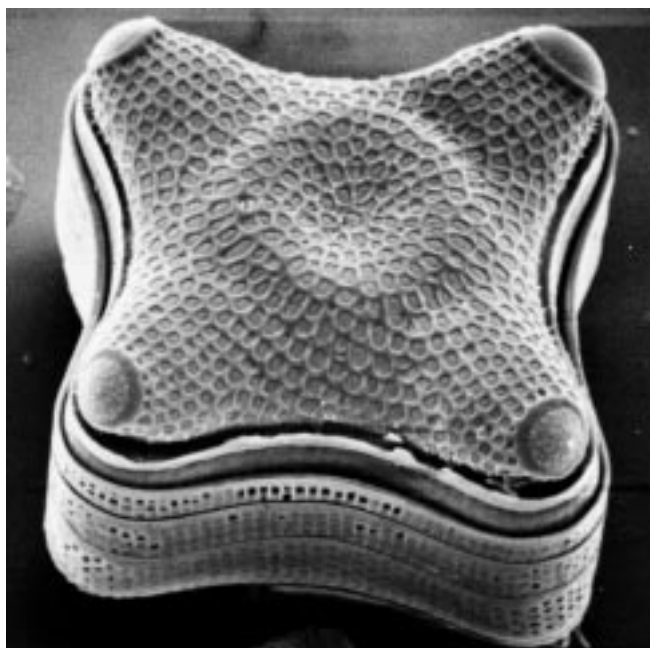


Figure 1. Scanning electron micrographs showing cells of the diatoms *Amphitetras antediluviana* (single cell; above) and *Paralia sulcata* (linked cells, fossil; below). The SEMs are reproduced with permission.^[11] ©1990 Cambridge University Press.

anhydrous hydrogen fluoride and are therefore named *HF*-extractable proteins (HEPs). Extensive studies with one of these proteins, the 200 kDa protein HEP200, have demonstrated that it is specifically located within the girdle band region of the cell wall. As shown by immunolocalization experiments with antibodies against frustulins and HEP200, the frustulins constitute the outer coat of the cell wall and exhibit a ubiquitous distribution, whereas HEP200 is located at a subset of about six out of about 30 silica strips that constitute the girdle band region of the cell wall.^[14] These results support the idea that the species-specific architecture

of the silica of the diatoms cell walls could be a consequence of differences in the structure of species-specific proteins associated with the silica scaffold.

Diatoms were also investigated for the mechanism of silicon transport that is an integral part of the silicification process.^[15, 16] As the environmental concentrations of dissolved silicon are rather low (see above), diatoms must have an efficient transport system. Silicon (as orthosilicic acid or silicate) must not only be transported into the cell, but also transported intracellularly into the SDV where silica formation occurs. The cells maintain pools of dissolved silicon (in whichever chemical form) in relatively high silicon concentrations. Silicon is taken up only during a specific time in the cell cycle (just prior to cell-wall synthesis), and the kinetic parameters for silicon transport were found to vary during the uptake period. Very recently a protein of the diatom *Cylindrotheca fusiformis* was characterized that transports silicon from solution (seawater) into the cell.^[15, 16] This discovery was accomplished by cloning and characterizing the DNA that codes for this protein. To test directly whether the isolated DNA encodes a silicon transporter, messenger RNA (obtained from the cloned DNA *in vitro*) was injected into *Xenopus laevis* oocytes, which were then investigated for the uptake of silicon (germanium) by using ⁶⁸Ge as a silicon-analogous tracer.^[15] Indeed, synthesis of the transporter protein and a significant silicon (germanium) uptake was observed with the RNA-injected frog cells, with the uptake being sodium-dependent. However, silicon transporter proteins of this particular type are not necessarily involved in intracellular transport.

A further major breakthrough in silicon biochemistry came from recent studies with the common marine sponge *Tethya aurantia*.^[17–21] Siliceous sponges deposit silica in needlelike spicules that support the organism and provide defense against predation. About 75% of the dry weight of *Tethya aurantia* is comprised of silica spicules (length 1–2 mm; diameter 30 μ m), each containing an axial central filament of protein (length 1–2 mm; diameter 1–2 μ m) that is fully occluded within the silica.^[17, 18] After dissolution of the silica with buffered hydrofluoric acid, these filaments can be isolated, purified, and resolved into three very similar silicon-free subunits, named silicatein (silica protein) α , β , and γ .^[17] Analyses of the amino acids demonstrated that the compositions of silicatein α (29 kDa), β (28 kDa), and γ (27 kDa) are highly similar, the relative proportions in the filaments being $\alpha:\beta:\gamma = 12:6:1$. Small-angle X-ray diffraction studies revealed evidence for a regular, repeating structure within the filaments (periodicity 17.245 nm), as would be predicted if a simple repeating subunit structure underlies the macroscopic filaments.^[17] Analysis of the DNA sequence for silicatein α (the principal subunit that comprises about 70% of the mass of the filaments) revealed that this protein is highly similar to members of the cathepsin L and papain family of proteases.^[17] The close relationship between silicatein α and cathepsin L is shown by the high similarities between their amino acid sequences, three-dimensional structures, and membrane-enclosed intracellular localizations. These and further findings strongly suggest a common evolutionary origin of these proteins.^[17] The fact that both proteins

are found within membrane-localized vesicles that are essential for their function (silicatein α in the SDV; cathepsin L in the lysosome) supports this suggestion.

These findings gave rise to the fascinating idea that the silicateins might possess an enzyme-like activity and might catalyze the hydrolysis of silicic acid esters.^[18] Since the homologous proteases function catalytically as hydrolases (cleavage of peptide and ester bonds under neutral conditions), related silicatein-catalyzed reactions were studied with substrates of the formula type $\text{RSi}(\text{OEt})_3$ ($\text{R} = \text{OEt}, \text{Me}, \text{Ph}$). Hydrolysis of such compounds, followed by condensation, should yield silica ($\text{SiO}_2 \cdot n\text{H}_2\text{O}$; $\text{R} = \text{OEt}$) or organyl-substituted silsesquioxanes ($(\text{RSiO}_{1.5})_n$; $\text{R} = \text{Me}, \text{Ph}$). The chemical (nonenzymatic) synthesis of such products typically requires acid or base catalysis, with the hydrolytic $\text{Si}-\text{OC}$ bond cleavage being the rate-limiting step. In contrast, the intact silicatein filaments were found to accelerate the formation of silica (from $\text{Si}(\text{OEt})_4$) and silsesquioxanes (from $\text{RSi}(\text{OEt})_3$; $\text{R} = \text{Me}, \text{Ph}$) in vitro at neutral pH.^[18] In addition, the resolved silicatein subunits (α, β, γ) and the purified and reconstituted silicatein α subunit (produced in bacteria from a cloned DNA template) were also found to accelerate the formation of silica from $\text{Si}(\text{OEt})_4$ under neutral conditions.^[18] Little or no product formation was observed in the absence of the silicatein filaments and subunits. Furthermore, the activity of the silicatein filaments and subunits was abolished by thermal denaturation and the related proteolytic enzymes papain and trypsin had no effect. This result clearly indicates the catalytic function of the silicateins (in their native three-dimensional structure) in accelerating the formation of silica and silsesquioxanes.^[18]

In addition to their catalytic activity, the macroscopic silicatein filaments also show a structure-directing activity: the macroscopic filaments were found to serve as scaffolds to organize the deposition of the resulting silica and silsesquioxane products; that is, they behave as templates that direct the growth of the product layers over the surface of the protein filaments.^[18]

In summary, silicateins can catalyze the formation of silica and organyl-substituted silsesquioxanes from the corresponding silicic acid esters $\text{RSi}(\text{OEt})_3$ ($\text{R} = \text{OEt}, \text{Me}, \text{Ph}$) at neutral pH and ambient temperature, and can direct the structures of the resulting products. However, it is still an open question as to whether the catalytic activity observed in vitro is of any physiological significance for the silicification process in vivo. The biological substrate (free orthosilicic acid or organic conjugates?) for silicification in the sponge still remains to be determined.^[18]

As the complete amino acid sequence and the three-dimensional structure of silicatein α are highly homologous to that of cathepsin L, parallels between the silicatein α -mediated catalysis and the known mechanism of action of the protease can be assumed. Thus, it has been proposed that silicatein α catalyzes the hydrolysis of $\text{Si}(\text{OEt})_4$ at neutral pH through the activity of the serine and histidine residues that occupy positions corresponding to the catalytically active, functionally related residues in the proteolytic enzymes of both the cathepsin L (cysteine–histidine) and trypsin/chymotrypsin (serine–histidine) types.^[19] Direct experimental evi-

dence for the proposed role of the specific serine-26 and histidine-165 residue came from site-directed mutagenesis, in which the cloned recombinant DNA that codes for silicatein α was modified in a site-specific manner in vitro, and the mutant DNAs were then used as templates to direct the synthesis of the corresponding proteins in bacteria.^[19] In these studies two structural variants of the silicatein α protein were produced, in which the serine-26 residue and histidine-165 residue were specifically replaced by an alanine moiety. Quantitative comparison of the catalytic activities of the resulting protein products with the activity of the original protein supports the suggestion that serine-26 and histidine-165 of silicatein α are indeed required for the efficient catalysis of silica formation from $\text{Si}(\text{OEt})_4$ at neutral pH.^[19] From these findings a detailed mechanistic model for the silicatein α -mediated catalysis was deduced.^[19]

In addition to site-directed mutagenesis, further methods of genetic engineering (for example, combinatorial mutagenesis) may be used to identify and optimize the catalytic and structure-directing activity of the silicateins.^[20, 21] Genetic engineering, in conjunction with biotechnological methods, offers the prospect of developing new, environmentally benign routes to the synthesis of organyl-substituted siloxanes.^[20, 21] It has been suggested “to use the information obtained from the studies of polysiloxane synthesis with the mutationally altered proteins to design synthetic peptide-based catalysts” and “to guide the design of synthetic non-peptide-based catalysts and structure-directing scaffolds that are both less expensive and more robust than the natural and genetically engineered proteins”.^[21]

The exciting results described in this article clearly demonstrate that significant progress has been made in the biochemistry of silicon. It can be expected that further studies of the proteins, genes, and molecular mechanisms controlling silicon metabolism in diatoms and sponges may also help to reveal the mechanisms for the essential requirement for silicon for optimal development and growth in many plants and animals. Furthermore, these studies may initiate the development of new technological methods for the shape-controlled production of new patterned silicone-based materials.

German version: *Angew. Chem.* **1999**, *111*, 3197–3200

Keywords: bioinorganic chemistry • enzyme catalysis • proteins • silica • silicon

- [1] M. G. Voronkov, G. I. Zelchan, E. Lukevitz, *Silizium und Leben* (Ed.: K. Rühlmann), Akademie, Berlin, **1975**.
- [2] *Biochemistry of Silicon and Related Problems* (Eds.: G. Bendz, I. Lindqvist), Plenum, New York, **1978**.
- [3] *Silicon and Siliceous Structures in Biological Systems* (Eds.: T. L. Simpson, B. E. Volcani), Springer, New York, **1981**.
- [4] *Silicon Biochemistry* (Eds.: D. Evered, M. O'Connor), Wiley, Chichester, **1986**.
- [5] R. Tacke, H. Linoh in *The Chemistry of Organic Silicon Compounds, Part 2* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1989**, pp. 1143–1206.
- [6] R. Tacke, S. A. Wagner in *The Chemistry of Organic Silicon Compounds, Part 3, Vol. 2* (Eds.: Z. Rappoport, Y. Apeloig), Wiley, Chichester, **1998**, pp. 2363–2400.

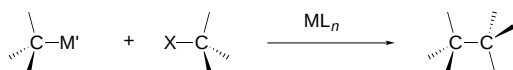
- [7] J. J. R. Fraústo da Silva, R. J. P. Williams, *The Biological Chemistry of the Elements: The Inorganic Chemistry of Life*, Clarendon, Oxford, **1991**.
- [8] C. Exley, *J. Inorg. Biochem.* **1998**, *69*, 139–144.
- [9] C. C. Perry, T. Keeling-Tucker, *J. Inorg. Biochem.* **1998**, *69*, 181–191.
- [10] P. Tréguer, D. M. Nelson, A. J. Van Bennekom, D. J. DeMaster, A. Leynaert, B. Quéguiner, *Science* **1995**, *268*, 375–379.
- [11] F. E. Round, R. M. Crawford, D. G. Mann, *The Diatoms: Biology & Morphology of the Genera*, Cambridge University Press, Cambridge, **1990**.
- [12] N. Kröger, C. Bergsdorf, M. Sumper, *EMBO J.* **1994**, *13*, 4676–4683.
- [13] N. Kröger, C. Bergsdorf, M. Sumper, *Eur. J. Biochem.* **1996**, *239*, 259–264.
- [14] N. Kröger, G. Lehmann, R. Rachel, M. Sumper, *Eur. J. Biochem.* **1997**, *250*, 99–105.
- [15] M. Hildebrand, B. E. Volcani, W. Gassmann, J. I. Schroeder, *Nature* **1997**, *385*, 688–689.
- [16] M. Hildebrand, K. Dahlin, B. E. Volcani, *Mol. Gen. Genet.* **1998**, *260*, 480–486.
- [17] K. Shimizu, J. Cha, G. D. Stucky, D. E. Morse, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 6234–6238.
- [18] J. N. Cha, K. Shimizu, Y. Zhou, S. C. Christiansen, B. F. Chmelka, G. D. Stucky, D. E. Morse, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 361–365.
- [19] Y. Zhou, K. Shimizu, J. N. Cha, G. D. Stucky, D. E. Morse, *Angew. Chem.* **1999**, *111*, 826–828; *Angew. Chem. Int. Ed.* **1999**, *38*, 780–782.
- [20] D. E. Morse, *Trends Biotechnol.* **1999**, *17*, 230–232.
- [21] D. E. Morse in *Organosilicon Chemistry IV—From Molecules to Materials* (Eds.: N. Auner, J. Weis), WILEY-VCH, in press.

Towards Efficient and Wide-Scope Metal-Catalyzed Alkyl–Alkyl Cross-Coupling Reactions*

Diego J. Cárdenas*

Cross-coupling between organic electrophiles and main group organometallic derivatives constitutes the most direct approach for the formation of carbon–carbon bonds. During the last two decades a great number of methods based mainly on Pd and Ni complexes have been reported.^[1, 2] Many different organometallic compounds can be employed as the nucleophile, ranging from the most reactive organolithium and Grignard reagents to the more functional group tolerant tin,^[3] boron,^[4] and even silicon derivatives.^[5] In general C(sp³), C(sp²), and C(sp) substituents may be coupled with suitable electrophiles. Diverse organic electrophiles such as those containing alkynyl, aryl, alkenyl, allyl, benzyl, and acyl groups as well as alkyl halides and pseudohalides have also been used as coupling partners.

Nevertheless, not all the reactions leading to the possible types of carbon–carbon bonds whose formation can be envisaged by crossing all the different nucleophiles and electrophiles have been equally developed. Whereas, for example, coupling between different kinds of C(sp²) centers can be achieved with a variety of reagents and substrates, the development of catalytic methods for the formation of C(sp³)–C(sp³) bonds between alkyl derivatives (Scheme 1)



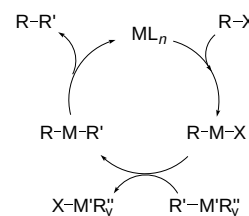
Scheme 1. A general metal-catalyzed alkyl–alkyl cross-coupling reaction. M' = Li, Mg, Zn, Al, Sn, B, Si, etc.; X = halide, OTf, etc.

[*] Dr. D. J. Cárdenas
Departamento de Química Orgánica
Facultad de Ciencias
Universidad Autónoma de Madrid
Cantoblanco, E-28049 Madrid (Spain)
Fax: (+349) 1-3973966
E-mail: diego.cardenas@uam.es

[**] The author thanks Prof. Antonio M. Echavarren for his comments on the manuscript.

has been much less successful. Cross-couplings between unactivated alkyl halides and organomagnesium compounds catalyzed by Cu salts are probably the most studied of such reactions.^[6, 7] Recently it has been demonstrated that alkyl-copper–zinc reagents, exhibiting a higher functional group tolerance, can be coupled with primary and benzyl halides.^[8]

However, a general metal-catalyzed cross-coupling reaction of unactivated alkyl halides and alkyl nucleophiles less reactive than organomagnesium compounds, and hence compatible with more functional groups, has not been developed yet. This is due to several possible drawbacks which can be rationalized on the basis of the general mechanism for metal-catalyzed cross-coupling reactions (Scheme 2). A coupling reaction usually starts with the oxidative addition of the electrophile to a coordinatively unsaturated low-valent metal complex, yielding an organometallic compound to which the second organic group is transferred from the nucleophile (transmetalation) in a second step. The resulting diorganometal complex finally gives rise to the coupling product by reductive elimination, regenerating the catalytically active species.^[9]



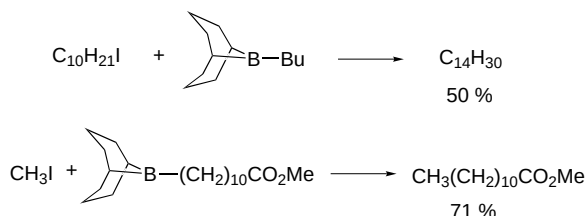
Scheme 2. General mechanism for a metal-catalyzed cross-coupling reaction between an organic electrophile and an organometallic nucleophile.

Difficulties are present in all these steps when unactivated alkyl halides and alkyl electrophiles are employed:

- 1) Alkyl halides (even CH₃I) react slowly with Pd⁰ complexes, in contrast with the behavior observed for allyl, benzyl, alkenyl, and aryl bromides and iodides.^[10] The reaction of CH₃I with phosphane–Ni⁰ complexes is about 10⁷ faster and follows a complex pathway in which radical species may be involved.^[11]

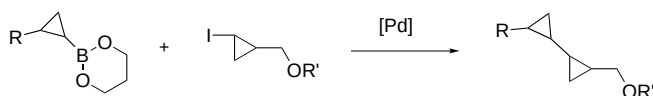
- 2) Once the alkyl–Pd^{II} complex has been formed, there should exist the possibility of decomposition by a fast β -elimination of hydrogen, which competes with the usually slower transmetalation. β -Elimination requires several conditions such as the existence of a vacant coordination site and the feasibility of arranging the M–C–C–H atoms in the same plane. This undesirable process may not be a problem in carbonylative couplings of C(sp³) centers since the fast CO insertion prevents decomposition of the alkyl–Pd intermediate.^[12]
- 3) Reductive elimination is slow for σ -alkyl– π -allyl–Pd^{II} and di- π -allyl–Pd^{II} complexes.^[13] In many cases this process can be accelerated by the addition of species capable of stabilizing the low-valent state of the metal, typically ligands with π -acceptor properties. Thus the choice of an additive with suitable coordinating properties could facilitate this step.

In spite of these problems, some examples of alkyl–alkyl coupling reactions have been reported. Suzuki et al. described some years ago the interesting Pd-catalyzed cross-coupling between alkyl halides and alkylboranes, although yields were not high (Scheme 3).^[14]



Scheme 3. Coupling of alkylboranes with iodoalkanes studied by Suzuki et al.^[14]

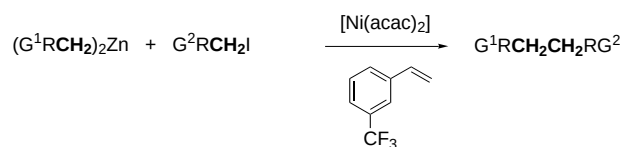
More recently, dicyclopropanes have been synthesized by Pd-catalyzed reaction of cyclopropylboronic acids and boronates with iodocyclopropanes (Scheme 4).^[15] In this case the instability of the cyclopropene that would be formed as well as the impossibility for the M–C–C–H atoms to reach a coplanar arrangement prevent decomposition by β -elimination of hydrogen.



Scheme 4. Suzuki-type cross-coupling between cyclopropyl derivatives. R = alkyl, alkoxy; R' = H, benzyl.

The results presented above^[12–15] show that the oxidative addition of primary and secondary alkyl iodides actually takes place on Pd⁰ complexes. These derivatives are by no means the only possible catalysts for alkyl–alkyl cross-coupling. Knochel et al. have reported an efficient Ni-catalyzed cross-coupling reaction for the formation of C(sp³)–C(sp³) bonds that employs organozinc compounds as nucleophiles.^[16] This work has important features; an efficient alkyl–alkyl cross-coupling has been attained for the first time in the presence of

different functional groups (thioacetal, thiophene, ketone, ester, amide; Scheme 5).



Scheme 5. A functional group tolerant Ni-catalyzed cross-coupling between iodoalkanes and functionalized dialkyl–Zn reagents. Functional group G¹ = alkyl, ester; G² = amide, ester, thioacetal, ketone.

Although only the use of primary alkyl iodides has been reported, the usual reactivity of other types of electrophiles with Ni complexes^[17] suggests that a wider scope may be discovered. A suitable cocatalyst is necessary to promote reductive elimination (or oxidative addition). It has been demonstrated that C–C reductive elimination in square-planar diorgano–Ni^{II} complexes follows an associative pathway that is accelerated by the addition of a suitable ligand.^[18] Among the reagents assayed, *m*-trifluoromethylstyrene afforded the cleanest and fastest reactions, although electron-deficient aromatic compounds and ketones were also effective. The presence of thioether or thioacetal moieties on the electrophile also makes the process favorable, probably by coordination to the metal. Nickel complexes react faster with alkyl iodides than their Pd analogues, and thus are of some advantage for reactions with such electrophiles.^[19] Knochel et al. point out that the oxidative addition may involve a radical pathway in this case since *p*-dinitrobenzene completely inhibits the reaction.^[20] On the other hand, β -elimination does not seem to be a problem here, which may be due to the occurrence of fast transmetalation and reductive elimination steps, although mechanistic studies would be necessary to ascertain this point.

The use of a coordinating cocatalyst may prevent the formation of vacant coordination sites necessary for β -elimination to occur, or it may simply accelerate the reductive elimination step. As far as the scope of the reaction in terms of the nucleophile is concerned, the coupling has been extended more recently to polyfunctional arylzinc derivatives.^[21] The possibility of preparing organozinc derivatives from metallic Zn and alkyl iodides means that the use of Grignard reagents or organolithium compounds can be avoided, thus allowing a greater functional group tolerance in the preparation of the nucleophiles.

In summary, the above-mentioned results show that the problems usually encountered in catalytic alkyl–alkyl cross-couplings can be overcome. Oxidative addition and reductive elimination can be tuned by the careful choice of additives. The ubiquitous β -elimination process can be avoided. The Ni-catalyzed reaction of alkyl halides with alkylzinc derivatives opens a new way for the formation of C(sp³)–C(sp³) bonds in the presence of different functional groups. A conceivable extension of this process to nucleophiles with higher functional group tolerance such as organotin, organoboron, or organosilicon compounds might widen the field of alkane

fragment coupling and solve one of the pending problems in synthetically useful organometallic chemistry.

German version: *Angew. Chem.* **1999**, *111*, 3201–3203

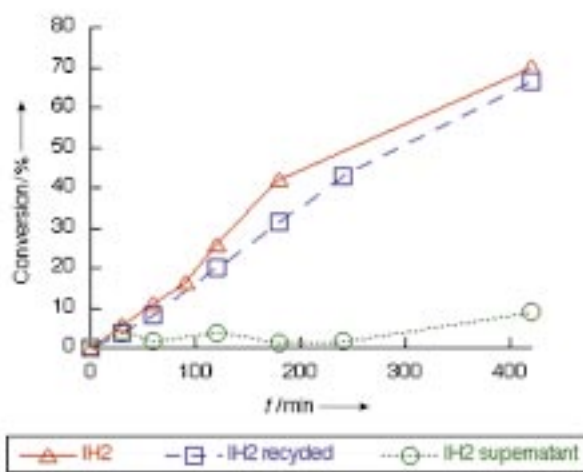
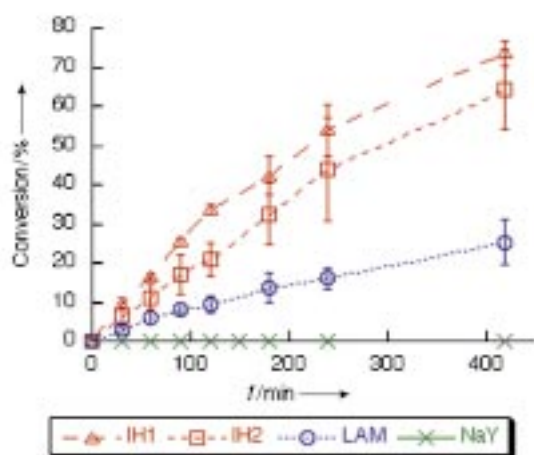
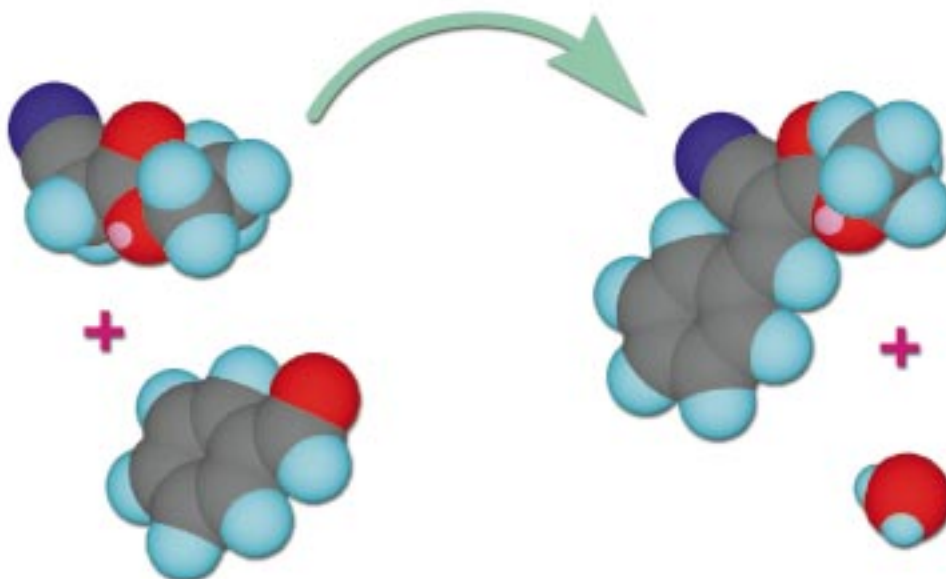
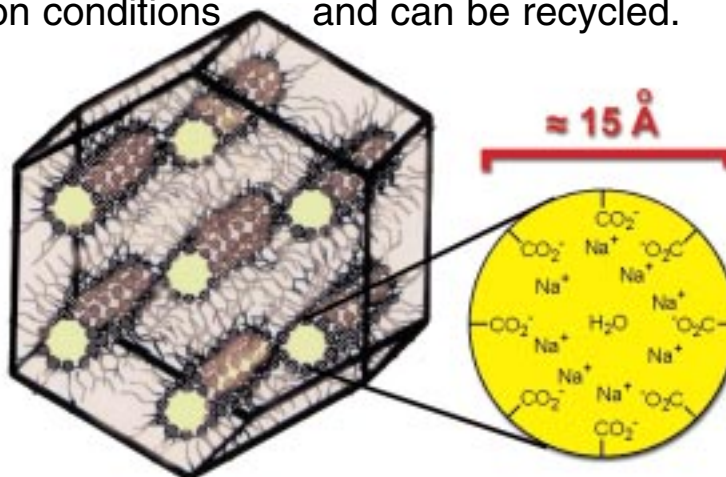
Keywords: cross-coupling • homogeneous catalysis • nickel • palladium • zinc

-
- [1] *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), WILEY-VCH, Weinheim, **1998**.
- [2] *Transition Metals for Organic Synthesis, Vol. 1* (Eds.: M. Beller, C. Bolm), WILEY-VCH, Weinheim, **1998**, chap. 2.10, pp. 158–183.
- [3] J. K. Stille, *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524.
- [4] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.
- [5] See, for example, a) Y. Hatanaka, K. Goda, T. Hiyama, *Tetrahedron Lett.* **1994**, *35*, 1279–1282; b) H. Matsubashi, S. Asai, K. Hirabayashi, Y. Hatanaka, A. Mori, T. Hiyama, *Tetrahedron Lett.* **1995**, *36*, 1539–1540.
- [6] Stoichiometric reactions of alkyl cuprates with alkyl halides have been known since the late 1960s.
- [7] B. H. Lipshutz, S. Sengupta, *Org. React. (N.Y.)* **1992**, *41*, 135–631.
- [8] C. E. Tucker, P. Knochel, *J. Org. Chem.* **1993**, *58*, 4781–4782.
- [9] This is, of course, a simplified general scheme. Other elemental steps may take place along the catalytic cycle depending on the nature of every different reaction. Even the generation of the active metal species may be complex.
- [10] J. K. Stille in *The Chemistry of the Metal–Carbon Bond, Vol. 2* (Eds.: F. R. Hartley, S. Patai), Wiley, New York, **1985**, chap. 9, pp. 625–787.
- [11] R. G. Pearson, P. E. Figdore, *J. Am. Chem. Soc.* **1980**, *102*, 1541–1547.
- [12] T. Ishiyama, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1991**, *32*, 6923–6926.
- [13] A. Goliaszewsky, J. Schwartz, *Tetrahedron* **1984**, *40*, 5779.
- [14] T. Ishiyama, S. Abe, N. Miyaura, A. Suzuki, *Chem. Lett.* **1992**, 691.
- [15] A. B. Charette, R. P. De Freitas-Gil, *Tetrahedron Lett.* **1997**, *38*, 2809–2812.
- [16] R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel, *Angew. Chem.* **1998**, *110*, 2512–2515; *Angew. Chem. Int. Ed.* **1998**, *37*, 2387–2392.
- [17] A. K. Smith in *Comprehensive Organometallic Chemistry II, Vol. 9* (Ed.: R. J. Puddephatt), Pergamon, Oxford, **1995**, pp. 29–106.
- [18] a) K. Tatsumi, A. Nakamura, S. Komiya, A. Yamamoto, T. Yamamoto, *J. Am. Chem. Soc.* **1984**, *106*, 8181–8188; b) R. J. McKinney, C. D. Roe, *J. Am. Chem. Soc.* **1985**, *107*, 261–262.
- [19] Nickel complexes have been also used in the coupling of allylamines and boronic acids, including methylboronic acid: B. M. Trost, M. D. Spagnol, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2083–2096.
- [20] The previously mentioned carbonylative coupling^[12] is accelerated by light.
- [21] R. Giovannini, P. Knochel, *J. Am. Chem. Soc.* **1998**, *120*, 11186–11187.
-

Organic zeolites ?

Nanostructures self-assembled from lyotropic liquid crystals can be stabilized by polymerization and used as base catalysts. The active sites in these assemblies are highly accessible, and the materials maintain order in reaction conditions and can be recycled.

More about this on the following pages



Heterogeneous Catalysis with Cross-Linked Lyotropic Liquid Crystal Assemblies: Organic Analogues to Zeolites and Mesoporous Sieves**

Seth A. Miller, Esther Kim, David H. Gray, and Douglas L. Gin*

The angstrom- and nanoscale structure of catalysts can dramatically alter their reactivity, selectivity, and efficiency. Zeolites, a class of crystalline aluminosilicates with uniform channels in the range of 3 to 15 Å, represent the pinnacle of nanostructured catalyst design (Figure 1 a).^[1] These materials

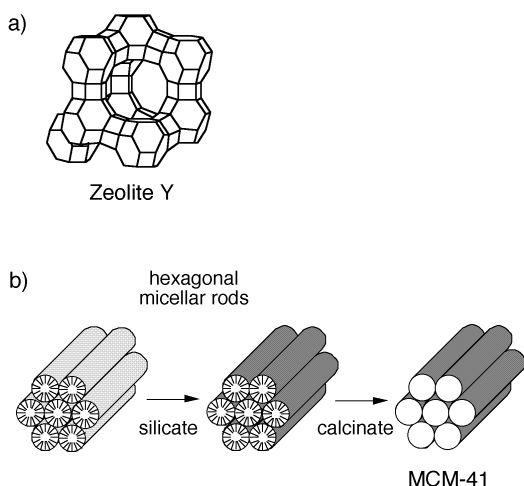


Figure 1. Nanoporous inorganic catalysts with regular structures: a) Zeolite Y, b) MCM-41.

exhibit high reactivity, recyclability, remarkable shape selectivity, and stability under extreme conditions. Consequently, they have been widely adopted as catalysts by industry for processes such as petroleum cracking and methane oxidation.^[2] However, zeolites are not amenable to processing, and their pore sizes and architectures are not easily adjustable for modulating reactivity. As a result, there has been considerable effort to find and develop materials that mimic the structure, reactivity, and selectivity of zeolites, but offer more control. For example, much attention has recently been given to mesoporous sieves, a family of templated silicate structures with tunable pore sizes from 20 to 100 Å (Figure 1 b).^[3] They have been explored with an eye towards novel reactivities but

their lack of stability in hydrolytic environments and low reactivity have so far prevented their adoption in industrial catalytic applications.^[4]

Organic analogues to zeolites and mesoporous sieves have been pursued with the goal of using the power of organic synthesis to tune the reactivity, processability, and architecture of the resulting systems. For example, noncovalent, crystalline organic supercages have been made that are highly porous and able to accommodate a variety of guests.^[5] These systems, however, are typically not stable to solvent or to removal of the guests. Cross-linked reverse microemulsions have successfully been used as heterogeneous organic catalysts for reactions such as phosphate hydrolysis.^[6] However, they too lack the selectivity and activity needed for many catalysis applications.

We present here a new class of catalytically active, nanoporous organic materials based on cross-linked lyotropic liquid crystals (LLCs). These solids have regular channel structures similar to those of mesoporous sieves but with much higher intrinsic reactivity. Size exclusion by the mesopores and enhanced basicity result from the nanoscale organization of the functional groups making up the channel walls. The activity of the materials is dependent on the channel structure. These materials function as efficient heterogeneous base catalysts for the Knoevenagel condensation.

Lyotropic liquid crystals are molecules composed of a polar head group and a hydrocarbon tail. Upon addition of water, these systems self-organize into phase-separated assemblies such as spheres, ordered cylinders, interconnected channels, and lamellae.^[7] We have used the LLC monomer **1**,^[8] which can pack into a lamellar or inverted hexagonal structure depending on the amount of water added.^[9] In the case of an inverted hexagonal structure, the carboxylate groups and their counterions pack densely together around extended aqueous channels approximately 10–15 Å in diameter to form a close-packed assembly of ions surrounded by a continuous organic medium (Figure 2).^[10] Monomer **1** contains a polymerizable styryl group, and upon addition of divinylbenzene (12 wt %), **1** can be photo-cross-linked into a “rigid” covalent polymer network that maintains the nanoscale order of the original LLC phase.^[8]

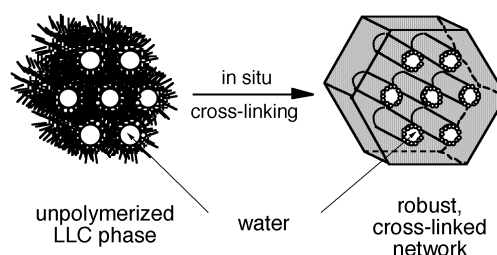
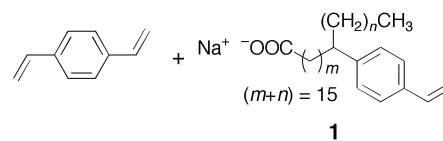
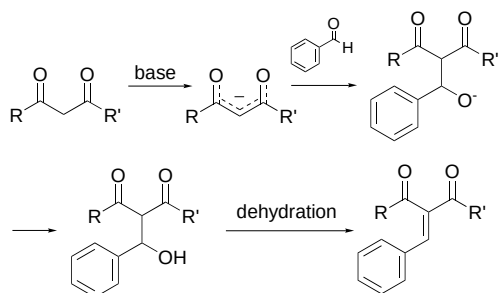


Figure 2. Synthesis of the cross-linked inverted hexagonal LLC phase using monomer **1** (a mixture of regioisomers).^[8]

[*] Prof. D. L. Gin, Dr. S. A. Miller, E. Kim, D. H. Gray
Department of Chemistry
University of California
Berkeley, California 94720 (USA)
Fax: (+1) 510-643-1846
E-mail: gin@cchem.berkeley.edu

[**] Financial support for this work was provided by the Office of Naval Research (N00014-97-1-0207), the Donors of the Petroleum Research Fund (33632-AC5,7), and the Exxon Education Fund. We would like to thank Dr. Jacek Klinowski of Cambridge University for supplying a sample of Na-MCM-41 and Zeolyst International for samples of NaY. We also thank Prof. Robert G. Bergman for helpful discussions at the initial stages of this project.

Cross-linked **1** was initially studied as a potential heterogeneous base catalyst, since the aqueous channels are lined with weakly basic carboxylate groups ($pK_a \approx 4.7$ in H_2O). Increased basicity may arise from the close packing of these charged groups inside the nanometer-scale pores. The Knoevenagel condensation of ethyl cyanoacetate with benzaldehyde (Scheme 1) was chosen as an initial test reaction of base



Scheme 1. Hann–Lapworth mechanism of the Knoevenagel condensation.^[23]

catalysis for two reasons: 1) This condensation is well-known to be catalyzed by weak bases,^[11] and the kinetics of the reaction can easily be modulated by changing the starting materials, temperature, or solvent;^[12] 2) This reaction has been previously examined using sodium-exchanged zeolite Y (NaY),^[13] mesoporous sieve (Na-MCM-41),^[14] and amine-modified MCM-41^[15] as catalysts. Thus, direct comparisons can be made between cross-linked **1** and existing inorganic, nanostructured catalysts.

The stability of cross-linked **1** was assessed before any kinetic experiments were run. Three batches of cross-linked **1** were prepared containing 8 (IH1), 15 (IH2), and 30 wt % water (LAM). Powder X-ray diffraction of these cross-linked phases showed IH1 and IH2 to be inverted hexagonal and LAM to be lamellar, as indicated by characteristic diffraction spacings of $(1, 1/\sqrt{3}, 1/2, \dots)$ and $(1, 1/2, 1/3, \dots)$, respectively.^[8] Each cross-linked phase was extracted with dry THF at reflux for four hours and retrieved by filtration under a nitrogen atmosphere. The inverted hexagonal matrices (IH1 and IH2) showed a slight decrease in overall order, as indicated by broadening of the X-ray diffraction peaks. However, their diffraction patterns and d-spacings are essentially similar (Figure 3). In contrast, the lamellar phase (LAM) showed greater disorder after cleaning, probably due to the tremendous volume loss as unbound water was removed from the matrix by THF extraction.

Phases IH1, IH2, and LAM were tested as base catalysts for the condensation of ethyl cyanoacetate with benzaldehyde (Scheme 1). The reaction was initially examined in water at reflux ($100^\circ C$), neat at room temperature, and in THF at reflux ($66^\circ C$) using 5 mol % catalyst loading. The reaction in water at reflux was highly efficient, with nearly quantitative conversion into products in only 15 min. In comparison, the use of Na-MCM-41 (5 mol %) under identical conditions in refluxing water yielded the product in 90 % yield after three hours.^[14] This was, however, too fast for a detailed kinetic analysis of our system. Running the reaction in THF allowed

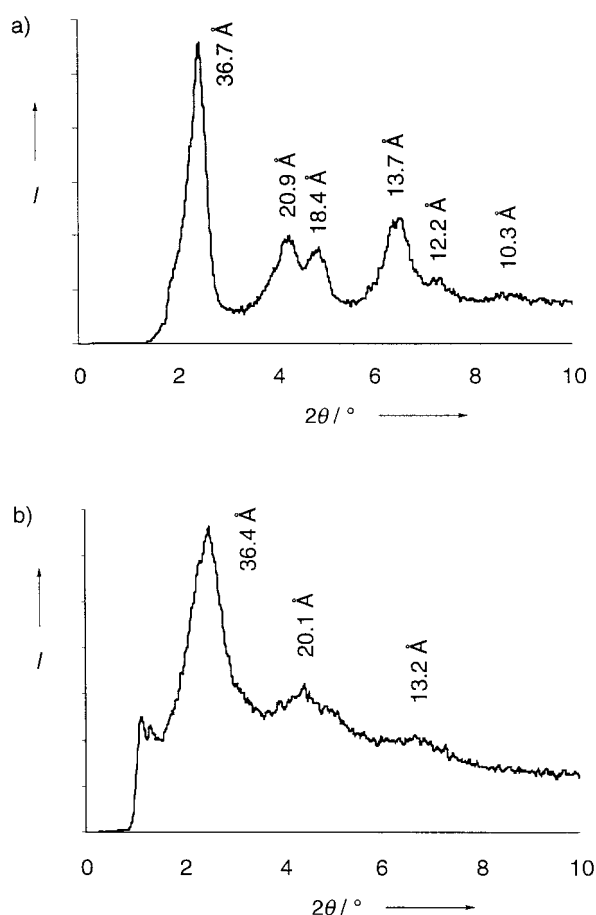


Figure 3. Powder X-ray diffraction profiles of IH1 a) before and b) after boiling in THF. After boiling in THF, the closely spaced peaks have grown together, but the spacing patterns are still indicative of an inverted hexagonal phase.

convenient monitoring of the reaction progress by gas chromatography (GC), and allowed for differentiation of the reactivities of each matrix and the NaY and Na-MCM-41 controls. In addition, 2 % cross-linked sodium polyacrylate was used as a secondary control in order to account for 1) any intrinsic basicity differences between carboxylates and anionic aluminosilicates, and 2) to compare an amorphous carboxylate system with one ordered into nanopores. The results reported below are for the reactions in THF, except where otherwise indicated.

The results of the runs in THF are shown in Figure 4. Phases IH1 and IH2 are first-order (a linear plot of $\ln c$ vs. t) with statistically equivalent rate constants ($k = 0.003$), but both show significantly more activity than LAM ($k = 0.001$). Na-MCM-41, NaY, and cross-linked sodium polyacrylate containing the same number of basic sites (as determined by elemental analysis for Na) show no activity under these conditions. In contrast, a reaction using sodium oleate as a homogeneous catalyst is second-order (a linear plot of $1/c$ vs. t) with respect to reactants, consistent with a bimolecular rate-limiting step in solution. The first-order rate constant for the LLC matrices indicates that deprotonation may be rate-limiting, and the reaction likely proceeds in a mass transport limited regime. No changes in reaction rate were seen by

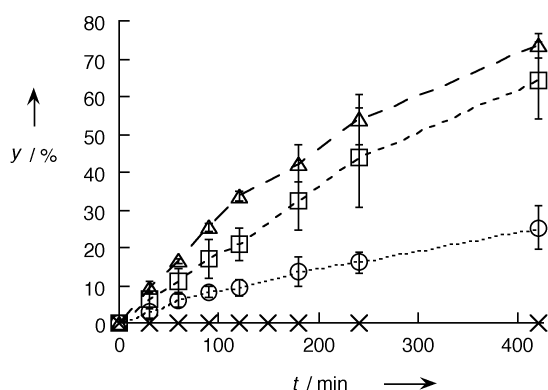


Figure 4. Results of the Knoevenagel condensation in refluxing THF; each point is the average of three runs. IH1 (Δ), IH2 ($\square$), LAM ($\circ$), NaY ($\times$); y = conversion. Na-MCM-41 and cross-linked sodium polyacrylate behave exactly as NaY.

varying the stirring rate, and the effect of particle size on reactivity could not be accurately assessed because the cross-linked particles were broken up over the course of the reaction. It is impossible to say whether the reactivities of NaY or Na-MCM-41 are so much lower due to limited transport or lower intrinsic basicities, although they are known to catalyze this reaction under more extreme conditions.^[13, 14]

Recycling experiments were performed to show that the catalytic activity of the cross-linked LLC matrices does not arise from soluble fractions leached out by the THF. After an initial reaction run, the supernatant was removed, filtered into a fresh flask, and charged with new reactants. The remaining solid was then washed and charged with fresh starting materials and THF. The supernatant repeatedly showed a very small but real activity as a base catalyst for the Knoevenagel reaction in THF. This activity was always considerably lower than that of the recycled solid, whose activity was not significantly degraded from that of the original run (Figure 5).

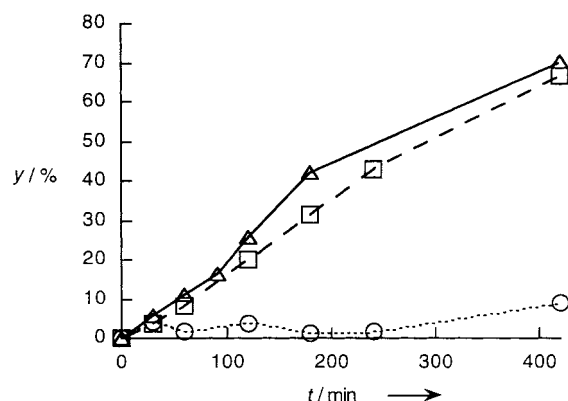


Figure 5. Recycling experiment for IH2. Original run of IH2 (Δ), recycled IH2 ($\square$), and the supernatant from the original run ($\circ$); y = conversion.

Phase IH2 was also tested as a catalyst for the condensation of ethyl cyanoacetate and benzaldehyde in the absence of solvent at room temperature; the catalyst loading level was 5 mol%. Reaction mixtures were stirred rapidly for two hours, then quenched by extracting the organic components

into ether, and analyzed by GC. Under these conditions, 70% of the starting material is converted into product by IH2. In contrast, Corma et al. showed that 20 wt% NaY in neat benzaldehyde and ethyl cyanoacetate only afforded 19% conversion after two hours at 140 °C.^[13] Since sodium oleate does not dissolve in neat benzaldehyde and ethyl cyanoacetate at room temperature, it was used as a nonporous heterogeneous control; it gives only 30% conversion after two hours. No product is seen using NaY or cross-linked sodium polyacrylate as heterogeneous catalysts in this neat system.

We rationalize these results in terms of two possible issues:

- 1) Basicity: Differences in the intrinsic basicity of the active sites (COO^- vs. aluminosilicate anions) may determine the ability of a system to catalyze the Knoevenagel condensation under certain conditions.
- 2) Accessibility: The LLC system under study is heavily cross-linked, and this may exclude species from the active sites. We anticipated the nanometer-scale order should keep the carboxylate groups largely accessible. However, size exclusion by the approximately 10–15 Å large pores may limit the ability of reagents to migrate into the channels, or the ability of products to leave the LLC matrix.

The basicity and accessibility of cross-linked **1** were determined by acid titration. Titration with strong acids yields the total amount of solvent-accessible basic groups, whereas titration with weaker acids shows the base strength of these sites. Previous studies of regular micelles containing carboxylate groups^[16] have generally shown increases in basicity from one to three $\text{p}K_a$ units, resulting from the decrease of the dielectric constant and an increase in surface potential as the ionic carboxylate groups pack together. Analogous work on close-packed, surface-exposed carboxylates have shown similar effects.^[17] These effects are not seen for unstructured polymers.^[18] Both volumetric and spectrophotometric methods were used in this work, and they yielded consistent results.

For the volumetric titration experiments, the three samples of cross-linked **1** (IH1, IH2, and LAM) were stirred in water containing two equivalents of acids of varying $\text{p}K_a$ values. After two days, an aliquot of the resulting supernatant liquid was titrated with sodium hydroxide, and the amount of acid absorbed by the matrices was determined. For weaker acids in water, **1** was stirred with one equivalent of phenol, 3-nitrophenol, or 4-nitrophenol in the absence of air, and the emergence of the deprotonated species was monitored by UV/Vis spectroscopy. The results of these experiments are summarized in Figure 6. The acids used for these volumetric titration experiments ranged in strength, from HCl to phenol ($\text{p}K_a$ range –7 to 10), and in ionicity (e.g. acetic acid, $\text{p}K_a = 4.7$, vs. pyridinium, $\text{p}K_a = 5.2$).

As can be seen in Figure 6, amorphous, cross-linked sodium polyacrylate behaves analogously to a free carboxylate group in solution. In addition, neither cross-linked sodium polyacrylate nor NaY deprotonate acids with $\text{p}K_a$ values greater than 6.8. However, nanostructured LLC networks IH1, IH2, and LAM deprotonated all the acids in this series. These experiments yielded two important results: 1) Approximately 80–90% of the carboxylate sites in the nanostructured LLC

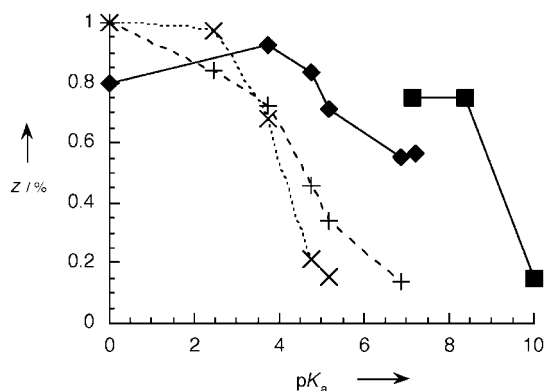


Figure 6. Titration of cross-linked LLC networks and controls in water. IH1 (♦), NaY (+), and cross-linked polyacrylic acid (X) were titrated volumetrically with acids of varying strength. IH1 was also titrated spectrophotometrically (■); z = amount of potential sites protonated.

networks (as determined from elemental analysis for Na) are accessible in water. 2) These sites are significantly more basic than those of amorphous carboxylate-containing polymers and NaY. The observed deprotonation of 4-nitrophenol ($pK_a=7$), 3-nitrophenol ($pK_a=8$), and phenol ($pK_a=10$) represents about five orders of magnitude greater apparent basicity than that of soluble carboxylate ions in water. This value is three orders of magnitude greater than that usually seen for micellar systems.^[16c] Such increased basicity likely arises from decreased stability of anions in the lower dielectric environment of the inverse hexagonal structures^[19] as well as an electrostatic effect from packing the carboxylates densely together.^[16a]

To account for the much lower catalytic activity exhibited by LAM compared to IH1 or IH2, experiments were performed to determine whether LAM differs owing to intrinsically lower basicity or lower accessibility as a result of its different nanostructure. For these experiments, each LLC matrix was boiled in THF for two hours with one equivalent of 4-nitrophenol ($pK_a=10.8$ in DMSO),^[20] and the amount of nitrophenoxide generated was assessed spectrophotometrically. Under these conditions, IH1 deprotonated 70% of the nitrophenol, compared with 30% deprotonated by LAM. Most strikingly, under the same conditions the LAM matrix only deprotonated 37% of the 2,4-dinitrophenol ($pK_a=5.1$ in DMSO).^[20] 2,4-Dinitrophenol is sufficiently acidic that it should easily protonate any accessible alkyl carboxylate group ($pK_a=11$ in DMSO). In THF, LAM appears to have equivalent basicity to IH1 and IH2 but fewer accessible carboxylate sites. The lower accessibility of the carboxylate groups in LAM fits well with the kinetic data, where the disappearance of about half of the active units correspondingly drops the catalytic rate by about a factor of two. This result also supports our model that nanostructural order in these materials is essential for obtaining high activity. The addition of water appears to swell the LAM matrix and can restore accessibility back to the level of IH1 and IH2.

Finally, simple size-exclusion experiments were performed on the cross-linked inverted hexagonal phase in order to get an indication of practical channel size selectivity independent of substrate reactivity. Extracted IH1 was stirred in water with

an excess of polycationic guest molecules of varying sizes, and the uptake by the anionic pore framework was monitored by UV/Vis or ^1H NMR spectroscopy (to determine the amount of remaining guests in the supernatant). Two polycations were chosen to encourage cation exchange by chelation. Alcian Blue (pyridine variant) is a fairly rigid tetracationic porphyrin-based dye with a diameter of approximately 15–20 Å, depending on its conformation. When one equivalent (based on cation content) of this compound is stirred with IH1, 7% of the dye is absorbed by the matrix after two hours and only 14% after two days. In contrast, over 70% of gallamine triiodide (1,2,3-tris[2-(triethylammonio)-ethoxy]-benzene triiodide), a smaller trication (<10 Å), was absorbed by the matrix after only one day. These two simple experiments confirm our rough estimate of the nanochannel size of 10–15 Å, and demonstrate that size exclusion may be one method to modulate catalytic activity. Given the small molecular size of our starting materials and products, it is unlikely that any sort of size exclusion is affecting the kinetics of the reactions and titrations under study.

The principles elucidated by these studies may be applicable to other classes of reactions as well. For instance, we have previously shown that we can substitute a variety of transition metals^[21] and lanthanides^[22] for the sodium ions in the nanochannels. These materials may serve as catalysts for other types of reactions.

Experimental Section

Instrumentation. ^1H NMR spectra were obtained using a Bruker AMX-300 FT spectrometer (300 MHz) and D_2O as the solvent. Low-angle X-ray diffraction profiles were obtained using an Inel CPS 120 powder diffraction system using monochromated $\text{CuK}\alpha$ radiation. UV/Vis spectra were obtained using a Hewlett-Packard 8453 diode array spectrophotometer. The GC traces were taken with a Hewlett-Packard 5890A gas chromatograph equipped with a Hewlett-Packard Ultra 2 column (length 25 m, diameter 0.2 mm). Measurements of pH were taken using an Accumet Model 15 pH meter.

Materials. Heavily cross-linked LLC matrices of **1** were made as previously described.^[8] The materials were ball-milled to a fine powder, and heated at reflux in distilled THF, captured by filtration, and stored under N_2 . Optima water was obtained from Fisher Scientific, and for air-free operations was degassed by purging with N_2 . THF, ethyl cyanoacetate, and benzaldehyde were purchased from Aldrich Chemical Company, distilled, and stored under N_2 prior to use. All other chemicals were used as purchased.

Catalysis experiments. A sample of the catalyst (ca. 40 mg, 5 mol% based on Na content) was refluxed with benzaldehyde (155 μL , 1.5 mmol) and ethyl cyanoacetate (163 μL , 1.5 mmol) in dry THF (7 mL) with *n*-dodecane (87 μL , 0.38 mmol; internal GC standard). The evolution of products was monitored by GC ($10^\circ\text{C min}^{-1}$, $70 \rightarrow 250^\circ\text{C}$, samples taken after 30, 60, 90, 120, 180, 240, and 420 min). Neat reactions were run at room temperature, quenched after 2 h, and analyzed by GC. Reactions in water were run at reflux for 15–30 min before quenching.

Volumetric titration experiments. A sample of catalyst (ca. 25 mg) was stirred for 48 h with 0.1M acid (1 mL, ca. 2 equiv). Acids used: HCl, cyanoacetic acid, formic acid, acetic acid, pyridinium tosylate, *N*-(2-acetamido)-2-aminoethane-sulfonic acid (ACES), and K_2HPO_4 . For each equilibration with acid, the suspension was centrifuged; and a 0.5-mL aliquot was removed and titrated with standardized 0.01505 M NaOH. The endpoints were detected using a pH meter.

Indicator experiments. An indicator solution was added to a few milligrams of cross-linked LLC and sonicated briefly. For quantitation in water, 10 mg of the heterogeneous base catalyst was stirred with a phenol solution (1 equiv in 2 mL of water) overnight in the absence of air. The resulting

phenoxide concentration was determined from UV/Vis spectroscopy at 288 nm (phenol), 390 nm (3-nitrophenol), 400 nm (4-nitrophenol), or 420 nm (2,4-dinitrophenol), within the linear Beer's Law regime as determined by a four-point calibration curve. For quantitation in THF, the matrix was heated at reflux in the absence of air with 1 equiv of nitrophenol in THF (4 mL) for 2 h. The concentration of phenoxide was measured spectroscopically as above.

Size-exclusion experiments. The cross-linked LLC matrix (10 mg) was stirred with 1 equiv, by cation content, of either Alcian Blue (pyridine variant) or gallamine triethiodide in D₂O (2 mL) in the absence of air. After one day of stirring, the suspensions were centrifuged and an aliquot was analyzed. Alcian Blue (pyridine variant) was analyzed quantitatively by UV/Vis spectroscopy at 615 nm. Measurements were taken within the linear regime for Beer's Law. Gallamine triethiodide concentrations were analyzed by integration of ¹H NMR signals using DMSO as an internal standard.

Received: May 17, 1999 [Z13430IE]

German version: *Angew. Chem.* **1999**, *111*, 3206–3210

Keywords: heterogeneous catalysis • liquid crystals • nanostructures • zeolite analogues

- [19] V. Ramesh, H.-S. Chien, M. M. Labes, *J. Phys. Chem.* **1987**, *91*, 5937–5940.
 [20] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463.
 [21] D. H. Gray, D. L. Gin, *Chem. Mater.* **1998**, *10*, 1827–1832.
 [22] H. Deng, D. L. Gin, R. C. Smith, *J. Am. Chem. Soc.* **1998**, *120*, 3522–2523.
 [23] A. C. O. Hann, A. Lapworth, *J. Chem. Soc.* **1904**, 85, 46–56.

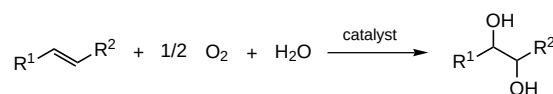
Atom-Efficient Oxidation of Alkenes with Molecular Oxygen: Synthesis of Diols**

Christian Döbler, Gerald Mehlretter, and Matthias Beller*

Dedicated to Professor Manfred Baerns on the occasion of his 65th birthday

The selective oxidation of alkenes with molecular oxygen involving the participation of both oxygen atoms is one of the most significant challenges in modern catalysis research. In spite of the advantages of oxygen over “classical” stoichiometric oxidizing agents (e.g. peracids, chlorates, periodates), only one oxygen atom is generally incorporated into the molecule in the oxidation of alkenes with molecular oxygen. The second oxygen atom reacts with a reducing agent present to form by-products, which are thus formed in stoichiometric amounts. Such processes are found in enzymatic oxidations,^[1] transition metal catalyzed reactions with O₂/H₂, and stoichiometric reactions with O₂/RCHO or O₂/alkylarenes.^[2] Groves et al. have been able for the first time to show that both oxygen atoms of molecular oxygen are used during epoxidation in the presence of a porphyrin–ruthenium catalyst.^[3]

Because of the industrial importance of diols, both as bulk chemicals (in particular propylene glycol)^[4] and as fine chemicals, we are interested in carrying out dihydroxylations with molecular oxygen as oxidant (Scheme 1).



Scheme 1. Metal-catalyzed dihydroxylation with molecular oxygen.

Osmium(VIII) compounds have proved to be the most reliable metal catalysts for dihydroxylations. On the basis of the pioneering work of Sharpless et al.^[5] it has been possible to demonstrate the preparative potential of the method,

- [1] J. M. Thomas, R. G. Bell, C. R. Catlow, *Handbook of Heterogeneous Catalysis*, Vol. 1 (Eds.: G. Ertl, H. Knozinger, J. Weitkamp), WILEY-VCH, Weinheim, **1997**, pp. 286–387.
 [2] a) G. T. Kokotailo, C. A. Fyfe, *J. Phys. Chem. Solids* **1989**, *50*, 441–447; b) N. Y. Chen, *Catalysis* (Ed.: J. W. Ward) Elsevier, Amsterdam, **1987**, pp. 153–163.
 [3] a) C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710–712; b) J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, *J. Am. Chem. Soc.* **1992**, *114*, 10834–10843.
 [4] a) A. Sayari, *Chem. Mater.* **1996**, *8*, 1840–1852; b) J. Y. Ying, C. P. Mehnert, M. S. Wong, *Angew. Chem.* **1999**, *111*, 58–82; *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 56–77.
 [5] a) V. A. Russell, C. C. Evans, W. J. Li, M. D. Ward, *Science* **1997**, *276*, 575–579; b) P. Brunet, W. Simard, J. D. Wuest, *J. Am. Chem. Soc.* **1997**, *119*, 2737–2738.
 [6] F. M. Menger, T. Tsuno, *J. Am. Chem. Soc.* **1990**, *112*, 1263–1264.
 [7] J. N. Israelachvili, *Intermolecular and Surface Forces*, Academic Press, London, **1985**.
 [8] D. H. Gray, S. Hu, E. Juang, D. L. Gin, *Adv. Mater.* **1997**, *9*, 731–736.
 [9] The very low water content in the mixture is consistent with an inverse mesophase, and addition of water leads to the expected lamellar structure. See also reference [8].
 [10] J. M. Seddon, *Biochim. Biophys. Acta* **1990**, *1031*, 1–69. Based on the known water content, approximate densities of the materials, and the interchannel distances (from X-ray diffraction), the pore diameters for IH1 and IH2 were calculated to be about 10–15 Å and the wall thicknesses about 30 Å.
 [11] G. Jones, *Org. React.* **1967**, *15*, 204–599.
 [12] a) S. Patai, Y. Israeli, *J. Chem. Soc.* **1960**, 2020–2024; b) S. Patai, Y. Israeli, *J. Chem. Soc.* **1960**, 2024–2030; c) S. Patai, J. Zabicky, *J. Chem. Soc.* **1960**, 2030–2038; d) S. Patai, J. Zabicky, Y. Israeli, *J. Chem. Soc.* **1960**, 2038–2044.
 [13] A. Corma, V. Fornés, R. M. Martín-Aranda, H. García, J. Primo, *Appl. Catal.* **1990**, *59*, 237–248.
 [14] K. R. Kloetstra, H. van Bekkum, *J. Chem. Soc. Chem. Commun.* **1995**, 1005–1006.
 [15] D. J. McQuarrie, D. B. Jackson, *Chem. Commun.* **1997**, 1781–1782.
 [16] a) M. S. Fernandez, P. Fromherz, *J. Phys. Chem.* **1977**, *81*, 1755–1761; b) F. Greiser, C. J. Drummond, *J. Phys. Chem.* **1988**, *92*, 5580–5593; c) O. A. El Seoud, *Adv. Colloid Interface Sci.* **1989**, *30*, 1–30.
 [17] a) S. R. Holmers-Farley, R. H. Reamey, T. J. McCarthy, J. Deutch, G. M. Whitesides, *Langmuir* **1985**, *1*, 725–740; b) S. R. Holmes-Farley, C. D. Bain, G. M. Whitesides, *Langmuir* **1988**, *4*, 921–927; c) J. Wang, L. M. Frostman, M. D. Ward, *J. Phys. Chem.* **1992**, *96*, 5224–5228.
 [18] J. E. Frommer, R. G. Bergman, *J. Am. Chem. Soc.* **1980**, *102*, 5227–534.

[*] Prof. Dr. M. Beller, Dr. C. Döbler, Dipl.-Chem. G. Mehlretter
 Institut für Organische Katalysforschung (IfOK)
 Buchbinderstrasse 5–6, D-18055 Rostock (Germany)
 Fax: (+49) 381-46693-24
 E-mail: matthias.beller@ifok.uni-rostock.de

[**] This work was supported by the Bildungsministerium des Landes Mecklenburg-Vorpommern and Bayer AG (Leverkusen). We thank I. Stahr for experimental support, and K. Kortus and Dr. C. Fischer for the GC and HPLC investigations.

Table 1. Dihydroxylation of 1-octene.^[a]

Entry	pH	Ligand	Os:L	Conversion [%]	Sel. [%]	Yield [%]	ee [%]
1	7	–	–	13	4	< 1	–
2	9	–	–	69	83	57	–
3	10.4	–	–	91	89	81	–
4	11.2	–	–	63	72	46	–
5	10.4	DABCO ^[b]	1:1	96	97	92	–
6	10.4	DABCO	1:3	99	97	96	–
7	10.4	quinuclidine	1:3	99	96	95	–
8	10.4	(DHQD) ₂ PHAL ^[c]	1:3	99	98	98	65 (R)
9	10.4	(DHQ) ₂ PHAL ^[d]	1:3	99	96	97	54 (S)

[a] In all reactions 1-octene (2.0 mmol) was allowed to react in the presence of 0.5 mol % $K_2[OsO_2(OH)_4]$ in a mixture of aqueous buffer solution (25 mL, phosphate buffer with the given pH value) and *tert*-butyl alcohol (10 mL) at 1 bar O_2 and 50 °C with stirring (reaction time 14–18 h). [b] DABCO = 1,4-diazabicyclo[2.2.2]octane. [c] (DHQD)₂PHAL = hydroquinidine 1,4-phthalazinediyl diether.^[6] [d] (DHQ)₂PHAL = hydroquinine 1,4-phthalazinediyl diether.^[6]

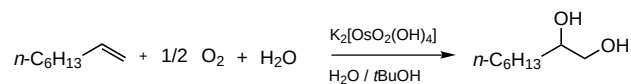
Table 2. Dihydroxylation of different alkenes with oxygen.^[a]

Entry	Alkene	Ligand ^[b]	Cat. [mol %]	Conversion [%]	Sel. [%]	Yield [%]	ee [%]
1	vinyl naphthalene	DABCO	1	75	75	56	–
2	vinyl naphthalene	(DHQD) ₂ PHAL	1	72	76	55	96 (R)
3	styrene	DABCO	2	66	77	51	–
4	styrene	(DHQD) ₂ PHAL	2	67	78	52	90 (R)
5	α -methylstyrene	DABCO	0.5	100	97	97	–
6	α -methylstyrene	(DHQD) ₂ PHAL	0.5	100	96	96	80 (R)
7	1-phenylcyclohexene	DABCO	2	90	95	85	–
8	1-phenylcyclohexene	(DHQD) ₂ PHAL	2	53	96	51	86 (R,R)
9	cyclohexene	DABCO	0.5	90	75	68	–

[a] The alkene (2.0 mmol) was allowed to react in the presence of $K_2[OsO_2(OH)_4]$ in a mixture of aqueous buffer solution (25 mL, pH 10.4) and *tert*-butyl alcohol (10 mL) at 1 bar O_2 and 50 °C with stirring (reaction time 16–24 h). [b] Ratio osmium/ligand = 1/3.

especially in asymmetric catalysis.^[6] In contrast, investigations on the use of molecular oxygen as oxidant for osmium-catalyzed dihydroxylations have been largely ignored,^[7] especially since in 1968 Cairns et al. demonstrated that diols were not formed during osmium-catalyzed dihydroxylations in the presence of oxygen.^[7a] More recent work by Krief et al. has shown with the example of the dihydroxylation of α -methylstyrene that such a reaction is possible, however, by light induction in the presence of sensitizers (8 mol % arylselenides).^[8]

We describe here for the first time highly selective (chemo- and enantioselective) osmium-catalyzed dihydroxylations of alkenes which can be carried out simply with molecular oxygen without the addition of cocatalysts, even under mild conditions. With the backdrop of the industrial importance of aliphatic diols^[9] we chose the transformation of 1-octene as model reaction (Scheme 2 and Table 1). Since the oxidative



Scheme 2. Dihydroxylation of 1-octene.

action of the Os/O_2 system is highly dependent upon the pH value of the reaction medium,^[7a] we first investigated the dihydroxylation of 1-octene in different aqueous buffer systems. To overcome the problem of further, nonselective oxidation of the diols, an organic solvent was added so that a second phase was formed under the reaction conditions.

As Table 1 shows (entry 1), no significant diol formation is observed at pH 7. In contrast, in the basic pH range (optimum: pH 10.4) osmium is reoxidized to active dihydroxylation catalysts (entries 2 and 3). At higher pH values the chemoselectivity of the reaction falls (entry 4). The oxygen consumption measured, which is almost 1 mmol for 2 mmol of substrate, shows that both oxygen atoms are used productively in the oxidation reaction. Since osmium-catalyzed dihydroxylation is a ligand-accelerated reaction (“ligand-accelerated catalysis”),^[10] the chemoselectivity of the catalyst should be improved by the addition of ligand. Indeed, higher yields are obtained by the addition of 1.5 mol % 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1.5 mol % quinuclidine as ligands (entries 6 and 7). Thus, 1-octene is oxidized to 99 % after 18 h in the presence of 0.5 mol % Os, and 1,2-octanediol is obtained with 97 % selectivity. To the best of our knowledge this is the highest selectivity obtained in transition metal catalyzed oxidation of alkenes with molecular oxygen.

The stereoselective dihydroxylation of 1-octene was also achieved with the use of chiral quinine and quinidine ligands developed by Sharpless et al.^[5] (entries 8 and 9). We explain the somewhat lower enantioselectivities compared to dihydroxylations with $K_3[Fe(CN)_6]$ as oxidant by the higher reaction temperatures in our system and the competition of hydroxide ions as ligands for the central metal.

Next we dihydroxylated different alkenes under the reaction conditions optimized for 1-octene. The results are summarized in Table 2.

In addition to aliphatic alkenes with a terminal double bond we investigated arylalkenes (styrene, vinyl naphthalene), the

1,1-disubstituted alkene α -methylstyrene, the 1,2-*cis*-disubstituted alkene cyclohexene, and the trisubstituted alkene 1-phenylcyclohexene. In all cases diol selectivities of over 75% are obtained, frequently greater than 90%. Calculations of oxygen consumption show that in all reactions both oxygen atoms are used productively for diol formation and catalyst regeneration. The aryl-substituted diols are formed with good to very good enantioselectivities (80–96% *ee*) which are only slightly lower than those achieved under the optimized Sharpless conditions. This is largely attributable to the higher temperature (50°C compared to 0°C).

In summary, osmium-catalyzed dihydroxylations may be carried out simply and practicably with oxygen at normal pressure in a basic two-phase system. Both oxygen atoms are incorporated into the product in an atom-efficient manner. The diols are obtained in excellent yields, and the catalyst can be recycled. Thus the method described here represents not only an improvement over the versatile Sharpless dihydroxylation, but also opens up new perspectives for by-product-free preparation of diols used on an industrial scale.

Received: June 22, 1999 [Z13598]

German edition: *Angew. Chem.* **1999**, *111*, 3211–3212

Keywords: dihydroxylations • homogeneous catalysis • osmium • oxidations • oxygen

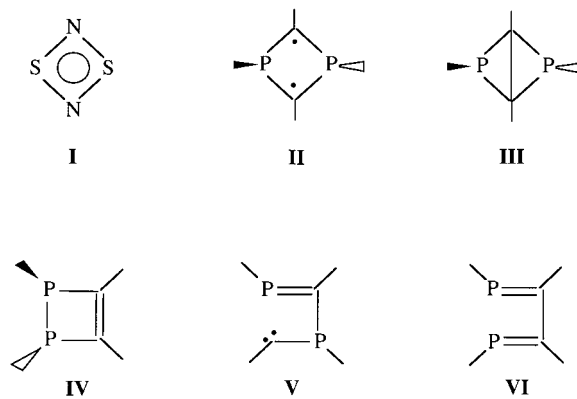
- [1] A. Archelas in *Enzyme Catalysis in Organic Synthesis* (Eds.: K. Drauz, H. Waldmann), VCH, Weinheim, **1995**, p. 667.
- [2] a) P. Laszlo, M. Levart, *Tetrahedron Lett.* **1993**, *34*, 1127–1130; b) T. Mukaiyama, T. Yamada, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 17–35; c) I. Klement, H. Lütjens, P. Knochel, *Angew. Chem.* **1997**, *109*, 1605–1607; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1454–1456; d) A. K. Mandal, J. Iqbal, *Tetrahedron* **1997**, *53*, 7641–7648; e) Z. Gross, A. Mahammed, *J. Mol. Catal.* **1999**, *142*, 367–372.
- [3] a) J. T. Groves, R. Qinn, *J. Am. Chem. Soc.* **1985**, *107*, 5790–5792; b) *Metalloporphyrins Catalyzed Oxidations* (Eds.: F. Montanari, L. Casella), Kluwer, Dordrecht, **1994**.
- [4] The worldwide annual production of propylene glycol in 1994 was over 1.1 million t. (Source: K. Weissmermel, H.-J. Arpe, *Industrielle Organische Chemie*, 5th ed., WILEY-VCH, Weinheim, **1998**, p. 302.)
- [5] a) E. N. Jacobsen, I. Markó, W. S. Mungall, G. Schröder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970; b) J. S. M. Wai, I. Markó, J. S. Svendsen, M. G. Finn, E. N. Jacobsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 1123–1125.
- [6] Review: a) H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547; b) M. Beller, K. B. Sharpless in *Applied Homogeneous Catalysis* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, pp. 1009–1024; c) H. C. Kolb, K. B. Sharpless in *Transition Metals for Organic Synthesis, Vol. 2* (Eds.: M. Beller, C. Bolm), WILEY-VCH, Weinheim, **1998**, pp. 219–242.
- [7] a) J. F. Cairns, H. L. Roberts, *J. Chem. Soc. C* **1968**, 640–642; b) Celanese Corp., GB-B 1028940, **1966** [*Chem. Abstr.* **1966**, *65*, 3064f]; c) R. S. Myers, R. C. Michaelson, R. G. Austin (Exxon Corp.), US-A 4496779, **1984** [*Chem. Abstr.* **1984**, *101*, P191362k].
- [8] A. Krief, C. Colaux-Castillo, *Tetrahedron Lett.* **1999**, *40*, 4189–4192.
- [9] G. Sienel, R. Rieth, K. T. Rowbottom in *Ullmanns Enzyklopädie der technischen Chemie, Vol. 9a*, 5th ed., VCH, Weinheim, **1992**, pp. 531–545.
- [10] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159–1171; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059–1071.

Valence Isomerization of a 1,3-Diphosphacyclobutane-2,4-diyl: Photochemical Ring Closure to 2,4-diphosphabicyclo[1.1.0]butane and Its Thermal Ring Opening to *gauche*-1,4-Diphosphabutadiene**

Edgar Niecke,* André Fuchs, and Martin Nieger

Dedicated to Professor Bernt Krebs on the occasion of his 60th birthday

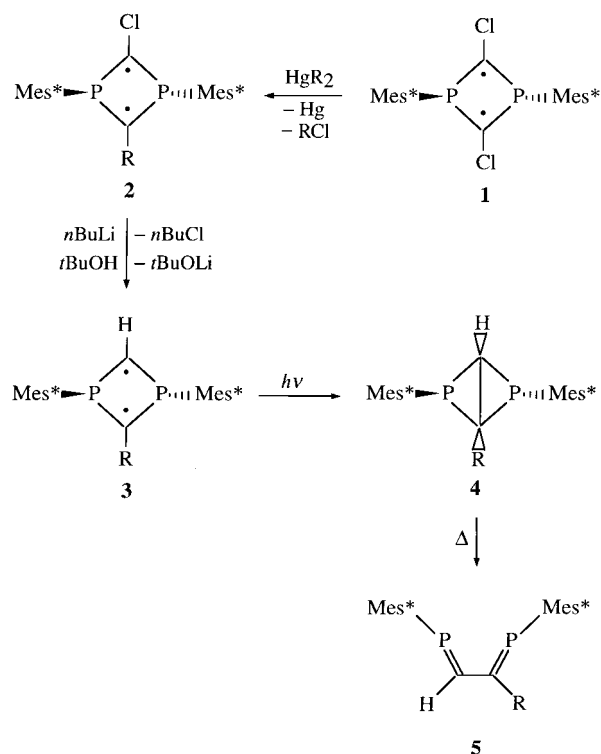
The disulfur dinitride **I** is generally considered as a prominent example of an electron-rich π -delocalized four-membered ring system.^[1] Valence isomerization to a bicyclobutane, butadiene, or cyclobutene analogue is unknown, although polymerization by means of diradical ring opening is known.^[2] Recently, we established^[3] the existence of a further four-membered ring system, isoelectronic with **I**, in the form of 1,3-diphosphacyclobutane-2,4-diyl **II** (a 2,4-diphosphabicyclo[1.1.0]butane bond stretch isomer^[4]) and characterized structurally the first derivatives.^[3, 5] Ab initio calculations confirm a substantial diradical contribution to the parent system of **II**^[6] which results from the high inversion barrier of the phosphorus atom. Transannular C–C bond formation to the thermodynamically favored 2,4-diphosphabicyclo[1.1.0]butane **III**,^[7] however, does not occur.^[8] Instead, thermal rearrangements are induced which, similar to **I**, were initiated by ring opening.^[3, 5] This includes the valence isomerization of **II** to 1,2-dihydro-1,2-diphosphete **IV** which we recently reported,^[9] and which proceeds via a phosphanylcarbene **V**.^[10] We report here on the photochemically induced ring closure of **II** to the 1,3-diphosphabicyclo[1.1.0]butane **III** and its thermal ring opening to *gauche*-1,4-diphosphabutadiene **VI**. Previously, phosphabicyclobutanes have only been known with phosphorus in the bridge position,^[11] for free phosphabutadienes only the *trans* form has been hitherto established.^[12]



[*] Prof. Dr. E. Niecke, Dr. A. Fuchs, Dr. M. Nieger
Institut für Anorganische Chemie der Universität
D-53121 Bonn (Germany)
Fax: (+49) 228-735327
E-mail: e.niecke@uni-bonn.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 334) and the Fonds der Chemischen Industrie. Published in part at the "XIV International Congress on Phosphorus Chemistry", Cincinnati, **1998**, Abstr. No. LM 2-3.

The crystalline 1,3-diphosphacyclobutane-2,4-diyl **2**, which is readily available from 1,3-diphosphacyclobutane-2,4-diyl [Mes*PCCl]₂ (**1**) (Mes* = 2,4,6-*t*Bu₃C₆H₂)^[3] by selective Cl/SiMe₃ exchange (0.5 equiv Hg(SiMe₃)₂), can be transformed into the protonated derivative **3** with *n*BuLi and subsequent *t*BuOH addition (Scheme 1). This product can be isolated in the form of a red crystalline solid. Whereas **3** is thermally extremely stable,^[13] irradiation (10% solution in *n*-pentane, −30 °C) induced a rapid conversion of **3** into the 1,3-diphosphabicyclo[1.1.0]butane **4**, which was isolated as a yellow solid and can be transformed into the 1,4-diphosphabutadiene **5** by heating (10% solution in mesitylene, 150 °C, 2 h) (Scheme 1; see Experimental Section).



Scheme 1. Synthesis of **2**–**5**. R = SiMe₃; Mes* = 2,4,6-*t*Bu₃C₆H₂.

The ³¹P and ¹³C NMR shifts of **2** and **3** correspond to those of the first 1,3-diphosphacyclobutane-2,4-diyls, [Mes*PCCl]₂^[3] and [2,2,6,6-Me₄C₅H₆NPCCl]₂.^[9] The observed A₂X pattern of the ring carbon atom signals in the ¹³C{¹H} NMR spectrum and the ideal 1:2:1 triplet structure of the signal of the ring proton in **3** (δ = 4.9, ²J(H,P) = 33.8 Hz) exclude the presence of the thermodynamically favored 1,2-dihydro-1,2-diphosphate **6**.^[14] The changes in the NMR spectrum observed during the irradiation of **3** are manifested in a strong deshielding of all ring atoms (δ(³¹P) = −83.4, −84.2, (²J(P,P) = 32.4 Hz; δ(¹³C) = 28.3 (¹J(C,P) = 74.8, 66.4 Hz), 28.3 (¹J(C,P) = 58.0, 47.7 Hz)). The position of the signals and the splitting pattern indicate the presence of the bicyclic valence isomer **4**. The chemical nonequivalence of the two phosphorus atoms confirm the axial/equatorial arrangement of the aryl residues, required for a stereoselective reaction course **3**→**4**.

The structures of **3** and **4** derived from the NMR data are proved by X-ray structural analysis^[15] (Figures 1a and 1b). This confirms the presence of a planar P₂C₂ ring for **3** with the

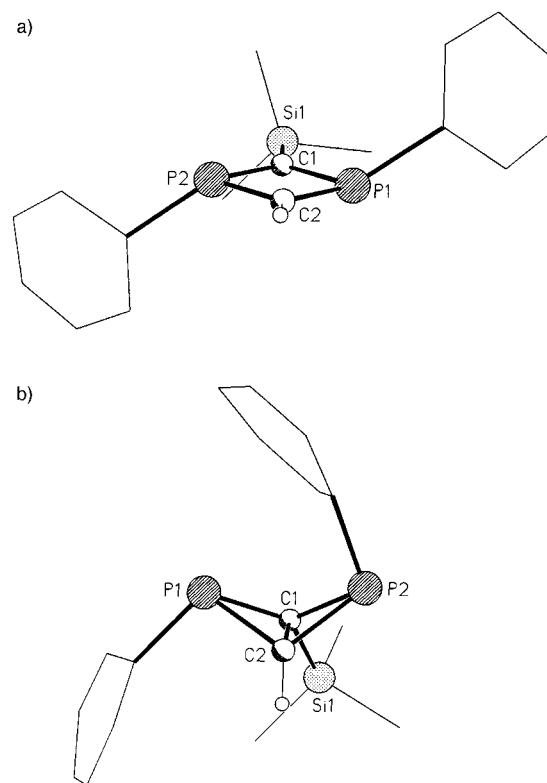


Figure 1. a) Simplified representation of the crystal structure of **3** (an independent molecule; without hydrogen atoms). Selected bond lengths [pm], bond angles [°], and torsion angles [°]: P1–C1 172.8(3), P1–C2 172.3(3), P2–C1 174.3(3), P2–C2 171.9(3); C1–P1–C2 91.5(1), P1–C1–P2 88.2(1), C1–P2–C2 91.1(1), P1–C2–P2 89.2(1); P1–C1...C2–P2 179.6(2). Sum of angles Σ at C1 360°, at C2 360°; P1, P2, C1 and C2 lie in one plane (deviation from the mean plane 0.2 pm). b) Simplified representation of the crystal structure of **4** (without hydrogen atoms). Selected bond lengths [pm], bond angles [°], and torsion angles [°]: P1–C1 187.0(3), P1–C2 182.0(3), P2–C1 186.1(3), P2–C2 181.2(3), C1–C2 151.6(4); C1–P1–C2 48.5(1), P1–C1–P2 100.3(1), P1–C1–C2 64.0(1), P1–C2–P2 104.1(1), C1–C2–P1 67.5(1), C1–P2–C2 48.7(1), P2–C1–C2 63.9(1), C1–C2–P2 67.3(1); P1–C1–C2–P2 = 117.3(1).

phosphorus atoms in the 1,3 position and *trans* aryl substituents (C_i symmetry). The pyramidalization at the phosphorus atoms in **3** (sum of the valence angle 337° and 341°) is similar to that in [Mes*PCCl]₂ (**3a**) (338°).^[3] Unlike in **3a**, the carbon atoms in **3** are trigonal-planar coordinated. This geometry causes comparatively shorter P–C distances (mean value: 173 pm; cf. 175 pm in **3a**),^[3] indicating a reinforcement of the cyclic electron delocalization (weakening of the diradical character) in comparison to **3a**. The transannular C–C linkage **3**→**4** (**3**: C1...C2 247, **4**: C1–C2 152 pm) is associated with a folding of the P₂C₂ four-membered ring (folding angle P1–C1–C2–P2 117°). The aryl substituents are thus forced into the axial/equatorial position, an indication of the retention of the configuration at the phosphorus atoms. The folding is associated with a loss of π-electron delocalization, which is expressed by an increase in the P–C distances to typical values for single bonds (mean value 184 pm).

The thermolysis of **4** (1,2-dimethoxyethane (DME), 150 °C, 2 h) proceeds smoothly to give a product which exhibited a strong deshielding of the phosphorus atoms in the ^{31}P NMR spectrum ($\delta = 298.2, 280.0$). The changes in the ^{13}C NMR shifts of the ring carbon atoms on transformation of **3** to **4** correlate with the $\delta(^{31}\text{P})$ values ($\delta = 184.3, 177.4$) and suggest the formation of a butadiene-like system with phosphorus atoms in the 1,4 positions. This constitution is supported by the low-field position and the multiplet structure of the ^1H NMR signal ($\delta = 7.46, J(\text{H},\text{P}) = 4.6, 28.7$ Hz). The large contribution of the P–P coupling constant of 167.8 Hz, which would be in agreement with neighboring lone pairs of electrons on the phosphorus atoms, is conspicuous.

Figure 2 shows the molecular structure of **5** in the crystal.^[15] Unlike the previously known, *trans*-configured 1,4-diphosphabutadienes,^[18] **5** exists in the *gauche*-(*cis,anti*) form

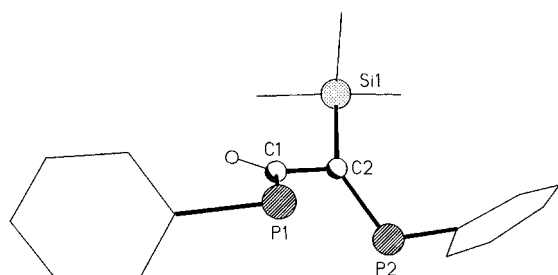


Figure 2. Simplified representation of the crystal structure of **5** (without hydrogen atoms). Selected bond lengths [pm], bond angles [°], and torsion angles [°]: P1–C1 168.5(2), C1–C2 146.4(2), C2–P2 169.7(2), C2–Si1 189.7(2), C1–H1 95; P1–C1–C2 123.2(1), C1–P1–C6 100.0(1), C1–C2–P2 110.8(1), C1–C2–Si1, 114.2(1), C2–P2–C24 108.0(1), P2–C2–Si1 134.9(1); P1–C1–C2–Si1 –142.3(1), P1–C1–C2–P2 41.0(2). Sum of angles Σ at C2 359.9°.

(torsion angle P1–C1–P2–C2 41°). This conformation, in which the two methylene carbon fragments, unlike a *cis* form,^[19] are transposed in opposite directions, leads to a reduction in the repulsive interactions between the lone pairs of electrons on the phosphorus atoms. The peripheral aryl substituents are located in the *exo,exo* position, which is to be expected for a contrarotatory ring opening **4** → **5**.^[5] Ab initio calculations also favor a contrarotatory process in the ring opening of the bicyclobutane to the *gauche* butadiene.^[20] The large value of the $^3J(\text{P},\text{P})$ coupling constant is equally compatible with the *gauche* conformation of **5**. The P–C distances (P1–C1 168.2(2), P2–C2 169.7(2) pm) and the C–C bond lengths (146.4 (2) pm) confirm the formation of a conjugated π -electron system. Steric factors impose the almost orthogonal alignment of the aryl moieties to the P_2C_2 fragment. The remaining bond lengths and angles show nothing conspicuous.

Experimental Section

2: A solution of **1** (1.30 g, 2 mmol) in THF (40 mL) was treated dropwise with a solution of $\text{Hg}(\text{SiMe}_3)_2$ in *n*-hexane (0.66 M, 3.2 mL) at 25 °C. The mixture was stirred for 2 h and the red solution was then withdrawn from the resulting mercury with a syringe. Cooling the reaction solution to 2 °C resulted in the crystallization of **2**. Yield 0.96 g (71 %); m.p. 140–142 °C; NMR spectra (25 °C, without signals of the aryl residues): $^{31}\text{P}\{^1\text{H}\}$ NMR (CH_2Cl_2): $\delta = 2.2$ (s); ^1H NMR (CH_2Cl_2): $\delta = -0.49$ (s, SiMe_3); ^{13}C NMR (CH_2Cl_2): $\delta = 1.71$ (t, $^3J(\text{C},\text{P}) = 3.4$ Hz, P_2SiC_3), 93.9 (t, $^1J(\text{C},\text{P}) = 27.9$ Hz,

P_2SiC_3), 104.5 (t, $^1J(\text{C},\text{P}) = 23.1$ Hz, P_2CCl_2); UV/Vis (pentane, $c = 2.60 \times 10^{-5}$ mol L $^{-1}$, 25 °C): λ [nm] (ϵ) = 205 (77000), 252 (36000), 321 (28000), 458 (2600); MS (70 eV): m/z (%): 684 (2) [M^+], 439 (100) [$M^+ - \text{Mes}^*$].

3: Compound **2** (0.45 g, 0.66 mmol) was dissolved in THF (3 mL) and metalated at –78 °C within 10 min by stirring with *n*BuLi (0.2 mL, 0.33 mmol) in *n*-hexane ($c = 1.6$ mol L $^{-1}$). Product **3** crystallized from the solution as yellow crystals after two days at +2 °C. Yield 97 %; m.p. 164–166 °C; NMR spectra (25 °C, without signals from the aryl residues): ^{31}P NMR (ext.): $\delta = 11.3$; ^1H NMR (C_6D_6): $\delta = 5.7$ (t, $^2J(\text{H},\text{P}) = 11.4$ Hz, P_2CHCl); ^{13}C NMR (C_6D_6): $\delta = 3.8$ (t, $^4J(\text{C},\text{P}) = 4.6$ Hz, PCSiC_3), 104.0 (t, $^2J(\text{C},\text{P}) = 4.8$ Hz, P_2CH), 111.0 (t, $^2J(\text{C},\text{P}) = 20.2$ Hz, P_2SiC_3); MS (70 eV): m/z (%): 482 (6) [M^+], 73 (100) [SiMe_3].

4: A solution of **3** (198 mg, 305 mmol) in DMF (5 mL) was irradiated at –25 °C with a Hg lamp for 2 h during which time the color of the reaction solution changed from red to yellow. In addition to an as yet unidentified species, **4** was formed as the main product (>90 % by ^{31}P NMR). The reaction solution was evaporated in vacuo and stored at –30 °C. Compound **4** crystallized after two days. Yield 1.21 g (67 %); m.p. 164–166 °C; NMR spectra (THF, 25 °C, without signals from the aryl residues): ^{31}P NMR (ext.): $\delta = -83.4, -84.2$ ($^2J(\text{P},\text{P}) = 32.4$ Hz); ^1H NMR (C_6D_6): $\delta = 2.73$ (dd, $^2J(\text{H},\text{P}) = 4.6, 28.7$ Hz); ^{13}C NMR (C_6D_6): $\delta = 28.3$ (dd, $^1J(\text{C},\text{P}) = 74.8, 66.4$ Hz), 28.3 ($^1J(\text{C},\text{P}) = 58.0, 47.7$ Hz); MS (70 eV): m/z (%): 482 (6) [M^+], 73 (100) [SiMe_3].

5: A solution of **4** (155 mg, 162 mmol) in mesitylene (20 mL) was stirred for 2 h at 150 °C. The solvent was then evaporated in vacuo and the residue was dissolved in a little DMF. After one day at 3 °C, yellow crystals of **5** were deposited. Yield 105 mg (68 %); m.p. 188–190 °C; NMR (THF, 25 °C; without signals from the aryl residues): ^{31}P NMR (ext.): $\delta = 298.2, 280.0$ ($^3J(\text{P},\text{P}) = 167.8$ Hz); ^1H NMR (C_6D_6): $\delta = -7.46$ (dd, $J(\text{H},\text{P}) = 15.5, 20.4$ Hz, C(H)CP); ^{13}C NMR (C_6D_6): $\delta = 177.4$ (dd, $J(\text{C},\text{P}) = 23.7, 40.1$ Hz, C(H)CP), 184.3 (dd, $J(\text{C},\text{P}) = 16.8, 79.0$ Hz, PC(Si)CP); MS (70 eV): m/z (%): 482 (6) [M^+], 73 (100) [SiMe_3].

Received December 17, 1998 [Z12792IE]
German version: *Angew. Chem.* **1999**, 3213–3216

Keywords: bond stretch isomers • phosphaaalkenes • phosphorus heterocycles • valence isomerization

- [1] For the electronic structure of S_2N_2 see: a) J. Bragin, M. V. Evans, *J. Chem. Phys.* **1969**, 51, 268; b) A. J. Banister, *Phosphorus Sulfur* **1979**, 6, 421; c) A. A. Bhattacharyya, A. Bhattacharyya, R. R. Adkins, A. G. Turner, *J. Am. Chem. Soc.* **1981**, 103, 7458; d) G. van Zandwijk, R. A. J. Jansen, H. M. Buck, *J. Am. Chem. Soc.* **1990**, 112, 4155; e) R. A. J. Janssen, *J. Phys. Chem.* **1993**, 97, 6384.
- [2] C. M. Mikulski, P. J. Russo, M. S. Saran, A. G. MacDiarmid, A. F. Garito, A. J. Haeger, *J. Am. Chem. Soc.* **1975**, 97, 6358, and references therein.
- [3] E. Niecke, A. Fuchs, F. Baumeister, M. Nieger, W. W. Schoeller, *Angew. Chem.* **1995**, 107, 640; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 555.
- [4] For the term “bond stretch isomer” see: W.-D. Stohrer, R. Hoffmann, *J. Am. Chem. Soc.* **1972**, 94, 779.
- [5] E. Niecke, M. Nieger, A. Fuchs, O. Schmidt, unpublished results
- [6] Diradical structures have also been discussed for S_2N_2 : R. D. Harcourt, T. M. Klapötke, A. Schulz, P. Wolyneć, *J. Phys. Chem.* **1998**, 102, 1850.
- [7] According to ab initio calculations on the parent system $(\text{HP})_2(\text{CH}_2)_2$, 2,4-diphosphabicyclobutane (**IIb**) should be thermodynamically more stable than 1,3-diphosphabutanediyl-2,4 (**IIa**) by 150 kJ mol $^{-1}$.^[5, 10]
- [8] According to the Woodward–Hoffmann rules, a 2,4-connection in 1,3-diphosphetane-2,4-diyl is a forbidden process.
- [9] O. Schmidt, A. Fuchs, D. Gudat, M. Nieger, W. Hoffbauer, E. Niecke, W. W. Schoeller, *Angew. Chem.* **1998**, 110, 995; *Angew. Chem. Int. Ed.* **1998**, 37, 949.
- [10] Stable phosphanylcarbenes are known: A. Igau, H. Grützmacher, A. Baccaredo, G. Bertrand, *J. Am. Chem. Soc.* **1988**, 110, 6463.
- [11] 1,2- and 1,3-diphosphabicyclo[1.1.0]butanes are known: E. Niecke, H. J. Metternich, R. Streubel, *Chem. Ber.* **1990**, 123, 67.

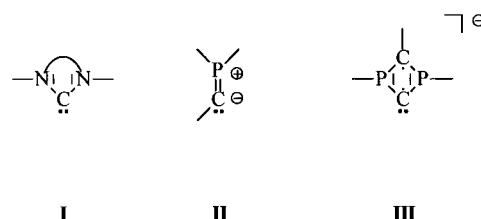
- [12] Transition metal complexes of *cis*-1,4-diphosphabutadienes are known: P. Le Floch, N. Maigrot, L. Ricard, C. Charrier, F. Mathey, *Inorg. Chem.* **1995**, *34*, 5070.
- [13] Short heating to 150 °C leads to no significant change in the compound.
- [14] C. Charrier, N. Maigrot, F. Mathey, F. Robert, Y. Jeannin, *Organo-metallics* **1986**, *5*, 623.
- [15] X-ray crystal analysis: **3**: $C_{41}H_{68}P_2Si$, red crystals, crystal dimensions $0.25 \times 0.40 \times 0.47$ mm; $M_r = 650.98$; triclinic, space group $P\bar{1}$ (no. 2), $a = 14.140(1)$, $b = 18.037(1)$, $c = 20.006(2)$ Å, $\alpha = 113.30(1)$, $\beta = 96.76(1)$, $\gamma = 109.82(1)^\circ$, $V = 4217.3(6)$ Å³, $Z = 4$, $\mu(Cu_{K\alpha}) = 1.37$ mm⁻¹, $T = 200(2)$ K, $F(000) = 1432$; $2\theta_{max} = 135^\circ$; 15 743 reflections, of which 15 209 were independent and used for all calculations, were measured on a Nonius MACH3 diffractometer with $Cu_{K\alpha}$ radiation. The structure was determined by direct methods and refined anisotropically on F^2 with the H atoms included with a riding model (programs: SHELXS-97,^[16] SHELXL-97^[17]). The final quality factor $wR2(F^2)$ was 0.193 with a conventional $R(F) = 0.065$ for 816 parameters and 190 restraints. An extinction correction and an empirical absorption correction was carried out on the basis of ψ scans (min. and max. transmission 0.430 and 0.916, respectively). In the second molecule, the phosphorus atoms and the trimethylsilyl group are disordered. **4**: $C_{41}H_{68}P_2Si$, yellow crystals, crystal dimensions $0.08 \times 0.10 \times 0.30$ mm; $M_r = 650.98$; monoclinic, space group $P2_1/c$ (no. 14), $a = 11.2020(3)$, $b = 20.5400(3)$, $c = 18.0230(5)$ Å, $\beta = 96.111(4)^\circ$, $V = 4123.3(2)$ Å³, $Z = 4$, $\mu(Mo_{K\alpha}) = 0.16$ mm⁻¹, $T = 123(2)$ K, $F(000) = 1432$; $2\theta_{max} = 50^\circ$; 23 102 reflections, of which 6554 were independent and used for all calculations, were measured on a Nonius-Kappa CCD diffractometer with $Mo_{K\alpha}$ radiation. The structure was determined by direct methods and refined anisotropically on F^2 with the H atoms included with a riding model (programs: SHELXS-97,^[16] SHELXL-97^[17]). The final quality factor $wR2(F^2)$ was 0.147 with a conventional $R(F) = 0.050$ for 400 parameters and one restraint. **5**: $C_{41}H_{68}P_2Si$, yellow crystals, crystal dimensions $0.10 \times 0.10 \times 0.25$ mm; $M_r = 650.98$; monoclinic, space group $P2_1/n$ (no. 14), $a = 14.9030(3)$, $b = 10.3010(2)$, $c = 26.6390(8)$ Å, $\beta = 90.992(5)^\circ$, $V = 4088.9(2)$ Å³, $Z = 4$, $\mu(Mo_{K\alpha}) = 0.16$ mm⁻¹, $T = 123(2)$ K, $F(000) = 1432$; $2\theta_{max} = 55^\circ$; 25 234 reflections, of which 7884 were independent and used for all calculations, were measured on a Nonius Kappa CCD diffractometer with $Mo_{K\alpha}$ radiation. The final quality factor $wR2(F^2)$ was 0.107 with a conventional $R(F) = 0.039$ for 397 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-112271 (**3**), 112272 (**4**), and 112273 (**5**). 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).
- [16] G. M. Sheldrick, SHELXS-97, *Acta Crystallogr. Sect. A* **1990**, *46*, 467.
- [17] G. M. Sheldrick, SHELXL-97, Universität Göttingen, **1997**.
- [18] R. Appel in *Multiple Bonding and Low Coordination in Phosphorus Chemistry* (Eds.: M. Regitz, O. J. Scherer), Thieme, **1990**, p. 367.
- [19] The *cis* form does not represent a minimum on the energy hypersurface: a) W. W. Schoeller, U. Tubbesing, A. B. Rozhenko, *Eur. J. Inorg. Chem.* **1998**, 951; b) S. M. Bachrach, M. Liu, *J. Org. Chem.* **1992**, *57*, 2040.
- [20] K. A. Nguyen, M. S. Gordon, *J. Am. Chem. Soc.* **1995**, *117*, 385.

1,3-Diphosphacyclobutane-2,4-diyl-2-ylidenide: A Unique Carbene and Its Trimethylalane Complex**

Edgar Niecke,* André Fuchs, Martin Nieger, Olaf Schmidt, and Wolfgang W. Schoeller

Dedicated to Professor Konrad Sandhoff on the occasion of his 60th birthday

The chemistry of N-heterocyclic carbenes **I** has, through the synthesis of stabilized derivatives by Arduengo et al.,^[1] experienced an unexpected renaissance.^[2] Heterocycles, in which the position neighboring the carbene atom is not occupied by nitrogen atoms, are not known in free form. On the other hand "push/pull" substituted λ^5 -phosphaacetylenes **II** ("kryptocarbenes"^[3]) are stable and reveal a carbene-

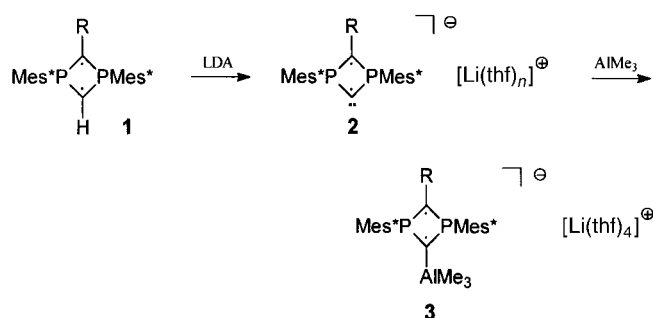


analogous reactivity.^[4] In connection with our work on four-membered π -delocalized phosphorus heterocycles (1,3-diphosphacyclobutane-2,4-diyls), which, owing to the pyramidalized carbon and^[5]/or^[6] phosphorus atoms, are ascribed more or less pronounced diradical character, we became interested in the corresponding isoelectronic anions **III** (1,3-diphosphacyclobutane-2,4-diyl-2-ylidenides). Here we report on the synthesis and bonding analysis of the first representative of this type as well as on the structure of its trimethylalane adduct.

Deprotonation of 1,3-diphosphacyclobutane-2,4-diyl^[6] **1** with one equivalent of lithium diisopropylamide (LDA) led to the formation of a deep red solution from which $2 \cdot [Li(thf)_n]^+$ can be isolated as a dark red, amorphous solid^[7] (Scheme 1). In the pure state $2 \cdot [Li(thf)_n]^+$ can be stored under an inert atmosphere without decomposition; in solution (25 °C, THF) **1** is re-formed within one day (ca. 60 % according to ³¹P NMR control). With the Lewis acid trimethylalane, **2** can easily be transformed into the adduct $2 \cdot AlMe_3$ (**3**), and isolated as the lithium salt $3 \cdot [Li(thf)_4]^+$ in the form of red, hydrolysis-sensitive crystals (Scheme 1).

[*] Prof. Dr. E. Niecke, Dr. A. Fuchs, Dr. M. Nieger, Dipl.-Chem. O. Schmidt
Institut für Anorganische Chemie der Universität
Gerhard-Domagk-Strasse 1, D-53121 Bonn (Germany)
Fax: (+49) 228-735-327
E-mail: e.niecke@uni-bonn.de
Prof. Dr. W. W. Schoeller
Fakultät für Chemie der Universität
Postfach 8640, D-33615 Bielefeld (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft (SSB 334) and the Fonds der Chemischen Industrie. Partly presented at the International Conference on Phosphorus Chemistry, Cincinnati, USA, July 12–17, 1998.



Scheme 1. Synthesis of **2**·[Li(thf)_n]⁺ and of **3**·[Li(thf)₄]⁺.

A comparison of the NMR data (³¹P, ¹³C) of **2**·[Li(thf)_n]⁺ with those of the protonated form **1**^[6] undoubtedly proves the cyclic structure of the anion as a 2,4-diphosphacyclobutane-2,4-diyl-2-ylidenide. The appearance of only one ³¹P NMR signal in solution (δ = 4.5) confirms the chemical equivalence of both phosphorus atoms, which reveal a chemical shift (δ = −11.3) comparable to that in **1**. The chemical equivalence of the phosphorus atoms is indicated in the ¹³C NMR spectrum by a triplet structure of the C(SiMe₃) signal (**2**: δ = 120.9, ¹J(C,P) = 21.0 Hz; **1**: δ = 111.0, ¹J(C,P) = 20.2 Hz). The signal of the C(H) ring carbon atom in **1** (δ = 104.1) experiences a strong deshielding upon protonation and is shifted downfield (**2**: δ = 158.8; Δδ = 55). Δδ values of 50–65 ppm indicate the difference between lithiated arenes and their corresponding protonated forms.^[7, 8] An even stronger deshielded carbene carbon atom is observed in the *push-pull* substituted “kryptocarbenes” of Bertrand et al., [(R₂N)₂P]CSiMe₃ (120 < δ < 145).^[3c] The ¹³C NMR spectra of ⁶Li-doped samples of **2**·[Li(thf)_n]⁺^[9] in THF show even at −90 °C no coupling with the carbene carbon atom, indicating a fast intermolecular exchange of the solvated lithium ion between the different anions **2**. In the case of the phosphanyl carbenoid, [Mes*P=CCl][Li(thf)₃]^[10] such an exchange mechanism can be proven by temperature-dependent ¹³C NMR experiments and can be frozen in at −100 °C. The adduct formation **2** → **3** causes no significant changes in the ³¹P or ¹³C NMR spectrum, apart from a considerable highfield shift of the “carbene carbon atom” signal (Δδ = 18.5). In the alane adduct of the 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene the deshielding of the carbene carbon atom is Δδ = 46.4.^[11]

The constitution of anion **3**, derived from the NMR data, is confirmed by X-ray analysis^[12] (Figure 1). It indicates the presence of a salt **3**·[Li(thf)₄]⁺ (thf = tetrahydrofuran). The anion is a planar P₂C₂ ring with phosphorus atoms in the 1,3-position; the aryl substituents are in a *trans* arrangement. The aluminum-substituted carbon atom lies in the ring plane (sum of angles Σ = 360°), while the carbon atom attached to the silicon is slightly pyramidalized (Σ = 357.4°). The C(sp²)–Al(sp³) distance (201.3(3) pm) is significantly longer than the terminal Al–C distance in (AlPh₃)₂ (195.8 pm)^[14] and corresponds to the one in the alane complex of the imidazol-2-ylidene.^[11] The significant pyramidalization of the phosphorus atoms (sum of valence angles: 336° (P1), 343° (P2)) leads to the formation of two distinct pairs of endocyclic P–C distances (P1–C1 175.6(3) and P1–C2 176.9(3) as well as P2–C1 173.2(3), P2–C2 172.6(3) pm), the shorter of which

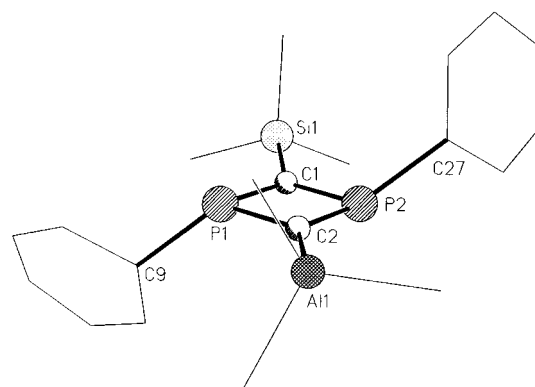
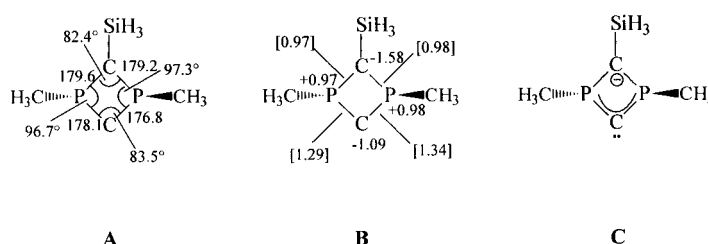


Figure 1. Molecular structure of the anion **3** (H atoms and peripheral groups omitted for clarity). Selected bond lengths [pm] and angles [°]: P1–C1 175.6(3), P1–C2 176.9(3), P2–C1 173.2(3), P2–C2 172.6(3), C1–Si1 182.9(3), C2–Al1 201.3(3), Al1–C6 200.9(3), Al1–C7 200.8(3), Al1–C8 201.1(3); C1–P1–C2 94.0(1), C1–P2–C2 96.4(1), P1–C1–P2 84.9(1), P1–C2–P2 84.7(1).

correspond to the less pyramidalized phosphorus atom P(2). The residual structural parameters are similar to the structural characteristics in the 1,3-diphosphetane-2,4-diyls.^[5, 6]

In order to understand the bonding situation in the 1,3-diphosphacyclobutane-2,4-diyl-2-ylidenide **2** and its Lewis acid adduct **3**, we performed ab initio calculations (B3LYP/6-31 + g*)^[15] on the model compounds *cyclo*–[(H₃C)PC(SiH₃)–P(CH₃)C][−] **X** and *cyclo*–[(H₃C)PC(SiH₃)P(CH₃)C(AlMe₃)][−] **Y**.^[16] The calculations indicate a planar P₂C₂ heterocycle with C_i symmetry for the anion **X**. Likewise, the silicon atom is situated in the plane with the ring, while the substituents at both pyramidalized phosphorus atoms are arranged *trans* to each other. The structural properties in the free anion **X** correspond to those of the lithium complex *cyclo*–[(H₃C)PC(SiH₃)P(CH₃)C][Li(Me₂O)₃].^[17] Scheme 2 presents



Scheme 2. Bonding parameters (**A**), charge densities and Wiberg indices (**B**), and canonical valence bond structure (**C**) of the 1,3-diphosphacyclobutane-2,4-diyl-2-ylidenide [(H₃C)PC(SiH₃)P(CH₃)C][−] (**X**).

structural data (**A**) as well as the results of a NBO analysis (**B**)^[18] for the anion **X**. Both carbon atoms bear a negative charge, which is preferentially localized in the p_π orbital orthogonal to the ring plane. The π population at the trigonal carbon atom is 1.63 (for the localization of two electrons in the p orbital 2.0 are expected). The empty p orbital at the carbene carbon atom suffers a homoallylic resonance with the neighboring lone pairs of electrons at the phosphorus atoms (the π population at the carbene carbon atom is 1.02). Hence, the 1,3-diphosphacyclobutane-2,4-diyl-2-ylidenide can be viewed as a cyclic, anionic bis(phosphanyl)carbene (**C**), which

is stabilized by p-electron density of the carbanionic center. A comparable bonding situation is given in the imidazol-2-ylidene ("Arduengo-carbene"); here the π -electron density of the C–C double bond distal to the carbene carbon center contributes to the stability of the cyclic bis(amino)carbene.^[19] The singlet–triplet energy separation for the parent compound of the cyclic, anionic bis(phosphanyl)carbene *cyclo*-[P₂C₂H₃][−] is calculated to be 7.4 kcal mol^{−1}.^[20] Hence it is comparable to that for dibromocarbene^[21] and the hypothetical bis(phosphanyl)carbene C(PH₂)₂ ($\Delta E(S/T)$ = 7.3 kcal mol^{−1}).^[22] Nevertheless, it is about a factor of 10 smaller than that of the imidazol-2-ylidene, *cyclo*-[C(NHCH)₂] ($\Delta E(S/T)$ kcal mol^{−1}).^[23]

The structural changes on going from **X** to the adduct **Y**, leads to a distortion of the ring moiety (C_i → C_i) giving two different pairs of P–C distances, in agreement with the solid-state structure of **3**. The electronic perturbation of the carbene fragments experienced by complexation with the Lewis acid AlMe₃ is evident from the NBO analysis^[18] of the density functional theory (DFT) wave function of **Y**. According to this, 0.28 electrons flow into the AlMe₃ fragment. The aluminum atom is bound weakly covalent to the carbene carbon atom (Wiberg bond index 0.48).^[24] The nature of the donor–acceptor complex is also apparent from the Laplace distribution of the electron density (Figure 2), which shows a domain of the electron pair at the carbene carbon, directing towards the aluminum atom.

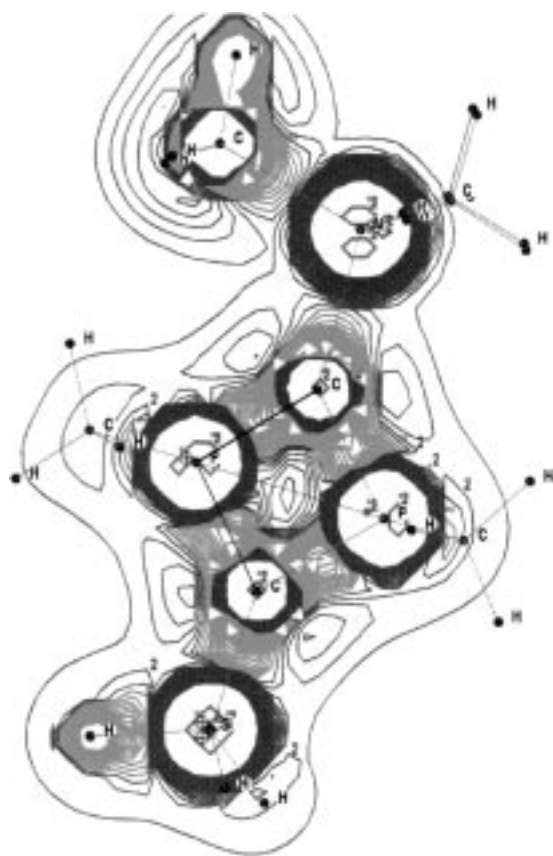


Figure 2. La Place distribution of the electron density of the 1,3-diphosphacyclobutane-2,4-diyl-2-ylidenide trimethylalane adduct *cyclo*-[(H₃C)PC(SiH₃)P(CH₃)C(AlMe₃)][−] (**Y**).

Experimental Section

2: A solution of **1** (325 mg, 0.5 mmol) in THF (10 mL) was added to a solution of LDA (0.25 mL, a 2 M solution in *n*-hexane) at room temperature. Further stirring of the red reaction mixture for 3 h resulted in a deepening of the color. After evaporation of the solvent and the resulting amine, the residue was washed with fresh cold *n*-pentane to give **2**·[Li(thf)_n]⁺ in the form of a deep red solid. NMR data (25 °C, without aryl groups): ³¹P{¹H} NMR (THF): δ = 4.6; ¹H NMR (THF): δ = −0.57 (s, SiCH₃); ¹³C NMR (THF): δ = 2.5 (t, ³J(C,P) = 2.7 Hz, P₂CSiC), 121.4 (t, ¹J(C,P) = 21.0 Hz, P₂CSi), 158.8 (br, *J*(C,P) = not resolved, P₂CLi).

3: To a stirred solution of **2** (0.2 mmol) in THF (10 mL) was added dropwise a equimolar solution of trimethylaluminum in toluene. Removal of the solvent in vacuo afforded **3**·[Li(thf)₄]⁺ in the form of red crystals (280 mg, 55 %). NMR (25 °C, without aryl groups): ³¹P{¹H} NMR (THF): δ = −0.1; ¹H NMR (THF): δ = −0.65, −0.18 (s, SiCH₃, AlMe₃); ¹³C NMR (THF): δ = 2.0, 2.6 (t, ³J(C,P) = 3.1, 3.6 Hz, P₂CSiC and P₂CAl), 118.3 (t, ¹J(C,P) = 28.4 Hz, P₂CSi), 140.3 (t, *J*(C,P) = 29.9 Hz, P₂CAl).

Received: April 6, 1999 [Z13243IE]

German version: *Angew. Chem.* **1999**, *111*, 3216–3219

Keywords: carbene complexes • carbenes • phosphorus heterocycles

- [1] A. J. Arduengo III, M. Kline, J. C. Calabrese, F. Davidson, *J. Am. Chem. Soc.* **1991**, *113*, 9704–9705.
- [2] Reviews: a) M. Regitz, *Angew. Chem.* **1996**, *108*, 791–794; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 725–728; b) W. A. Hermann, C. Köcher, *Angew. Chem.* **1997**, *109*, 2257–2282; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162–2188, and references therein.
- [3] a) A. Igau, H. Grützmacher, A. Bacciredo, G. Bertrand, *J. Am. Chem. Soc.* **1988**, *110*, 6463–6466; b) M. Soleilhavoup, H. Grützmacher, A. Bacciredo, O. Treutler, R. Ahlrichs, M. Nieger, G. Bertrand, *J. Am. Chem. Soc.* **1992**, *114*, 10959–10961; c) G. Bertrand, R. Reed, *Coord. Chem. Rev.* **1994**, *137*, 323–355.
- [4] Concerning the problem: phosphaacetylene or phosphanylcarbene of H₂PCH see: L. Nyulási, D. Szieberth, J. Réffy, T. Veszprémi, *J. Mol. Struct.* **1998**, *455*, 91–95, and references therein.
- [5] a) E. Niecke, A. Fuchs, M. Nieger, W. W. Schoeller, *Angew. Chem.* **1995**, *107*, 640–642; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 555–557; b) O. Schmidt, A. Fuchs, D. Gudat, M. Nieger, W. Hoffbauer, E. Niecke, W. W. Schoeller, *Angew. Chem.* **1998**, *110*, 995–998; *Angew. Chem. Int. Ed.* **1998**, *37*, 949–952.
- [6] E. Niecke, A. Fuchs, M. Nieger, *Angew. Chem.* **1999**, *111*, 3213–3216; *Angew. Chem. Int. Ed.* **1999**, *38*, 3028–3031.
- [7] a) D. Seebach, R. Hässig, J. Gabriel, *Helv. Chim. Acta*, Vol. 66, **1983**, 27, 309–338; b) H. Günther, D. Moskau, P. Bast, D. Schmalz, *Angew. Chem.* **1987**, *99*, 1242–1250; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1212–1220;
- [8] W. Bauer, P. von R. Schleyer in *Advances in Carbanion Chemistry*, Vol. 1 (Ed.: V. Snieckus), Jai Press, Greenwich, CT, **1992**, p. 89, and references therein.
- [9] Obtained by reaction of **1** with *n*Bu⁶Li in THF.
- [10] E. Niecke, M. Nieger, O. Schmidt, D. Gudat, W. W. Schoeller, *J. Am. Chem. Soc.* **1999**, *121*, 519–522.
- [11] A. J. Arduengo III, H. V. R. Dias, J. C. Calabrese, F. Davidson, *J. Am. Chem. Soc.* **1992**, *114*, 9724–9725.
- [12] Crystal data for **3**: [C₄₄H₇₆AlP₂Si][−][Li(C₄H₈O)₄]⁺: red crystals, crystal dimensions 0.15 × 0.40 × 0.50 mm; *M*_r = 1017.41; monoclinic space group *P*2₁/*c* (No. 14), *a* = 10.7024(4), *b* = 25.4123(9), *c* = 24.0149(7) Å, β = 102.670(2)°, *V* = 6372.4(4) Å³, *Z* = 4, μ (MoK α) = 0.141 mm^{−1}, *T* = 123(2) K, *F*(000) = 2240. A total of 54165 reflections were collected up to $2\theta_{\max}$ = 50° on an Enraf Nonius Kappa CCD diffractometer with MoK α radiation, of these 10547 were independent and were used for calculations. The structure was solved by direct methods^[13a] and refined on *F*² anisotropically;^[13b] the H atoms were refined by using a riding model. The final *R* values are *wR*2(*F*²) = 0.1524 and *R*(*F*) = 0.0516 for 614 parameters and 386 restraints. The

p-*t*Bu groups and two THF molecules are disordered. 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-130277. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [13] a) G. M. Sheldrick, SHELXS-97, *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473; b) G. M. Sheldrick, SHELXL-97, Universität Göttingen, **1997**.
- [14] J. F. Malone, W. S. McDonald, *J. Chem. Soc. Dalton Trans.* **1972**, 2646–2648.
- [15] a) M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Avala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, *Gaussian-94 (Revision A.1)*, Gaussian, Inc., Pittsburgh, PA, **1995**; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.
- [16] Calculated structure data^[15] (B3LYP/6-31+G*) for *cyclo*-(H₃C)PC-(SiH₃)P(CH₃)C[−] (C₃ symmetry): distances [pm]: P–C(Si) 179.2 and 179.6, P–C 176.8 and 178.1, C–Si 179.8; angles [°]: C–P–C 96.7 and 97.3, P–C–P 82.4 and 83.5; sum of angles Σ [°]: Σ(C) = 359.2, Σ(P) = 326.3 and 328.5°. Calculated structure data^[15] (B3LYP/6-31+G*) for *cyclo*-(H₃C)PC(SiH₃)P(CH₃)C(AlMe₃)[−]: distances [pm]: P–C(Al) 173.1 and 178.7, P–C(Si) 175.9 and 179.8, C–Si 180.7 and C–Al 204.0; angles [°]: C–P–C 92.7 and 96.0, P–C–P 86.3 and 85.1; sum of angles Σ [°]: Σ(C(Al)) = 359.9; Σ(C(Si)) = 360.0, Σ(P) = 317.9 and 334.9°.
- [17] W. W. Schoeller, personal communication.
- [18] A. F. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899–926.
- [19] A. J. Arduengo III, H. V. Rasika, D. A. Dixon, R. C. Harlow, W. J. Klooster, T. F. Koetzle, *J. Am. Chem. Soc.* **1994**, *116*, 6812–6822.
- [20] The energy difference (S → T) was performed at the CCSD(t)/6-311+G**//B3LYP/6-31+G, the triplet states were obtained on the UB3LYP-level. All values were corrected by zero point vibration corrections on the (U)B3LYP/6-31+G* level.
- [21] K. K. Ikura, W. A. Goddard III, J. L. Beauchamp, *J. Am. Chem. Soc.* **1992**, *114*, 48–51.
- [22] W. W. Schoeller, *Eur. J. Inorg. Chem.* **1999**, in press.
- [23] D. A. Dixon, A. J. Arduengo III, *J. Phys. Chem.* **1991**, *95*, 4180–4182.
- [24] Further Wiberg bond indices for **Y** are: P–C(Al): 1.33, 1.14; P–C(Si) 1.07, 0.99; C–Si: 0.90; P–C(H₃) 0.86, 0.89; all Al–C(H₃): 0.56.

Charting No-Man's Land in d⁰ Transition Metal Six-Coordination: Structure Predictions for the Complexes [WCl₅CH₃], [WCl₄(CH₃)₂], and [WCl₃(CH₃)₃]*

Martin Kaupp*

Among the growing number of early, high-valent transition metal complexes that defy the traditional structural rules, the computationally predicted^[1–3] and experimentally confirmed^[4] distorted trigonal-prismatic structure of hexamethyltungsten, [W(CH₃)₆], holds a central role. Related, more ionic d⁰ complexes such as [Zr(CH₃)₆]^{2−} or [Ta(CH₃)₆][−] have regular trigonal-prismatic structures.^[2c, 4b, 5] In contrast to these fascinating compounds, the majority of hexacoordinate d⁰ systems are octahedral, such as the Group 6 hexahalides.^[3, 6] A major difference^[1, 3, 7] between these two sets of complexes is that cylindrical π-donor halide (or related) ligands favor the octahedron, whereas exclusively σ-bonding ligands prefer nonoctahedral arrangements (the latter preference can be rationalized within relatively simple valence bond^[2a, 8] or molecular orbital^[1, 2b,c, 3, 7, 9] frameworks). We are thus facing two seemingly very different structural paradigms within closely related series of compounds. This suggests that one should be able to find complexes with preferences *between* octahedral and distorted or regular trigonal-prismatic structures. There are different routes into this “no-man's land”. One route consists of replacing the cylindrical halide π-donor ligands by effectively single-faced π donors, for example as in thiolate complexes. This leads into the large and interesting field of dithiolene, dithiolate, and related complexes, the trigonal twist angles of which do indeed cover a large range between octahedral and trigonal prismatic,^[10] depending on bond polarity and on the actual π-donor abilities of the ligands. Herein are reported the first computational results along a different route into this intermediate region, on which practically nothing has been known: Starting from octahedral WCl₆ complexes, we replace successively π-donor chloride ligands by σ-donor methyl groups. Structural predictions for the first three members of this [WCl_{6−n}(CH₃)_n] series (*n* = 1–3) and for the fluoride complex [WF₅CH₃] are made.

Figure 1 shows the most important stationary points computed at the gradient-corrected density functional theory (DFT) level^[11] for [WCl₅CH₃] (**1**). We note that this complex has been prepared and was characterized by IR and ¹H NMR spectroscopy,^[12] but nothing is known about its structure. The

[*] Priv.-Doz. Dr. M. Kaupp
Max-Planck-Institut für Festkörperforschung
Heisenbergstrasse 1, D-70569 Stuttgart (Germany)
Fax: (+49) 711-689-1702
E-mail: kaupp@vsibm1.mpi-stuttgart.mpg.de

[**] This work was supported by Deutsche Forschungsgemeinschaft (DFG) by a Heisenberg scholarship, and by Fonds der Chemischen Industrie. I am grateful to Prof. Dr. A. Haaland (Oslo) for stimulating discussions, and to Dr. M. Bühl (Zürich) for helpful comments on the manuscript.

 Supporting information for this article (one Figure with computed IR spectra for [WCl₅CH₃]) is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

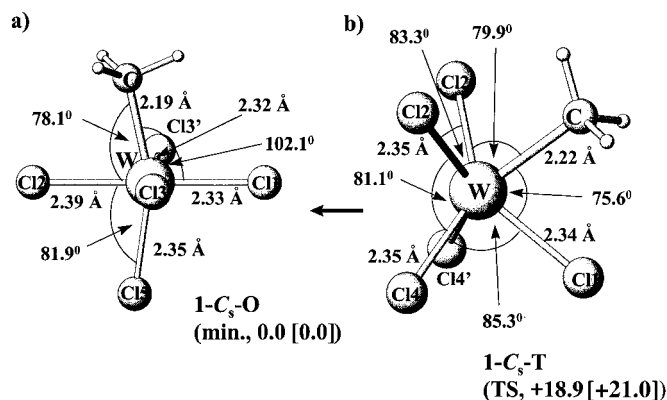


Figure 1. DFT-optimized stationary points for $[\text{WCl}_5\text{CH}_3]$ (**1**). Relative energies in kJ mol^{-1} (values in brackets include zero-point vibrational energy corrections). a) Distorted octahedral minimum (**1-C_s-O**), further angles [°]: Cl1-W-Cl5 97.9, Cl1-W-Cl2 179.8, Cl3-W-Cl3' 166.3, Cl1-W-Cl3 87.0; b) trigonal-prismatic transition state (**1-C_s-T**).

calculations give a distorted octahedral C_s -symmetrical minimum energy structure (**1-C_s-O**, Figure 1 a). The methyl group and its *trans* chloride ligand are bent characteristically towards one of the *cis* ligands. This leads to a moderate energy gain relative to a C_{4v} heavy-atom skeleton (by ca. 7 kJ mol^{-1}) and is shown by population analyses to be due to slightly improved W–C bonding.^[13] A configuration with the methyl group bisecting the angle between two *cis* ligands is energetically almost indistinguishable (but has a small imaginary vibrational frequency of about $i17 \text{ cm}^{-1}$ at this level), and we conclude that the tilted methyl group and its *trans* chloride ligand may rotate essentially without barrier above the plane of the *cis* ligands. A trigonal-prismatic structure, also with C_s symmetry (**1-C_s-T**, Figure 1 b), is characterized as a low-lying transition state (TS), only about 20 kJ mol^{-1} above the distorted octahedral minimum. This is remarkable considering that we compute at the same theoretical level a D_{3h} TS for WCl_6 to be about 80 kJ mol^{-1} above the octahedral minimum. Thus, the introduction of one methyl group leads already to drastic changes in the structural behavior, and to a compound that may be considered fluxional at room temperature. Population analyses show that this behavior is due to a delicate balance between maximization of W–C σ bonding (which is most covalent in **1-C_s-T**), as well as maximization of W–Cl π bonding and minimization of ligand repulsion (both favored in an octahedral arrangement). Our computed IR spectra for **1-C_s-O** and **1-C_s-T** (Figure S1 in Supporting Information) agree well with the experimental data but are not diagnostic with respect to the structure. Similarly, the ^1H chemical shifts are not helpful in this respect.

Introducing the second methyl group in $[\text{WCl}_4(\text{CH}_3)_2]$ leads to the possibility of various isomeric structures; Figure 2 summarizes only the most important stationary points located on the potential energy surface. The relations between the stationary points may be described roughly by rotations of opposite trigonal faces from distorted trigonal antiprismatic (distorted octahedral) to trigonal-prismatic arrangements (see fat arrows in Figure 2; details of these transformations are presently being explored). We have found two minima. One is a *trans*-octahedral C_{2v} -symmetrical structure (**2-C_{2v}-tO**), the

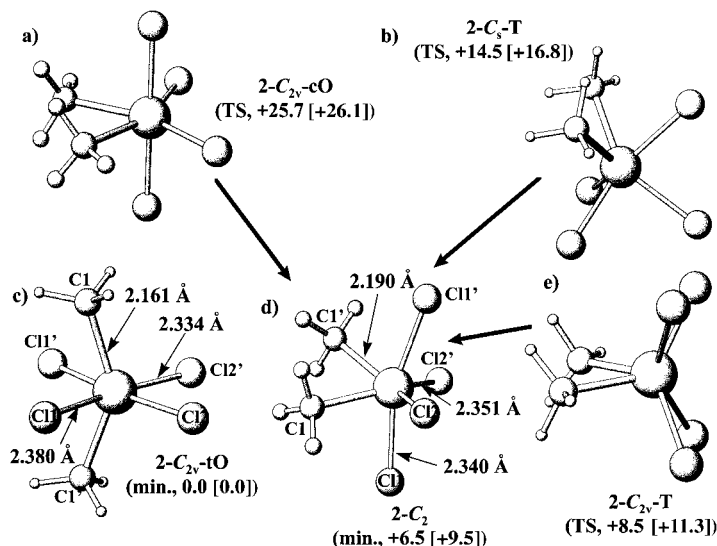


Figure 2. DFT-optimized stationary points for $[\text{WCl}_4(\text{CH}_3)_2]$ (**2**). Relative energies in kJ mol^{-1} (values in brackets include zero-point vibrational energy corrections). a) **2-C_{2v}-cO**; b) **2-C_s-T**; c) **2-C_{2v}-tO**. Angles [°]: Cl1-W-Cl1' 144.0, Cl1-W-Cl1 78.9, Cl1-W-Cl2 103.2, Cl1-W-Cl1' 102.8, Cl2-W-Cl2' 84.6, Cl1-W-Cl2 86.3; d) **2-C₂**. Angles [°]: Cl1-W-Cl1' 73.4, Cl1-W-Cl1 82.0, Cl1-W-Cl1' 113.4, Cl1-W-Cl1' 161.5, Cl2-W-Cl2' 130.9, Cl1-W-Cl2 88.9, Cl1-W-Cl2' 83.4; e) **2-C_{2v}-T**.

other is a C_2 structure (**2-C₂**), which lies about 10 kJ mol^{-1} higher in energy (including zero-point vibrations). This latter minimum **2-C₂** is very interesting, as its coordination arrangement is not uniquely characterizable as an octahedron or prism. It is somewhat closer to **2-C_{2v}-T**, a trigonal-prismatic TS with the two methyl groups in opposite trigonal faces but in an eclipsed position, than to the *cis*-octahedral **2-C_{2v}-cO** TS, which is already about 26 kJ mol^{-1} higher in energy. The **2-C_{2v}-tO** minimum is again characteristically distorted, like the minimum **1-C_s-O** of $[\text{WCl}_5\text{CH}_3]$ (see Figure 1), and for similar reasons. Another trigonal-prismatic TS, **2-C_s-T**, is connected to **2-C₂** by rotation of a $\text{W}(\text{CH}_3)_2\text{Cl}$ face. The TS that connects **2-C_{2v}-tO** with **2-C₂** has not yet been located but is expected to be also at low energy. We conclude that the energy differences between octahedral and prismatic structures have essentially vanished already at this point, and we suspect the system to be highly fluxional.

Introducing the third methyl group in $[\text{WCl}_3(\text{CH}_3)_3]$ changes the picture again significantly (Figure 3). Now the only minima found are the two trigonal-prismatic isomers **3-C₁-T** and **3-C_{3v}-T**, of which the latter has all three methyl groups in the same trigonal face and appears to be very slightly higher in energy. Structures **3-C_s-O** and **3-C_{3v}-O** derived from meridional and facial octahedra, respectively, are only transition states. While the former is still at moderate energy, the latter is not competitive. Thus, the trigonal prism is already notably more favorable than an octahedral coordination for $[\text{WCl}_3(\text{CH}_3)_3]$. We note for comparison that for $[\text{W}(\text{CH}_3)_6]$ at the same computational level,^[1b,c] a distorted octahedral C_{3v} -structure analogous to **3-C_{3v}-O** is already about 132 kJ mol^{-1} above the distorted trigonal-prismatic C_3 symmetrical minimum structure (which is analogous to **3-C_{3v}-T**). Thus, octahedral arrangements become even less favorable upon substitution of the remaining three chloride ligands by

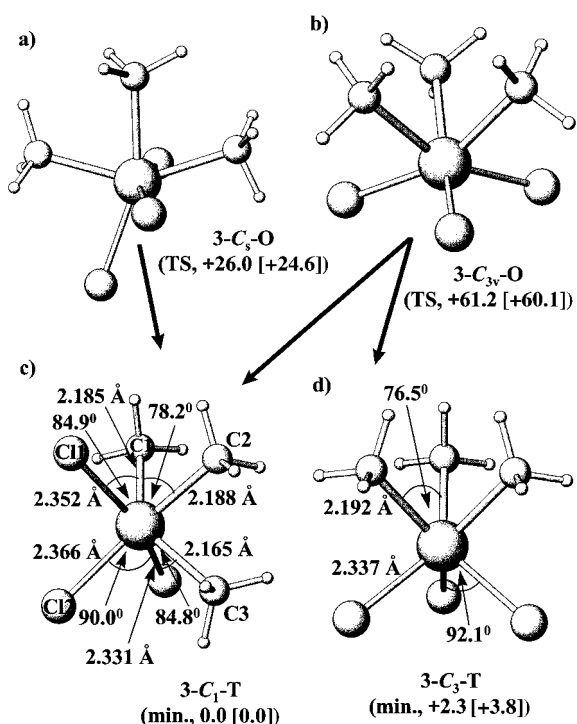


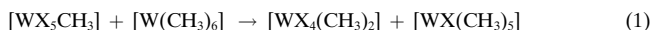
Figure 3. DFT-optimized stationary points for $[\text{WCl}_3(\text{CH}_3)_3]$ (**3**). Relative energies in kJ mol^{-1} (values in brackets include zero-point vibrational energy corrections). a) $3\text{-C}_{3v}\text{-O}$; b) $3\text{-C}_{3v}\text{-O}$; c) $3\text{-C}_1\text{-T}$, further angles $^\circ$: Cl1-W-C2 80.2, Cl2-W-C2 87.7; d) $3\text{-C}_3\text{-T}$.

methyl groups, as one might expect from the interplay between σ - and π -donor ligands.

At the theoretical level used here, we compute the trigonal prism to be only about 43 kJ mol^{-1} above the octahedron for WF_6 compared to about 80 kJ mol^{-1} for WCl_6 . This is due to the weaker π -donor character of the fluoride ligands (it cannot be due to ligand repulsion, as the latter would favor the octahedron more strongly for WF_6), as confirmed by our bonding analyses. The trigonal prism should thus become competitive even earlier along our substitution pathway for the $[\text{WF}_{6-n}(\text{CH}_3)_n]$ series. Indeed, our first calculations confirm that for $[\text{WF}_5\text{CH}_3]$, the trigonal-prismatic structure (cf. **1-C_{3v}-T** in Figure 1) is a minimum at this theoretical level, already 2 kJ mol^{-1} below the best distorted octahedral arrangement. Kleinhenz et al.^[4b] assigned two peaks in the ^{19}F NMR spectra obtained when dissolving $[\text{W}(\text{CH}_3)_6]$ in WF_6 to $[\text{WF}_5\text{CH}_3]$. From the doublet and quintet character of the high-frequency and low-frequency peaks, respectively, they concluded that the structure is octahedral. Obviously, our calculations are not consistent with a rigid octahedral structure for the free complex.^[14] However, in view of the very small energy differences involved, we cannot exclude the stabilization of a regular structure in the environment of the WF_6 matrix. Similar structural behavior as for the analogous chloro complexes is also indicated by our calculations for $[\text{WF}_4(\text{CH}_3)_2]$ and $[\text{WF}_3(\text{CH}_3)_3]$,^[15] with a somewhat larger preference for arrangements derived from a trigonal prism.

While there is experimental evidence for the existence of the monosubstituted complexes $[\text{WX}_5\text{CH}_3]$ ($\text{X} = \text{F}, \text{Cl}$),^[4b, 12] no indications for multiply methyl-substituted complexes have been seen. Our preliminary calculations of isodesmic

reaction energies indicate that thermodynamically the mixed compounds are more stable than the sum of the homoleptic complexes. Also, reactions such as that in Equation (1) are



computed to be exothermic (by -31 and -44 kJ mol^{-1} for $\text{X} = \text{Cl}, \text{F}$, respectively, including zero-point vibrational energy corrections) and should also be favored entropically. It appears that kinetic rather than thermodynamic factors limit the access to these complexes. Reductive elimination reactions will of course have to be considered. We are presently studying systematically the entire range of heteroleptic complexes $[\text{WX}_{6-n}(\text{CH}_3)_n]$ ($n = 1-5$; $\text{X} = \text{F}, \text{Cl}$) by quantum chemical methods.^[15] This includes predictions of spectroscopic parameters that may help to experimentally characterize these species, once they have been prepared.

Received: March 29, 1999

Revised version: June 14, 1999 [Z13220IE]

German version: *Angew. Chem.* **1999**, *111*, 3219–3221

Keywords: density functional calculations • transition metals • tungsten

- [1] For the first computational prediction of trigonal-prismatic structures for $d^0 \text{ MH}_6$ systems, see: S. K. Kang, T. A. Albright, O. Eisenstein, *Inorg. Chem.* **1989**, *28*, 1611.
- [2] a) C. R. Landis, T. Cleveland, T. K. Firman, *J. Am. Chem. Soc.* **1995**, *117*, 1859; b) M. Kaupp, *J. Am. Chem. Soc.* **1996**, *118*, 3018; c) M. Kaupp, *Chem. Eur. J.* **1998**, *4*, 1678.
- [3] S. K. Kang, H. Tang, T. A. Albright, *J. Am. Chem. Soc.* **1993**, *115*, 1971.
- [4] a) V. Pfenning, K. Seppelt, *Science* **1996**, *271*, 626; b) S. Kleinhenz, V. Pfenning, K. Seppelt, *Chem. Eur. J.* **1998**, *4*, 1687; see also: c) A. Haaland, A. Hammel, K. Rypdal, H. V. Volden, *J. Am. Chem. Soc.* **1990**, *112*, 4547.
- [5] P. M. Morse, G. S. Girolami, *J. Am. Chem. Soc.* **1989**, *111*, 4114; S. Kleinhenz, M. Schubert, K. Seppelt, *Chem. Ber.* **1997**, *130*, 903.
- [6] See, for example: F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, 5th ed., Wiley, New York, **1988**.
- [7] a) A. Demolliens, Y. Jean, O. Eisenstein, *Organometallics* **1986**, *5*, 1457; see also: b) C. A. Jolly, D. S. Marynick, *Inorg. Chem.* **1989**, *28*, 2893; c) M. Kaupp, P. von R. Schleyer, *J. Am. Chem. Soc.* **1992**, *114*, 491.
- [8] See also: C. R. Landis, T. K. Firman, D. M. Root, T. Cleveland, *J. Am. Chem. Soc.* **1998**, *120*, 1842; R. B. King, *Inorg. Chem.* **1998**, *37*, 3057.
- [9] See also: C. A. Bayse, M. B. Hall, *J. Am. Chem. Soc.* **1999**, *121*, 1348.
- [10] For the most recent overviews see, for example: a) J. L. Martin, J. Takats, *Can. J. Chem.* **1989**, *67*, 1914; b) T. B. Karpishin, T. D. P. Stack, K. N. Raymond, *J. Am. Chem. Soc.* **1993**, *115*, 182, and references therein.
- [11] a) All calculations employed the BP86 functional^[11b] and were carried out with the Gaussian series of programs.^[11c] We used a quasirelativistic effective-core potential (ECP) with a $6s5p3d$ basis on tungsten,^[11d] ECPs and DZP basis sets on C, Cl, and F,^[11e] as well as a DZ basis on hydrogen.^[11f] This computational level has been shown previously for closely related compounds to give excellent structures, and relative energies in good agreement with more sophisticated methods (e.g. CCSD(T); cf. ref. [2b]). As a further confirmation, we have performed CCSD(T) calculations for the energy difference between **1-C_{3v}-O** and **1-C_{3v}-T**. We obtain 15.7 kJ mol^{-1} in favor of **1-C_{3v}-O**, in excellent agreement with the DFT result of 18.9 kJ mol^{-1} (Figure 1); b) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098; J. P. Perdew, *Phys. Rev. B* **1986**, *33*, 8822; c) Gaussian 94, Revisions B2, G.2, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A.

- Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh, **1995**; d) D. Andrae, U. Häußermann, M. Dolg, H. Stoll, H. Preuss, *Theor. Chim. Acta* **1990**, 77, 123; e) A. Bergner, M. Dolg, W. Küchle, H. Stoll, H. Preuss, *Mol. Phys.* **1993**, 80, 1431; f) T. H. Dunning, H. Hay in *Methods of Electronic Structure Theory; Modern Theoretical Chemistry, Vol. 3* (Ed.: H. F. Schaefer III), Plenum, New York, **1977**.
- [12] C. Santini-Scampucci, J. G. Riess, *J. Chem. Soc. Dalton Trans.* **1976**, 195. See also: W. Grahlert, K.-H. Thiele, *Z. Anorg. Allg. Chem.* **1971**, 383, 144.
- [13] Related distortions have been discussed for complexes such as $[\text{TiCl}_3\text{RL}_2]$ ($\text{R} = \text{CH}_3, \text{C}_2\text{H}_5$; $\text{L}_2 = \text{diphosphane ligand}$),^[7a] or $[\text{MCl}(\text{OAr})_2\text{H}_2\text{L}]$ ($\text{M} = \text{Nb, Ta}$) (J. R. Clark, A. L. Pulvirenti, P. E. Fanwick, M. Sigalas, O. Eisenstein, I. P. Rothwell, *Inorg. Chem.* **1997**, 36, 3623). For related distortions in heteroleptic five-coordinate complexes, see: T. R. Ward, H.-B. Bürgi, F. Gillardoni, J. Weber, *J. Am. Chem. Soc.* **1997**, 119, 11974; M. Kaupp, *Chem. Eur. J.* **1998**, 4, 2059.
- [14] Preliminary DFT calculations of ^{19}F shifts give surprisingly poor agreement with experiment and let us suspect the presence of significant intermolecular interactions in the WF_6 solutions.
- [15] M. Kaupp, unpublished results.

Trapping of an Organic Radical by an $\text{O}=\text{Cr}^{\text{VI}}$ Function**

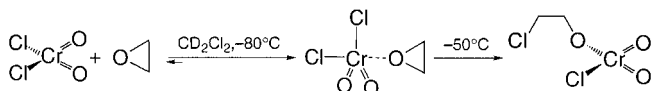
Tobias Wistuba, Christian Limberg,* and Peter Kircher

Dedicated to Professor Helmut Werner
on the occasion of his 65th birthday

Traditionally H-atom transfer onto metal oxo species in nature and technology was rationalized based on an analogy with organic radical chemistry, that is unpaired electron density was thought to be transferred to the oxygen atoms of the metal compounds, which are then ready to undergo radical reactions.^[1] In the meantime it has been established that d^0 -metal oxo systems (thus systems without unpaired spin density) can abstract hydrogen atoms from saturated organic systems, and a progression has occurred from thinking about radicals and spin density to an approach based on the thermochemistry of the H-atom transfer step.^[2] Furthermore from the results of kinetic studies and radiolysis experiments it has been inferred that the $\text{M}=\text{O}$ functions ($\text{M} = \text{metal}$) of d^0 -metal oxo compounds such as CrO_2Cl_2 ,^[3] CrO_4^{2-} ,^[4] and MnO_4^- ^[2, 4] are also capable of trapping organic radicals. For instance the radicals resulting from the H-abstraction step in

oxidations of aliphatic compounds with CrO_2Cl_2 were proposed to add to $\text{Cr}=\text{O}$ groups of excess CrO_2Cl_2 to yield Cr^{V} alkoxides, which then release the alcohols found among the oxidation products after aqueous workup. Here we provide evidence for this type of reactivity for the first time through the isolation of such a Cr^{V} primary intermediate.

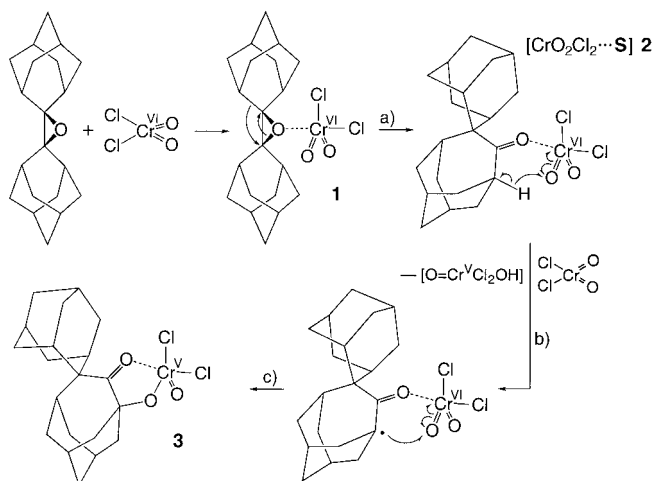
Examining Cr^{VI} alkoxides^[5] produced by epoxide cleavage with CrO_2Cl_2 (Scheme 1), we noticed their strong tendency to decompose^[6] by α -proton-coupled electron transfers onto the



Scheme 1. Oxirane cleavage with CrO_2Cl_2 .

$\text{Cr}=\text{O}$ functions, yielding paramagnetic complexes of chlorinated carbonyl compounds.^[5] To prepare stable $[\text{Cl}(\text{O})_2\text{Cr}(\text{OCR}_2\text{CR}_2\text{Cl})]$ derivatives we therefore set out by employing epoxides that lack α -H atoms. Brought into contact with CrO_2Cl_2 , tetramethyl- and tetraphenylloxirane, however, isomerized to the corresponding ketones already at very low temperatures, while epoxides like perfluoropropene oxide were too electron poor to react at all. Hence the ideal epoxide substrate should be fully substituted at the α -position, electron-rich, and not prone to rearrangements.

Bisadamantylidene epoxide (BAE) fulfils these requirements, and thus its reaction with CrO_2Cl_2 was studied by NMR spectroscopy at -50°C . The ^{13}C NMR resonance for the epoxide ring carbon atoms of BAE were shifted by $\Delta\delta = 0.5$ to lower field, indicating the formation of a complex $[\text{CrO}_2\text{Cl}_2 \cdot \text{BAE}]$ (**1**) (Scheme 2). However, comparing the shift differ-



Scheme 2. Proposed mechanism for the formation of **3**.

ence found for oxirane (Scheme 1) on complexation ($\Delta\delta = 9.6$) it has to be concluded that—probably as a result of its steric bulk—BAE is comparatively weakly complexed by the Cr center.

As we had hoped, the incorporation of the epoxide function into the adamantane framework prevented the epoxide/ketone isomerization within **1** quite effectively up to a temperature of -5°C , but a formal $\text{Cr}-\text{Cl}$ bond insertion of

[*] Dr. C. Limberg, T. Wistuba, Dr. P. Kircher
Anorganisch-chemisches Institut der Universität
Im Neuenheimer Feld 270, D-69120 Heidelberg (Germany)
Fax: (+49) 6221-545-707
E-mail: Limberg@sun0.urz.uni-heidelberg.de

[**] We are grateful to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for a scholarship (C. L.) and funding as well as to Professor G. Huttner for his generous support and to Professor J. M. Mayer for valuable discussions.

the epoxide failed to occur, too. However, further warming led to the formation of a paramagnetic main product, **3**, which could be crystallized when the reaction was performed on a preparative scale. A single-crystal X-ray analysis^[7] (Figure 1)

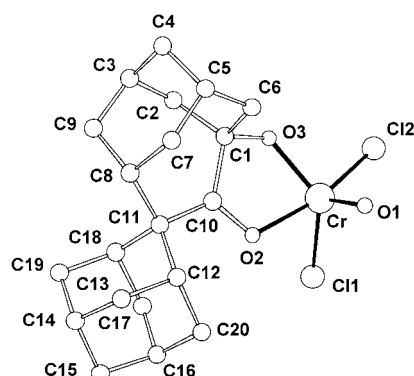


Figure 1. Molecular structure of **3**; all hydrogen atoms were omitted for clarity. Selected bond lengths [Å] and angles [°]: Cr–O1 1.561(2), Cr–O2 2.032(2), Cr–O3 1.781(2), Cr–Cl1 2.1991(8), Cr–Cl2 2.2139(7), C1–O3 1.432(2), O2–C10 1.240(2), C1–C10 1.527(3); O2–Cr–O3 78.83(6), O2–Cr–Cl2 164.77(5), Cl1–Cr–Cl2 93.35(3), O1–Cr–O2 93.09(7), Cr–O3–C1 120.1(1).

identified **3** as dichlorooxo(η^1, η^1)-spiro(adamantane-2,2'-homoadamantan-3-on-4-oate)chromate(v). The coordination sphere of its chromium center can be described as distorted trigonal bipyramidal with Cl2 and O2 as axial ligands (the O2–Cr–Cl2 angle is 164.88(3)°). Consequently, the Cl1–Cr–Cl2 angle of 93.35(3)° approximates a right angle, while O3–Cr–Cl1 is close to 120° (125.80(6)°). Compound **3** displays an ESR signal typical for d¹-Cr systems and to our knowledge it is the first structurally characterized neutral O=Cr^V alkoxide. However, the structures of a few charged species are known^[8] and can serve for comparison. All bond lengths in **3** appear to lie within characteristic regions, that is they are very similar, for instance, to those found in [OCr(O₂CCOMeEt)₂][–] (where [–]O₂CC(OH)MeEt = 2-hydroxy-2-methylbutyrate).^[8a]

The formation of **3** is of particular interest and it can be rationalized by the mechanism shown in Scheme 2. The first step (a) consists of a Cr^{VI}-catalyzed epoxide/ketone isomerization that yields a spiro(adamantane-2,2'-homoadamantan-3-one) (**S**),^[9] which remains coordinated at the Cr center to give **2**. In the next step (b) an α -H atom is selectively abstracted leading to a radical. In principle this could be envisaged to occur in the form of an intracomplex reaction or bimolecular reaction of **2** with free CrO₂Cl₂; the latter is known to be very selective in C–H activations,^[3] and in fact there is some evidence for a preference with respect to the α -keto positions in certain systems.^[3] However, the abstraction rates found so far were—even at 70 °C—comparatively low, and correspondingly we found that a reaction of the type as shown in Scheme 2 proceeds only to an insignificant extent when for instance CH₃C(O)CH(CH₃)₂ is employed under our conditions (0 °C). If on the other hand the spiro-ketone **S** is treated with CrO₂Cl₂ directly, that is if the investigation is started from **2** rather than **1**, the formation of paramagnetic centers can be detected already at temperatures below –50 °C, so that in the reaction of BAE the formation of **2**

(step a in Scheme 2) must be rate-determining. Both the site-selectivity^[10] and the high rate of the abstraction step (step b) can only be explained by a chelation-assisted intracomplex reaction—that is by a positioning of the α -H-atom directly beside a Cr=O group within **2** (compare the density functional theory (DFT)-optimized structure of **2** in Figure 2), so that the

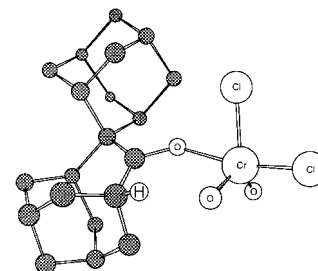


Figure 2. Structure of **2** as optimized by DFT methods (B3LYP, LANL2DZ); $d(\text{Cr}=\text{O} \cdots \text{H}_\alpha) = 2.18 \text{ Å}$.

system sets out already at a relatively high level of the C–H activation barrier. After the abstraction, Cr(OH)(O)Cl₂ formed initially, indicating an inefficient radical trap.^[3] However, it was rapidly exchanged by excess CrO₂Cl₂ (perhaps only formally in a redox reaction), thus leading to the situation shown in Scheme 2 for step (b).

The final step (c) is of a kind that has been subject to intense discussion in the past:^[2, 3] the radical formed adds to a Cr^{VI}=O function to yield an O=Cr^V alkoxide. Exactly this type of reactivity, which is manifested in **3**, has been put forward^[2, 3] to explain alcohol formation in alkane oxidations with CrO₂Cl₂ (vide supra; hydrolysis of **3** provides—as expected—the corresponding α -hydroxy ketone in good yields). Moreover the addition of organic radicals to d⁰-M=O bonds had been proposed before, for example: 1) to rationalize the trapping of radicals by CrO₄^{2–} and MnO₄[–],^[4] 2) to explain the formation of acrolein during the propene oxidation at MoO₃/Bi₂O₃ catalysts, which is assumed to proceed via allyl radicals,^[11] and 3) to understand the electron transfer from methyl radicals to d⁰ metal ions during methane oxidation on metal oxide surfaces^[12] as well as in the gas phase.^[13] The identification of the molecular compound **3**, whose isolation and characterization following reaction of BAE with CrO₂Cl₂ was possible due to special advantageous settings, provides forthright evidence for this fundamental type of reaction on a molecular level.

Experimental Section

3 · CH₂Cl₂: A solution of BAE (2.00 g, 7.03 mmol)^[9] in CH₂Cl₂ (20 mL) was frozen to –196 °C and CrO₂Cl₂ (3.25 g, 20.98 mmol) were condensed on top of the frozen block. The mixture was allowed to warm to 0 °C and then stirred at that temperature for 5 h. Avoiding further warming, all volatiles were removed under vacuum, and after washing with *n*-hexane the brown residue was extracted with CH₂Cl₂. Cooling of the filtrate yielded analytically pure **3 · CH₂Cl₂** as brown crystals. Yield: 2.60 g, 70.7%. IR (KBr): $\tilde{\nu} = 1568(\text{s})$ ($\nu(\text{C}=\text{O})$), 988(vs) ($\nu(\text{Cr}=\text{O})$) cm^{–1}; ESR (298 K): $g = 1.9864$, $\Delta H_{\text{pp}} = 20.6 \text{ G}$.

Received: April 16, 1999 [Z13285IE]
German version: *Angew. Chem.* **1999**, *111*, 3222–3224

Keywords: alkoxides • chromium • epoxides • oxidations • radicals

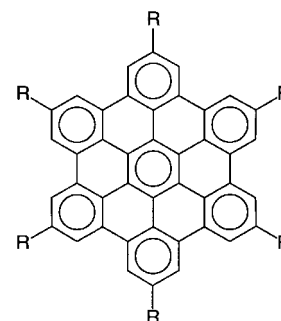
- [1] H. K. Singh in *Cytochrome P-450: Structure, Mechanism, and Biochemistry* (Ed.: R. R. Ortiz de Montellano), Plenum, New York, **1986**.
- [2] J. M. Mayer, *Acc. Chem. Res.* **1998**, *31*, 441.
- [3] G. K. Cook, J. M. Mayer, *J. Am. Chem. Soc.* **1994**, *116*, 1855; G. K. Cook, J. M. Mayer, *J. Am. Chem. Soc.* **1995**, *117*, 7139; J. M. Mayer, *Polyhedron* **1995**, *14*, 3273; K. Wang, J. M. Mayer, *J. Org. Chem.* **1997**, *62*, 4248.
- [4] M. Al-Sheikhly, W. L. McLaughlin, *Radiat. Phys. Chem.* **1991**, *38*, 203; S. Steenken, P. Neta, *J. Am. Chem. Soc.* **1982**, *104*, 1244.
- [5] C. Limberg, S. Cunsis, A. Frick, *Chem. Commun.* **1998**, 225; C. Limberg, T. Wistuba, *J. Org. Chem.* **1999**, *64*, 6169.
- [6] A. Leo, F. H. Westheimer, *J. Am. Chem. Soc.* **1952**, *74*, 4383.
- [7] $3 \cdot \text{CH}_2\text{Cl}_2$: $\text{C}_{20}\text{H}_{27}\text{Cl}_2\text{CrO}_3 \cdot \text{CH}_2\text{Cl}_2$, $M_r = 523.26$, monoclinic, space group $C2/c$, $Z = 8$, $a = 22.574(5)$, $b = 10.534(2)$, $c = 20.629(4)$ Å, $\beta = 117.06(3)^\circ$, $V = 4368.5(15)$ Å³, $4.1 < 2\theta < 52.1^\circ$, ω scan, $T = 200$ K, $\rho_{\text{calcd}} = 1.591$ g cm⁻³, 34 592 measured reflections, 4300 independent, and 3534 observed reflections with $I > 2\sigma(I)$, L_p -correction ($\mu = 1.035$ mm⁻¹), 264 refined parameters with $R = 0.032$, residual electron density: max/min: 0.404/−0.309 e Å⁻³; $\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å, the structure was solved by direct methods (SHELXS-97), and refined versus F^2 (SHELXL-97) with anisotropic temperature factors for all non-hydrogen atoms. 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-115684. 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).
- [8] a) M. Krumpolc, B. G. DeBoer, J. Rocek, *J. Am. Chem. Soc.* **1978**, *100*, 145; b) for salen complexes, see: E. G. Samsel, K. Srinivasan, J. K. Kochi, *J. Am. Chem. Soc.* **1985**, *107*, 7606; K. Srinivasan, J. K. Kochi, *Inorg. Chem.* **1985**, *24*, 4671; c) H. Nishino, J. K. Kochi, *Inorg. Chim. Acta* **1990**, *174*, 93.
- [9] G. B. Gill, D. Hands, *Tetrahedron Lett.* **1971**, 181; H. Wynberg, E. Boelema, J. H. Wieringa, J. Strating, *Tetrahedron Lett.* **1970**, 3613.
- [10] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529.
- [11] Review: R. K. Grasselli, J. D. Burrington, *Ind. Engl. Chem. Prod. Res. Dev.* **1984**, *23*, 394.
- [12] Y. Tong, J. H. Lunsford, *J. Am. Chem. Soc.* **1991**, *113*, 4741.
- [13] I. Kretschmar, A. Fiedler, J. N. Harvey, D. Schröder, H. Schwarz, *J. Phys. Chem. A* **1997**, *101*, 6253.

Highly Ordered Columnar Structures from Hexa-*peri*-hexabenzocoronenes—Synthesis, X-ray Diffraction, and Solid-State Heteronuclear Multiple-Quantum NMR Investigations**

Andreas Fechtenkötter, Kay Saalwächter, Martha A. Harbison, Klaus Müllen,* and Hans Wolfgang Spiess*

The generation of new functional materials requires both intelligent design and the high-yield synthesis of tailor-made building blocks, as well as methods that enable the highly selective characterization of their organization into supermolecular structures.^[1] Interdisciplinary studies involving advanced physical characterization methods, closely coupled with the synthetic work, is the key to success. Herein, we present an example of such an endeavor through the development of new columnar structures.

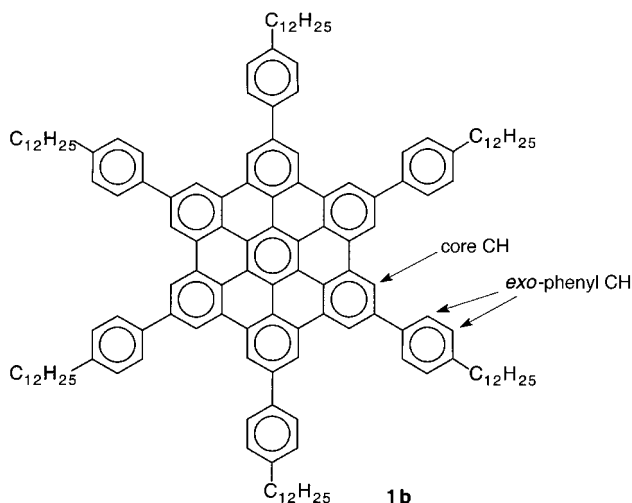
Hexa-*peri*-hexabenzocoronene (HBC, **1**) with long chain alkyl substituents, such as $\text{C}_{12}\text{H}_{25}$ (HBC- C_{12} **1a**) or $\text{C}_{14}\text{H}_{29}$, is of considerable interest on account of the unusually large liquid crystalline (LC) phase widths and favorable physical, electronic, and optoelectronic properties that are obtained. An example of such a property is their very high one-dimensional charge carrier mobility.^[2] In addition, HBC- C_{12} has the ability to form adsorbate layers on graphite, which have been investigated by scanning tunneling microscopy (STM).^[3] These substituted HBCs form columnar liquid crystals,^[4] in which the aromatic cores undergo rapid axial rotation on the μs time scale, although the order parameter of the discs, $S = 0.84$, is found to be considerably lower than in other columnar discotics.^[5] Since high mobility and low order limit the charge carrier mobility, we set out to synthesize a less mobile mesogen, which at the same time should improve the hexagonal columnar ordering. With this in mind, phenyl rings were inserted between the planar HBC discs and the pendent alkyl chains. In this communication we report the synthesis of hexa(*para*-*n*-dodecylphenyl)-substituted HBC (HBC-Ph C_{12} ,



1 (R = H)
1a (R = *n*- $\text{C}_{12}\text{H}_{25}$)

[*] Prof. Dr. K. Müllen, Prof. Dr. H. W. Spiess, A. Fechtenkötter, K. Saalwächter, M. A. Harbison
Max-Planck-Institut für Polymerforschung
Postfach 3148, D-55021 Mainz (Germany)
Fax: (+49) 6131-379-320

[**] The authors wish to thank Steven P. Brown and Ingo Schnell for helpful discussions, J. Diederich Brand for the synthesis of HBC- C_{12} , and Christoph Kayser for supplying the X-ray diffractogram of HBC- C_{12} . Financial support was supplied by the Deutsche Forschungsgemeinschaft (SFB 262), the European Commission TMR Project "SISITOMAS", and the Volkswagen Stiftung.



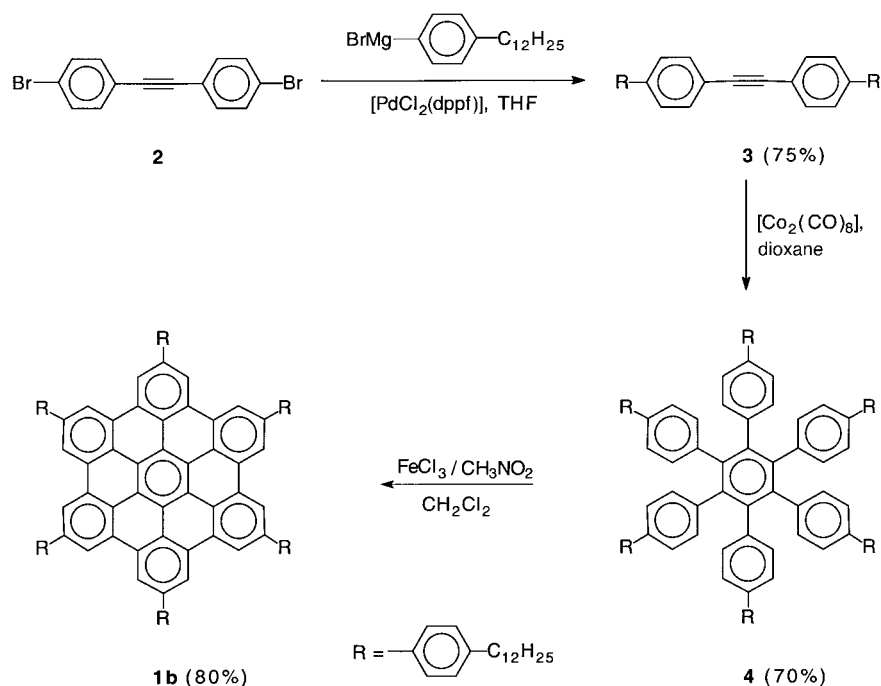
1b), and probe its order and mobility by X-ray diffraction and solid-state NMR spectroscopy.

The synthesis of HBC-PhC₁₂ is outlined in Scheme 1. First, in a Kumada-type Grignard reaction catalyzed with [PdCl₂(dppf)]^[6] (dppf = 1,1'-bis(diphenylphosphanyl)ferrocene), 4,4'-dibromotoluene (**2**) reacts with 4-*n*-dodecylphenylmagnesium bromide to give di(4-*n*-dodecylbiphenyl)acetylene (**3**) in 75% yield. Cyclotrimerization of **3**, catalyzed by [Co₂(CO)₈], in dioxane then afforded hexa(4-*n*-dodecylbiphenyl)benzene (**4**) in 70% yield after workup. The key step for the synthesis of HBCs is the oxidative cyclodehydrogenation.^[7] Here, **4** was dissolved in CH₂Cl₂ and flushed with argon for several minutes, before adding a solution of FeCl₃ in CH₃NO₂. Precipitation with MeOH and work-up finally afforded HBC-PhC₁₂ (**1b**) in 80% yield. The synthesis of **1a** has been published recently.^[7]

Both HBC-PhC₁₂ (**1b**) and HBC-C₁₂ (**1a**) form thermotropic mesophases. The differential scanning calorimetry (DSC) results showed that the transition from the room-temperature phase occurs at 80 °C for HBC-PhC₁₂, while that for HBC-C₁₂ occurs at 107 °C, and in addition, the temperature range over which the phase transition occurs is broader in HBC-PhC₁₂. Furthermore, HBC-PhC₁₂ exhibits a much higher solubility in common organic solvents than any other reported HBC derivative, for example, HBC-PhC₁₂ has a solubility greater than 10 g L⁻¹ in THF while that for HBC-C₁₂ is less than 1 g L⁻¹. The X-ray diffraction patterns for both **1a** and **1b** demonstrat-

ed that the high-temperature LC mesophases exist as ordered columnar hexagonal (Col_{h0}) superstructures. For a perfect hexagonal lattice reflections at small angles with relative spacings of 1:√3:√4:√7:√9 are expected, where the intensities depend on the perfection of the lattice and the order parameter. As shown in Figure 1, only the first three peaks (100), (110), and (200) are observed for HBC-C₁₂, while for HBC-PhC₁₂ the fourth peak (210) is apparent above the noise level, which indicates an improved long-range packing of the columns into a hexagonal arrangement. In addition, the packing of the cores within the columns is improved, as indicated by the sharp (001) reflection at 2θ ≈ 25.6°. This reflection corresponds to an intermolecular distance of 0.350 nm between the aromatic cores, which should be compared to a spacing of about 0.355 nm in the LC phase of HBC-C₁₂, where the (001) reflexion is significantly broader.^[5]

Structure and dynamics on a molecular level can be probed in detail by advanced solid-state NMR spectroscopy.^[8] The rapid rotation of the disc-shaped molecules about the



Scheme 1. Synthesis of hexaphenyl-substituted HBC (HBC-PhC₁₂).

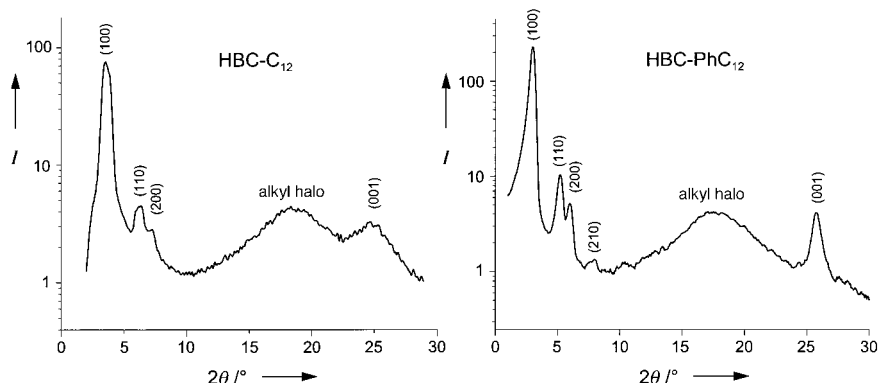


Figure 1. X-ray diffraction patterns of the Col_{h0} mesophases of HBC-PhC₁₂ and HBC-C₁₂ obtained with CuK_α radiation. The intensities (arbitrary units) are plotted on a logarithmic scale.

columnar axis in the high-temperature LC phase has been confirmed by ^2H NMR measurements,^[5] and more recently by ^1H double-quantum (DQ) magic-angle spinning (MAS) NMR spectroscopy.^[7] This rotation leads to an averaging of the respective interaction tensors, namely, the quadrupolar coupling tensor in the case of ^2H NMR, and the homonuclear dipolar coupling tensor in the case of ^1H DQ MAS NMR spectroscopy. Thus, fast motional processes can be quantified by measuring the reduction of the coupling constants. If the symmetry axes of the tensors (the CH bond vector and the H-H internuclear vector of the two core CH protons) lie in a plane perpendicular to the rotational axis, the coupling constants are reduced by a factor of 0.5. With the two methods employed, reduction factors of 0.40 and 0.42 have been observed, which corresponds to order parameters^[4] for the discs of 0.80 and 0.84, respectively, and is indicative of additional out-of-plane or librational motions.

The application of both methods mentioned above is limited. ^2H NMR spectroscopy requires specifically isotopically labeled samples, which represents a considerable synthetic challenge, while ^1H DQ MAS NMR spectroscopy is unsuitable in the case of HBC-PhC₁₂ (**1b**), since the core CH and the *exo*-phenyl CH proton resonances can not be differentiated. Both limitations are overcome by a recently developed heteronuclear multiple-quantum correlation method. REPT-HMQC (*Recoupled Polarization-Transfer Heteronuclear Multiple-Quantum Correlation*)^[8] is a two-dimensional correlation experiment for solids under very fast MAS, which exploits the concept of “separated local field” spectroscopy.^[9] An advantage of this technique is the enhanced site resolution that is made available by the observation of ^{13}C rather than ^1H resonances. As in ^1H solid-state DQ MAS spectra, the signal in the MQ dimension can be distributed over several orders of spinning side bands, with intensities depending on the dipolar coupling and the spinning frequency.^[10] These side-band intensities can then be used to quantitatively evaluate the heteronuclear dipolar coupling of site-resolved ^{13}C atoms to their neighboring protons. The sensitivity of the technique to dipolar couplings of different magnitudes can be chosen by simply changing the so-called recoupling time τ_{recpl} , which corresponds to the number of rotor periods (τ_{R}) used to excite the MQ modes.

By measuring the dipolar coupling within a CH moiety, one can use such 2D experiments to obtain site-resolved dynamical information in complex molecules without the need for isotopic labeling. It should be emphasized that the REPT-HMQC method is applicable to samples naturally abundant in ^{13}C , and only requires small amounts of sample (typically 10–15 mg). Both the heteronuclear dipolar and quadrupolar coupling tensor of a C- ^1H and a C- ^2H group, respectively, exhibit the same symmetry; hence the results from the experiments described here can be seen as being analogous to those obtained by ^2H NMR spectroscopy, the latter being a well-established method for the investigation of liquid crystals.^[4]

In Figure 2 the MQ spinning side-band patterns corresponding to the core CH signals of HBC-C₁₂ and HBC-PhC₁₂ are displayed for different temperatures and different recoupling times. In the latter case, as shown in the ^{13}C CP MAS

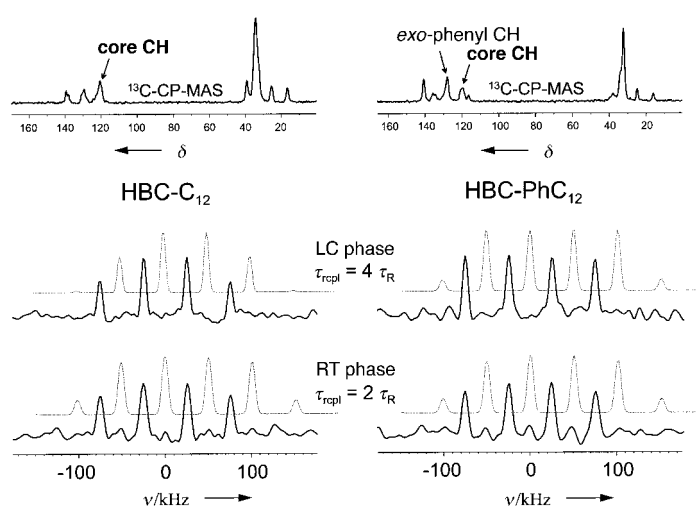


Figure 2. Solid-state ^1H - ^{13}C heteronuclear multiple-quantum spinning side-band patterns, obtained at a spinning frequency of 25 kHz, using the REPT-HMQC pulse sequence. The patterns are the sum projections over the core ^{13}CH signal in the 2D spectra of HBC-C₁₂ and HBC-PhC₁₂. The spectra for the room temperature and high temperature LC phases were recorded at 35 °C and 120 °C, respectively. The dotted traces represent simulated spectra, obtained by taking into account the best-fit dipolar coupling constants for the CH groups. The recoupling time τ_{recpl} is given in rotor periods τ_{R} . The top diagrams are ^{13}C -CP-MAS spectra taken at a spinning speed of 15 kHz, with the signal positions of the aromatic CH signals identified.

spectra, the *exo*-phenyl CH signals are resolved from the core CH signals. The side-band pattern for very fast MAS^[11, 12] is that of an isolated spin pair, namely being composed of odd-order side bands only, with the observed intensity distribution depending on the product of the recoupling time and the dipolar coupling constant.^[8, 10] The shown side-band patterns for the room-temperature and high-temperature LC phases of both materials are similar, but the recoupling times are $2\tau_{\text{R}}$ and $4\tau_{\text{R}}$ for the RT and LC phases, respectively. This means that the dipolar couplings are reduced by approximately 50%. A closer inspection reveals that the side-band pattern for the LC phase of HBC-C₁₂ exhibits less intense third-order side bands, which indicates a weaker coupling than in HBC-PhC₁₂.

The dipolar coupling constants were evaluated quantitatively by numerically fitting the side-band patterns to the analytical solution for the case of a heteronuclear spin pair; such best-fit spectra are shown as dotted lines in Figure 2. The average dipolar coupling constant for a rigid, aromatic CH group—as found in the RT phase of both materials—was determined from various independent measurements to be 20.9 ± 0.5 kHz, which corresponds to an internuclear distance of 113 ± 1 pm, while the motionally reduced coupling constants for the LC phases were determined to be 8.2 ± 0.9 and 9.7 ± 0.9 kHz for HBC-C₁₂ and HBC-PhC₁₂, respectively. Thus, reduction factors of 0.39 ± 0.04 and 0.46 ± 0.04 were calculated for the motional processes in the two materials, which corresponds to order parameters of 0.78 ± 0.09 and 0.93 ± 0.09 . The value for HBC-C₁₂ thus agrees with the earlier findings within the limits of experimental error.^[5, 7] In contrast, the order parameter for the discs in HBC-PhC₁₂ has increased by 15%, which means that the rotational motion is better defined and that additional out-of-plane motions are

suppressed more effectively. It should be emphasized that the increase in the order parameter is better defined than its absolute value, the latter being subject to systematic deviations.

It may further be noted that the MQ measurements were carried out at 120 °C, such that the motional processes in both HBC samples are assured to be fast on the NMR time scale, namely at least in the μ s range. In this respect, the decrease of line widths in the ^1H MAS spectra upon heating the sample made it become clear that the degree of motional averaging for HBC-PhC₁₂, despite its lower calorimetric phase transition temperature of 80 °C, still increases up to about 110 °C. One should keep in mind that these thermally activated motions, though fast on an NMR time scale, are not expected to interfere with the dynamics of the hopping process of charge transport, which takes place on a time scale of less than 1 ns.

These NMR investigations strongly support the conclusion of the existence of high intracolumnar order as drawn from the X-ray data, and thus we can state that order phenomena in the LC phase of HBC-PhC₁₂ not only extend to longer ranges—as detected by scattering experiments—but also manifest themselves in a well-defined packing of the rotating discs on a molecular level. We also note that preliminary results concerning motional processes in the side chains at different temperatures indicate an initially surprising higher mobility in HBC-PhC₁₂ relative to HBC-C₁₂, which indicates that a higher order of the HBC cores does not necessarily lead to an overall reduction of mobility in the system. Since the charge-carrier transport properties in such systems are limited by the degree of long-range order within the columns, the possibility of the system undergoing molecular reorientations as a result of this motional freedom, thus allowing for self-healing, is highly desirable.

In summary, the design, synthesis, and mesophase characterization of a hexaphenyl-substituted HBC has indicated that symmetric substitution can inhibit out-of-plane mesogen mobility without interrupting the columnar hexagonal superstructure. Both MQ NMR results and X-ray diffraction patterns indicate higher inter- and intracolumnar ordering in the mesophase. The possibility of studying the motional processes of the mesogens in a site-resolved way using technologically advanced heteronuclear multiple-quantum NMR methods, without the synthetic difficulties of isotopic labeling, has greatly enhanced our ability to understand the mesogenic properties of these fascinating materials.

Experimental Section

3: A 1 M solution of 4-*n*-dodecylphenylmagnesium bromide (18 mL) was added dropwise to a solution of **2** (1 g, 3 mmol) in dry THF (100 mL) in a 250-mL Schlenk flask. [PdCl₂(dppf)] catalyst (200 mg) was added to this solution. The resulting mixture was stirred under reflux in an inert atmosphere for 20 h. While cooling the mixture to room temperature, a white solid precipitated. The solid was then filtered and washed several times with petrol ether and methanol to yield **3** (1.5 g, 75 %). ^1H NMR (500 MHz, C₂D₂Cl₄): δ = 7.58 (s, 8H; CH), 7.51 (d, $^3J(\text{H,H})$ = 7 Hz, 4H; CH), 7.24 (d, $^3J(\text{H,H})$ = 7 Hz, 4H; CH), 2.65 (m, 4H; α -CH₂), 1.67 (m, 4H; β -CH₂), 1.25–1.45 (m, 36H; CH₂), 0.91 (t, $^3J(\text{H,H})$ = 6 Hz, 6H; CH₃); ^{13}C NMR (125 MHz, C₂D₂Cl₄): δ = 143.10, 141.40, 138.0, 132.50, 129.30, 127.23, 127.17, 122.60, 90.70, 36.00, 32.30, 31.50, 30.04, 30.03, 30.00, 29.96,

29.87, 29.76, 29.67, 23.00, 14.36; MS (FD, 8 kV): m/z (%): 666.9 (100) [M^+] (calcd for C₅₀H₆₆: 666.5)

4: A suspension of **3** (1 g, 1.5 mmol) in dioxane (50 mL) was degassed several times in a 100-mL round bottom flask equipped with a reflux condenser. [Co₂(CO)₈] (78 mg, 0.23 mmol) was then added and the resulting mixture was refluxed for 3 h. The solvent was evaporated under vacuum, and the residue purified by column chromatography on silica gel with petrol ether/CH₂Cl₂ (8/2) to yield **4** (0.7 g, 70 %) as an off-white solid. ^1H NMR (500 MHz, C₂D₂Cl₄): δ = 7.31 (d, $^3J(\text{H,H})$ = 8 Hz, 12H; CH), 7.1 (d, $^3J(\text{H,H})$ = 8 Hz, 12H; CH), 7.06 (d, $^3J(\text{H,H})$ = 8 Hz, 12H; CH), 6.88 (d, $^3J(\text{H,H})$ = 8 Hz, 12H; CH), 2.51 (m, 12H; α -CH₂), 1.52 (m, 12H; β -CH₂), 1.30–1.15 (m, 108H; CH₂), 0.83 (t, $^3J(\text{H,H})$ = 6 Hz, 18H; CH₃); ^{13}C NMR (125 MHz, C₂D₂Cl₄): δ = 142.05, 140.37, 139.94, 138.10, 137.26, 132.27, 128.91, 126.83, 125.18, 35.82, 32.21, 31.76, 29.98 (2 $\times$ CH₂), 29.94, 29.90, 29.82, 29.70, 29.65, 23.02, 14.52; MS (FD, 8 kV): m/z (%): 2002.1 (100) [M^+] (calcd for C₁₅₀H₁₉₆: 2001.2).

1b: A 250-mL two-necked round bottom flask was charged with **4** (0.53 g, 0.27 mmol) and CH₂Cl₂ (70 mL). A constant stream of argon was bubbled into the solution through a glass capillary. A solution of FeCl₃ (0.8 g, 5 mmol) in CH₃NO₂ was then added dropwise with a syringe. After 30 min the mixture was quenched with MeOH and the precipitate was filtered off. The resulting yellow solid was recrystallized from hot THF and dried under vacuum to yield **1b** (0.42 g, 80 %). ^1H NMR (500 MHz, *p*-C₆D₄Cl₂, 85 °C): δ = 8.57 (s, 12H; CH), 7.92 (d, $^3J(\text{H,H})$ = 6.5 Hz, 12H; CH), 7.58 (d, $^3J(\text{H,H})$ = 6.5 Hz, 12H; CH), 3.18 (m, 12H; α -CH₂), 2.25 (m, 12H; β -CH₂), 1.95 (m, 12H; γ -CH₂), 1.88 (m, 12H; δ -CH₂), 1.8–1.45 (m, 84H; CH₂), 1.13 (m, 18H; CH₃); ^{13}C NMR (125 MHz, C₂D₂Cl₄, 85 °C): δ = 141.87, 140.65, 136.73, 129.83, 129.35, 128.93, 122.63, 120.31, 118.32, 37.37, 33.25, 33.22, 31.40, 31.34, 31.27, 31.21, 31.08, 30.90, 30.7, 23.91, 15.12; MS (MALDI-TOF): m/z (%): 1989.1 (100) [M^+] (calcd for C₁₅₀H₁₈₆: 1989.1).

NMR spectroscopy: All NMR experiments were carried out on a Bruker DSX 300 spectrometer equipped with a commercial Bruker 2.5 mm double-resonance MAS probe and operating at 300.23 MHz for ^1H and 75.49 MHz for ^{13}C . The 90° pulse lengths were 2 μ s on both channels, and proton dipolar decoupling with a B₁ frequency of 125 kHz. CP contact times were 2 ms, and the repeating time amounted to 1 s. Details concerning the REPT-HMQC pulse sequence can be obtained from reference [8].

Received: May 11, 1999 [Z13407IE]

German version: *Angew. Chem.* **1999**, *111*, 3224–3228

Keywords: coronene • liquid crystals • NMR spectroscopy • X-ray scattering

- [1] *Electronic Materials: The Oligomer Approach* (Eds.: K. Müllen, G. Wegner), WILEY-VCH, Weinheim, **1998**.
- [2] A. M. van de Craats, J. M. Warman, K. Müllen, Y. Geerts, J. D. Brand, *Adv. Mater.* **1998**, *10*, 36.
- [3] A. Stabel, P. Herwig, K. Müllen, J. P. Rabe, *Angew. Chem.* **1995**, *107*, 1768; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1609.
- [4] *Handbook of Liquid Crystals* (Eds.: D. Demus, J. W. Goodby, G. W. Gray, H. W. Spiess, V. Vill), WILEY-VCH, Weinheim, **1998**.
- [5] P. Herwig, C. W. Kayser, K. Müllen, H. W. Spiess, *Adv. Mater.* **1996**, *8*, 510.
- [6] T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* **1984**, *106*, 158.
- [7] S. P. Brown, I. Schnell, J. D. Brand, K. Müllen, H. W. Spiess, *J. Am. Chem. Soc.* **1999**, *121*, 6712.
- [8] K. Schmidt-Rohr, H. W. Spiess, *Multidimensional Solid-State NMR and Polymers*, Academic Press, New York, **1994**.
- [9] K. Saalwächter, R. Graf, H. W. Spiess, *J. Magn. Reson.*, in press.
- [10] H. Geen, J. J. Titman, J. Gottwald, H. W. Spiess, *Chem. Phys. Lett.* **1994**, *227*, 79; J. Gottwald, D. E. Demco, R. Graf, H. W. Spiess, *Chem. Phys. Lett.* **1995**, *243*, 314.
- [11] K. Saalwächter, R. Graf, D. E. Demco, H. W. Spiess, *J. Magn. Reson.* **1999**, *139*, 287.
- [12] C. Filip, S. Hafner, I. Schnell, D. E. Demco, H. W. Spiess, *J. Chem. Phys.* **1999**, *110*, 423.

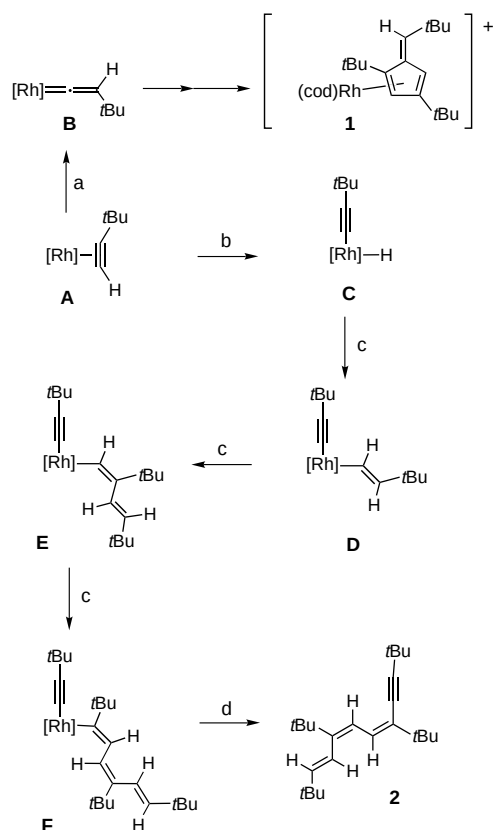
Rhodium-Promoted Linear Tetramerization and Cyclization of 3,3-Dimethylbut-1-yne**

Andrew D. Burrows, Michael Green,* John C. Jeffery, Jason M. Lynam, and Mary F. Mahon

Dedicated to Professor Helmut Werner on the occasion of his 65th birthday

Following the early work of Reppe et al.^[1] and continuing throughout the development of modern organotransition metal chemistry^[2] there has been a sustained interest in the reactions of alkynes with transition metal centers. Recently attention has focused on both linear oligomerization reactions^[3–5] and on the trimerization of alkynes to form fulvenes,^[6–8] potential synthons for substituted cyclopentadienyl ligands.^[7, 9]

We had earlier found^[6] that reaction of $[\text{Rh}_2(\mu\text{-Cl})_2(\text{cod})_2]$ (cod = cycloocta-1,5-diene) with $t\text{BuC}_2\text{H}$ and AgPF_6 in CH_2Cl_2 led to the selective formation of the cationic fulvene complex **1** (Scheme 1), from which the free fulvene could be



Scheme 1. Proposed pathway to the triene-yne **2**. $[\text{Rh}] = [\text{Rh}(\text{cod})]^+$. a) CH_2Cl_2 ; b) THF; c) $t\text{BuC}_2\text{H}$; d) $[\text{Rh}(\text{cod})(\text{thf})]^+$.

[*] Prof. M. Green, Dr. A. D. Burrows, Dr. J. M. Lynam, Dr. M. F. Mahon
Department of Chemistry, University of Bath
Claverton Down, Bath BA2 7AY (UK)
Fax: (+44) 1225-826-231
E-mail: m.green@bath.ac.uk
Dr. J. C. Jeffery
School of Chemistry, University of Bristol (UK)

[**] The EPSRC is thanked for financial support.

readily displaced by acetonitrile. In seeking to establish a catalytic version of this chemistry we added $t\text{BuC}_2\text{H}$ to a solution of the labile complex $[\text{Rh}(\text{NMe})_2(\text{cod})][\text{BF}_4]$ ^[10] in dichloromethane, but were surprised to observe that there was no reaction at 40 °C. However, using the same reactants with tetrahydrofuran (THF) as the solvent, in which the more labile complex $[\text{Rh}(\text{thf})_2(\text{cod})][\text{BF}_4]$ could be formed by ligand displacement, the color of the reaction mixture changed rapidly (0.5 h, 50 °C) from yellow to deep red. Following removal of the solvent an orange solid was isolated, which showed in its ^1H NMR spectrum resonances corresponding to a single organic product in addition to $[\text{Rh}(\text{cod})]^+$ species. The organic compound was purified by column chromatography (silica gel; diethyl ether) and recrystallization (acetone/ethanol, 1/1) to give crystals of **2** (70% yield), which was shown by MS and ^1H NMR measurements to be a tetramer of 3,3-dimethylbut-1-yne.^[11] A single crystal X-ray crystallographic analysis^[12] demonstrated that **2** was a linear tetramer, and this was confirmed spectroscopically as being a triene-yne (Scheme 1).

Although there are recent reports of the formation of ene-yne,^[3] butatrienes,^[4] and diene-yne^[5] from metal-promoted linear dimerization and trimerization reactions of alkynes, the regio- and stereoselective synthesis of **2** represents the first example of a linear tetramerization reaction, which is especially interesting because of its solvent dependency.

It is suggested that in the reaction between $[\text{Rh}_2(\mu\text{-Cl})_2(\text{cod})_2]$, AgPF_6 , and $t\text{BuC}_2\text{H}$ in dichloromethane an η^2 -alkyne complex **A** (Scheme 1) is formed, which selectively rearranges into the vinylidene species **B**, a clear precursor of the fulvene ligand.^[6, 8] However, a different pathway is followed in THF, the η^2 -alkyne complex **A** transforms into the hydridoacetylide–rhodium(III) complex **C**,^[13] thus opening the way to the sequential “insertion”^[14, 15] of $t\text{BuC}_2\text{H}$ ($\text{C} \rightarrow \text{D} \rightarrow \text{E} \rightarrow \text{F}$) and the formation, through reductive elimination, of the triene-yne **2**. Each of these steps is highly selective and although in principle both **D** and **E** could reductively eliminate to form an ene-yne or diene-yne, respectively, it is only when the third alkyne inserts ($\text{E} \rightarrow \text{F}$) with different selectivity^[14] to the two previous steps that reductive elimination intervenes and halts the oligomerization process.^[16]

With this insight the way seemed to be clear to establish a catalytic procedure for the formation of the triene-yne **2**, and consequently a solution of $[\text{Rh}(\text{NMe})_2(\text{cod})][\text{BF}_4]$ in THF was treated with 100 molar equivalents of $t\text{BuC}_2\text{H}$ at 50 °C for 1 h. The color of the reaction mixture rapidly changed from yellow to red, but surprisingly on work up it was evident that only a relatively small amount of **2** had been formed. However, there was a new product present (60% yield), which was separated and purified by column chromatography (silica gel; hexane). The ^1H , ^{13}C NMR, and MS data^[17] of this hydrocarbon-soluble material showed it to be a mononuclear rhodium complex **3** containing a cod ligand and an unusual organic ligand assembled from four $t\text{BuC}_2\text{H}$ molecules. In this ligand one of the $t\text{Bu}$ groups has been transformed into a CH_2CMe_2 fragment, and loss of H^+ has occurred: consequently the product **3** is neutral. Attempts to establish the structural identity of **3** by X-ray crystallography were

frustrated by the high solubility of the material. However treatment of **3** with $[\text{FeCp}_2][\text{BF}_4]$ (CH_2Cl_2 , -78°C) led to a 17e cationic species formed by a one electron oxidation reaction. Loss of $\text{H}^\bullet$ from this intermediate gave the diamagnetic cationic complex **4**. An X-ray diffraction study^[18] of **4** following recrystallization ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$) established the structure of the cation in this complex as that shown in Figure 1. Complex **4** contains two linked C_5 rings and is formed by a type of alkyne coupling reaction previously unobserved.

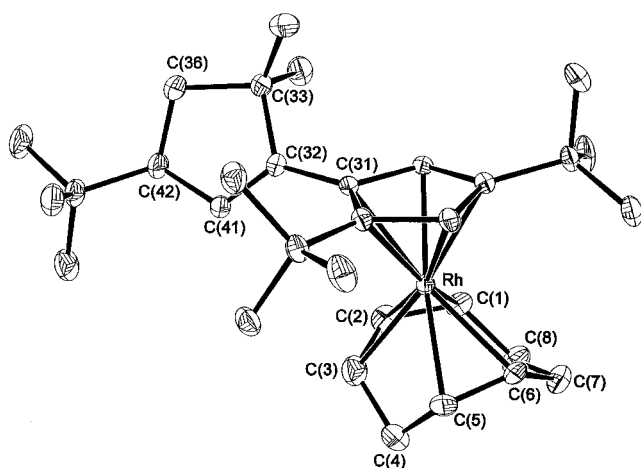
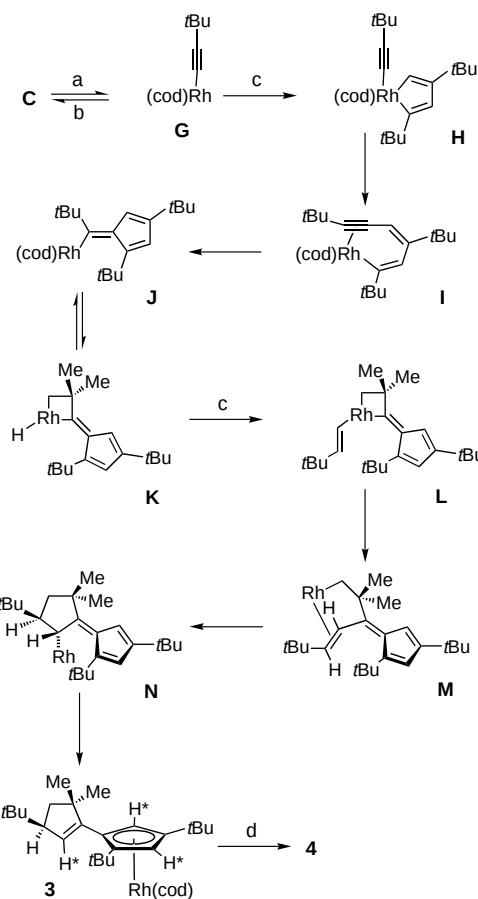


Figure 1. Solid-state structure of **4** (the hydrogen atoms and the BF_4^- counterion are removed for clarity). Selected bond lengths [Å]: Rh-C(1) 2.182(3), Rh-C(2) 2.143(3), Rh-C(3) 2.303(3), Rh-C(5) 2.228(3), Rh-C(6) 2.222(3), C(31)-C(32) 1.484(4), C(32)-C(41) 1.333(3), C(32)-C(33) 1.542(4), C(33)-C(36) 1.547(4), C(36)-C(42) 1.540(4), C(41)-C(42) 1.507(4).

Comparison of the NMR data for **3** with that of the cation **4** clearly showed that the redox reaction involved only the cycloocta-1,5-diene ligand, which was transformed into an ene- η^3 -allyl system.^[19] Therefore, with the structural identity of **3** (Scheme 2) established it is reasonable to consider a possible reaction pathway to this novel product. In agreement with the pathway outlined in Scheme 1, the reaction in THF at low concentrations of $t\text{BuC}_2\text{D}$ afforded the triene-yne **2**, in which only the vinylic CH bonds had been replaced by CD. However, at high $t\text{BuC}_2\text{D}$ concentrations, when the catalytic reaction stops because of the formation of the neutral complex **3**, deuterium atoms are incorporated into the three asterisked positions of **3**, (Scheme 2), which suggests that a terminal alkyne hydrogen atom is lost.

The formation of **3** and the results from the deuterium labeling experiments can be rationalized if it is assumed that the hydridoacetylide **C** is reversibly deprotonated in the basic solvent THF to give the neutral complex **G** (Scheme 2), which is presumably stabilized by the coordination of THF. At high alkyne concentrations **G** can be captured by $t\text{BuC}_2\text{H}$ resulting in the formation of the rhodacyclopentadiene **H** and the diversion of the rhodium away from the triene-yne forming process. Once formed, **H** could be expected to undergo a reductive elimination reaction to form the alkyne complex **I**, thus providing access to the σ -bonded fulvene derivative **J**. As a result of the proximity of the α - $t\text{Bu}$ substituent to the



Scheme 2. Proposed pathway to complex **3** in THF. a) $-\text{H}^\bullet$; b) $+\text{H}^\bullet$; c) $t\text{BuC}_2\text{H}$; d) $[\text{FeCp}_2][\text{BF}_4]$; the cod ligands have been omitted for clarity in species **K–N**.

rhodium center **J** would be expected to readily undergo a reversible C–H activation reaction leading, via the intermediates **L**, **M**, and **N**, to complex **3**.

There is no precedent for a reaction of this type, and it is especially interesting that the course of the reaction between a putative $[\text{Rh}(\text{cod})]^+$ fragment and $t\text{BuC}_2\text{H}$ is dependent in a subtle way on both the choice of the reaction solvent and on the alkyne concentration. We have also found in a preliminary study of the corresponding system in which the cod ligand is replaced by norbornadiene that although the triene-yne **2** is formed, there is no evidence for the formation of a norbornadiene-substituted analogue of **3**. This observation has interesting consequences for the development of a catalytic synthesis of the triene-yne.

Received: May 19, 1998 [Z13445IE]

German version: *Angew. Chem.* **1999**, *111*, 3228–3230

Keywords: alkynes • C–C coupling • cyclizations • oligomerizations • rhodium

- [1] W. Reppe, N. von Kutepow, A. Magin, *Angew. Chem.* **1969**, *81*, 717–723; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 727–733.
- [2] Reviews: a) K. P. C. Vollhardt, *Angew. Chem.* **1984**, *96*, 525–541; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539–556; b) J. L. Templeton, *Adv. Organomet. Chem.* **1989**, *29*, 1–100; c) N. E. Schore in

- Comprehensive Organic Synthesis*, Vol. 5 (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, pp. 1129–1162; d) G. G. Melikyan, K. M. Nicholas in *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**, pp. 99–138.
- [3] a) C. Bianchini, P. Innocenti, A. Meli, M. Peruzzini, F. Zanolini, P. Zanello, *Organometallics* **1990**, *9*, 2514–2522; b) M. Schäfer, N. Mahr, J. Wolf, H. Werner, *Angew. Chem.* **1993**, *105*, 1377–1379; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1315–1318; c) C. Bianchini, P. Frediani, D. Masi, M. Peruzzini, F. Zanolini, *Organometallics* **1994**, *13*, 4616–4632; d) H. Werner, M. Schäfer, J. Wolf, K. Peters, H. G. von Schnering, *Angew. Chem.* **1995**, *107*, 213–215; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 191–194.
- [4] a) Y. Wakatsuki, H. Yamazaki, N. Kumegawa, T. Satoh, J. Y. Satoh, *J. Am. Chem. Soc.* **1991**, *113*, 9604–9610; b) R. Wiedemann, J. Wolf, H. Werner, *Angew. Chem.* **1995**, *107*, 1359–1361; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1244–1246.
- [5] H.-F. Klein, M. Mager, S. Isringhausen-Bley, U. Flörke, H.-J. Haupt, *Organometallics* **1992**, *11*, 3174–3175.
- [6] G. Moran, M. Green, A. G. Orpen, *J. Organomet. Chem.* **1983**, *250*, C15–C20.
- [7] E. S. Johnson, G. J. Balaich, P. E. Fanwick, I. P. Rothwell, *J. Am. Chem. Soc.* **1997**, *119*, 11086–11087.
- [8] J. M. O'Connor, K. Hiibner, R. Merwin, P. K. Gantzel, B. S. Fong, M. Adams, A. L. Rheingold, *J. Am. Chem. Soc.* **1997**, *119*, 3631–3632.
- [9] T. A. Mobley, R. G. Bergman, *J. Am. Chem. Soc.* **1998**, *120*, 3253–3254.
- [10] M. Green, T. A. Kuc, S. H. Taylor, *J. Chem. Soc. A* **1971**, 2334–2337.
- [11] **2**: ^1H NMR (CDCl_3): δ = 1.08 (s, 9H; CMe_3), 1.10 (s, 9H; CMe_3), 1.12 (s, 9H; CMe_3), 1.32 (s, 9H; CMe_3), 5.61 (d, ^3J = 15.9 Hz, 1H; CH), 5.85 (d, ^3J = 15.9 Hz, 1H; CH), 6.57 (d, ^3J = 10.8 Hz, 1H; CH), 6.62 (d, ^3J = 10.8 Hz, 1H; CH); ^{13}C NMR (CDCl_3): δ = 28.3 (CMe_3), 29.4 (CMe_3), 29.5 (CMe_3), 29.6 (CMe_3), 31.3 (CMe_3), 33.6 (CMe_3), 35.7 (CMe_3), 36.1 (CMe_3), 77.1 ($\text{C}=\text{C}$), 106.4 ($\text{C}=\text{C}$), 121.1 ($=\text{CH}$), 121.3 ($=\text{CH}$), 129.0 ($=\text{CH}$), 132.6 ($=\text{C}(\text{Bu})$), 147.6 ($=\text{CH}$), 151.1 ($=\text{C}(\text{Bu})$); EI-MS: m/z : 328.3 [M^+], 271.3 [$M^+ - \text{CMe}_3$], 215.2 [$M^+ - 2\text{CMe}_3$].
- [12] Crystal structure analysis of **2**, $\text{C}_{24}\text{H}_{40}$: M_r = 328.56, monoclinic, space group $P2_1/c$, a = 10.001(3), b = 12.231(3), c = 10.237(3) Å, β = 113.55(2)°, V = 1147.9(6) Å³, Z = 2, μ = 0.052 mm⁻¹, crystal dimensions 0.25 × 0.25 × 0.2 mm. $2\theta_{\text{max}}$ = 50°, $\text{MoK}\alpha$ radiation (λ = 0.71069 Å), T = 170(2) K, 2181 measured reflections, of which 2016 were unique and 1058 observed with $F_o > 4\sigma(F_o)$. Lorentz and polarization corrections were applied and the structure solved by direct methods (SHELX86) with full-matrix least-squares (SHELXL93) refinement based on F^2 , 115 parameters. $R1$ = 0.1111, $wR2$ = 0.3159.^[20] The asymmetric unit consists of one half of the triene-yne with the remainder generated by an inversion center, hence there is disorder between the terminal double and triple bonds.
- [13] It is also possible that the vinylidene complex **B** is formed via the hydridoacetylide complex **C**.
- [14] A. M. La Pointe, M. Brookhart, *Organometallics* **1998**, *17*, 1530–1537. In this study of the reactions of alkynes with the cationic complexes $[\text{Pd}(\text{CH}_3)(\text{N}-\text{N})\text{L}][\text{BAR}_4^+]$ ($\text{N}-\text{N}$ = phenanthroline or diimine, L = Et_2O or MeCN , Ar^1 = 3,5-(CF_3)₂ C_6H_3) the regiochemistry of the “insertion” step has been related to the steric demands of both the metal center and the alkyne. It is also reported in this paper that an excess of alkyne results in the formation of a palladium–trieryl species that can then undergo an intramolecular cyclization reaction to form a 5-ethylidene-2-cyclopentene-1-yl complex. Although a related intramolecular cyclization reaction with the rhodium–trieryl intermediate **F** (shown in Scheme 1) can be envisaged, such a process does not provide a pathway to the fulvene complex **1**.
- [15] M. Etienne, R. Mathieu, B. Donnadieu, *J. Am. Chem. Soc.* **1997**, *119*, 3218–3228, and references therein.
- [16] In the case of the cobalt system studied by Klein and co-workers^[5] a shut down of the oligomerization process is also observed on reversal of the regiochemistry of the insertion of a monosubstituted alkyne (PhC_2H). However, in contrast with the rhodium system this occurs earlier in the oligomerization process.
- [17] The ^1H NMR data for **3** indicated the presence of three compounds in the approximate ratio 8:2:1. The fact that all three species possessed near-identical NMR spectra led us to conclude that they were all stereoisomers. In contrast, the ^1H NMR spectrum of the crystals of **4** showed evidence for the presence of only one stereoisomer. NMR data for the major stereoisomer of **3**: ^1H NMR (CDCl_3): δ = 0.85 (s, 9H; CMe_3), 0.89 (s, 3H; CMe_2), 1.01 (s, 3H; CMe_2), 1.19 (s, 9H; CMe_3), 1.21 (s, 9H; CMe_3), 1.45 (dd, ^2J = 11.7, ^3J = 8.8 Hz, 1H), 1.67 (dd, ^2J = 11.7, ^3J = 6.3 Hz, 1H), 1.73 (m, 2H; cod CH_2), 1.98 (m, 2H; cod CH_2), 2.08 (m, 2H; cod CH_2), 2.18 (m, 2H; cod CH_2), 2.54 (ddd, ^3J = 8.8, ^3J = 6.3, ^3J = 1.5 Hz, 1H), 3.58 (m, 2H; cod CH), 3.83 (m, 2H; cod CH), 4.28 (d, ^4J = 2.4 Hz, 1H; Cp), 4.50 (d, ^4J = 2.4 Hz, 1H; Cp), 5.80 (d, 1.5 Hz, 1H); ^{13}C NMR (CDCl_3): δ = 27.2 (s; CMe_2), 27.9 (s; CMe_3), 28.5 (s; CMe_2), 31.6 (s; cod CH_2), 32.3 (s; CMe_3), 33.4 (s; CMe_3), 33.5 (s; cod CH_2), 44.5 (s; CH_2), 47.4 (s; CMe_2), 53.8 (s; $\text{CH}(\text{Bu})$), 63.5 (d, $^1J_{\text{RhC}}$ = 14.4 Hz; cod CH), 66.8 (d, $^1J_{\text{RhC}}$ = 14.4 Hz; cod CH), 80.6 (d, $^1J_{\text{RhC}}$ = 3.3 Hz; Cp CH), 81.9 (d, $^1J_{\text{RhC}}$ = 4.4 Hz; Cp CH), 101.6 (d, $^1J_{\text{RhC}}$ = 4.4 Hz; Cp CC), 116.1 (d, $^1J_{\text{RhC}}$ = 4.4 Hz; Cp CC), 117.7 (d, $^1J_{\text{RhC}}$ = 3.3 Hz; Cp CC), 133.8 (s; $\text{CH}=\text{C}$), 146.8 (s; $\text{CH}=\text{C}$); FAB MS of **3**: m/z : 538.2 [M^+], 481.1 [$M^+ - \text{CMe}_3$].
- [18] Crystal structure analysis of **4**, $\text{C}_{32}\text{H}_{50}\text{BF}_4\text{Rh}$: M_r = 624.44, triclinic, space group $P\bar{1}$, a = 8.931(2), b = 9.389(2), c = 20.404(9) Å, α = 103.12(3), β = 90.14(3), γ = 110.72(2)°, V = 1552.1(8) Å³, Z = 2, μ = 0.593 mm⁻¹, crystal dimensions 0.40 × 0.20 × 0.05 mm. $2\theta_{\text{max}}$ = 55°, $\text{MoK}\alpha$ radiation (λ = 0.71073 Å), T = 173(2) K, 16005 measured reflections, of which 7020 were unique (R_{int} = 0.0332) and observed. Full-matrix least-squares refinement based on F^2 , 382 parameters.^[20] $R1$ = 0.0361, $wR2$ = 0.0807. NMR data for **4**: ^1H NMR (CDCl_3): δ = 0.91 (s, 9H; CMe_3), 1.05 (s, 3H; CMe_2), 1.26 (s, 3H; CMe_2), 1.33 (s, 9H; CMe_3), 1.34 (s, 9H; CMe_3), 1.59 (dd, ^2J = 11.8, ^3J = 10.8 Hz, 1H), 1.80 (dd, ^2J = 11.8, ^3J = 6.5 Hz, 1H), 2.29 (m), 2.55 (m), 2.74 (dd, ^3J = 10.8, ^3J = 6.5 Hz, 1H), 2.88 (m), 3.32 (m), 3.83 (m), 4.59 (m), 4.71 (m), 5.04 (m), 5.23 (d, ^4J = 1.7 Hz, 1H; Cp), 5.46 (d, ^4J = 1.7 Hz, 1H; Cp), 5.85 (m), 6.01 (d, ^3J < 1 Hz, 1H).
- [19] A similar reaction has been observed on treatment of $[\text{Rh}(\text{cod})\text{Cp}]$ with one-electron oxidants: M. D. Kitchen, PhD thesis, University of Bristol (UK), **1978**; N. G. Connelly, personal communication.
- [20] 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-118903 (**2**) and -118904 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

An Atmospherically Driven Optical Switch

James J. La Clair*

An effective switch translates an external force through components of minimal complexity into a signal that regulates a desired output. A series of macromolecular switches have now been constructed that can be initiated by chemical, electrochemical, photochemical, or thermal stimuli.^[1] Recent attention now focuses on adapting these materials into machines or electronic components.^[2] A new device is presented that translates a change in the atmosphere into an electrical output through a photophysical change within a small group of molecules.

Here, a change is defined in units of molecules and measured by monitoring the viability of twisted intramolec-

[*] Prof. J. J. La Clair
Department of Molecular Biology
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037 (USA)

ular charge transfer (TICT) state formation.^[3–4] Materials that contain a large dielectric constant, such as **1**, undergo facile rotation about unrestricted sp³ bonds to form TICT states upon being excited to the singlet state (Figure 1). The

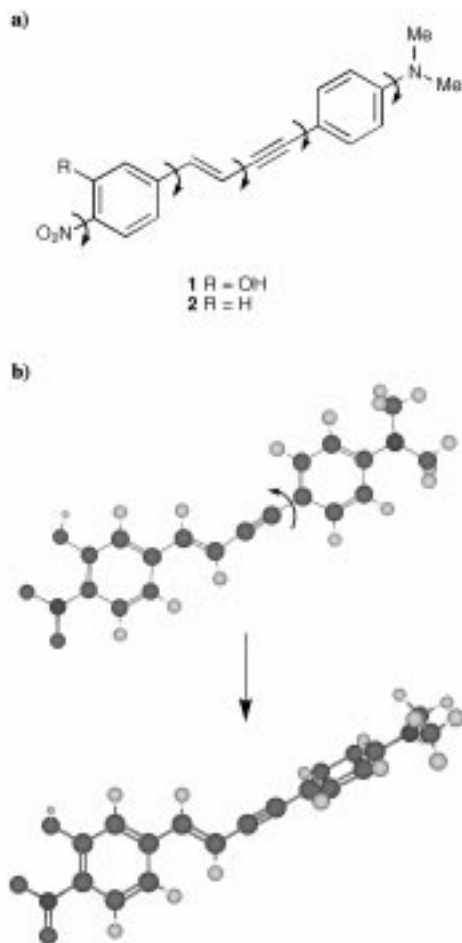


Figure 1. a) Compounds **1** and **2** contain five bonds (shown with arrows), which rotate in the excited state to provide a series of TICT states. b) Schematic representation depicting the formation of an orthogonal TICT state (bottom) from a planar conformation (top).

orthogonal alignment of these states restricts their relaxation back to the ground state by nonemissive processes. Overall, the presence of a TICT state acts as a funnel that removes the potential for individual molecules to fluoresce.

The formation of a TICT state is encouraged in polar media as a consequence of the relative increase in charge separation.^[4] For **1**, changing the solvent from *n*-heptane to methanol red-shifted the fluorescence maxima^[5] and decreased the relative quantum yield, as indicated by a change of $\lambda_F = 527$ nm ($\Phi_F = 0.10$) and $\lambda_F = 541$ ($\Phi_F = 0.0049$) in *n*-heptane to $\lambda_F = 483$ nm ($\Phi_F \sim 10^{-6}$) in methanol. This solvent effect was so pronounced that the addition of 0.005 % methanol provided only 10% of the fluorescence normally obtained from a 1 μ M solution of **1** in *n*-heptane.

The switching process was monitored using confocal single molecule spectroscopy. This technique was chosen as it is applicable to a small volume and provides a signal that requires a minimum number of molecules. Fluorescence from

1 was examined as individual molecules diffused through a 2.8 fL (2.8×10^{-15} L) conical fluorescent element. An illuminated cavity was generated by imaging the fluorescence, which arises from excitation with a 488 nm line (10 mW) of an argon ion laser through a 1 μ m diameter pinhole and a 545 nm cutoff filter, onto a photoavalanche detector (Figure 2). Single

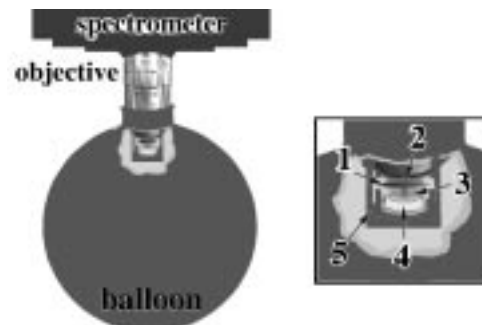


Figure 2. Schematic representation of the optical switch.^[8] Left: An 80 ± 10 μ L droplet of a 100 pM solution of **1** in benzene or toluene, enclosed within a balloon, is placed in contact with the objective of a confocal fluorescence spectrometer. Right: enlarged view of the probe. A laser beam (2) passes from the objective into the sample (3). The sample is held in a 50 μ L gold well housed within a silver case (4). The sample holder is fixed to the objective using small strips of wood and tape (5). A small cover slip (1) is held between the objective and sample by a 20 μ L drop of water to prevent contamination. Fluorescence is collected back through the objective, passed through a 1.0 μ m diameter pinhole, and focused on the tip of the photoavalanche detector. The final probe volume is 2.8 fL (10^{-15} L). The chamber can be filled with argon, carbon dioxide, or nitrogen without altering the temperature of the probe.

molecules of **1** were readily detected in 0.1–1 nM solutions of *n*-heptane, benzene, or toluene in an argon or nitrogen atmosphere.^[6, 7] In contrast, comparable detection was not possible in a variety of polar solvents, including methanol, ethanol, DMSO, DMF, 1,4-dioxane, and THF. This solvent sensitivity served as an effective switching element.

When the atmosphere surrounding a 100 pM solution of **1** in benzene or toluene was changed from nitrogen to carbon dioxide, single molecules were no longer detected (Figure 3). Interestingly, the solubility of carbon dioxide in benzene or toluene was sufficient to decrease the net fluorescence from **1**. Single molecules were again detected after removal of the carbon dioxide and re-filling the chamber with argon or nitrogen.^[9] This switching was limited only by the evaporation of the solvent. The presence of fluorescent molecules could be determined with a 99.1 ± 0.7 % certainty over 900 runs after 1.5 s. The speed of switching was not restricted by the detection element but rather by the ability to de-gas and refill the chamber.

A two-stage switch was constructed on the basis of the ability to detect single molecules of **1** as they diffused through a 2.8 fL cylinder.^[7] The positions of the switch were defined as ON in an argon or nitrogen atmosphere and OFF in the presence of carbon dioxide. The lack of fluorescence in the OFF position likely arose from a combination of solvent-induced alteration in the access to the TICT state as well as carbonylation of the free phenol. Evidence for both factors come from a comparison of the results obtained with **1** with

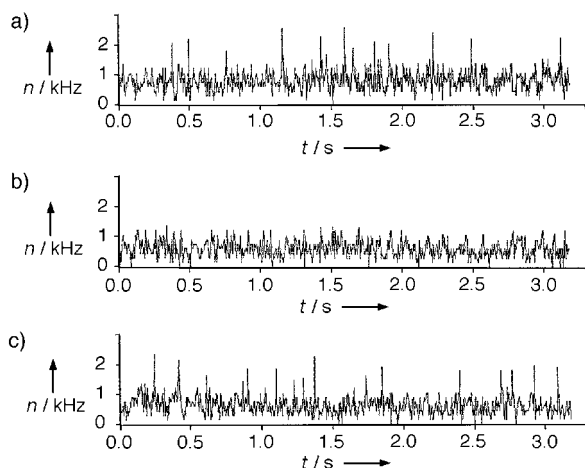


Figure 3. Traces of single molecules of **1** diffusing through a 2.8 fL (10^{-15} L) fluorescence element. a) Single molecules are readily detected in *n*-heptane solution in an argon or nitrogen atmosphere. b) Transients from these molecules disappear as the atmosphere is changed to carbon dioxide and c) reappear upon returning to an argon or nitrogen atmosphere.

those from **2**. While both materials share comparable spectroscopic properties and solvent sensitivity, the number of single molecule events was decreased but not eliminated when **2** was subjected to the same conditions as those used in Figures 2 and 3.

The fluorescence observed from the switching of **1** was translated into a graphical display (Figure 3) by conversion of the fluorescent photons into an electrical signal by means of a single-photon counting photoavalanche detector. The relay of the interaction between atmosphere and molecular photo-physics to an electrical signal provides a novel approach for the design of future optical mechanical and electronic devices.

Experimental Section

Measurements were conducted on a conventional confocal single molecule spectrometer.^[6, 7] A 20 μ L drop of water was placed on the upper side of a circular cover-slip (Fischer) and attached to the head of a microscope objective (Zeiss Plan-neofluar Multi-immersion 40X). A 50 μ L gold well encased in a silver holder ($2 \times 2 \times 0.6$ cm) and loaded with 80 ± 10 μ L of a 100 pM solution of **1** in benzene or toluene was slowly brought into contact with the cover-slip. The assembly was held in place by mounting the sample holder on to the objective with four beams (see Figure 2). The droplet of **1** was open to the atmosphere. A balloon was placed over the entire sample housing and filled with gas. Confocal single molecule examinations were made repetitively on solutions of **1** in argon, nitrogen, and carbon dioxide atmospheres.

Received: April 26, 1999

Revised version: July 5, 1999 [Z133181E]

German version: *Angew. Chem.* **1999**, *111*, 3231–3233

Keywords: atmospheric chemistry • charge transfer • fluorescence • molecular switches • single molecule spectroscopy

- [1] a) V. Balzani, M. Gomez-Lopez, J. F. Stoddart, *Acc. Chem. Res.* **1998**, *31*, 405; b) J. P. Sauvage, *Acc. Chem. Res.* **1998**, *31*, 611; c) B. Kenda, F. Diederich, *Angew. Chem.* **1998**, *110*, 3162; *Angew. Chem. Int. Ed.* **1998**, *37*, 3154; d) W. B. Davis, W. A. Svec, M. A. Ratner, M. R. Wasielewski, *Nature* **1998**, *396*, 60; e) C. D. Mao, W. Q. Sun, Z. Y. Shen, N. C. Seeman, *Nature* **1999**, *397*, 144; f) E. Zahavy, M. A. Fox, *Chem. Eur. J.* **1998**, *4*, 1647; g) R. A. English, S. G. Davison, Z. L. Miskovic, F. O.

- Goodman, *J. Phys. Condens. Matter* **1998**, *10*, 4423; h) D. Gosztola, M. P. Niemczyk, M. R. Wasielewski, *J. Am. Chem. Soc.* **1998**, *120*, 5118.
- [2] a) S. J. Tans, A. R. M. Verschueren, C. Dekker, *Nature* **1998**, *393*, 49; b) F. Kulzer, S. Kummer, R. Matzke, C. Bräuchle, T. Basché, *Nature* **1997**, *387*, 688; c) C. Joachim, J. K. Gimzewski, *Chem. Phys. Lett.* **1997**, *265*, 353; d) A. D. Mehta, J. T. Finer, J. A. Spudich, *Methods Enzymol.* **1998**, *298*, 436; e) K. Kinoshita, Jr., R. Yasuda, H. Noji, S. Ishiwata, M. Yoshida, *Cell* **1998**, *93*, 21.
- [3] a) J. J. La Clair, *J. Am. Chem. Soc.* **1997**, *119*, 7676; b) J. J. La Clair, *Angew. Chem.* **1998**, *110*, 339; *Angew. Chem. Int. Ed.* **1998**, *37*, 325.
- [4] W. Rettig, *Angew. Chem.* **1986**, *98*, 969; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 971.
- [5] C. Reichardt, *Chem. Rev.* **1994**, *94*, 2319.
- [6] a) P. Schwill, F. J. Meyer-Almes, R. Rigler, *Biophys. J.* **1997**, *72*, 1878; b) M. Eigen, R. Rigler, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 5740; c) R. A. Keller, W. P. Ambrose, P. W. Goodwin, J. H. Jett, J. C. Martin, M. Wu, *Appl. Spectrosc.* **1996**, *50*, 12A; d) X. S. Xie, *Acc. Chem. Res.* **1996**, *29*, 598; e) D. T. Chiu, A. Hsiao, A. Gaggari, R. A. Garzalopez, O. Orwar, R. N. Zare, *Anal. Chem.* **1997**, *69*, 1801; f) J. Enderlein, D. L. Robbins, W. P. Ambrose, P. M. Goodwin, R. A. Keller, *Bioimaging* **1997**, *5*, 88; g) H. P. Lu, X. S. Xie, *Nature* **1997**, *385*, 143; h) S. Xie, R. N. Zare, *Ann. Rev. Biophys. Biomol. Struct.* **1997**, *26*, 567.
- [7] Single molecules were detected using a confocal fluorescence spectrometer as designed by Eigen–Rigler.^[6a,b] Fluorescent photons were harvested by passing the filtered fluorescent beam through a 1 μ m diameter pinhole and focusing this light on to a single photon counting silicon avalanche detector (EG&G SPCM-100).
- [8] The switch was flipped by changing the atmosphere within the balloon between argon or nitrogen and carbon dioxide. This was conveniently accomplished by slowly purging and filling with the appropriate gas.
- [9] The fact that the regenerated signal (Figure 3, bottom trace) originated from **1** was verified by two observations. Firstly, the detected transients displayed an identical diffusion time ($t_d = 55 \pm 5$ ms) with that of **1**, as given by their auto-correlated function (not shown). Secondly, the reaction of **1** with carbon dioxide was reversible as indicated by independent ^1H NMR characterization of a scaled-up version of this process.

Novel Catalytic Hydrogenolysis of Trimethylsilyl Enol Ethers by the Use of an Acidic Ruthenium Dihydrogen Complex**

Yoshiaki Nishibayashi, Izuru Takei, and Masanobu Hidai*

Since the first report on a tungsten complex with an η^2 -bound H_2 ligand, $\text{W}(\eta^2\text{-H}_2)$, by Kubas and co-workers in 1984,^[1] a great number of this unique class of complexes have

[*] Prof. Dr. M. Hidai, Dr. Y. Nishibayashi, I. Takei
Department of Chemistry and Biotechnology
Graduate School of Engineering
The University of Tokyo, Hongo 7-3-1
Bunkyo-ku, Tokyo 113-8656 (Japan)
Fax: (+81)3-5841-7265
E-mail: hidai@chembio.t.u-tokyo.ac.jp

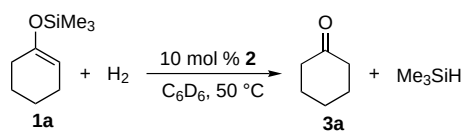
[**] This work was supported by a Grant-in-Aid for Specially Promoted Research (09102004) from the Ministry of Education, Science, Sports, and Culture, Japan. We thank Dai Masui and Shin Takemoto for assistance with NMR analysis.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

been found and their structures and reactivities have been delineated.^[2, 3] Dihydrogen complexes allow the design of a simple fascinating pathway for the heterolytic activation of molecular dihydrogen (H_2) on a transition metal center. Actually, the heterolytic cleavage of coordinated H_2 has been achieved by treatment with a variety of bases.^[2, 3] This has led to systematic investigation of ligand effects on the reactivity of coordinated H_2 and to the synthesis of highly acidic $M(\eta^2-H_2)$ complexes.^[2, 3] However, the catalytic reactions that proceed through heterolytic activation of H_2 by acidic $M(\eta^2-H_2)$ complexes are limited.^[3f, 4–7] Very recently, we have succeeded in the formation of NH_3 by the protonation of the coordinated N_2 on a tungsten atom with an acidic $Ru(\eta^2-H_2)$ complex under mild conditions.^[8] This finding has led us to develop a novel catalytic reaction in which the heterolytic activation of H_2 is catalyzed by an acidic $Ru(\eta^2-H_2)$ complex.

Transition metal catalyzed hydrogenation of a variety of unsaturated substrates is an important and conventional method in preparative organic chemistry.^[9] The Wilkinson complex, $[RhCl(PPh_3)_3]$, is probably one of the most widely used catalysts for the homogeneous hydrogenation of carbon–carbon double bonds in the laboratory.^[9] For example, trimethylsilyl enol ethers are converted into saturated trimethylsilyl ethers in the presence of $[RhCl(PPh_3)_3]$ under an atmospheric pressure of H_2 .^[10, 11] In this case, the addition of H_2 to the carbon–carbon double bond occurs. In sharp contrast to the conventional hydrogenation, we have now found that employment of an acidic $Ru(\eta^2-H_2)$ complex as catalyst results in hydrogenolysis of the Si–O bond. In this reaction, H_2 is heterolytically cleaved into H^+ and H^- on the Ru center and transferred to the enol oxygen^[12] and the trimethylsilyl silicon atom, respectively, affording a ketone and Me_3SiH . This provides a conceptually new type of catalytic reaction. Preliminary results on this catalytic reaction are described here.

Treatment of 1-trimethylsilyloxy-1-cyclohexene (**1a**) in the presence of a catalytic amount of $[RuCl(dppe)_2]OTf$ (**2**) (10 mol %) ($dppe$ = 1,2-bis(diphenylphosphanyl)ethane, Tf = trifluoromethanesulfonyl) under 1 atm of H_2 in anhydrous C_6D_6 at 50 °C for 3 h in an NMR tube afforded cyclohexanone (**3a**) and Me_3SiH in almost quantitative yields by NMR spectroscopy (Scheme 1). This novel reaction proceeded

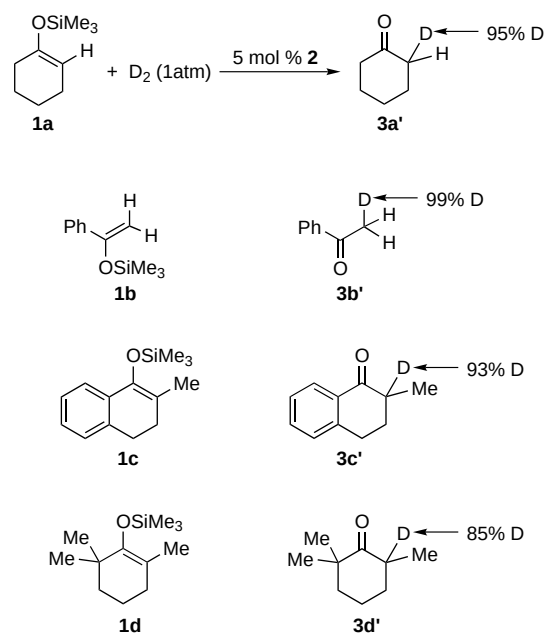


Scheme 1. Hydrogenolysis of **1a** into **3a** and Me_3SiH . $^{29}Si\{^1H\}$ NMR of **1a** (C_6D_6): δ = 14.6; $^{29}Si\{^1H\}$ NMR of Me_3SiH (C_6D_6): δ = –16.4.

smoothly at 50 °C, however, very slowly at room temperature. The formation of Me_3SiH was confirmed by the ^1H and $^{29}Si\{^1H\}$ NMR spectra of the reaction mixture. No other products were observed by NMR spectroscopy, gas–liquid chromatography (GLC), and gas chromatography mass spectrometry (GC-MS). Under 1 atm of H_2 , complex **2** was quantitatively converted into $[RuCl(\eta^2-H_2)(dppe)_2]OTf$ (**4**) within 5 min at ambient temperature. Since complex **4** has

relatively high acidity,^[14] **1a** is considered to be protonated at the oxygen atom by the coordinated H_2 in **4** to give **3a**, while the Me_3Si group in **1a** eventually binds with the remaining hydride to form Me_3SiH (vide infra). Interestingly, the reaction between **1a** and $[RuH(\eta^2-H_2)(dppe)_2]OTf$ with low acidity^[15] did not occur.

The direct proton transfer from H_2 to **1a** catalyzed by complex **2** was confirmed by the experiment employing D_2 gas. The reaction of **1a** was carried out under 1 atm of D_2 at 50 °C for 48 h in the presence of 5 mol % of **2** in anhydrous dichloroethane. This reaction resulted in **3a'** in >95 % yield (GLC) with monodeuteration at the α -position (Scheme 2).



Scheme 2. Hydrogenolysis of **1a–d** with D_2 .

Other trimethylsilyl enol ethers (**1b–d**) were also protonated with D_2 to give ketones (**3b'–d'**) in >95 % yields (GLC) with monodeuteration at the α -position. Incorporation of D at the α -position of **3a'–d'** was quantitatively analyzed by ^1H NMR spectroscopy and GC-MS (see Scheme 2 and Supporting Information for experimental details). These results indicate that one of the deuterium atoms of the coordinated D_2 is catalytically transferred to the oxygen atom, and the resultant enol then tautomerizes to form the corresponding ketone with monodeuteration at the α -position. When THF or benzene was used as solvent in place of dichloroethane, almost the same results were obtained.

By contrast, the catalytic hydrogenation of trimethylsilyl enol ethers using $[RhCl(PPh_3)_3]$ under the same reaction conditions led to the formation of the corresponding trimethylsilyl ethers. For example, treatment of **1b** in the presence of 5 mol % of $[RhCl(PPh_3)_3]$ under 1 atm of H_2 in anhydrous C_6H_6 at 50 °C for 24 h afforded (1-phenyl-1-trimethylsilyloxy)ethane in >95 % yield (GLC).

Figure 1 shows the unequivocal effect of H_2 on the conversion of **1a** into **3a** catalyzed by complex **2**. Under 1 atm of N_2 the reaction of **1a** in the presence of 1 mol % of **2**

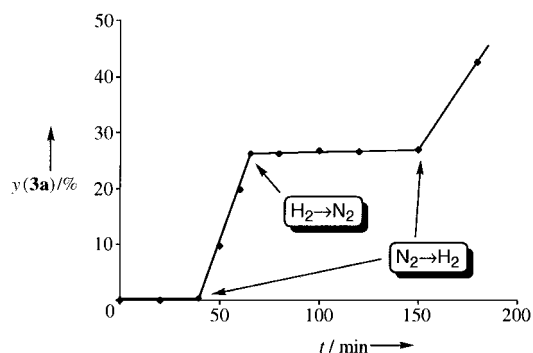
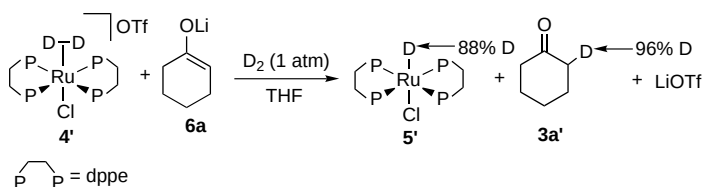


Figure 1. Effect of the reaction atmosphere on the conversion of **1a** into **3a**. y = yield.

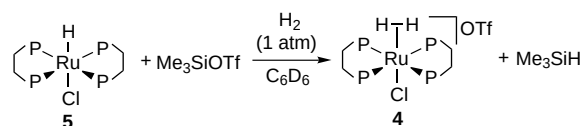
in THF at 50 °C did not occur at all. When the N₂ atmosphere was replaced by 1 atm of H₂ after 45 min, the reaction began and **3a** was rapidly produced. However, the reaction was again stopped after 60 min when the reaction atmosphere was changed back to 1 atm of N₂. Further production of **3a** started when the N₂ atmosphere was again replaced by 1 atm of H₂ after 150 min. This result demonstrates that H₂ is essential to this catalytic reaction.

To elucidate the mechanism of this novel catalytic reaction, the following stoichiometric and catalytic reactions were investigated. First, treatment of lithium enolate **6a**, which was prepared from **1a** and MeLi, with one equivalent of [RuCl(η²-D₂)(dppe)₂](OTf) (**4'**) under 1 atm of D₂ in anhydrous THF at room temperature afforded **3a'** with monodeuteration at the α-position in >95 % yield (GLC) and a deuteride complex [RuClD(dppe)₂] (**5'**) in 85 % yield of isolated product (Scheme 3). This provides the direct evidence of heterolytic



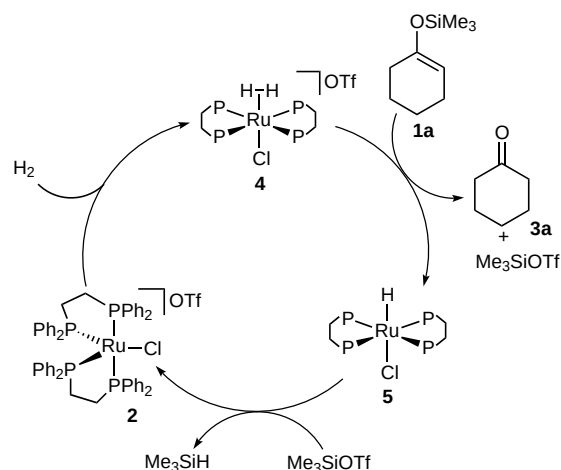
Scheme 3. Reaction between D₂ complex **4'** and lithium enolate **6a**.

cleavage of D₂ coordinated on the ruthenium atom: D⁺ is probably transferred to the sp² carbon of **6a** to form **3a'** (vide infra), while D[−] remains at the ruthenium atom as a deuteride. Furthermore, treatment of 2-cyclohexen-1-one in the presence of a catalytic amount of **2** under 1 atm of H₂ at 50 °C did not give **3a** at all. This result indicates that the hydrogenolysis of **1a** does not proceed via 2-cyclohexen-1-one, which might be formed from dehydrosilylation of **1a**.^[16] Second, the reaction of [RuClH(dppe)₂]^[14a] (**5**) with one equivalent of Me₃SiOTf under 1 atm of H₂ in anhydrous C₆D₆ at room temperature rapidly gave **4** in quantitative NMR yield together with Me₃SiH (Scheme 4). In this stoichiometric reaction Me₃SiOTf behaves as a hydride acceptor. Thus, complex **2** may be initially formed from complex **5** by reaction with Me₃SiOTf, which is immediately converted into the starting Ru(η²-H₂) complex **4** under 1 atm of H₂.



Scheme 4. Conversion of **5** into **4**. ³¹P{¹H} NMR of **4** (C₆D₆): δ = 51.6 (s); ³¹P{¹H} NMR of **5** (C₆D₆): δ = 62.7 (s).

Based on these findings we propose a mechanism for the formation of **3a** and Me₃SiH from **1a** and H₂ (Scheme 5). The initial step is the protonation of the trimethylsilyl enol ether

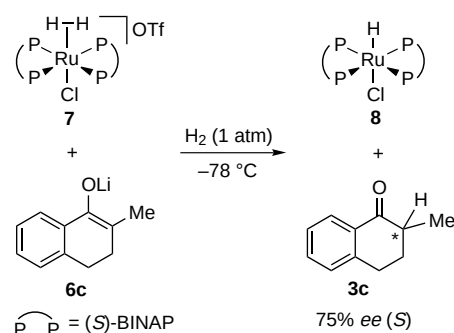


Scheme 5. A mechanism for the hydrogenolysis of **1a**.

probably at the oxygen atom with H₂ coordinated on the Ru atom; this yields **3a** and Me₃SiOTf together with **5**. Subsequent reaction of Me₃SiOTf with **5** under 1 atm of H₂ results in the formation of the starting Ru(η²-H₂) complex **4** via **2**, concurrent with Me₃SiH. We believe that a delicate balance of the acidity of the Ru(η²-H₂) complex **4** and the nucleophilicity of the hydride complex **5** might rationalize this novel hydrogenolysis.

Finally, the present hydrogenolysis has been extended to the asymmetric protonation of silyl enol ether **1c** and the corresponding lithium enolate **6c** with [RuCl(η²-H₂)((*S*)-BINAP)₂](OTf) (**7**) (BINAP = (2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl). Treatment of **1c** with one equivalent of **7** at −78 °C in CH₂Cl₂ under 1 atm of H₂ afforded **3c** in >95 % yield (GLC) with no enantioselectivity. On the other hand, the reaction of lithium enolate **6c** with 1 equiv of **7** at −78 °C in CH₂Cl₂ under 1 atm of H₂ produced **3c** with 75 % *ee* (*S*) and **8**^[17] in >95 % yields (Scheme 6).^[18] The enantioselective protonation of prochiral enolates has attracted much attention,^[19] thus providing a new approach to the asymmetric protonation of enol ethers. Further work on the effect of chiral ligands around the Ru atom is currently in progress.

In summary, we have found novel catalytic hydrogenolysis of trimethylsilyl enol ethers with H₂ catalyzed by [RuCl(η²-H₂)(dppe)₂](OTf) (**4**). In this reaction, the Si–O bond is heterolytically cleaved by coordinated H₂ to form a ketone and Me₃SiH. We have also demonstrated the stoichiometric, but enantioselective ruthenium-assisted protonation of a



Scheme 6. Asymmetric protonation of **6c**.

prochiral lithium enolate with H_2 to give a chiral ketone with high enantioselectivity (up to 75% *ee*).

Experimental Section

Preparation of $2 \cdot (\text{CH}_2\text{Cl}_2)_{0.5}$: This complex was prepared from *cis*- $[\text{RuCl}_2(\text{dppe})_2]$ and NaOTf by a procedure similar to that for reported for $[\text{RuCl}(\text{dppe})_2]\text{PF}_6$.^[14a] A solution of NaOTf (2.13 g, 12.4 mmol) and *cis*- $[\text{RuCl}_2(\text{dppe})_2]$ (10.0 g, 10.3 mmol) in THF (100 mL) and EtOH (50 mL) was stirred at room temperature for 12 h under 1 atm of Ar. After evaporation of the solvents, the residue was extracted with CH_2Cl_2 (20 mL). Addition of hexane to the concentrated solution gave **2** (CH_2Cl_2)_{0.5} (8.96 g, 7.97 mmol, 77%) as dark red crystals; ^1H NMR (CDCl_3): δ = 1.65 (br. s, 4H), 2.56 (br. s, 2H), 2.65 (br. s, 2H), 6.78–7.76 (m, 40H); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3): δ = 55.6 (br. t, J = 12 Hz), 83.7 (br. t, J = 12 Hz); elemental analysis (%) calcd for $\text{C}_{53}\text{H}_{48}\text{ClF}_3\text{O}_3\text{P}_4\text{SRu} \cdot (\text{CH}_2\text{Cl}_2)_{0.5}$: C 57.12, H 4.39; found: C 57.13, H 4.57.

7: To a solution of **8** (1.152 g, 0.83 mmol) in dichloromethane (10 mL) and THF (10 mL) was added HOTf (80 μL) by syringe under 1 atm of H_2 . The reaction mixture was stirred at room temperature for 30 min. The color of the solution turned from yellow to red during the reaction. Hexane (50 mL) was then added to the reaction mixture to give a pale red solid **7**, which was collected by filtration, washed with hexane (3×20 mL), and dried under reduced pressure (1.050 g, 0.68 mmol, 82%); ^1H NMR (CD_2Cl_2): δ = −9.11 (br., 2H), 5.2–8.8 (m, 64H); a minimum T_1 value of 21 ms (400 HMz) at 243 K was obtained for the broad signal at δ = −9.11, assignable to $\eta^2\text{-H}_2$; $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): δ = 2.5 (t, J = 27 Hz), 26.3 (t, J = 27 Hz); elemental analysis (%) calcd for $\text{C}_{89}\text{H}_{66}\text{ClF}_3\text{O}_3\text{P}_4\text{SRu}$: C 69.73, H 4.34; found: C 69.74, H 4.38.

Asymmetric protonation of **6c with **7** (Scheme 6):** A solution of **6c** was prepared by lithiation of **1c** (25.0 mg, 0.10 mmol) with methylolithium (0.10 mL of 1.02 N solution in diethyl ether, 0.10 mmol) in Et_2O (3 mL) at room temperature for 2 h under 1 atm of N_2 . A solution of complex **7** (150 mg, 0.10 mmol) in dry dichloromethane (5 mL) was then added to the above solution of **6c** at −78 °C under 1 atm of H_2 . The mixture was stirred at that temperature for 4 h under 1 atm of H_2 . Then the reaction mixture was gradually warmed up to room temperature and stirred at room temperature for 12 h. GLC analysis showed the formation of **3c** (>95%). The solvent was removed under reduced pressure, and the residue was extracted with Et_2O (3×5 mL). The extract was purified by TLC (SiO_2 , hexane/ EtOAc = 7/3 as eluent) to afford **3c** as a pale yellow liquid (12 mg, 0.075 mmol, 75%). The remaining residue was recrystallized from CH_2Cl_2 / Et_2O to give **8** as a yellow solid (95 mg, 0.069 mmol, 69%). The absolute configuration of (*S*)-**3c** was determined by its optical rotation; $[\alpha]_D^{25} = -30$ (c = 0.40 in dioxane); the 75% *ee* value of (*S*)-**3c** was determined by GLC (helium carrier gas, 120 °C column temperature, 20:1 split ratio) on a cyclodextrin phase (Chiraldex GT-A, 30 m); retention time of (*R*)-**3c** = 22.87 min (12.6%); retention time of (*S*)-**3c** = 24.01 min (87.4%).

Received: May 18, 1999 [Z13438IE]

German version: *Angew. Chem.* **1999**, *111*, 3244–3247

Keywords: asymmetric synthesis • enols • protonations • ruthenium • silicon

- [1] G. J. Kubas, R. R. Ryan, B. I. Swanson, P. J. Vergamini, H. J. Wasserman, *J. Am. Chem. Soc.* **1984**, *106*, 451.
- [2] For recent examples, see: a) A. C. Ontko, J. F. Houllis, R. C. Schnabel, D. M. Roddick, T. P. Fong, A. J. Lough, R. H. Morris, *Organometallics* **1998**, *17*, 5467; b) D. H. Lee, B. P. Patel, E. Clot, O. Eisenstein, R. H. Crabtree, *Chem. Commun.* **1999**, 297; c) Z. Xu, I. Bytheway, G. Jia, Z. Lin, *Organometallics* **1999**, *18*, 1761.
- [3] For recent reviews, see: a) P. G. Jessop, R. H. Morris, *Coord. Chem. Rev.* **1992**, *121*, 155; b) D. M. Heinekey, W. J. Oldham, *Chem. Rev.* **1993**, *93*, 913; c) R. H. Morris, *Can. J. Chem.* **1996**, *74*, 1907; d) R. H. Crabtree, *J. Organomet. Chem.* **1998**, *577*, 111; e) S. Sabo-Etienne, B. Chaudret, *Chem. Rev.* **1998**, *98*, 2077; f) M. A. Esteruelas, L. A. Oro, *Chem. Rev.* **1998**, *98*, 577.
- [4] a) R. T. Hembre, S. McQueen, *J. Am. Chem. Soc.* **1994**, *116*, 2141; b) R. T. Hembre, J. S. McQueen, V. W. Day, *J. Am. Chem. Soc.* **1996**, *118*, 798.
- [5] a) W. C. Chan, C. P. Lau, Y. Z. Chen, Y. Q. Fang, S. M. Ng, G. Jia, *Organometallics* **1997**, *16*, 34; b) H. S. Chu, C. P. Lau, K. Y. Wong, W. T. Wong, *Organometallics* **1998**, *17*, 2768.
- [6] V. I. Bakmutov, E. V. Vorontsov, D. Y. Antonov, *Inorg. Chim. Acta* **1998**, *278*, 122.
- [7] The first examples of the direct involvement of $\text{M}(\eta^2\text{-H}_2)$ complexes in catalytic hydrogenation are found in the following articles: a) C. Bianchini, A. Meli, M. Peruzzini, P. Frediani, C. Bohanna, M. A. Esteruelas, L. A. Oro, *Organometallics* **1992**, *11*, 138; b) C. Bianchini, C. Bohanna, M. A. Esteruelas, P. Frediani, A. Meli, L. A. Oro, M. Peruzzini, *Organometallics* **1992**, *11*, 3837; c) M. A. Esteruelas, J. Herrero, A. M. Lopez, L. A. Oro, M. Schulz, H. Werner, *Inorg. Chem.* **1992**, *31*, 4013.
- [8] Y. Nishibayashi, S. Iwai, M. Hidai, *Science* **1998**, *279*, 540.
- [9] “Reductions in Organic Chemistry”: M. Hudlicky, *ACS Symp. Ser.* **1996**, *188*.
- [10] For examples, see a) M. Tanaka, Y. Watanabe, T. Mitsudo, Y. Yasunori, Y. Takegami, *Chem. Lett.* **1974**, 137; b) R. Kuwano, S. Okuda, Y. Ito, *J. Org. Chem.* **1998**, *63*, 3499.
- [11] In the catalytic hydrogenation of trimethylsilyl enol ethers, the corresponding ketones are sometimes observed as by-products. This is explained by the reaction of trimethylsilyl enol ethers with adventitious water in the solvent.
- [12] Since no enantioselectivity was observed in the stoichiometric reaction of **1c** (see Scheme 2) with **7** (see Scheme 6), we consider that the hydrogenolysis of trimethylsilyl enol ethers catalyzed by **4** (see Scheme 4) proceeds through O-protonation by the activated H_2 ligand.^[13] Thus, in this novel reaction an enol product is initially produced, which isomerizes to the corresponding keto form.
- [13] A study on protonolysis of several silyl enol ethers showed that C-protonation occurred in the case of *tert*-butyldimethylsilyl enol ethers while no conclusion was made for trimethylsilyl enol ethers; M. H. Novice, H. R. Seikaly, A. D. Seiz, T. T. Tidwell, *J. Am. Chem. Soc.* **1980**, *102*, 5835.
- [14] a) B. Chin, A. J. Lough, R. H. Morris, C. T. Schweitzer, C. D’Agostino, *Inorg. Chem.* **1994**, *33*, 6278. b) The $\text{p}K_a$ value of $[\text{RuCl}(\eta^2\text{-H}_2)(\text{dppe})_2]\text{PF}_6$ was estimated to be 6.0.
- [15] a) E. P. Cappellani, S. D. Drouin, G. Jia, P. A. Maltby, R. H. Morris, C. T. Schweitzer, *J. Am. Chem. Soc.* **1994**, *116*, 3375. b) The $\text{p}K_a$ value of $[\text{RuH}(\eta^2\text{-H}_2)(\text{dppe})_2]\text{PF}_6$ was estimated to be 15.0.
- [16] The formation of 2-cyclohexen-1-one by the Pd^{II} -catalyzed dehydro-silylation of **1a** was reported; Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011.
- [17] H. Kawano, T. Ikariya, Y. Ishii, M. Saburi, S. Yoshikawa, Y. Uchida, H. Kumobayashi, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1571.
- [18] We suspect that the reaction of lithium enolate **6c** with **7** favors C-protonation by the activated H_2 ligand because high enantioselectivity was achieved in this case, in contrast to the reaction of **1c**.^[12]
- [19] a) A. Yanagisawa, K. Ishihara, H. Yamamoto, *Synlett* **1997**, 411, and references therein; b) C. Fehr, *Angew. Chem.* **1996**, *108*, 2726; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2566, and references therein.

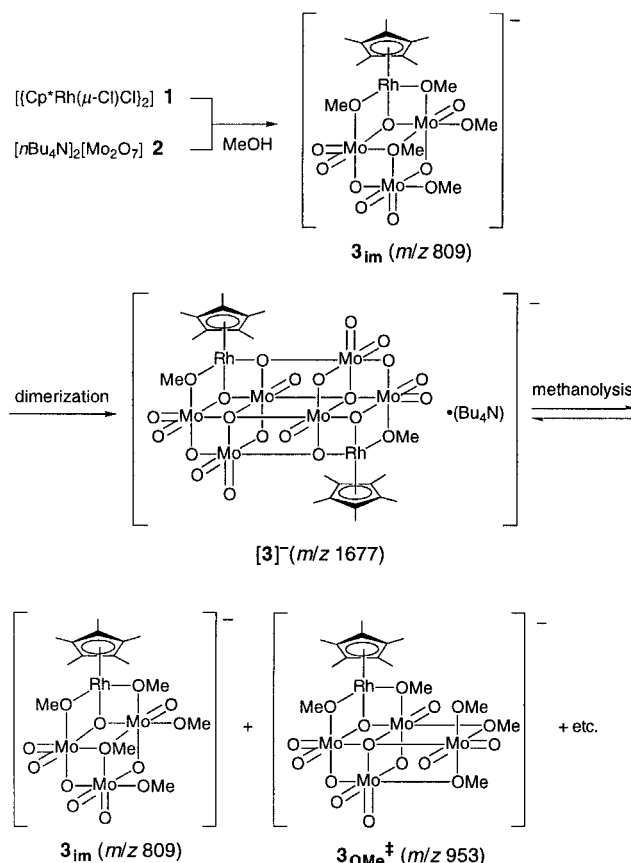
Direct Observation by Electrospray Ionization Mass Spectrometry of $[\text{Cp}^*\text{RhMo}_3\text{O}_8(\text{OMe})_5]^-$, a Key Intermediate in the Formation of the Double-Bookshelf-Type Oxide Cluster $[(\text{Cp}^*\text{Rh})_2\text{Mo}_6\text{O}_{20}(\text{OMe})_2]^{2-}$

Satoshi Takara, Seiji Ogo,* Yoshihito Watanabe, Koji Nishikawa, Isamu Kinoshita, and Kiyoshi Isobe*

Organometallic oxide clusters with cubic and incomplete cubic frameworks are very useful as homogeneous and heterogeneous catalysts in the oxidation and metathesis of unsaturated hydrocarbons.^[1] Recently, we found that the reaction of $[(\text{Cp}^*\text{Rh}(\mu\text{-Cl})\text{Cl})_2]$ (**1**, $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) with four equivalents of $[\text{nBu}_4\text{N}]_2[\text{Mo}_2\text{O}_7]$ (**2**) in MeOH quantitatively yields the double-bookshelf-type oxide cluster $[\text{nBu}_4\text{N}]_2[(\text{Cp}^*\text{Rh})_2\text{Mo}_6\text{O}_{20}(\text{OMe})_2]$ (**3**) with an incomplete cubic framework in which many of the vertices are lacking (Scheme 1).^[2] Furthermore, **3** is converted into the face-sharing triple-cubane-type cluster $[(\text{Cp}^*\text{Rh})_4\text{Mo}_4\text{O}_{16}]$, the incomplete double-cubane-type cluster $[(\text{Cp}^*\text{Rh})_2\text{Mo}_3\text{O}_9(\text{OMe})_4]$, and the face-sharing quadruple-cubane-type cluster $[(\text{Cp}^*\text{Rh})_4\text{Mo}_6\text{O}_{22}]$ under different conditions.^[2, 3] Understanding the mechanism of formation for these clusters may provide strategies for the synthesis of desired oxide cluster catalysts for hydrocarbon transformations.

We have investigated the formation mechanism of **3** by electrospray ionization mass spectrometry (ESI-MS),^[4] which allows us to detect unstable species generated in solution.^[5] Herein, we report a direct observation by ESI-MS of $[\text{Cp}^*\text{RhMo}_3\text{O}_8(\text{OMe})_5]^-$ (**3_{im}**; m/z 809), a key intermediate in the formation of **3** from the reaction of **1** and **2** in MeOH at -78°C .

The ^{95}Mo NMR spectrum of **2** in MeOH showed one broad signal ($\delta = -15$, reference: Na_2MoO_4) even at -50°C because of the rapid exchange of Mo centers between several species in equilibrium.^[6] As shown in Figure 1 a, the negative-ion ESI mass spectrum of a cooled solution (-78°C in an acetone/dry ice bath) of **2** in MeOH in the range of m/z 1200 to 250 confirmed that **2** exists as an equilibrium mixture of di- ($[\text{nBu}_4\text{N}][\text{Mo}_2\text{O}_7]^-$; m/z 546; $[\text{Mo}_2\text{O}_4(\text{OMe})_5]^-$; m/z 412;^[7] and $[\text{H}_3\text{Mo}_2\text{O}_7(\text{OMe})_2]^-$; m/z 369^[7]), tri- ($[\text{nBu}_4\text{N}][\text{Mo}_3\text{O}_{10}]^-$, **Mo₃**; m/z 690), tetra- ($[\text{nBu}_4\text{N}][\text{Mo}_4\text{O}_{13}]^-$; m/z 834), penta- ($[\text{nBu}_4\text{N}][\text{Mo}_5\text{O}_{16}]^-$; m/z 973), and hexamolybdates ($[\text{HMo}_6\text{O}_{18}(\text{OMe})_2]^-$; m/z 926^[7]). Although all of these equilibrium



Scheme 1. Proposed mechanism for the formation of **3** via the intermediate **3_{im}**, generated from the reaction of **1** with two equivalents of **2** in MeOH at -78°C . Methanolysis and equilibrium of **3** yields **3_{im}**, **3OMe⁺**, and other products.

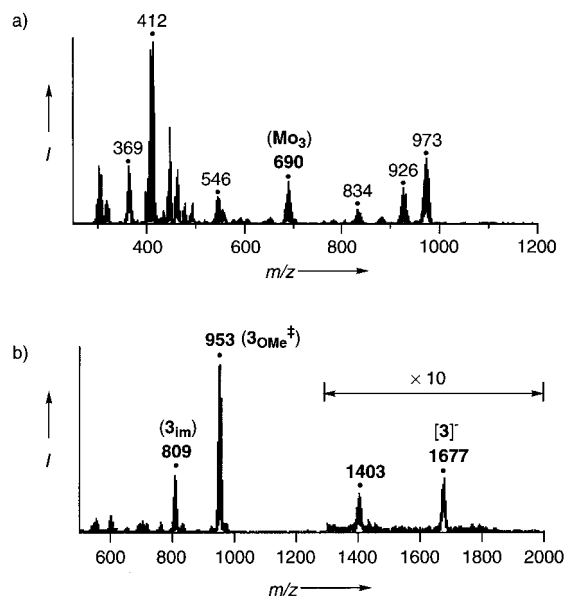


Figure 1. Negative-ion ESI mass spectra of cooled solutions (-78°C) of **2** (a) and **3** (b) in MeOH. See text for details. I = relative intensity.

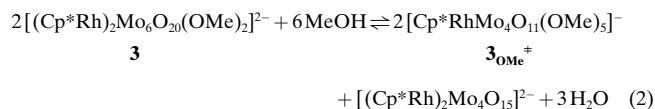
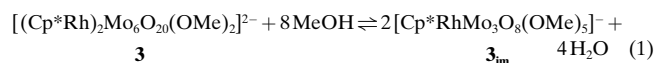
species of **2** could participate in the formation of **3**, the trimolybdate species **Mo₃** could be selected preferentially as an essential building block because the $[\text{Mo}_3\text{O}_{10}]^{2-}$ unit in **Mo₃** is also found in **3** as a key $\{\text{Mo}(\text{O})_2\}_3(\mu_3\text{-O})(\mu_2\text{-O})_3$ unit.^[8]

[*] Prof. K. Isobe, Dr. S. Takara, K. Nishikawa, Dr. I. Kinoshita
Department of Material Science, Graduate School of Science
Osaka City University, 3-3-138 Sugimoto
Sumiyoshi-ku, Osaka 558-8585 (Japan)
Fax: (+81) 6-6690-2753
E-mail: isobe@sci.osaka-cu.ac.jp

Dr. S. Ogo, Prof. Y. Watanabe
Institute for Molecular Science
Myodaiji, Okazaki 444-8585 (Japan)
Fax: (+81) 564-54-2254
E-mail: ogo@ims.ac.jp

[**] Financial support of this research by a Grant-in-Aid for Scientific Research on Priority Areas to K.I. (no. 10149101), S.O. (no. 09740503), and Y.W. (Molecular Biomaterials) from the Ministry of Education, Science, and Culture, Japan, is acknowledged.

The negative-ion ESI mass spectrum of a cooled solution (-78°C) of **3** in MeOH in the range of m/z 2000 to 1300 shows two weak envelopes at m/z 1677 and 1403, which correspond to the molecular ion of **3** ($[\text{3}]^{-}$: $[\text{nBu}_4\text{N}(\text{Cp}^*\text{Rh})_2\text{Mo}_6\text{O}_{20}(\text{OMe})_2]^{-}$) and a fragment ion of **3** ($[\text{3} - \text{nBu}_4\text{N} - \text{OMe}]^{-}$: $[(\text{Cp}^*\text{Rh})_2\text{Mo}_6\text{O}_{20}(\text{OMe})]^{-}$), respectively (Figure 1 b). In the range of m/z 1300 to 100, the mass spectrum shows two prominent envelopes at m/z 953 (relative intensity $I = 100\%$) and 809 ($I = 34\%$). They correspond to the methanolysis species $[\text{Cp}^*\text{RhMo}_4\text{O}_{11}(\text{OMe})_5]^{-}$ (**3_{OMe}⁺**) and $[\text{Cp}^*\text{RhMo}_3\text{O}_8(\text{OMe})_5]^{-}$, respectively; the latter has the same molecular mass as **3_{im}** [Scheme 1, Eqs. (1), (2)].^[9] It is noteworthy that cluster **3** undergoes methanolysis to yield the same species as the intermediate **3_{im}**, which is produced from the reaction between **1** and **2** (see below). Measurements with the mass spectrometry/mass spectrometry (MS/MS) method have also been performed with **3_{im}** and **3_{OMe}⁺**.^[10]



We have simultaneously monitored the intensity changes of three selected envelopes—namely, those at m/z 690 (**Mo₃**), 809 (**3_{im}**), and 953 (**3_{OMe}⁺**)—during the reaction of **1** with two equivalents of **2** in MeOH (-78°C) by rapid scanning^[11] (Figure 2). After mixing of the reagents, the envelope at m/z

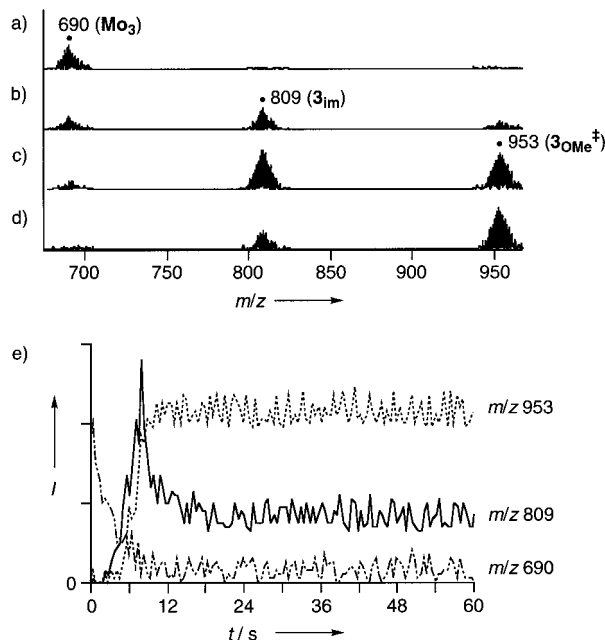


Figure 2. Time-dependent behavior of the three selected envelopes at m/z 690 (**Mo₃**), 809 (**3_{im}**), and 953 (**3_{OMe}⁺**) during the reaction of **1** with two equivalents of **2** in cooled MeOH (-78°C). The reaction was monitored by simultaneous and rapid scanning of ESI-MS (see ref. [11] and Experimental Section). a) Before mixing of **1** and **2**; b) 5.4 s after mixing; c) 7.8 s after mixing; d) 12.6 s after mixing; e) the changes in intensity of the three selected envelopes as a function of time.

690 decreased immediately in intensity (Figure 2 b, c, e), concomitant with the appearance and increase in intensities of the envelopes at m/z 809 and 953. Fortunately, we observed a time lag (ca. 2.4 s) in the appearance of the envelope at m/z 953 with respect to that at m/z 809 (compare Figure 2 b with 2 c). These results suggest that the intermediate **3_{im}** was first generated by the reaction of **1** with **2** in MeOH, and then **3_{im}** dimerized to **3**, which exists as equilibrium mixtures with **3_{im}** and **3_{OMe}⁺** [Eqs. (1), (2); Scheme 1].^[9] The processes of forming **3** and the equilibrium will cause the time lag. After 7.8 s of mixing (Figure 2 c–e), the intensity of the envelope at m/z 953 increased somewhat and remained constant, while the intensity of the envelope at m/z 809 dramatically decreased and then remained constant. The decrease in intensity of the envelope at m/z 809 is probably due to 1) the predominant consumption of the intermediate **3_{im}** for the formation of **3** and 2) a low supply of **3_{im}** resulting from the methanolysis of **3**.^[12] Finally, after the disappearance of **Mo₃** (Figure 2 d, e), the intensities of the envelopes at m/z 809 and 953 became constant.^[13]

To confirm the existence of the methoxo ligands in **3_{im}**, the reaction of **1** with **2** has been carried out in CD_3OD at -78°C . The ESI-MS results show that the envelope at m/z 809 ($[\text{Cp}^*\text{RhMo}_3\text{O}_8(\text{OCH}_3)_5]^{-}$) shifts to m/z 824 ($[\text{Cp}^*\text{RhMo}_3\text{O}_8(\text{OCD}_3)_5]^{-}$); that is, the labeled methoxo ligands (OCD_3) are incorporated into **3_{im}**. Although many geometrical isomers are assumed for **3_{im}**, we propose the isomer depicted in Scheme 1, where two **3_{im}** units are spontaneously assembled into **3** with release of methoxo ligands. Such spontaneous self-assembly by utilizing methoxo ligands as leaving groups was similarly demonstrated in $[(\text{Cp}^*\text{Rh})_4\text{Mo}_6\text{O}_{22}]^{3-}$.^[3b] The MS/MS fragmentation pattern of **3_{im}** indicates that the proposed structure is appropriate.^[10]

The employment of MeCN as the solvent for the reaction of **1** with **2**^[6] leads to the selective formation of the triple-cubane-type oxide cluster $[(\text{Cp}^*\text{Rh})_4\text{Mo}_4\text{O}_{16}]^{2-}$,^[2, 3a] but no **3**. These results clearly show that the use of MeOH as the solvent is essential for the formation of **3** with two methoxo ligands via the intermediate **3_{im}** with five methoxo ligands.

Experimental Section

It was confirmed that the observed distribution of isotopomers of all ions discussed in this study matches well with the calculated values.

Procedure: Before each measurement, the flow pass (fused silica capillary, ca. 400 mm long, 0.075 mm inner diameter) in the system was precooled by flushing with MeOH cooled to -78°C in a acetone/dry ice bath. The temperature of the sprayer of the API 300 triple quadrupole mass spectrometer (PE-Sciex), measured by a thermocouple (Anritu, HFT-50), was approximately 25°C . A solution of **1** (0.25 mM) in MeOH (2 mL) was added rapidly to a solution of **2** (0.50 mM) in MeOH (2 mL) at -78°C by standard Schlenk technique. The resulting solution was then delivered immediately (within 1 s after mixing) to the sprayer through the fused silica capillary under a constant Ar pressure (0.1 MPa). The sprayer was held at a potential of -4.5 kV , and compressed N_2 was employed to assist liquid nebulization. The orifice potential was maintained at -25 V . The negative-ion ESI mass spectra were measured in the range of m/z 100 to 2000. The MS/MS measurements were carried out at room temperature.

Received: January 22, 1999

Revised version: July 12, 1999 [Z12949IE]

German version: *Angew. Chem.* **1999**, *111*, 3233–3235

Keywords: catalysts • cluster compounds • intermediates • mass spectrometry

- [1] a) C. Zhang, Y. Ozawa, Y. Hayashi, K. Isobe, *J. Organomet. Chem.* **1989**, 373, C21–C25; b) K. Isobe, A. Yagasaki, *Acc. Chem. Res.* **1993**, 26, 524–529; c) K. Takahashi, M. Yamaguchi, T. Shido, H. Ohtani, K. Isobe, M. Ichikawa, *J. Chem. Soc. Chem. Commun.* **1995**, 1301–1303; d) M. Ichikawa, W. Pan, Y. Imada, M. Yamaguchi, K. Isobe, T. Shido, *J. Mol. Catal. A* **1996**, 107, 23–38.
- [2] S. Takara, T. Nishioka, I. Kinoshita, K. Isobe, *Chem. Commun.* **1997**, 891–892.
- [3] a) Y. Hayashi, K. Toriumi, K. Isobe, *J. Am. Chem. Soc.* **1988**, 110, 3666–3668; b) Y. Do, X. Z. You, C. Zhang, Y. Ozawa, K. Isobe, *J. Am. Chem. Soc.* **1991**, 113, 5892–5893.
- [4] a) C. M. Whitehouse, R. N. Dreyer, M. Yamashita, J. B. Fenn, *Anal. Chem.* **1985**, 57, 675–679; b) J. B. Fenn, M. Mann, C. K. Meng, S. F. Wong, C. M. Whitehouse, *Science* **1989**, 246, 64–70; c) R. D. Smith, J. A. Loo, C. G. Edmonds, C. J. Barinaga, H. D. Udseth, *Anal. Chem.* **1990**, 62, 882–899; d) I. Jardine, *Nature* **1990**, 345, 747–748; e) J. B. Fenn, M. Mann, C. K. Meng, S. F. Wong, C. M. Whitehouse, *Mass Spectrom. Rev.* **1990**, 9, 37–70; f) P. Kebarle, L. Tang, *Anal. Chem.* **1993**, 65, 972A–986A, and references therein; g) R. Colton, A. D'Agostino, J. C. Traeger, *Mass Spectrom. Rev.* **1995**, 14, 79–106.
- [5] a) J. W. Sam, X. J. Tang, J. Peisach, *J. Am. Chem. Soc.* **1994**, 116, 5250–5256; b) J. Kim, Y. Dong, E. Larka, L. Que, Jr., *Inorg. Chem.* **1996**, 35, 2369–2372; c) C. Hinderling, D. A. Plattner, P. Chen, *Angew. Chem.* **1997**, 109, 272–274; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 243–244; d) D. Feichtinger, D. A. Plattner, *Angew. Chem.* **1997**, 109, 1796–1798; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1718–1719; e) M. Okamoto, H. Doe, K. Mizuno, T. Fukuo, R. Arakawa, *J. Am. Soc. Mass Spectrom.* **1998**, 9, 966–969.
- [6] The form of **2** in solution is dependent on the solvent. In contrast to the case of MeOH, **2** exists intact in MeCN. This was confirmed by ESI-MS and ^{17}O NMR spectroscopy: a) The negative-ion ESI mass spectrum of a solution of **2** in MeCN in the range of m/z 100 to 1000 showed only two envelopes at m/z 303 ($[\text{HMo}_2\text{O}_7]^-$) and 546 ($[\text{nBu}_4\text{NMo}_2\text{O}_7]^-$); b) ^{17}O NMR spectroscopy: V. W. Day, M. F. Fredrich, W. G. Klemperer, *J. Am. Chem. Soc.* **1977**, 99, 6146–6148.
- [7] The existence of the methoxo ligands in these species was confirmed by isotopic labeling experiments using CD_3OD as solvent.
- [8] The MS/MS spectra of **Mo₃** (m/z 690) exhibit peaks at m/z 448 and 432, which correspond to the negative ions of $[\text{Mo}_3\text{O}_{10}]^-$ and $[\text{Mo}_3\text{O}_9]^-$, respectively, suggesting that the proposed structure of **Mo₃**, $[\{\text{Mo}(\text{O})_2\}_3(\mu_3\text{-O})(\mu_2\text{-O})_3]^{2-}$, is appropriate.
- [9] ^{95}Mo NMR experiments of **3** have been performed both in CD_3OD and CD_2Cl_2 at room temperature. Although the spectrum in CD_2Cl_2 shows three signals with nearly equal intensity at $\delta = 30.0$ ($I = 78\%$), 86.6 ($I = 100\%$), and 167.2 ($I = 89\%$)—supporting preservation of the solid-state structure—the spectrum in CD_3OD is much more complicated and gives five broad signals with different intensities at $\delta = -9.0$ ($I = 53\%$), 50.8 ($I = 100\%$), 95.5 ($I = 56\%$), 113.5 ($I = 51\%$), and 155.3 ($I = 43\%$). The results of ^{95}Mo NMR and ESI-MS experiments (the observation of the envelopes for **3_{im}** (m/z 809) and **3_{ome}⁺** (m/z 953)) suggest that in MeOH, cluster **3** exists as equilibrium mixtures [Eqs. (1), (2)]. These equilibria, which lie far to the right, may be reached very quickly. The species $[(\text{Cp}^*\text{Rh})_2\text{Mo}_4\text{O}_{15}]^{2-}$ in Equation (2), which was not detected by ESI-MS, may react with further MeOH to establish a new equilibrium.
- [10] The MS/MS spectra of **3_{im}** (m/z 809) exhibit peaks at m/z 778, 685, 587, 399, and 368, which correspond to the negative ions of $[\text{Cp}^*\text{RhMo}_3\text{O}_8(\text{OMe})_4]^-$, $[\text{Cp}^*\text{RhMo}_3\text{O}_8(\text{OMe})_3]^-$, $[\text{Cp}^*\text{RhMo}_2\text{O}_7(\text{OMe})_3]^-$, $[\text{Cp}^*\text{RhMo}_2\text{O}_7(\text{OMe})_2]^-$, and $[\text{Cp}^*\text{RhMo}_2\text{O}_7]^-$, respectively. The MS/MS spectra of **3_{ome}⁺** (m/z 953) exhibit peaks at m/z 763, 732, 588, 541, and 540, which correspond to the negative ions of $[\text{Cp}^*\text{RhMo}_3\text{O}_9(\text{OMe})_3]^-$, $[\text{Cp}^*\text{RhMo}_3\text{O}_9(\text{OMe})_2]^-$, $[\text{Cp}^*\text{RhMo}_2\text{O}_8(\text{OMe})_2]^-$, $[\text{Cp}^*\text{RhMo}_2\text{O}_8(\text{OMe})_1]^-$, and $[\text{Cp}^*\text{RhMo}_2\text{O}_8]^-$, respectively. These results indicate that the proposed structures of **3_{im}** and **3_{ome}⁺** shown in Scheme 1 are appropriate.
- [11] Scan range: 674.9–705.1, 794.9–825.1, and 936.9–967.1 amu (atomic mass unit); step size: 0.2 amu; dwell time per step: 0.001 s; scan time: 0.47 s. The envelope of the molecular ion of **3** at m/z 1677 was not selected in the rapid scanning experiments because the intensity was too weak.
- [12] We have conducted a reaction of **2** with **3** in MeOH at room temperature in order to check whether there are routes for the formation of **3_{ome}⁺** through **3_{im}**, which would account for the reduction in intensity of **3_{im}** between ca. 8–14 s (Figure 2e). However, **3_{im}** does not react with the dimolybdate or any heavier species produced from **2** in MeOH; intensity changes in the envelopes at m/z 809 and 953 are not observed during the reaction of **2** with one equivalent of **3**. Furthermore, the fragmentation patterns of **3_{im}** are different from that of **3_{ome}⁺**,^[10] suggesting that there is no relationship between **3_{im}** and **3_{ome}⁺**. Therefore, we believe that the existence of the intermediate **3_{im}** is essential.
- [13] The spectrum after 18 s of reaction is essentially identical to that of **3** (Figure 1b).

The First Bismuth Phosphide Complex: [Li(thf)₄]⁺[(*i*BuP)₃Bi][−]*

Michael A. Beswick,* Nick Choi,
Alexander D. Hopkins, Yvonne G. Lawson,
Mary McPartlin, Alexander Rothenberger,
Dietmar Stalke, Andrew E. H. Wheatley, and
Dominic S. Wright*

Although amide^[1] and imido^[2] complexes of the heavier Group 15 elements (Sb and Bi) have been reported in recent years, for the related phosphorus compounds (containing R_2P^- or RP^{2-} groups) only those of Sb have appeared in the literature.^[3] Moreover, the only examples of complexes containing Bi–P bonds to be structurally characterized are Bi^{III} halides in which neutral phosphane ligands coordinate the metal centers.^[4] In recent studies of the reactions of $[\text{E}(\text{NMe}_2)_3]$ ($\text{E} = \text{As}, \text{Sb}$) with primary phosphido alkali metal complexes ($[\text{RPHM}]$; $\text{M} = \text{Li}, \text{Na}$), we showed that heterocyclic anions of the type $[(\text{RP})_n\text{E}]^-$ are generated^[5] prior to the ultimate formation of Zintl compounds containing E_7^{3-} ions.^[6] Prompted by the absence of structurally characterized Bi phosphides, which would have the potential for the formation of elusive polyatomic Bi_5^{3-} and Bi_3^{3-} ions by this low-temperature route,^[7] we decided to investigate the

[*] Dr. M. A. Beswick, Dr. D. S. Wright, A. D. Hopkins,
Dr. Y. G. Lawson, Dr. A. E. H. Wheatley
Chemistry Department, University of Cambridge
Lensfield Road, Cambridge CB2 1EW (UK)
E-mail: dsw1000@cus.cam.ac.uk.

Dr. N. Choi, Prof. M. McPartlin
School of Chemistry, University of North London
London N7 8DB (UK)

A. Rothenberger, Prof. D. Stalke
Institut für Anorganische Chemie
Universität Würzburg (Germany)

[**] We gratefully acknowledge the EPSRC (A.D.H., Y.G.L., M.McP.), the Leverhulme Trust (M.A.B.), Electron Industries (A.D.H.), Gonville and Caius College, Cambridge (A.E.H.W.), the Gottlieb Daimler-und-Karl-Benz-Stiftung (A.R.) and the ARC (D.S., D.S.W.) for financial support. We also thank Dr. P. Grice (Cambridge) for running the COSY and *J*-spectra.

analogous reactions of $[\text{Bi}(\text{NMe}_2)_3]$. We report here the synthesis and structural characterization of the first bismuth phosphide complex $[\text{Li}(\text{THF})_4][\text{Bi}\{(\text{tBuP})_3\}_2]$ (**1**).

The reaction of $[\text{Bi}(\text{NMe}_2)_3]$ with $[\text{tBuP}(\text{H})\text{Li}]$ (ratio 1:3) in THF/hexane gives metallic Bi and a yellow solution at room temperature. Prolonged storage of the filtrate (-30°C) gives yellow crystals of **1** (see Experimental Section). Although moderately stable in solution, the complex proved to be too thermally unstable to isolate and therefore could not be characterized satisfactorily by standard spectroscopic and analytical means. Room-temperature ^{31}P NMR spectra of fresh and aged reaction solutions show that **1** and $[\text{tBuP}]_4$ (s , $\delta = -57.0$) are the major products. The formation of the latter suggests that the reaction involved is similar to that occurring between $[\text{E}(\text{NMe}_2)_3]$ ($\text{E} = \text{As}, \text{Sb}$) and primary phosphido-lithium complexes.^[5, 6] A surprising feature of the $[\text{tBuP}]_3^{2-}$ ligands of **1** is that they appear as two double doublets at $\delta = -69.8$ and -108.9 (ratio 2:1) rather than the anticipated doublet and triplet (as is observed for $[(\text{tBuP})_3\text{As}]^-$).^[8] This ABX pattern is consistent with an essentially static structure for the $[\text{Bi}\{(\text{tBuP})_3\}_2]^-$ ion in solution, in which the axial and equatorial P centers $[\text{P}(\text{A}, \text{B})]$ are rendered marginally inequivalent and couple separately to the central P atom $[\text{P}(\text{X})]$. The lack of Berry pseudorotation in the $[\text{Bi}\{(\text{tBuP})_3\}_2]^-$ ion (even up to 60°C in THF) presumably stems from the steric congestion of the *t*Bu groups of the terminal P centers which would arise in a square-base pyramidal intermediate (Figure 1).^[9]

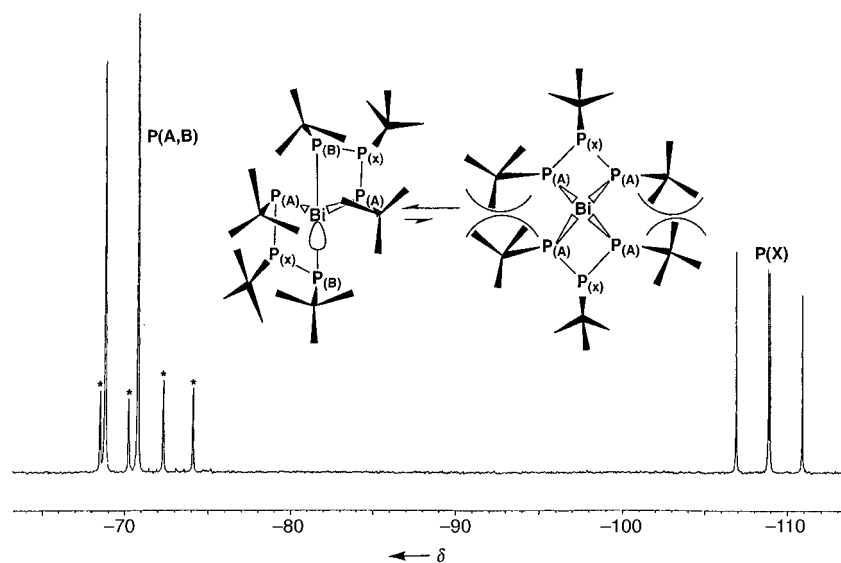


Figure 1. ^{31}P NMR spectrum of fresh and aged reactions mixtures from $[\text{Bi}(\text{NMe}_2)_3]$ and $[\text{tBuP}(\text{H})\text{Li}]$ (50:50 in $[\text{D}_8]\text{THF}$, $+25^\circ\text{C}$), as well as a representation of the Berry pseudorotation (see text for details).

The low-temperature X-ray crystal structure of **1**^[10] reveals that the complex has an ion-separated structure, $[\text{Li}(\text{thf})_4]^+[\text{Bi}\{(\text{tBuP})_3\}_2]^-$. The anion of **1** consists of a Bi^{III} center which is coordinated by two crystallographically independent $[\text{tBuP}]_3^{2-}$ ions (Figure 2). The resulting pseudo-trigonal bipyramidal geometry of the metal center (10e), whose vacant coordination site is characteristic of a stereochemically active metal

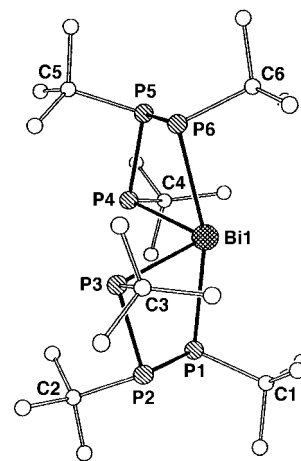


Figure 2. Structure of the anion of **1**. H atoms are omitted for clarity. Key bond lengths [Å] and angles [$^\circ$]: Bi1–P1 2.911(3), Bi1–P6 2.885(3), Bi1–P3 2.630(4), Bi1–P4 2.651(3), P1–P2 2.177(5), P5–P6 2.174(5), P2–P3 2.240(5), P4–P5 2.236(5); P1–Bi1–P3 76.12(10), P4–Bi1–P6 75.78(11), P1–Bi1–P6 162.10(11), P1–Bi1–P4 91.50(11), P3–Bi1–P6 90.67(10), P1–P2–P3 101.6(2), P4–P5–P6 101.1(2).

lone pair, is comparatively rare for Bi^{III} ; here the high Lewis acidity of the metal center almost always leads to an increase in coordination number above four,^[11] and only a few examples of discrete Bi^{III} anions having a pseudo-trigonal bipyramidal geometry have been structurally characterized.^[12] More significantly, it was only relatively recently that the synthesis of the first binary phosphide of Bi^{III} itself (BiP) was

realized^[13] and there are no reported examples of molecular species containing bonds between anionic P centers and Bi. This situation presumably reflects the generally high thermal instability of these species (as is the case with solid **1**).

Within the anion of **1**, the axial P–Bi bonds (Bi1–P1 2.911(3), Bi1–P6 2.885(3) Å) are considerably longer than the equatorial ones (Bi1–P3 2.630(4), Bi1–P4 2.651(3) Å). Overall, these bond lengths are similar to those found in structurally characterized complexes between Bi^{III} halides and neutral phosphanes (range 2.654(8)–3.090(3) Å), in which the Bi cations are all six-coordinate.^[4] The adoption of a pseudo-trigonal bipyramidal geometry for the $[\text{Bi}\{(\text{tBuP})_3\}_2]^-$ ion and the large ionic radius of Bi^{III} results in considerable strain in the heterocyclic P_3Bi ring units. This is most apparent in the significant expansion of the angles at the central P atom of the $[\text{tBuP}]_3^{2-}$ ligands (mean 101.4°) compared to that occurring in the $[(\text{tBuP})_3\text{As}]^-$ ring of $[(\text{tBuP})_3\text{As}]\text{Li}(\text{tmeda})(\text{thf})$ ($91.4(2)^\circ$),^[5] and in the irregular pattern of P–P bond lengths found in these units. These bond lengths mirror the extent of interaction of the terminal P centers of the $[\text{tBuP}]_3^{2-}$ ligands with the Bi atom; the P–P bonds to the axial P centers (P2,5–P1,6, mean 2.176(5) Å) are significantly shorter than those made with the equatorial P

atoms (P2,5–P3,4, mean 2.238(5) Å; cf. ca. 2.20 Å for both the P–P bonds in [(tBuP)₃As][−] [5]).

In summary, studies of the reaction of [Bi(NMe₂)₃] with [tBuPHLi] have led to the structural characterization of the first bismuth phosphide complex. We have found no evidence so far for the formation of Zintl compounds containing Bi_n^{x−} ions in this system. However, by using appropriate ligands (such as cryptands) we hope to stabilize these potential products in future.

Experimental Section

1: To a solution of tBuPHLi (6.0 mmol) in THF (4 mL)/hexane (5 mL) at −78 °C was added dropwise a solution of Bi(NMe₂)₃ (2.0 mmol, 0.8 mL, 2.5 mol L^{−1} in THF). The mixture was stirred (3 h), giving a deep red solution and considerable deposition of Bi metal. The mixture was allowed to warm slowly to room temperature. At about −20 °C the color began to change and a yellow solution was formed at room temperature. The mixture was stirred (15 min) and then filtered slowly through a thick bed of celite. Storage of the solution for up to four months gave **1** in low yield as large yellow crystals. Attempts to isolate the complex resulted in decomposition into a black solid. However, ³¹P NMR spectra (101.256 MHz +25 °C, rel. to 80% H₃PO₄/D₂O) obtained on several fresh and aged reaction solutions (50:50 [D₈]THF) show that **1** is always formed as the major product together with [tBuP]₄ (only minor by-products are observed in the range δ = 0 to −50). J_{AX} = 195.9 Hz, J_{BX} = 205.8 Hz (error = ±1.7 Hz). The interdependence of the two resonances was confirmed by ³¹P COSY and J-spectrum NMR experiments. Although heating of the solution results in broadening of the resonances, no coalescence occurs in the range 25–60 °C.

Received: March 19, 1999 [Z13189IE]

German version: *Angew. Chem.* **1999**, *111*, 3236–3238

Keywords: bismuth • phosphides • structure elucidation

- [1] W. Clegg, N. A. Compton, R. J. Errington, N. C. Norman, N. Wishart, *Polyhedron* **1989**, *8*, 1579; W. Clegg, N. A. Compton, R. J. Errington, G. A. Fisher, M. E. Green, D. R. Hockless, N. C. Norman, *Inorg. Chem.* **1991**, *30*, 4680.
- [2] M. Noltemeyer, H. W. Roesky, H. Schmidt, U. Warringa, *Inorg. Chem.* **1994**, *33*, 4607; D. Barr, M. A. Beswick, A. J. Edwards, J. R. Galsworthy, M. A. Paver, M.-A. Rennie, C. A. Russell, P. R. Raithby, K. L. Verhorevoort, D. S. Wright, *Inorg. Chim. Acta* **1996**, *248*, 9; S. C. James, N. C. Norman, A. G. Orpen, M. J. Quayle, *J. Chem. Soc. Dalton Trans.* **1996**, 1455.
- [3] P. Jutzi, U. Meyer, S. Opiela, M. M. Olmstead, P. P. Power, *Organometallics* **1990**, *9*, 1459; M. A. Beswick, J. M. Goodman, C. A. Harmer, A. D. Hopkins, M. A. Paver, P. R. Raithby, A. E. H. Wheatley, D. S. Wright, *Chem. Commun.* **1997**, 1879.
- [4] W. Clegg, R. J. Errington, G. A. Fisher, M. E. Green, D. C. R. Hockless, N. C. Norman, *Chem. Ber.* **1991**, *124*, 2457; W. Clegg, R. J. Errington, R. J. Flynn, M. E. Green, D. C. R. Hockless, N. C. Norman, V. C. Gibson, K. Tavakkoli, *J. Chem. Soc. Dalton Trans.* **1992**, 1753; W. Clegg, M. R. J. Elsegood, N. C. Norman, N. L. Pickett, *J. Chem. Soc. Dalton Trans.* **1994**, 1753; W. Clegg, M. R. J. Errington, V. Graham, N. C. Norman, N. L. Pickett, K. Tavakkoli, *J. Chem. Soc. Dalton Trans.* **1994**, 1743; G. R. Willey, L. T. Daly, M. G. B. Drew, *J. Chem. Soc. Dalton Trans.* **1996**, 1063.
- [5] M. A. Beswick, N. Choi, A. D. Hopkins, M. McPartlin, M. E. G. Mosquera, P. R. Raithby, A. Rothenberger, D. Stalke, D. S. Wright, *Chem. Commun.* **1998**, 2485.
- [6] M. A. Beswick, N. Choi, A. D. Hopkins, C. N. Harmer, M. McPartlin, D. S. Wright, *Science* **1998**, *281*, 1500.
- [7] Although Zintl had reported that these ions can be prepared in liquid ammonia, there is still no structural evidence for their existence. See: E. Zintl, J. Goubeau, W. Dullenkoff, *Z. Phys. Chem. A* **1931**, *154*, 1.
- For evidence of the related Sb₃^{3−} ion, see: M. Okada, R. Guidotti, J. D. Corbett, *Inorg. Chem.* **1968**, *7*, 2118.
- [8] The nature of the [RP]₃^{2−} ion has been the subject of some controversy. For [PhP]₃^{2−} an AB₂ pattern is observed; K. Issleib, E. Fluck, *Angew. Chem.* **1966**, *78*, 597; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 587; P. R. Hoffman, K. G. Caulton, *J. Am. Chem. Soc.* **1975**, *97*, 6370.
- [9] Calculational and spectroscopic studies give values of about 3.92–2.16 kcal mol^{−1} for the activation energy for pseudorotation in PF₅ and AsF₅, see: V. P. Spiridonov, L. S. Berstein, J. J. Kim, K. S. Pitzer, S. Abramowitz, I. W. Levin, *J. Phys. Chem.* **1975**, *63*, 3671; L. S. Berstein, S. Abramowitz, I. W. Levin, *J. Chem. Phys.* **1976**, *64*, 3228; A. A. Ischenko, L. S. Ivashkevich, *J. Mol. Struct.* **1981**, *72*, 153; C. Marsden, *J. Chem. Soc. Chem. Commun.* **1984**, 401.
- [10] Crystal data for **1**: C₄₀H₈₆BiLiO₄P₆, *M*_r = 1032.83, monoclinic, space group P2₁/n, *Z* = 4, *a* = 11.727(2), *b* = 17.710(3), *c* = 26.131(4) Å, β = 102.268(4)°, *V* = 5303.2(15) Å³, ρ_{calcd} = 1.292 Mg m^{−3}, *F*(000) = 2136, μ(MoKα) = 3.538 mm^{−1}, *T* = 223(2) K. The crystal (0.30 × 0.30 × 0.15 mm), mounted in inert oil, diffracted weakly at high angle; 7316 data were collected on a Siemens P4 diffractometer (θ range 1.79–21.00°). The structure was solved by direct methods. Relatively high displacement parameters for the atoms of the THF ligands indicated some conformational disorder and three carbon atoms were each resolved into two components of about 0.5 site occupancy; chemically equivalent bonds within the ligands were constrained to be equal within an esd of 0.01 Å. Hydrogen atoms of the methylene and methyl carbon atoms were included in idealized positions and assigned *U*_{iso} = 1.2 and 1.5 *U*_{eq} of the parent carbon atom, respectively. Anisotropic thermal parameters were applied to all the fully occupied non-hydrogen atoms. Full-matrix least-squares refinement with 5696 independent absorption corrected data (*R*_{int} = 0.0884, *T*_{max} = 0.756, *T*_{min} = 0.327) on *F*² with 467 parameters. Final *R*₁ = 0.0654 [*I* > 2σ(*I*)] and *wR*₂ = 0.1423 (all data). Largest peak and hole in the final difference map 1.063 and −1.270 e Å^{−3}. Programs used see reference [14]. 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-114097. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [11] For examples of Bi^{III} halides: A. Schier, J. M. Wallis, G. Muller, H. Schmidbauer, *Angew. Chem.* **1986**, *98*, 742; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 757; N. J. Mammona, A. Zalkin, A. Landers, A. L. Rheingold, *Inorg. Chem.* **1977**, *16*, 297; C. L. Raston, G. L. Rowbottom, A. H. White, *J. Chem. Soc. Dalton Trans.* **1981**, 1372; L. P. Battaglia, A. B. Corradi, I. M. Vezzosi, F. A. Zanolli, *J. Chem. Soc. Dalton Trans.* **1990**, 1675.
- [12] D. H. R. Barton, B. Charpoit, E. T. H. Dau, W. B. Motherwell, C. Pascard, C. Pichon, *Helv. Chim. Acta* **1984**, *67*, 586; X. Chen, Y. Yamamoto, K. Akiba, S. Yoshida, M. Yasui, F. Iwasaki, *Tett. Lett.* **1992**, *33*, 6653; S. Satoshi, M. Yasui, F. Iwasaki, Y. Yamamoto, X. Chen, K. Akiba, *Acta Crystallogr. Sect. B* **1994**, *50*, 151.
- [13] C. J. Carmalt, A. H. Cowley, A. L. Hector, N. C. Norman, I. P. Parkin, *J. Chem. Soc. Chem. Commun.* **1994**, 1987; G. C. Allen, C. J. Carmalt, A. H. Cowley, A. L. Hector, S. Kamepalli, Y. G. Lawson, N. C. Norman, I. P. Parkin, L. K. Pickard, *Chem. Mater.* **1997**, *9*, 1385.
- [14] a) N. Walker, D. Stuart, *Acta Crystallogr. Sect. A* **1983**, *39*, 158; b) SHELXTL PC version 5.03, Siemens Analytical Instruments, Madison, WI, **1994**.

α -Alkyl- α -Amino- β -Lactam Peptides: Design, Synthesis, and Conformational Features**

Claudio Palomo,* Jesus M. Aizpurua,* Ana Benito, Regina Galarza, Uttam K. Khamrai, Jordi Vazquez, Beatriz de Pascual-Teresa, Pedro M. Nieto, and Anthony Linden

The concept of linking two neighboring α -amino acids in peptide **1** (Figure 1) to stabilize a single conformation was established by Freidinger et al. in the early 1980s.^[1] Since then,

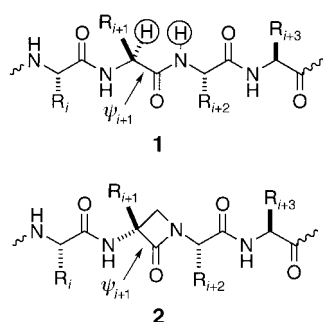


Figure 1. The approach for the introduction of conformational constraints into peptides by the $C\alpha_{i+1}$ – N_{i+2} linkage. A methylene bridge generates the constraint in **2**, and the R_{i+1} group mimics the original residue in the parent peptides **1**.

several lactam peptides of various ring sizes and β -turn mimetics have been prepared either to control the conformation of peptides and/or as potential pharmaceuticals.^[2] How-

ever, despite considerable success to date,^[3] it is not always easy to confidently predict the optimal structure which will generate a desired type of conformational restriction.^[4] There are various reasons to consider β -lactam peptides of type **2** (Figure 1) as potential candidates for β -turn mimetics and/or as promising leads for pharmaceutical drug discovery:

- 1) They possess the rigid azetidin-2-one ring^[5] and therefore the same ψ_{i+1} torsion angle (120°) as ideal type II and type VI β -turns.^[6]
- 2) They show minimum structural divergence with respect to the parent peptides **1**, retaining the R_{i+1} substituent of the original residue and thus facilitating recognition by receptors or enzymes.^[7]
- 3) Owing to the presence of the α,α -disubstitution pattern, they are expected to exhibit enhanced resistance to chemical and enzymatic hydrolysis by proteases.^[8]

However, access to this kind of lactam peptide is hampered by the difficulty in forming β -unsubstituted β -lactams with quaternary stereogenic centers at the $C\alpha$ position.^[9] In particular, the asymmetric α -alkylation of a 4-unsubstituted 3-aminoazetidin-2-one, which would be the most straightforward method for creating a quaternary center, has remained elusive until now.^[10] The main reason is probably the lack of efficient methodology to generate an appropriate chiral building block.^[11] Recently we reported the synthesis of the β -lactam **3**^[12] (see Scheme 1), which has a removable chiral tether whose stereogenic center is close to the $C\alpha$ position of the β -lactam ring. We now report that this synthetic building block acts as a new and very useful β -amino alaninate equivalent, which makes possible the preparation and study of β -lactam peptides of type **2** for the first time.

Upon deprotonation with a base at the C3 methine, **3** should probably generate an enolate with W-type geometry (Scheme 1). If so, the reaction of the latter with alkyl halides should take place from the enolate side opposite to that occupied by the phenyl group, and a certain degree of diastereoselectivity should be observed. The reaction of representative alkyl halides with the lithium enolate of **3** proceeded as expected to give products **4/5** with good to excellent diastereoselectivities. According to the data collected in Table 1, the diastereomeric ratios attained depend upon the nature of the alkyl halide used, but allyl and benzyl halides lead to the formation of **4** essentially as the sole diastereomer. The stereochemical course of these reactions was assumed to be uniform, as established by hydrogenation of the double bond in **4d** to give **4b**, which was identical to that produced by the direct route. The R configuration at the $C\alpha$ position for the major products **4** was assigned by single-crystal X-ray analysis of **4b** and **4f**. Finally, deprotection of the carbamate and azetidinone nitrogen atoms according to our procedure^[12] led to the desired α -alkyl- β -aminoalanine equivalents **6–8** in good overall yields.

With these compounds in hand, a variety of α,α -disubstituted β -lactam-derived peptides became accessible, and provided insight into the conformational preferences of these compounds. For instance, N -alkylation of **8** with benzyl bromoacetate gave, after hydrogenolytic cleavage of the benzyl ester group, the Boc-Phe-Gly dipeptide analogue **9** (Scheme 2). Coupling of **9** with α -amino isobutyric acid

[*] Prof. Dr. C. Palomo, Prof. Dr. J. M. Aizpurua, A. Benito, Dr. R. Galarza, Dr. U. K. Khamrai
Departamento de Química Orgánica
Universidad del País Vasco, Facultad de Química
Apdo 1072, E-20080 San Sebastián (Spain)
Fax: (+349)43-212-236
E-mail: qoppanic@sc.ehu.es.

Dr. J. Vazquez
Departament de Química Orgànica
Universitat de Barcelona, Barcelona (Spain)

Dr. B. de Pascual-Teresa
(computational analysis)
Departamento de Química Orgánica y Farmacéutica
Universidad San Pablo, Madrid (Spain)

Dr. Pedro M. Nieto
(NMR analysis)
Instituto de Investigaciones Químicas
Centro de Investigaciones Científicas Isla de la Cartuja
Sevilla (Spain)

Dr. A. Linden
(X-ray analysis)
Organisch-chemisches Institut der Universität
Zürich (Switzerland)

[**] This work was supported by the University of the Basque Country (projects UPV 170.215-EA172/97 and 170.215-G47/98) and, in part, by the Ministerio de Educación y Cultura, Spanish Government (project SAF-98-0159-CO2-01) and by Gobierno Vasco (GV PI-123/98). We thank the CIEMAT (Spain) for computer time and facilities.

Supporting information for this contribution is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

Table 1. Asymmetric alkylation of **3**.^[a]

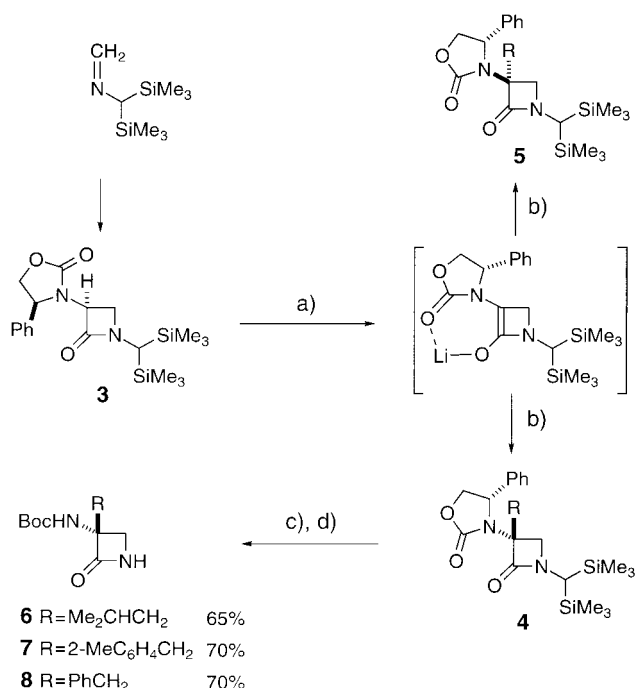
R-X	4 : 5 ^[b]	Yield of 4 [%]	M.p. [°C]	$[\alpha]_D^{25}$
CH ₃ -I	70:30	— ^[c] (4a)	oil	—
CH ₃ CH ₂ CH ₂ -Br	80:20	40 (4b)	oil	+ 82.1 ^[d]
(CH ₃) ₂ CHCH ₂ -Br	91:9	62 (4c)	99–100	– 26.8 ^[d]
CH ₂ =CHCH ₂ -Br	> 98:2	70 (4d)	111–112	– 16.8
2-MeC ₆ H ₄ CH ₂ -Br	> 98:2	80 (4e)	152–153	+ 32.1
PhCH ₂ -Br	> 98:2	90 (4f)	168–169	+ 21.5

[a] Reactions were carried out in THF with 4×10^{-3} mol of β -lactam using a LDA:**3**:RX ratio of 1.5:1:5.0. [b] Determined by ¹H NMR spectroscopy (300 MHz) of the crude reaction mixture. [c] Not isolated. The yield of the mixture of isomers **4**/**5** was 65 %. [d] Measured on analytically pure samples separated by preparative HPLC.

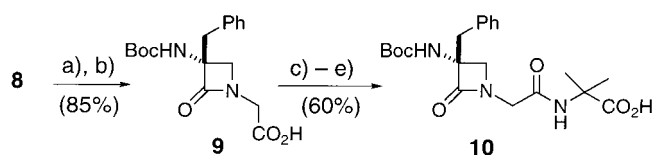
Table 2. Solid-state (X-ray), solution (NMR), and theoretical structure data (RHF/3–21G) for compound **10**.

	(ϕ_1, ψ_1); (ϕ_2, ψ_2) [°]	C=O...HN [Å]	=O...N [Å]	=O...H-N [°]
ideal type II β -turn	(– 60.0, 120.0); (80.0, 00.0)	1.8–2.5	—	≈ 160
X-ray ^[a]	(– 40.9, 122.5); (100.5, – 2.1)	2.32	3.05	164
X-ray ^[a]	(– 47.1, 122.5); (104.5, – 13.7)	2.37	3.12	167
NMR ^[b]	(– 41.7, 114.6); (132.9, – 59.5)	1.81	2.68	136
RHF/3–21G ^[c]	(– 46.2, 122.0); (116.2, – 31.1)	2.04	2.98	155

[a] Two symmetry-independent structures in the cell unit. [b] Measured in CDCl₃ (10^{-3} mol L^{–1}).^[16] [c] The relative energy difference between the β -turn and the γ -turn conformers of **10** was estimated at 9.91 kcal mol^{–1} (the extended conformation could not be characterized as a proper energy minimum). This value was calculated by a Monte Carlo random variational search using the Amber force field and the solution model GB/SA, followed by a RHF/3–21G full optimization of the relative energies and structural parameters. The Amber force field was used as implemented in MacroModel, version 5.5.^[17]



Scheme 1. Asymmetric synthesis of 4-unsubstituted 3-alkyl-3-amino-azetidin-2-ones **6**–**8**. a) Lithium diisopropylamide (LDA), THF, –78 °C; b) R-X (5 equiv, see Table 1), –78 °C → room temperature, overnight; c) Li, NH₃, THF, then (Boc)₂O; d) (NH₄)₂Ce(NO₃)₆, then NaHCO₃. Boc = *tert*-butoxycarbonyl. See reference [12] for the synthesis of **3**.



Scheme 2. Synthesis of Boc-tripeptide **10**. a) BrCH₂CO₂Bn, Cs₂CO₃; b) H₂, Pd/C; c) cyanuric fluoride, pyridine; d) H₂NCMe₂CO₂Bn, *N*-methylpyrrolidine; e) H₂, Pd. Bn = benzyl.

benzyl ester (AibOBn) according to the procedure of Carpino et al.^[13] and subsequent O-debenzylation provided the tripeptide **10** (m.p. 183–185 °C, $[\alpha]_D^{25} = +89.7$ (CH₂Cl₂, *c* = 0.24)).

The X-ray analysis of a single crystal of **10**^[14] showed two symmetry-independent molecules in the asymmetric unit having quite similar conformations (Table 2, Figure 2 a) which displayed a S(10) graph set^[15] for intermolecular hydrogen

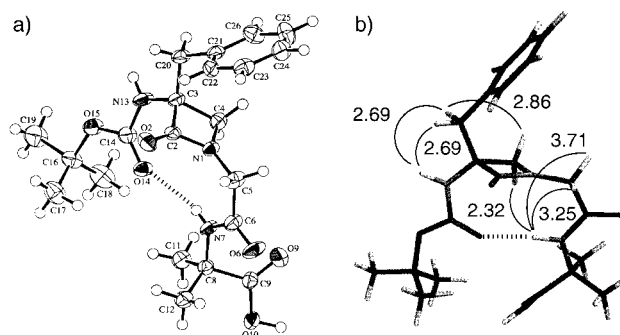


Figure 2. The type II β -turn conformation of **10**. a) Ortep plot of the solid-state X-ray structure (only one of the two symmetry-independent structures in the cell unit is represented). b) Conformation derived from ¹H NMR spectroscopy^[16] in CDCl₃ (10^{-3} mol L^{–1}, 20 °C). Representative measured interprotonic distances [Å] are shown.

bonds. Most remarkably, each conformer of **10** presented intramolecular N–H...O hydrogen bonds forming a β -turn motif which fitted reasonably well with the structural parameters of a slightly deformed type II β -turn. Finally, high-resolution structural analysis of **10** by ¹H NMR spectroscopy (500 MHz, CDCl₃, NOESY, ROESY)^[16] and molecular modeling^[17] confirmed the presence of a very stable type II β -turn conformation at 20 °C (Table 2, Figure 2 b).

In conclusion, we have found a new family of molecular scaffolds that can open the way to new dual-action peptido-

mimetics combining the biological activity of β -lactams and the countless bioactive properties of conformationally restricted oligopeptides.

Received: March 12, 1999 [Z13156IE]
German version: *Angew. Chem.* **1999**, *111*, 3241–3244

Keywords: alkylations • conformation analysis • lactams • peptides • peptidomimetics

- [1] a) R. M. Freidinger, D. F. Veber, D. S. Perlow, J. R. Brooks, R. Saperstein, *Science* **1980**, *210*, 656–658; b) D. F. Veber, R. M. Freidinger, *Trends Neurosci.* **1985**, 392–396.
- [2] a) C. Toniolo, *Int. J. Pept. Protein Res.* **1990**, *35*, 287–300; b) A. Giannis, T. Kolter, *Angew. Chem.* **1993**, *105*, 1303–1326; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244–1267; c) J. Gante, *Angew. Chem.* **1994**, *106*, 1780; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699–1720; d) R. M. J. Liskamp, *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 1–19.
- [3] M. S. Wolfe, D. Dutta, J. Aubé, *J. Org. Chem.* **1997**, *62*, 654–663, and references therein.
- [4] A well-known approach to the formation of type I and type II β -turns is, for instance, the incorporation of L-proline at the second of the four amino acid residues: T. S. Haque, J. C. Little, S. H. Gellman, *J. Am. Chem. Soc.* **1996**, *118*, 6975–6978, and references therein.
- [5] For a complete theoretical study on the structure of azetidin-2-ones, see a) E. Sedano, J. M. Ugalde, F. P. Cossio, C. Palomo, *J. Mol. Struct. (THEOCHEM)* **1988**, *166*, 481–486; b) J. Frau, J. Donoso, F. Muñoz, F. García-Blanco, *Helv. Chim. Acta* **1996**, *79*, 353–362.
- [6] For a classification of β -turns, see a) J. S. Richardson, *Adv. Protein Chem.* **1981**, *34*, 167–339; b) C. M. Wilmot, J. M. Thornton, *Protein Eng.* **1990**, *3*, 479–493.
- [7] U. Sreenivasan, R. K. Mishra, R. L. Johnson, *J. Med. Chem.* **1993**, *36*, 256–263.
- [8] Z. Wu, G. I. Georg, B. E. Cathers, J. V. Schloss, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 983–986.
- [9] Review: J. Backes in *Houben-Weyl, Methoden der Organischen Chemie*, Band E 16B (Eds.: E. Müller, O. Bayer), Thieme, Stuttgart, **1991**, p. 31.
- [10] For the asymmetric α -alkylation of β -substituted β -lactams, see I. Ojima, *Acc. Chem. Res.* **1995**, *28*, 383–398.
- [11] B. Alcaide, A. Rodríguez-Vicente, M. A. Sierra, *Tetrahedron Lett.* **1998**, *39*, 163–166.
- [12] C. Palomo, J. M. Aizpurua, M. Legido, R. Galarza, *Chem. Eur. J.* **1997**, *3*, 1432–1441.
- [13] L. A. Carpino, E.-S. M. E. Masour, D. Sadat-Aalae, *J. Org. Chem.* **1991**, *56*, 2611–2614.
- [14] Crystal data for **10**: $C_{21}H_{29}N_3O_6$, $M_r = 419.47$, triclinic, space group $P1$, $a = 9.912(2)$, $b = 11.953(2)$, $c = 9.904(1)$ Å, $\alpha = 96.46(1)$, $\beta = 102.87(1)$, $\gamma = 83.31(1)^\circ$, $V = 1131.6(3)$ Å³, $Z = 2$, $\rho = 1.231$ g cm⁻³, crystal dimensions $0.15 \times 0.28 \times 0.43$ mm, $T = -100^\circ\text{C}$, Rigaku AFC5R diffractometer, MoK_α radiation, $\lambda = 0.71069$ Å, $\mu = 0.0906$ mm⁻¹, $\omega/2\theta$ scans, $2\theta_{\text{max}} = 55^\circ$, all 5485 measured reflections were unique. The refinement of 563 parameters using 4359 observed reflections with $I > 2\sigma(I)$ gave $R = 0.0402$, $wR = 0.0339$, $S = 1.476$, and $\Delta\rho_{\text{max}} = 0.19$ e Å⁻³. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-113857 (**10**), CCDC-113858 (**4b**), and CCDC-113859 (**4f**). 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).
- [15] For a detailed information on graph set definitions, see J. Bernstein, R. E. Davis, L. Shimoni, N.-L. Chang, *Angew. Chem.* **1995**, *107*, 1689–1708; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1555–1573.
- [16] Interprotonic distances were calculated using the full relaxation matrix approach (MARGIGRAS+) with data obtained from NOESY and ROESY experiments at mixing times of 200 and 400 ms. The conformation in solution was calculated by a restrained molecular mechanics minimization using the SYBYL software and TRIPOS

force field; see a) B. A. Borgias, T. L. James, *J. Magn. Reson.* **1990**, *87*, 475–487; b) M. Clark, R. D. Cramer III, N. Van Opdenbosch, *J. Comput. Chem.* **1989**, *10*, 982–1012.

- [17] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440–467; Gaussian 94, revision C.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, J. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defress, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1995**.

Double Insertion of Coordinated Phosphanylalkyne Ligands into a Pt–C₆F₅ Bond**

Jonathan P. H. Charmant, Juan Forníes,* Julio Gómez, Elena Lalinde,* M. Teresa Moreno, A. Guy Orpen, and Santiago Solano

Carbon–carbon bond forming reactions promoted by transition metals are among the basic goals of organometallic chemistry and play an important role in the design of efficient and selective processes.^[1] The intramolecular coupling of alkyne and related C₂ ligands (alkynyl, vinyl, vinylidene) is particularly interesting because it constitutes an effective method for the synthesis of useful organic products.^[2] The facile migratory insertion of C $\equiv$ C units into M–H and M–C bonds seems to be decisive not only for these reactions but also for many catalytic processes.^[1, 2] Usually bonds between a metal and a perfluorocarbon atom are quite inert towards insertion reactions, and there is currently little or no knowledge on the insertion of acetylene fragments into the robust M–R_F bonds.^[3]

[*] Prof. Dr. J. Forníes
Departamento de Química Inorgánica
Instituto de Ciencia de Materiales de Aragón
Universidad de Zaragoza-Consejo Superior de
Investigaciones Científicas
E-50009 Zaragoza (Spain)
Fax: (+349) 76-761187
E-mail: forniesj@posta.unizar.es

Dr. E. Lalinde, Dr. M. T. Moreno, S. Solano
Departamento de Química
Universidad de La Rioja
E-26001 Logroño (Spain)
Fax: (+349) 41-259431
E-mail: elena.lalinde@dq.unirioja.es

Dr. J. P. H. Charmant, J. Gómez, Prof. Dr. A. G. Orpen
School of Chemistry, University of Bristol (UK)

[**] This work was supported by the D.G.E.S. (Spain, project PB95-0003C02-01 02) and the University of La Rioja (project API-99/B17 and a grant to J.G.).

 Supporting information for this article (experimental procedures and spectral data of products) is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

Herein we report on the unprecedented double insertion of coordinated (phenylethynyl)phosphane $\text{PPh}_2\text{C}\equiv\text{CPh}$ into a $\text{Pt}-\text{C}_6\text{F}_5$ bond. Phosphanylalkynes $\text{PPh}_2\text{C}\equiv\text{CR}$ are extremely versatile molecules which display a very rich chemistry. They are not only capable of binding in a variety of coordination modes,^[4] but in some cases the ligands undergo cleavage of the $\text{P}-\text{C}(\text{alkyne})$ bond to yield phosphide and alkynyl fragments, which may take part in further coupling reactions in the presence of suitable unsaturated molecules.^[4a,b,5] Insertions into reactive $\text{M}-\text{H}$ or $\text{M}-\text{C}$ bonds are also known,^[6] and several recent papers describe oxidative alkyne coupling processes with these unsaturated phosphorous-substituted alkynes.^[7]

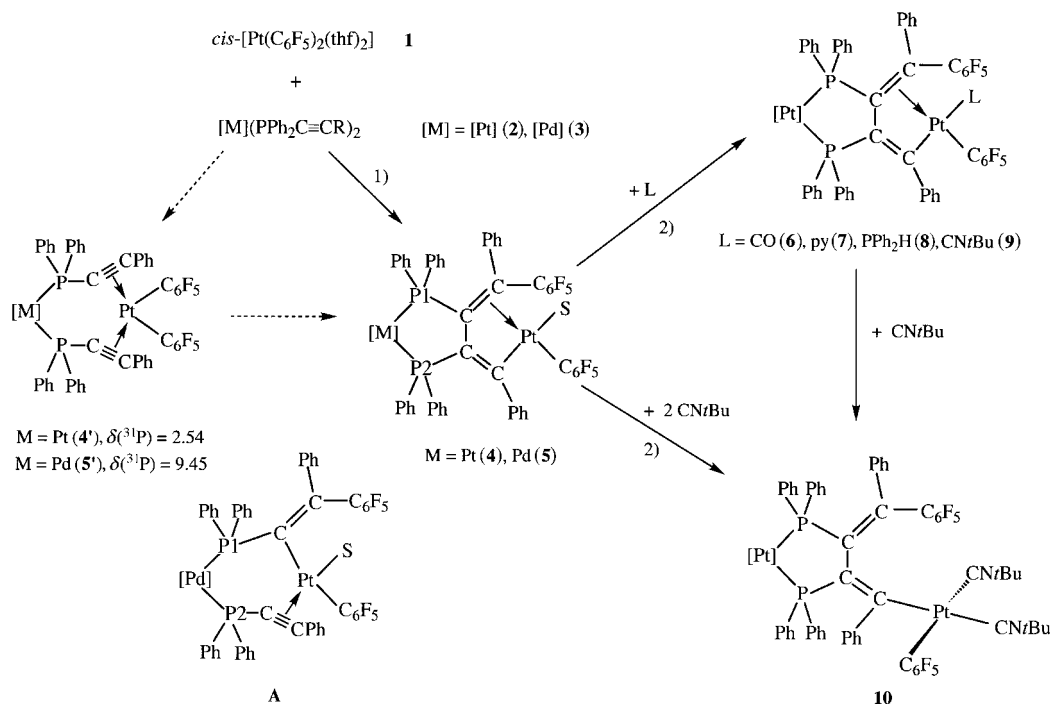
We have recently shown that the tetrahydrofuran molecules of the very reactive compound $\text{cis}[\text{Pt}(\text{C}_6\text{F}_5)_2(\text{thf})_2]$ (**1**) are easily displaced by alkynes^[8a] or alkynylmetal complexes.^[8b-d] However, the reaction of **1** with $\text{cis}[\text{PtX}_2(\text{PPh}_2\text{C}\equiv\text{CR})_2]$ ($\text{X} = \text{Cl}$, $\text{C}\equiv\text{CR}$; $\text{R}' = \text{Ph}$, $t\text{Bu}$) yields only homobridged—($\mu\text{-X}$)₂ ($\text{X} = \text{Cl}$,^[8e] $\text{C}\equiv\text{CR}$ ^[8f])—or heterobridged—($\mu\text{-PPh}_2\text{C}\equiv\text{CR}$)($\mu\text{-Cl}$)^[8e]—binuclear complexes. To force the coordination of two $\text{PPh}_2\text{C}\equiv\text{CR}$ molecules as bridging ligands, we have investigated the reaction of **1** with complexes $\text{cis}[\text{M}(\text{C}_6\text{F}_5)_2(\text{PPh}_2\text{C}\equiv\text{CR})_2]$ ($\text{M} = \text{Pt}$ (**2**), Pd (**3**); $\text{R} = \text{Ph}$ (**a**), $t\text{Bu}$ (**b**)), which were prepared by standard methods (see the Supporting Information). To our surprise these reactions did not lead to the expected bis[$\mu\text{-}\kappa\text{P}:(\eta^2)\text{-(PPh}_2\text{C}\equiv\text{CR})$]-bridged η^2 -alkyne complexes **4'** and **5'** (see Scheme 1), but to unusual coupling products.

As outlined in Scheme 1 the *tert*-butyl derivatives **2b** and **3b** did not react with **1**, even under reflux conditions (CH_2Cl_2 , 5 h for **2b** or 1 h for **3b**). However, the phenylethynyl complexes **2a** and **3a** react with an equimolar amount of **1** in CH_2Cl_2 to give the yellow binuclear complexes **4** (82 %) and **5** (66 %), respectively, which contain an unusual 2,3-bis(di-

phenylphosphanyl)-1,3-butadien-1-yl ligand acting as a bis-chelating $\mu\text{-}1(3,4\text{-}\eta,\kappa\text{C}^1):2\kappa^2\text{P,P'}$ bridging ligand. IR and ^{19}F NMR (282.4 MHz) spectroscopy of **4** and **5** clearly established not only the presence of a $\text{C}-\text{C}_6\text{F}_5$ unit, but also the existence of four different types of C_6F_5 moieties, indicating an asymmetrical structure. Similarly two different ^{31}P resonances are seen ($^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3): **4**: $\delta = 24.81$ (d, $^1J_{\text{Pt2,P2}} = 2284$, $^3J_{\text{Pt1,P2}} = 276$ Hz), 36.03 (d, $^1J_{\text{Pt2,P1}} = 2251$, $J_{\text{P2,P1}} \approx 7$ Hz); **5**: $\delta = 37.71$ (br, $^3J_{\text{Pt1,P2}} = 270$ Hz), 42.14 (brs); Pt1 stems from **1**), but X-ray analysis was needed to determine unambiguously the nature of the unsymmetric bridging ligand.

Complex **4** crystallizes easily in different solvent systems, but none of the crystals obtained were suitable for X-ray crystallography. An X-ray crystallographic investigation of **5** was also tried; however, disorder associated with the solvent coordination site at Pt (partial occupancy for thf or H_2O) prevented a satisfactory refinement.^[9] This study notwithstanding indicated that the two acetylenic fragments of the precursor **2** or **3** had condensed with one of the C_6F_5 groups of **1** to form a 2,3-bis(diphenylphosphanyl)butadienyl ligand that bridges the two metal centers (Scheme 1). This is confirmed by X-ray studies on complexes resulting from the substitution of ligand S (see below). A few similar η^3 -butadienyl ($3,4\text{-}\eta,\kappa\text{C}^1$) backbones have been previously obtained by insertion of two alkynes into $\text{Ru}-\text{X}$ ($\text{X} = \text{H}$, Me)^[10a] or $\text{Pd}-\text{X}$ bonds ($\text{X} = \text{Cl}$, Ph)^[10b,c] or into cyclometalated Pd^{II} or Ni^{II} complexes.^[11] In other systems, the butadienyl unit invariably displays symmetric or asymmetric η^3 -allylic (through C2–C4) or η^1 (through C2) bonding modes.^[12]

When the reaction of **1** with **2a** or **3a** was monitored at room temperature no intermediates were detected. However, on the basis of preliminary experimental evidence at low



Scheme 1. Synthesis of **4**–**10**. 1) CH_2Cl_2 , 0–10 °C, 45 min. 2) CH_2Cl_2 , room temperature, 5–30 min. [$\text{M} = \text{cis-M}(\text{C}_6\text{F}_5)_2$, $\text{M} = \text{Pt}$, Pd ; $\text{R} = \text{Ph}$ (**a**), $t\text{Bu}$ (**b**). $\text{py} = \text{pyridine}$, $\text{S} = (\text{thf})_x(\text{H}_2\text{O})_{1-x}$. ^{31}P NMR data at –30 °C.

temperature (^{31}P and ^{19}F NMR spectroscopy between -50 and -10°C) we postulate that the formation of **4** and **5** proceeds stepwise. Thus when the reaction between **2a** and **1** was performed at -50°C , the expected η^2 -alkyne adduct **4'** was detected together with the precursors (**2a**:**1**:**4'** $\approx$ 1:1:0.4) and fully characterized ($\delta(^{31}\text{P})=2.15$ ($^1J_{\text{Pt,P}}=2341$ Hz); $\delta(^{19}\text{F})\approx -116.1$ (br), -120.1 (br, *o*-F), -153.98 (t), -160.5 (*p*-F, overlap with the signal for *p*-F of **1**), -163.0 (m, *m*-F)). The presence of complex **4** was detected at -20°C . Its formation, accompanied by the gradual and simultaneous disappearance of **4'** and reactants, is clean at -10°C and complete within about 6 h.

In the **2a/1** system no other intermediate could be observed. However, in the reaction of **3a** with **1**, the ^{31}P and ^{19}F NMR spectra recorded at -50°C reveal that in addition to the precursors and the η^2 -alkyne adduct **5'** ($\delta(\text{P})=9.27$), a new intermediate (**A**, Scheme 1) is also formed (**3a**:**5'**:**A** $\approx$ 0.54:0.29:0.17). This intermediate shows two different ^{31}P resonances ($\delta(\text{P})=11.16$ (br), -3.29 (br)), and particularly the ^{19}F resonances for one C_6F_5 group ($\delta(\text{F})=-127.14$, -129.5 (*o*-F), -151.5 (*p*-F), -156.8 , -158.6 (*m*-F)) are at chemical shifts typical of a $\text{C}-\text{C}_6\text{F}_5$ unit and support a formulation of the monoinserted alkyne/vinyl species **A**. If the reaction temperature is allowed to increase, the formation of **5** can be observed clearly at -10°C . At this temperature the NMR signals of **3a**, **5'**, and **A** gradually disappear (with a nearly constant ratio), and the signals due to **5** grow concomitantly. Again the transformation is very slow, requiring around 12 h to go to completion.

Although we have no experimental evidence of an analogous monoinserted product in the Pt/Pt system and the structural assignment of the intermediate **A** is only tentative, the participation of **A** in the proposed reaction pathway seems reasonable on chemical grounds and is in agreement with previous results on cyclometalated palladium(II) complexes and acetylenes.^[11b] Curiously, in a donor solvent such as acetone there is formation of neither **4/5** nor **4'/5'**, suggesting that the proximity of the acetylene fragments in the initial adduct probably play a major role in the activation process. The formation of asymmetric diphosphanes by activation^[13] or coupling^[7a,c] of two alkynylphosphanes mediated by metal centers has been previously reported, but, as far as we know, the migratory insertion of an acetylenic fragment into a $\text{M}-\text{C}_6\text{F}_5$ bond has no precedent. In this context it is worth noting that a few examples of pentafluorobenzimidoyl derivatives ($\text{C}(\text{C}_6\text{F}_5)=\text{NR}$) of Ti and Pd have been obtained through insertion reactions of isocyanides into $\text{M}-\text{C}_6\text{F}_5$ bonds.^[14] More recently Espinet et al. have shown that the addition of $\text{Pd}-\text{C}_6\text{F}_5$ to coordinated olefins is also a relatively easy process.^[15]

To confirm the structure of the new bridging ligand we have explored the reactivity of the more stable complex **4** towards different neutral ligands. As expected, the diplatinum derivatives **6–9** (Scheme 1) are easily obtained as yellow (**6**, **9**) or orange (**7**, **8**) air-stable microcrystalline solids by treatment of **4** with stoichiometric amounts of the corresponding ligands **L** (see the Supporting Information for details). The η^2 -olefin interaction seems to be rather strong because only the reaction of **4** with CNiBu (1:2 molar ratio) results in the

opening of the chelating ring to give **10** as a lemon yellow microcrystalline solid (78% yield).

In addition to full spectroscopic and analytical characterization of complexes **6–10**, the solid-state structures of **8** and **10** were determined by single-crystal X-ray diffraction.^[16] The molecular structure of **8** (Figure 1) confirms unequivocally

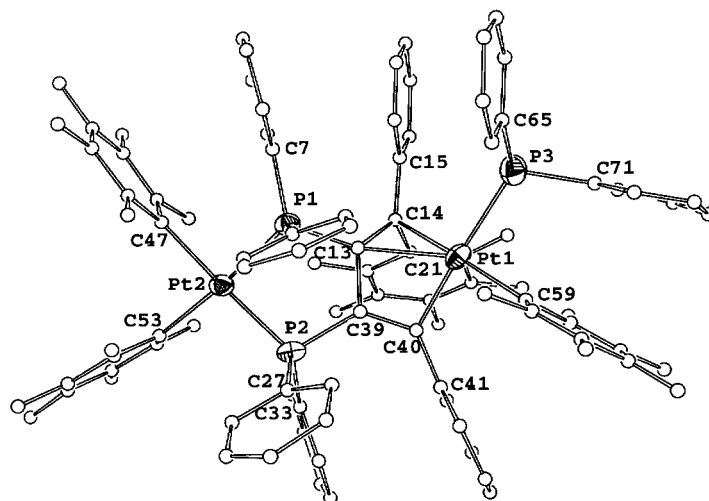


Figure 1. Molecular structure of **8**. Hydrogen atoms have been omitted for clarity. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Pt1–C40 2.022(9), Pt1–C14 2.322(9), Pt1–C13 2.396(9), Pt2–P1 2.300(3), Pt2–P2 2.279(3), C13–C14 1.430(13), C13–C39 1.516(12), C39–C40 1.369(15); C14–C13–C39 118.2(9), C14–C13–P1 130.5(7), C39–C13–P1 108.1(7), C13–C14–Pt1 75.2(5), C40–C39–C13 111.1(9), C40–C39–P2 129.8(7), C13–C39–P2 118.7(7), C39–C40–Pt1 101.0(7).

that the reaction between **1** and **2a** results in the formation of a butadienyldiphosphane ligand which coordinates to the $\text{Pt}_2(\text{C}_6\text{F}_5)_2$ unit as a typical diphosphane ligand and to the $\text{Pt}_1(\text{C}_6\text{F}_5)\text{PPh}_2\text{H}$ fragment as a vinyl-olefin ligand ($\sigma:\eta^2$). The interatomic distances and angles about the butadienyl chain are within the expected range.^[10, 11] The phenyl and PPh_2 groups are mutually *cis* not only in the vinyl unit but also in the η^2 -alkene fragment, indicating that the overall insertion process is probably highly regioselective. A *trans* arrangement about the η^2 -alkene bond is usually displayed in related butadienyl backbones formed by double insertion of alkynes into cyclopalladate complexes.^[11]

In summary these results confirm previous indications of the enhanced reactivity of uncoordinated $\text{C}\equiv\text{C}$ bonds held in the proximity of a metal in phosphanylacetylene complexes. Work to extend these reactions to other $\text{PPh}_{3-x}(\text{C}\equiv\text{CR})_x$ phosphanes ($x=1-3$) and to study the chemical reactivity of the final species is in progress.

Received: March 5, 1999

Revised version: July 5, 1999 [Z13115IE]

German version: *Angew. Chem.* **1999**, *111*, 3238–3241

Keywords: alkynes • insertions • P ligands • platinum

- [1] a) J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, **1987**; b) D. B. Grotjahn in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds.: E. W.

- Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, chap. 7.3, p. 741, and references therein.
- [2] a) J. R. Berenguer, J. Forniés, E. Lalinde, F. Martínez, L. Sanchez, B. Serrano, *Organometallics* **1998**, *17*, 1640; b) F. Guerin, D. H. Conville, J. J. Vittal, G. A. P. Yap, *Organometallics* **1998**, *17*, 1290; c) A. Evenzahav, N. J. Turro, *J. Am. Chem. Soc.* **1998**, *120*, 10835; d) E. D. Jemmis, K. T. Gijn, *J. Am. Chem. Soc.* **1998**, *120*, 6952, and references therein; e) H.-F. Klein, M. Heiden, M. He, T. Jung, *Organometallics* **1997**, *16*, 2003; f) B. M. Trost, M. T. Sorvum, C. Chan, A. E. Harms, G. Rühler, *J. Am. Chem. Soc.* **1997**, *119*, 698, and references therein.
- [3] a) A. J. Carty in *Comprehensive Organometallic Chemistry*, Vol. 9 (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, chap. 5; b) P. M. Maitlis, P. Espinet, M. J. Russell in *Comprehensive Organometallic Chemistry*, Vol. 6 (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1982**, chap. 38.4; c) R. Usón, J. Forniés, *Adv. Organomet. Chem.* **1988**, *28*, 219; d) J. Browning, M. Green, J. L. Spencer, F. G. A. Stone, *J. Chem. Soc. Dalton Trans.* **1974**, 97.
- [4] Reviews: a) M. J. Went, *Polyhedron* **1995**, *14*, 465, and references therein; b) A. J. Carty, *Pure Appl. Chem.* **1982**, *54*, 113; see also R. S. Dickson, T. Simone, R. J. Parker, G. D. Fallou, *Organometallics* **1997**, *16*, 1531; E. Lonattani, A. Lledós, J. Suades, A. Alvarez-Lorena, J. F. Piniella, *Organometallics* **1995**, *14*, 1053.
- [5] a) E. Delgado, Y. Chi, W. Wang, G. Hogart, P. J. Low, G. D. Enright, S.-M. Peng, G.-H. Lee, A. J. Carty, *Organometallics* **1998**, *17*, 2936; b) P. Blenkiron, G. D. Enright, P. J. Low, J. F. Corrigan, N. J. Taylor, Y. Chi, J.-Y. Saillard, A. J. Carty, *Organometallics* **1998**, *17*, 2447; c) M. H. A. Benvenutti, M. D. Vargas, D. Braga, F. Grepioni, B. E. Mann, S. Naylor, *Organometallics* **1993**, *12*, 2947, and references therein.
- [6] a) P. Rosa, P. Le Floch, L. Ricard, F. Mathey, *J. Am. Chem. Soc.* **1997**, *119*, 9417; b) Y. Miquel, A. Igau, B. Donnadieu, J. P. Majoral, L. Dupuis, N. Pirio, P. Meunier, *Chem. Commun.* **1997**, 279; *J. Am. Chem. Soc.* **1998**, *120*, 3504; c) W. Imhof, B. Eber, G. Huttner, C. Emmerich, *J. Organomet. Chem.* **1993**, *447*, 21; d) D. Montlo, J. Suades, F. Dahan, R. Matthieu, *Organometallics* **1990**, *9*, 2933; e) E. Sappa, G. Pasquinelli, A. Tiripicchio, M. Tiripicchio Camellini, *J. Chem. Soc. Dalton Trans.* **1989**, 601.
- [7] a) M. A. Bennett, C. J. Cobley, E. Wenger, A. C. Willis, *Chem. Commun.* **1998**, 1307; b) A. Mahieu, Y. Miquel, A. Igau, B. Donnadieu, J. P. Majoral, *Organometallics* **1997**, *16*, 3086; c) D. K. Johnson, T. Rukachaisirikul, Y. Sun, N. J. Taylor, A. J. Carty, *Inorg. Chem.* **1993**, *32*, 5544.
- [8] a) R. Usón, J. Forniés, M. Tomás, B. Menjón, C. Fortuño, A. J. Welch, D. E. Smith, *J. Chem. Soc. Dalton Trans.* **1993**, 275; b) J. Forniés, M. A. Gómez-Saso, E. Lalinde, F. Martínez, M. T. Moreno, *Organometallics* **1992**, *11*, 2873; c) I. Ara, J. R. Berenguer, E. Eguizabal, J. Forniés, E. Lalinde, A. Martín, F. Martínez, *Organometallics* **1998**, *17*, 4578; d) J. R. Berenguer, L. R. Falvello, J. Forniés, E. Lalinde, M. Tomás, *Organometallics* **1993**, *12*, 6; e) J. Forniés, E. Lalinde, A. Martín, M. T. Moreno, A. J. Welch, *J. Chem. Soc. Dalton Trans.* **1995**, 1333; f) I. Ara, L. R. Falvello, S. Fernández, J. Forniés, E. Lalinde, A. Martín, M. T. Moreno, *Organometallics* **1997**, *16*, 5923.
- [9] I. Ara, Universidad de Zaragoza, personal communication.
- [10] a) M. I. Bruce, A. Catlow, M. G. Humphrey, G. A. Koutsantonis, M. R. Snow, E. R. T. Tiekink, *J. Organomet. Chem.* **1988**, *338*, 59, and references therein; b) P. M. Maitlis, *J. Organomet. Chem.* **1980**, *200*, 161; c) E. A. Kelley, P. M. Maitlis, *J. Chem. Soc. Dalton Trans.* **1979**, 167.
- [11] a) J. Albert, J. Granell, J. Sales, J. Xolans, *J. Organomet. Chem.* **1989**, *379*, 177; b) A. D. Ryabov, R. van Eldik, G. Le Borgne, M. Pfeffer, *Organometallics* **1993**, *12*, 1386; c) J. P. Sutter, M. Pfeffer, A. De Cian, J. Fisher, *J. Organomet. Chem.* **1992**, *11*, 386; d) G. Zhao, Q.-G. Wang, T. C. W. Mak, *Tetrahedron: Asymmetry* **1998**, *9*, 2253; e) J. Vicente, I. Saura-Llamas, J. Turpin, M. C. Ramirez de Arellano, P. G. Jones, *Organometallics* **1999**, *18*, 2689.
- [12] a) C. Slugove, K. Mereiter, R. Schmid, K. Kirchner, *J. Am. Chem. Soc.* **1998**, *120*, 6175; b) C. P. Casey, S. Chung, Y. Ha, D. R. Powell, *Inorg. Chim. Acta* **1997**, *265*, 127; c) D. Huang, M. Olivan, J. C. Huffman, O. Eisenstein, K. G. Caulton, *Organometallics* **1998**, *17*, 4700; d) Ch. S. Yi, N. Liu, A. L. Rheingold, L. M. Liable-Sands, *Organometallics* **1997**, *16*, 3910; e) H. Werner, R. Wiedemann, P. Steiner, J. Wolf, *Chem. Eur. J.* **1997**, *3*, 127; f) A. C. Dema, C. M. Lukehart, *Inorg. Chim. Acta* **1997**, *264*, 193; g) S. A. Benyunes, L. Brandt, A. Fries, M. Green, M. F. Mahon, T. M. Papworth, *J. Chem. Soc. Dalton Trans.* **1993**, 3785; h) A. C. Dema, C. M. Lukehart, A. T. McPhail, D. R. McPhail, *J. Am. Chem. Soc.* **1990**, *112*, 7229; i) A. Furlani, M. V. Russo, A. C. Villa, A. G. Manfredoti, C. Guastini, *J. Chem. Soc. Dalton Trans.* **1977**, 2154.
- [13] a) A. J. Carty, S. E. Jacobson, R. T. Simpson, N. J. Taylor, *J. Am. Chem. Soc.* **1975**, *97*, 7254; b) A. J. Carty, D. K. Johnson, S. E. Jacobson, *J. Am. Chem. Soc.* **1979**, *101*, 5612; c) N. J. Taylor, S. E. Jacobson, A. J. Carty, *Inorg. Chem.* **1975**, *11*, 2648; see also d) A. J. Carty, G. Hogarth, G. Enright, G. Frapper, *Chem. Commun.* **1997**, 1883.
- [14] a) A. Dormond, A. Dahchour, *J. Organomet. Chem.* **1980**, *193*, 321; b) R. Usón, J. Forniés, P. Espinet, E. Lalinde, P. G. Jones, G. M. Sheldrick, *J. Organomet. Chem.* **1985**, *288*, 249, and references therein.
- [15] A. C. Albeniz, P. Espinet, Y.-S. Lin, *J. Am. Chem. Soc.* **1996**, *118*, 7145, and references therein.
- [16] Crystal data for **8** ($C_{74}F_{20}H_{36}P_3Pt_2$): orthorhombic, space group $Pca2_1$, $a = 23.197(2)$, $b = 14.068(2)$, $c = 23.264(2)$ Å, $V = 7591.8(11)$ Å³, $Z = 4$, $\mu = 3.83$ mm⁻¹, $T = 173(2)$ K. A total of 47 379 reflections were collected, of which 17 225 were unique ($R(\text{int}) = 0.0534$). The refinement converged to $R1 = 0.048$, $wR2 = 0.116$, and $S = 0.999$. 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-115339 and 115340. 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).

Exploiting the Self-Assembly Strategy for the Design of Selective Cu^{II} Ion Chemosensors**

Patrizia Grandini, Fabrizio Mancin, Paolo Tecilla,*
Paolo Scrimin, and Umberto Tonellato*

Chemosensors, small abiotic molecules that signal the presence of analytes, typically combine two components: a recognition site that binds the target substrate and a readout system that signals binding.^[1] In the case of metal ion sensors the recognition site is a metal-chelating molecule designed to bind the target ion selectively and the readout system is very often a fluorophore. The two components are usually covalently linked through a spacer and the complexation of the metal ion results in a variation of the position and/or intensity of the emission band of the fluorophore. With this set-up a large number of molecular sensors has been devised for the detection of alkali and transition metal ions in solution.^[1] Among the latter group, Cu^{II} has attracted

[*] Prof. P. Tecilla,^[+] Prof. U. Tonellato, Dr. P. Grandini, Dr. F. Mancin, Prof. P. Scrimin
Dipartimento di Chimica Organica e Centro
CNR Meccanismi di Reazioni Organiche
Università di Padova
Via Marzolo 1, I-35131 Padova (Italy)
Fax: (+390) 49-8275239
E-mail: tecilla@mail.chor.unipd.it
tonum@mail.chor.unipd.it

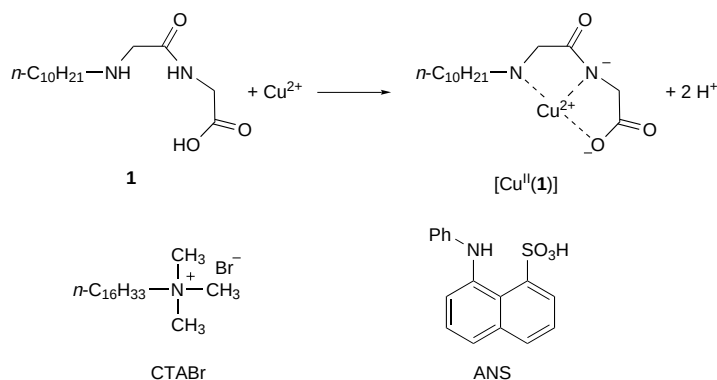
[+] New address:
Dipartimento di Scienze Chimiche, Università di Trieste
Via L. Giorgieri 1, I-34127 Trieste (Italy)

[**] This work was supported by funds from the Italian Ministry of the University, MURST, under the framework of the "Supramolecular Devices" project.

particular attention.^[2] For instance, Fabbri et al.,^[3] Czarnik et al.,^[4] Imperiali et al.,^[5] and Marchelli et al.^[6] have connected fluorescent probes to different types of selective Cu^{II} ligand subunits. The binding of the metal ion causes a quenching of the fluorescence emission of the probe and allows its detection in the micro- or submicromolar range. In these systems the quenching is ascribed to a photoinduced metal-to-fluorophore electron-transfer mechanism.^[3] However, sensors in which the binding of a Cu^{II} ion causes an increase in the fluorescence emission or in which the fluorophore and the metal ion do not interact directly have been reported by the groups of Bharadwaj^[7] and Arnold,^[8] respectively.

A common feature of all the sensors described so far is a covalent linkage between the two components. While this ensures their proximity, it requires a proper design and synthetic efforts. Our goal was to realize a system in which the active components assemble spontaneously to give a sensor, without the need for any covalent link between them.^[9] We reasoned that a lipophilic ligand, a fluorophore, and a surfactant would self-assemble in water to give a comicellar aggregate.^[10] The proximity between the ligand and the fluorophore inside this aggregate should ensure contact between the complexed metal ion and the dye. Herein we present a sensor for Cu^{II} ions that is able to compete in selectivity and sensitivity with other more sophisticated systems. This is realized by simply mixing, under suitable conditions, commercially available surfactants and fluorophores with a dipeptide-based ligand. We have also applied a combinatorial approach to emphasize the versatility of this self-assembly strategy.

To achieve strong and highly specific binding of Cu^{II} ions in neutral water we selected the glycylglycine dipeptide **1**, bearing a C₁₀ linear alkyl chain at the N-terminus, as the ligand. The dipeptide is known^[11] to coordinate Cu^{II} ions by means of its amino group, the deprotonated amido nitrogen atom, and the carboxylate group as shown in Scheme 1. The



Scheme 1.

key feature for the selective formation of a strong complex is the deprotonation of the amido nitrogen atom, which occurs under slightly acidic or neutral pH exclusively with Cu^{II} ions, and not with other metal ions such as Zn^{II}, Ni^{II}, or Co^{II}. While ligand **1** dissolves in water up to millimolar concentrations in the pH range 2–9, the neutral complex [Cu^{II}(**1**)] is only

slightly soluble above pH 5. Clear and stable solutions of the complex can be obtained by addition of a surfactant such as CTABr when [CTABr]/[Cu^{II}(**1**)] ≥ 2/1. The uncomplexed ligand also partitions in CTABr and the resulting comicelles have a critical micellar concentration (cmc) of 2.6 × 10^{−4} M (CTABr). The commercial fluorophore 8-anilino-1-naphthalenesulfonic acid (ANS) strongly binds to the above aggregates as highlighted by the strong increase in the fluorescence associated with its transfer from the aqueous solution to the less polar micellar environment.^[1b] The binding is very effective and ultrafiltration experiments show that, even at a concentration of CTABr as low as the cmc, the fluorophore is fully bound to the aggregate. Thus, the ligand and the fluorophore spontaneously self-assemble in water containing CTABr aggregates. Titration of such assemblies at pH 7 with Cu(NO₃)₂ results in the almost total quenching of the fluorescence emission of ANS, which reaches a plateau at about 5 % of its initial intensity (Figure 1). Formation of the

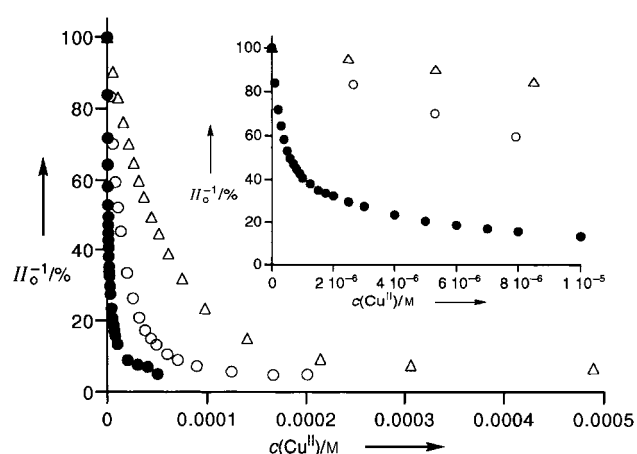


Figure 1. Spectrofluorimetric titrations of CTABr/1/ANS comicelles with Cu(NO₃)₂ in HEPES buffer 0.01 M, pH 7. Conditions: [ANS] = 5.0 × 10^{−7} M; [CTABr]/[**1**] = 2; [CTABr] = 9.4 × 10^{−4} M (Δ); 4.7 × 10^{−4} M (○); 2.4 × 10^{−4} M (●). Inset: enlargement of the first part of the titrations. II₀^{−1} = ratio of fluorescence intensity and original fluorescence intensity.

complex [Cu^{II}(**1**)] is the essential prerequisite to observe the fluorescence quenching. No effect is observed in the absence of the ligand, or in the presence of an excess of the hydrophilic ligand ethylenediaminetetraacetic acid (EDTA), or at a pH value below 5 where the complex is not formed. The system is rather stable and reproducible: titrations made with different micellar preparations or measurement of the fluorescence emission of the same solution at different times give identical results within experimental error (<2%). Only in the case of the more diluted comicelles (● of Figure 1) has a relatively higher (<5%) variation of the fluorescence data been observed.

The sensitivity of the system strongly depends on the ratio [CTABr]/[ANS] reaching the micromolar range while the concentration of the surfactant is close to the cmc (Figure 1). At high surfactant concentration, when the number of micelles exceeds the number of dye molecules, it is reasonable to assume that some micelles do not contain ANS. As a consequence, binding of Cu^{II} ions to the empty aggregates is

ineffective relative to the quenching process. Hence, the dependence of the quenching efficacy on the total concentration of surfactant allows one to tune the sensitivity of the system. For example, the amount of Cu^{II} ions that reduces the initial fluorescence intensity to 50% ($[\text{Cu}^{\text{II}}]_{50\%}$) decreases from 4×10^{-5} to 1×10^{-6} M on changing the concentration of CTABr (and **1**, the ratio being 2/1) from 9.45×10^{-4} to 2.34×10^{-4} M. The ratio $[\text{CTABr}]/[\text{ligand}]$ is another important factor that determines the sensitivity. By keeping the concentration of ANS (5×10^{-7} M) and **1** (2.3×10^{-4} M) constant and increasing the ratio $[\text{CTABr}]/[\text{1}]$ from 2/1 to 5/1 and 10/1, $[\text{Cu}^{\text{II}}]_{50\%}$ increases from 1×10^{-5} , to 5×10^{-5} , and 1.5×10^{-4} M, respectively. Thus, dilution of the ligand in the aggregate inhibits the quenching process, making the contact between the fluorophore and the Cu^{II} complex less favorable.

Selectivity is of paramount importance for a chemosensor and to prove it for the present system we have titrated (Figure 2) comicelles made from CTABr, **1**, and ANS with

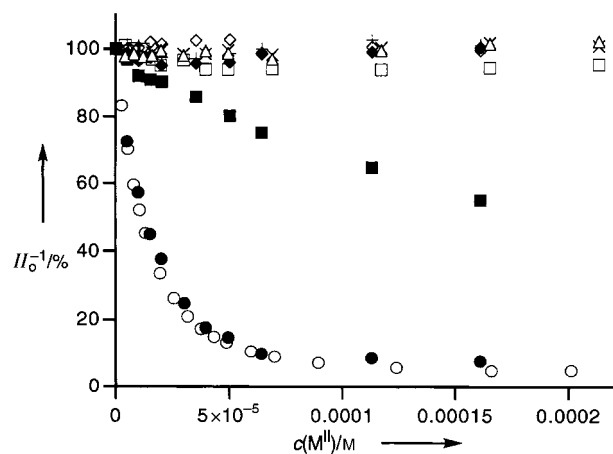
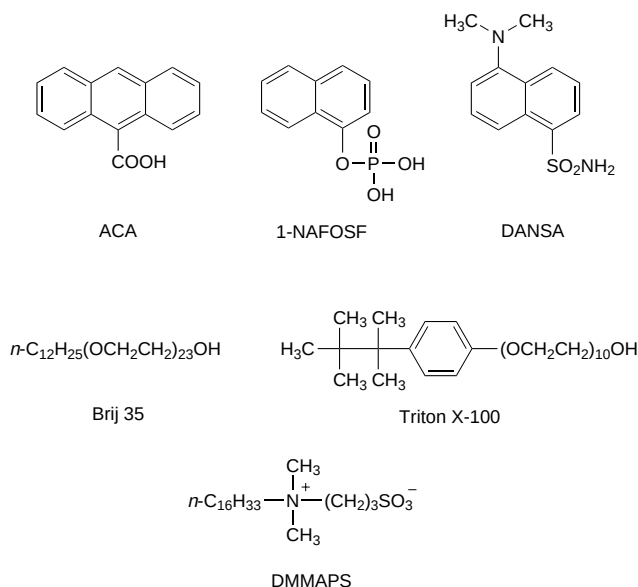


Figure 2. Spectrofluorimetric titrations of CTABr/**1**/ANS comicelles (4.7×10^{-4} M/ 2.3×10^{-4} M/ 5.0×10^{-7} M) in HEPES buffer 0.01 M, pH 7 with different metal ions: Mn^{II} (+); Fe^{II} (■); Co^{II} (◇); Ni^{II} (◆); Zn^{II} (x); Cd^{II} (□); Pb^{II} (△); Cu^{II} (○); Cu^{II} in the presence of all the other metal ions each 1×10^{-4} M (●).

other divalent metal ions, mainly belonging to the 3d series. No effect was observed with all cations investigated, except Fe^{II} .^[12] With this latter metal ion the $[\text{Fe}^{\text{II}}]_{50\%}$ is 2.0×10^{-4} M from which a $\text{Cu}^{\text{II}}/\text{Fe}^{\text{II}}$ selectivity of 20 may be determined. More importantly a titration of Cu^{II} in the presence of all cations listed in Figure 2 (each 1.0×10^{-4} M) gives a curve superimposable to the one obtained exclusively in the presence of Cu^{II} ions. Therefore, the sensor not only does not respond to other metal ions but is also selective towards Cu^{II} ions in their presence.

A major advantage in using the self-assembling strategy is the easy interchange of the different components to achieve the desired properties and the facile set up of a combinatorial approach for the selection of the most effective system. To investigate this aspect we performed a series of experiments checking all combinations of **1**, surfactants, and dyes. The results are summarized in Figure 3 as the percentage of residual fluorescence in the presence of Cu^{II} ions (5×10^{-5} M), fluorophore (5.0×10^{-7} M), **1** (2.3×10^{-4} M), and the minimum



amount of surfactant needed to solubilize the complex (see caption of Figure 3 for details). Of the systems investigated that made up of CTABr and 1-naphthylphosphate (1-NAFOSF) proved to be the most effective. This result is

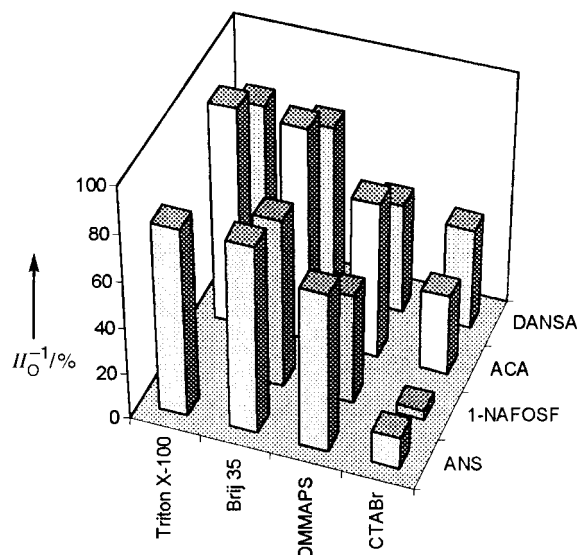


Figure 3. Percentage of residual fluorescence in the presence of 5.0×10^{-5} M Cu^{II} measured for the different comicellar systems. Conditions: HEPES buffer 0.01 M, pH 7; [fluorophore] = 5.0×10^{-7} M; [**1**] = 2.3×10^{-4} M; [surfactant]/[**1**] = 2 (CTABr); 6 (DMMAPS); 10 (Brij 35); 10 (Triton X-100). The couple Triton X-100/1-NAFOSF was not investigated because of the high background level of fluorescence emitted by the surfactant when irradiated at 286 nm.

probably related to: a) the low $[\text{surfactant}]/[\text{ligand}]$ ratio attainable with CTABr and b) a possible weak interaction of the phosphate group with the Cu^{II} complex. A more detailed investigation is under way to assess the role played by other factors, such as the charge of the surfactant and the structure of the dye.

In conclusion, we have demonstrated that the self-assembly strategy can be conveniently used for the construction of a Cu^{II} sensor. The components of the system employed in this

study are commercially available or can be easily synthesized. They spontaneously self-assemble in neutral water giving rise to an assembly that displays some of the most important features of a sensor, such as sensitivity and selectivity. This modular approach allows for the easy variation of the components, which makes the process of system optimization very simple. Work is in progress to extend such a concept to ligands selective towards other metal ions and to widen its scope to the sensing of neutral molecules.

Experimental Section

N-Decylglycylglycine (**1**) was synthesized following a reported procedure^[13] and was isolated as the CF₃COOH salt. All spectral and analytical data were in agreement with the proposed structure. Representative data for **1**: m.p. 109–110 °C; elemental analysis calcd for C₁₆H₂₉N₂O₅F₃: C 49.7, H 7.56, N 7.25; found: C 50.1, H 7.51, N 7.27; ¹H NMR (250 MHz, CD₃OD, 25 °C, TMS): δ = 0.94 (t, *J* = 6.5 Hz, 3H), 1.38 (m, 14H), 1.74 (m, 2H), 3.07 (t, *J* = 6.7 Hz, 2H), 3.88 (s, 2H), 4.03 (s, 2H).

Critical micellar concentrations were obtained from surface tension measurements using a Krüss K6 apparatus. Ultrafiltrations were performed with a 8010 Amicon cell equipped with a regenerated cellulose Millipore filter with a cut-off of 10⁴ Daltons. Emission spectra were recorded on a Perkin–Elmer LS-50B spectrofluorimeter. Titrations were performed in a 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid (HEPES) buffer 0.01M, pH 7, and 25 °C. Excitation and emission wavelengths (nm) were, respectively: 375 and 500 for ANS; 286 and 360 for 1-NAFOSF; 362 and 415 for 9-anthracenecarboxylic acid (ACA); 325 and 530 for dansylamide (DANSA).

Received: May 10, 1999 [Z13396IE]

German version: *Angew. Chem.* **1999**, *111*, 3247–3250

Keywords: copper • fluorescent sensor • micelles • self assembly • supramolecular chemistry

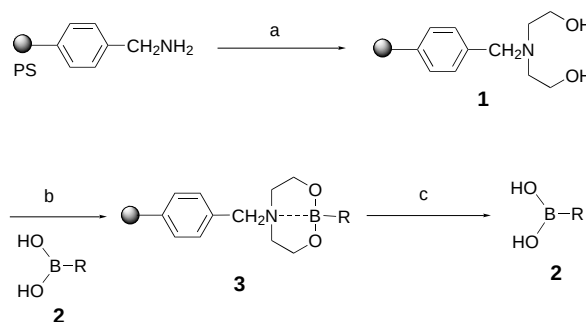
- [1] a) “Fluorescent Chemosensors for Ion and Molecule Recognition”: *ACS Symp. Ser.* **1993**, 538; b) A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.* **1997**, *97*, 1515–1566.
- [2] R. Krämer, *Angew. Chem.* **1998**, *110*, 804–806; *Angew. Chem. Int. Ed.* **1998**, *37*, 772–773.
- [3] G. De Santis, L. Fabbri, M. Lichelli, C. Mangano, D. Sacchi, N. Sardone, *Inorg. Chim. Acta* **1997**, *257*, 69–76.
- [4] J. Yoon, N. E. Ohler, D. H. Vance, W. D. Aumiller, A. W. Czarnik, *Tetrahedron Lett.* **1997**, *38*, 3845–3848.
- [5] A. Torrado, G. K. Walkup, B. Imperiali, *J. Am. Chem. Soc.* **1998**, *120*, 609–610.
- [6] R. Corradini, A. Dossena, G. Galaverna, R. Marchelli, A. Panagia, G. Sartori, *J. Org. Chem.* **1997**, *62*, 6283–6289.
- [7] P. Ghosh, P. K. Bharadwaj, S. Mandal, S. Ghosh, *J. Am. Chem. Soc.* **1996**, *118*, 1553–1554.
- [8] D. Y. Sasaki, D. R. Shnek, D. W. Pack, F. H. Arnold, *Angew. Chem.* **1995**, *107*, 994–996; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 905–907.
- [9] A different approach to a self-assembling sensor is based on the competition between the target substrate and the dye for the receptor. For a recent example, see A. Metzger, E. V. Anslyn, *Angew. Chem.* **1998**, *110*, 682–684; *Angew. Chem. Int. Ed.* **1998**, *37*, 649–651.
- [10] For a different strategy to self-assembling systems, see J. W. Canary, B. C. Gibb, *Prog. Inorg. Chem.* **1997**, *45*, 1.
- [11] H. Siegel, R. B. Martin, *Chem. Rev.* **1982**, *82*, 385–426.
- [12] The observed quenching is at least partly due to the absorbance of the Fe(NO₃)₃ solution at the wavelength used for the excitation of ANS ($\epsilon \approx 1000 \text{ M}^{-1} \text{ cm}^{-1}$ at 375 nm). Experiments performed in the presence of excess EDTA show that at least 30% of the quenching observed is a result of the absorption of the exciting light.
- [13] M. C. Cleij, P. Scrimin, P. Tecilla, U. Tonellato, *J. Org. Chem.* **1997**, *62*, 5592–5599.

N,N-Diethanolaminomethyl Polystyrene: An Efficient Solid Support to Immobilize Boronic Acids**

Dennis G. Hall,* Jyoti Tailor, and Michel Gravel

Insoluble resins that selectively couple to a functional group are vital in combinatorial chemistry to immobilize substrates to be derivatized by solid-phase synthesis.^[1] They are also employed as scavenger or “fishing out” resins in the solution-phase parallel synthesis of small molecule libraries.^[2] Despite the use of boronic acids as intermediates in reactions such as the Suzuki cross-coupling^[3] and in biological applications including sugar recognition^[4] and inhibition of serine proteases,^[5] there are currently no solid supports available that couple to the boronic acid functionality. Herein we report on the preparation of *N,N*-diethanolaminomethyl polystyrene (DEAM-PS), the first resin capable of immobilizing boronic acids, along with a preliminary assessment of its usefulness toward combinatorial chemistry applications. DEAM-PS resin can immobilize aryl, alkenyl, and alkyl boronic acids almost quantitatively in a wide range of organic solvents. Moreover, it is easily synthesized at low cost and can be recycled.

Diethanolamine boronate adducts have long been employed to stabilize, purify, and characterize boronic acids.^[6] We looked at several ways to derivatize polystyrene resin to include such a diethanolamine anchor. We have best achieved this goal through the reaction of aminomethylated polystyrene (AM-PS) with excess ethylene oxide at 50 °C in a THF/water solvent mixture in a sealed, pressure-resistant tube (Scheme 1). Under these conditions, quaternization to give the triethanolalkylammonium hydroxide salt and oxirane



Scheme 1. Synthesis of DEAM-PS resin **1**. Immobilization and subsequent release of boronic acids **2**. a) Ethylene oxide (excess), THF/H₂O 9/1 (sealed tube), 50 °C, 24 h; b) boronic acid **2** (see Table 1), solvent, RT, 15 min; c) THF/H₂O/AcOH 90/5/5, RT, 1 h; or THF/H₂O 9/1, RT, 2 h.

[*] Prof. D. G. Hall, J. Tailor, M. Gravel
Department of Chemistry, University of Alberta
Edmonton, AB, T6G 2G2 (Canada)
Fax: (+1) 780-492-8231
E-mail: dennis.hall@ualberta.ca

[**] Financial support for this research by the Natural Sciences and Engineering Research Council (NSERC) of Canada and by the University of Alberta is gratefully acknowledged. D.G.H. also acknowledges receipt of a Research Innovation Award from the Research Corporation. M.G. thanks NSERC for a Postgraduate Scholarship.

alcoholysis are known to be minimal.^[7] Indeed, the resulting resin possessed characteristics and a loading level that suggested clean and complete dialkylation of AM-PS to give DEAM-PS (**1**).^[8]

Preliminary experiments showed that resin **1** can couple almost quantitatively to equimolar amounts of arylboronic acids **2** in dry THF after a few minutes (Scheme 1). The formation of a stable resin-bound boronate adduct **3** is highly favored, and as expected,^[6] there is no need to remove the water produced in this operation. The use of glycerol-PS resin^[10] led to less than 50% coupling under the same conditions, clearly underlining the benefit of possible nitrogen coordination with DEAM-PS (**1**).^[11] The boronic ester linkage in **3** can be quickly hydrolyzed with a THF/water/acetic acid (90/5/5) mixture to release the free boronic acids (**2**). In the case of acid-sensitive boronic acids the resin can also be cleaved under neutral conditions with prolonged exposure to THF/water (9/1). Since an excess of water is sufficient to release the boronic acid, albeit slowly, resin **1** is not recommended for the immobilization of boronic acids from aqueous solvent mixtures. A solvent profile study using *p*-tolylboronic acid (**2a**) as a model and a slight excess of resin **1** (1.25 equiv) showed that a broad range of organic solvents is suitable for scavenging applications (Table 1, entries 1–6).

Resin **1** was found to be very efficient in immobilizing a wide variety of electron-rich and electron-poor arylboronic acids in near quantitative yields in THF (entries 6–12).^[12] These values were determined from the amounts of boronic acids recovered after subsequent hydrolytic release from the support. Concentration of the filtrate from exhaustive rinsing of the resin after immobilization revealed none or very little unbound boronic acid. Most interestingly, resin **1** can also couple efficiently with alkenylboronic acids (entry 13) and even with air-sensitive alkylboronic acids, although with a lower yield in this case (entry 14). The boronic acids **2a–i** were all recovered intact after cleavage from the solid support, and DEAM-PS resin **1** can be recycled with no apparent loss of efficiency after neutralization with base washings (for example, CH₂Cl₂/Et₃N 3/1).

The use of scavenger resins to eliminate excess reagents is a promising strategy in the solution-phase synthesis of parallel libraries.^[2] In this regard, DEAM-PS resin **1** could be very useful to scavenge unreacted boronic acids employed in the Suzuki cross-coupling^[3] and other reaction processes. Similarly, it can be utilized to capture boronic acid products from complex reaction mixtures either for purification or to perform solid-phase transformations.^[13] As a significant demonstration of such applications resin **1** was employed in the purification of crude dienyboronic acid **6**.^[14] The latter is produced by treating 2-methyl-1-buten-3-yne (**4**) with dicyclohexylborane followed by oxidative workup (Scheme 2). The purification of alkenylboronic acids such as compound **6** can be considerably troublesome. However, the use of resin **1** to capture **6** and eliminate excess reagents and the cyclohexanol by-products greatly facilitates its purification through simple rinsing of its resin-bound form **5**.

Of particular interest to combinatorial chemistry is the use of resin **1** to immobilize functionalized boronic acid templates and plan different solid-phase transformations. For instance,

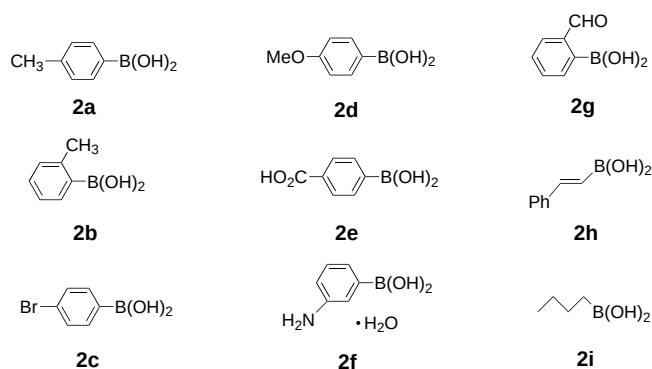
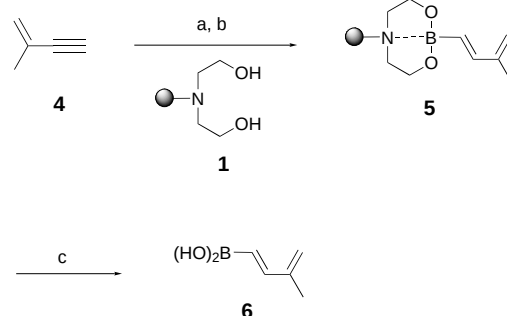


Table 1. Coupling of different boronic acids **2** with DEAM-PS resin **1**.^[a]

Entry	Boronic acid	Solvent	Yield [%] ^[b]	Purity [%] ^[c]
1	2a	CH ₂ Cl ₂	> 95	> 95
2	2a	DMF	87	> 95
3	2a	toluene	> 95	> 95
4	2a	CH ₃ OH	53	> 95
5	2a	Et ₂ O	90	> 95
6	2a	THF	> 95	> 95
7	2b	THF	> 95	> 95
8	2c	THF	> 95	> 95
9	2d	THF	> 95	> 95
10	2e	THF	> 95	> 95
11	2f	THF	> 95	> 90
12	2g	THF	90	> 95
13	2h	THF	91	> 90
14	2i	THF	50	> 90

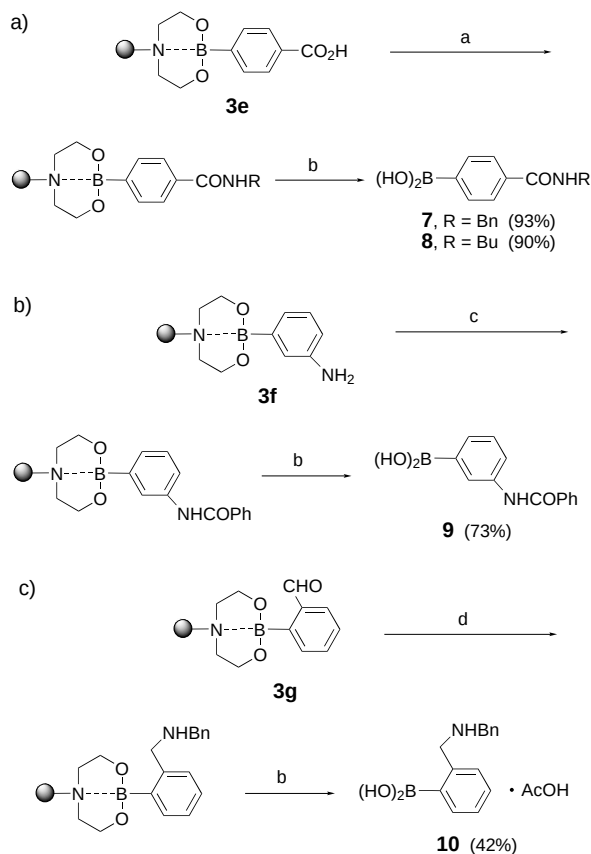
[a] The coupling reactions were conducted by shaking a slight excess of resin **1** (200 mg, 0.92 mmol g⁻¹ substitution) with the boronic acid (0.8 equiv) in the indicated solvent (2 mL) at RT for 15 min in a polypropylene vessel equipped with a fritted filter. [b] Based on the amount of boronic acid recovered after cleavage of the resin for 1 h in a THF/H₂O/AcOH mixture (90/5/5). A slight imprecision must be ascribed to these values as a result of exhaustive drying, which may lead to partial dehydration to give boronic acid anhydrides. [c] Estimated through comparison of the ¹H NMR spectra of the recovered boronic acids and the starting material.



Scheme 2. Purification of dienyboronic acid **6** with resin **1** following dicyclohexylboration/oxidation of **4**. a) Addition of **4** to (C₆H₁₁)₂BH (1.0 equiv) in THF, 0 °C, 0.5 h; RT, 0.5 h; then (CH₃)₃NO · 2H₂O (2.0 equiv), 0 °C to RT, 12 h; b) DEAM-PS resin **1** (0.5 equiv), CH₂Cl₂, 1.5 h; c) THF/H₂O 9/1, RT, 1.5 h, 95% (overall yield based on **1**).

this would allow the elaboration of diverse libraries of new arylboronic acids with potential use as inhibitors of serine proteases.^[15] In addition, whereas boronic acids are important building blocks for solid-phase Suzuki reactions in combina-

torial chemistry,^[16] few are commercially available. The *N,N*-diethylaminomethyl-PS boronate linkage (**3**, Scheme 1) was found to be resistant to standard carbodiimide methods for amide bond formation. Benzylamine and butylamine were coupled with high efficiency to resin-bound *p*-carboxyphenylboronic acid (**3e**), to afford the corresponding amides **7** and **8** in high yields after cleavage (Scheme 3a).^[17] Similarly, resin-



Scheme 3. Immobilization and solid-phase transformations of resin-bound arylboronic acids **3e–g**. Synthesis of new boronic acid derivatives **7–10**. a) RNH_2 (2.5 equiv), *N*-hydroxybenzotriazole $\cdot$ H_2O (2.5 equiv), *N,N*-diisopropylcarbodiimide (2.5 equiv), DMF, RT, 6 h; b) THF/ H_2O /AcOH 90/5/5, RT, 1 h; c) PhCOCl (10 equiv), iPr_2EtN (11 equiv), THF, RT, 24 h; d) PhCH₂NH₂ (2.0 equiv), NaBH(OAc)₃ (2 equiv), $(ClCH_2)_2$, RT, 2 h.

bound *m*-aminophenylboronic acid (**3f**) was transformed into anilide **9** upon treatment with benzoyl chloride (Scheme 3b) and reductive amination of **3g** with benzylamine afforded **10** (Scheme 3c).^[17] Further work on applications of DEAM-PS resin is currently in progress.

Experimental Section

Preparation of DEAM-PS resin **1**: 1% DVB (DVB = divinylbenzene) cross-linked aminomethylated polystyrene (3.0 g, 1.00 mmol g⁻¹ substitution) was weighed out in a large thick-walled pressure tube equipped with a stirring bar. A THF/water solvent mixture (9/1, 25 mL) was added, followed by excess ethylene oxide (ca. 2 mL). The tube was quickly closed through its teflon screw cap equipped with a seal and immersed into an oil bath at 50–55 °C. The tube was hand shaken periodically when magnetic stirring became inefficient. After 24 h the tube was allowed to cool to RT and uncapped. The tube contents were passed through a medium-porosity fritted glass filter and the resin was rinsed with THF (5 $\times$), CH₂Cl₂/Et₃N (3/

1, 3 $\times$), then CH₂Cl₂ (5 $\times$), and dried under high vacuum for a few days (the resin was pulverized to powder after a few hours of drying), to afford 3.35 g of a white colored resin (theoretical: 3.26 g, 0.92 mmol g⁻¹).

Immobilization of **3e**, followed by amide coupling with butylamine and cleavage to give **8**: A slight excess of *p*-carboxyphenylboronic acid (**2e**) (45 mg, 0.27 mmol) was added to a polypropylene filter vessel containing a suspension of resin **1** (200 mg, 0.18 mmol) in dry THF (2 mL). The vessel was shaken for 2 h after which the resin was rinsed with dry THF (5 $\times$) and dry DMF (2 $\times$). Unbound boronic acid (13 mg) was recovered from the first three THF rinses, which corresponds almost exactly to the theoretical unbound excess. Dry DMF (2 mL) was then added to resin **3e** and a solution of *N*-hydroxybenzotriazole (70 mg, 0.46 mmol) and butylamine (50 μ L, 0.46 mmol) in DMF (1 mL) was added to the suspension. The latter was homogenized by gentle vortexing followed by the addition of diisopropylcarbodiimide (72 μ L, 0.46 mmol). The vessel was shaken for 5 h then rinsed with dry DMF (3 $\times$) and dry THF (5 $\times$). The resulting resin was treated with a THF/water/acetic acid mixture (90/5/5, 2 mL) for 1 h. The liquid phase was drained and the resin rinsed with the above cleavage mixture (1 $\times$) and THF (3 $\times$). The combined filtrates were concentrated and dried under high vacuum (>12 h) to afford arylboronic acid **8** as a white powder (41 mg, 90%). ¹H NMR (300 MHz, 5% D₂O in CD₃OD, 25 °C): δ = 7.7–8.0 (m, 4H; Ar), 3.37 (t, ³J(H,H) = 7 Hz, 2H; NCH₂), 1.59 (m, 2H; CH₂CH₂CH₃), 1.40 (m, 2H; CH₂CH₂), 0.96 (t, ³J(H,H) = 7 Hz, 3H; CH₃); ¹³C NMR (75 MHz, 5% D₂O in CD₃OD, 25 °C): δ = 170.4 (CONH), 134.9, 134.8, 129.6, 127.1 (4s, Ar), 40.7 (NCH₂), 32.6 (CH₂CH₂CH₃), 21.1 (CH₂CH₂), 14.1 (CH₃); MS (positive ES): *m/z* (%): 244 (45) [*M*⁺+Na], 222 (100) [*M*⁺]; HR-MS (positive ES): *m/z*: calcd for C₁₁H₁₇NO₃B [*M*⁺]: 222.1303; found: 222.1301.

Received: April 29, 1999 [Z13344IE]

German version: *Angew. Chem.* **1999**, *111*, 3250–3253

Keywords: boronic acid • immobilization • solid-phase synthesis

- [1] R. J. Booth, J. C. Hodges, *Acc. Chem. Res.* **1999**, *32*, 18–26.
- [2] B. J. Backes, J. A. Ellman, *Curr. Opin. Chem. Biol.* **1997**, *1*, 86–93.
- [3] A. Suzuki, *Pure Appl. Chem.* **1991**, *63*, 419–422.
- [4] T. D. James, S. Sandanayake, S. Shinkai, *Angew. Chem.* **1996**, *108*, 2038–2050; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1910–1922.
- [5] For a recent example, see V. Martichonok, J. B. Jones, *J. Am. Chem. Soc.* **1996**, *118*, 950–958.
- [6] For an example, see P. B. Tripathy, D. S. Matteson, *Synthesis* **1990**, 200–206.
- [7] P. K. Sundaram, M. M. Sharma, *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3141–3147.
- [8] The resulting resin gave a negative outcome with Kaiser's ninhydrin assay,^[9] which indicated the absence of any primary and secondary amines originating from incomplete alkylation. The presence of a basic tertiary amine site, however, was shown through a positive reaction with bromophenol blue. The absence of over-alkylation to give a triethanolalkylammonium hydroxide resin was indirectly confirmed by exhaustive acylation with FmocGlyOH (1-hydroxy-1*H*-benzotriazole, diisopropylcarbodiimide, 4-dimethylaminopyridine; DMF, RT, 6 h) followed by UV spectroscopic quantitation of the resulting fulvene–piperidine adduct (Fmoc = fluorenylmethoxycarbonyl). The loading level obtained therein was in agreement with the formation of two ethanolamine arms per aminomethyl site according to the initial loading of commercial AM-PS. However, a slightly high O/N ratio from combustion analysis of the resin (theoretical = 2.3, experimental = 2.6) may indicate the presence of residual water, or of a few hydroxyethoxyethyl arms formed by ethylene oxide solvolysis. These inhomogeneities do not seem to affect the resin's efficiency.
- [9] E. Kaiser, R. L. Colescott, C. D. Bossinger, P. I. Cook, *Anal. Biochem.* **1970**, *34*, 595–598.
- [10] Purchased from Advanced Chemtech, Inc.
- [11] Another control experiment ruled out the possibility that a tertiary amine site alone (through formation of a tight acid-base complex)

- could be sufficient. Diisopropylaminomethyl polystyrene (Argonaut Technologies) failed to couple with **2a** under the usual conditions.
- [12] All boronic acids used in Table 1 were obtained from commercial sources (Lancaster or Aldrich) except **2h**, which was synthesized according to: H. C. Brown, S. K. Gupta, *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371.
- [13] For an example of the resin capture of diboronic acids using a Suzuki coupling, see S. D. Brown, R. W. Armstrong, *J. Am. Chem. Soc.* **1996**, *118*, 6331–6332.
- [14] M. Vaultier, F. Truchet, B. Carboni, R. W. Hoffmann, I. Denne, *Tetrahedron Lett.* **1987**, *28*, 4169–4172.
- [15] For example, benzenboronic acid is an effective competitive inhibitor of α -chymotrypsin and subtilisin: M. Philipp, M. L. Bender, *Proc. Natl. Acad. Sci. USA* **1971**, *68*, 478–480.
- [16] For example, see S. Wendeborn, S. Berteina, W. K.-D. Brill, A. De Mesmaeker, *Synlett* **1998**, 671–675.
- [17] Nonoptimized yields of crude isolated compounds of satisfying purity, all characterized by NMR spectroscopy and mass spectrometry.

Electrochemical Synthesis of $\text{Ba}_2\text{Ag}_8\text{S}_7$, a Quasi-One-Dimensional Barium Silver(I) Sulfide Containing Mixed $\text{S}^{2-}/\text{S}_2^{2-}$ Ligands**

He Li and Shiou-Jyh Hwu*

There has been renewed interest in the synthesis of solid-state inorganic materials by means of chemical electrolysis.^[1, 2] The versatility of the electrochemical technique for exploratory synthesis has been demonstrated by a number of recent reports in materials synthesis.^[2] Compared to conventional thermal methods, electrochemical synthesis allows greater control over the electronic state of extended solids and possibly structural frameworks as well as product stoichiometry. We have enjoyed numerous successes in the electrochemical crystal growth of copper(I) sulfides in nonaqueous solvents.^[3] Systematic studies on the electrochemically grown series of compounds $\text{KCu}_{7-x}\text{S}_4$, for example, have revealed some unusual stoichiometry-dependent transport anomalies.^[2a, 3] In light of the fascinating physical properties, we have expanded our search of new coinage metal chalcogenides to include silver. We report here a novel barium silver(I) sulfide obtained in our recent exploratory synthesis of alkaline earth silver(I) sulfides. The $\text{Ba}_2\text{Ag}_8\text{S}_7$ structure is quasi-one-dimensional and contains mixed S^{2-} and S_2^{2-} ligands. This discovery provides new insights with respect to possible electrochemical routes for the rational synthesis of inorganic solids.

[*] Prof. S.-J. Hwu, H. Li
Department of Chemistry
Clemson University
Clemson, SC 29634-0973 (USA)
Fax: (+1) 864-656-6613
E-mail: shwu@clemson.edu

[**] Financial support from the Donors of The Petroleum Research Fund, administered by the American Chemical Society, and from, in part, the National Science Foundation (DMR-9612148) is gratefully acknowledged.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

Prior to this study, all the reported $\text{A}/\text{Ag}^{\text{I}}/\text{S}$ compounds (A^+ = alkali metal cation, TI^+ , NH_4^+) contained monovalent electropositive cations. A dozen sulfides based on the general formula $m\text{A}_2\text{S} \cdot n\text{Ag}_2\text{S}$ have been reported thus far. For silver-rich phases ($m = 1$; $\text{A}_2\text{S} \cdot n\text{Ag}_2\text{S}$), there exist TIAgS ($n = 1$),^[4] $\text{A}_2\text{Ag}_4\text{S}_3$ ($\text{A} = \text{K}, \text{Rb}$; $n = 2$),^[5] AAg_3S_2 ($\text{A} = \text{Rb}, \text{Cs}, \text{TI}$; $n = 3$),^[6] $\text{A}_2\text{Ag}_6\text{S}_4$ ($\text{A} = \text{Na}, \text{K}$; $n = 3$),^[7] AAg_5S_3 ($\text{A} = \text{K}, \text{Rb}$; $n = 5$),^[8] and CsAg_7S_4 ($n = 7$).^[8] For $m = 3$, the only known phase is Na_3AgS_2 ($\equiv 3\text{Na}_2\text{S} \cdot \text{Ag}_2\text{S}$).^[9] In addition, $\text{TI}\text{Ag}_{5.4}\text{S}_{3.5}$,^[10] a nonstoichiometric compound whose structure has not yet been reported, is known. The compounds listed above were synthesized by high-temperature and/or high-pressure techniques, whereby no compound containing polysulfide has yet been isolated. The silver-based polysulfides known, thus far, are $[\text{Ag}_2\text{S}_{20}]^{4-}$, $[\text{Ag}(\text{S}_9)]^{1-}$, and $[\text{Ag}(\text{S}_5)]^{-}$.^[11] The title compound, $\text{Ba}_2\text{Ag}_8\text{S}_7$, was prepared by electrolysis, a method in favor of selective synthesis of low-dimensional conducting solids.^[2a] It is the first ternary alkaline earth metal silver sulfide known.

Single crystals of $\text{Ba}_2\text{Ag}_8\text{S}_7$ were grown from a BaS_3 /ethylenediamine solution in a simple two-electrode chemical cell. The crystal structure was determined by single-crystal X-ray diffraction methods.^[12] The UV/Vis diffuse reflectance spectrum of $\text{Ba}_2\text{Ag}_8\text{S}_7$ was taken in the range of 200 nm (6.2 eV) to 2500 nm (0.50 eV).^[13]

The crystal structural analysis of $\text{Ba}_2\text{Ag}_8\text{S}_7$ reveals an interesting “stingray” pattern. Figure 1 shows a projected view of the structure where the extended Ag–S framework

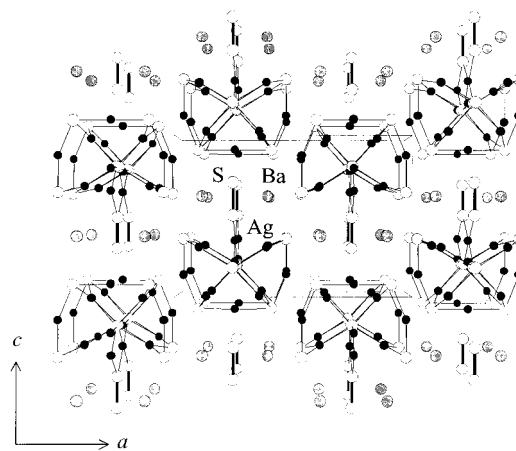


Figure 1. A projected view onto the ac plane of the $\text{Ba}_2\text{Ag}_8\text{S}_7$ structure revealing a stingray pattern; see text for details.

exhibits arrays of alternating stingray units. The structure propagates along the $[100]$ direction with respect to the 2_1 screw axis. The parallel arrays of stingray units are stacked head-to-tail in the $[001]$ direction to create voids where the barium atoms reside.

$\text{Ba}_2\text{Ag}_8\text{S}_7$ adopts a pseudo-one-dimensional structure with respect to the $\infty[\text{Ag}_8\text{S}_7]$ columns. The projected view of the column resembles the shape of the aforementioned stingray. Figure 2 presents a tilted view showing the coordination environments of the silver atoms. Each column is made of fused $[\text{Ag}_8\text{S}_5]$ units, each of which is weakly linked to one end of an $[\text{S}_2]$ unit. The $[\text{Ag}_8\text{S}_5]$ unit structure consists of a stacked

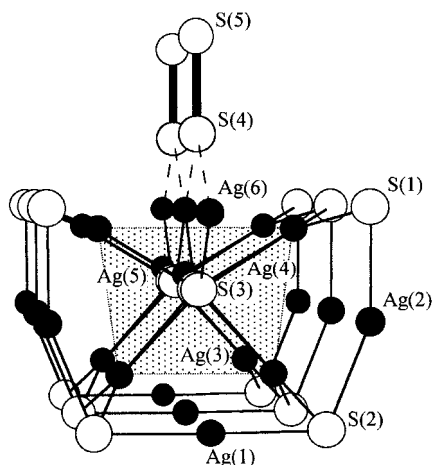


Figure 2. View of the partial structure of a $[\text{Ag}_8\text{S}_7]$ column consisting of two fused $[\text{Ag}_8\text{S}_5]$ units; see text for details. A tilted view is shown to discern the coordination environments of the silver atoms. The dashed lines represent the weak linkages between the disulfide units and the "body" of the column. The shaded frame outlines the Ag_4 core. Selected bond distances [Å]: Ag(1)–S(2) 2.450(3) ($\times 2$), Ag(2)–S(1) 2.446(3), Ag(2)–S(2) 2.498(3), Ag(3)–S(2) 2.551(2) ($\times 2$), Ag(3)–S(3) 2.567(5) ($\times 2$), Ag(4)–S(3) 2.568(4), Ag(4)–S(3) 2.569(4), Ag(4)–S(1) 2.577(2) ($\times 2$), Ag(5)–S(3) 2.581(8) ($\times 2$), Ag(6)–S(3) 2.520(9) ($\times 2$), Ag(6)–S(4) 2.804(5) ($\times 2$), S(4)–S(5) 2.146(6).

C-shaped Ag_3S_4 unit ($\equiv \text{Ag}(1)_{2/2}\text{Ag}(2)_{4/2}\text{S}(1)_{4/2}\text{S}(2)_{4/2}$), a distorted square-planar Ag_4 core ($\equiv \text{Ag}(3)_{2/1}\text{Ag}(4)_{2/1}$, indicated by the shaded frame) centered by an $\text{S-Ag}_x\text{-S}$ unit ($\equiv \text{Ag}(5)_x\text{S}(3)_{2/2}$), and additional $\text{Ag}(6)_{1-x}$. The Ag(5) and Ag(6) sites are partially occupied ($x = 0.576(7)$).^[14] The latter is 0.11 Å above the center of the edge across two tips ($2 \times \text{S}(1)$) of the Ag_3S_4 unit. The planar Ag_4 core is made of two crystallographically independent silver atoms (Ag(3) and Ag(4)).^[12] The silver atoms adopt three different coordination environments with respect to sulfur atoms: approximately linear coordination for Ag(1), Ag(2), and Ag(5) ($\angle(\text{S-Ag-S}) = 178.4(2)$, $158.5(1)$, and $168.8(4)^\circ$, respectively), slightly distorted trigonal planar coordination for Ag(3) and Ag(4) ($\Sigma(\angle(\text{S-Ag-S})) = 359.6$ and 358.9° , respectively), and distorted square planar coordination for Ag(6) ($\Sigma(\angle(\text{S-Ag-S})) = 360.1^\circ$).

The $[\text{Ag}_8\text{S}_5]$ sulfide unit possesses a reasonably strong covalent framework, judging from the observed Ag–S bond distances (2.45–2.58 Å). All the Ag–S bond distances are comparable to either 2.43 Å, observed in Ag_2S ,^[15] or 2.51 Å, the sum of Shannon crystal radii for Ag^+ (0.81 Å for coordination number 2) and S^{2-} (1.70 Å),^[16] with the exception of the long bond between Ag(6) of the $[\text{Ag}_8\text{S}_5]$ unit and one atom of the S_2^{2-} anion (2.80 Å).

The $[\text{Ag}_8\text{S}_5]$ framework may also possess some bonding interactions between silver(I) cations. It is known that $d^{10}\text{--}d^{10}$ interactions exist.^[17] Although the Ag–Ag distances are somewhat long (3.26–3.40 Å for the Ag_4 unit and 2.98–3.19 Å between the Ag_4 unit and the Ag_3S_4 unit) compared to that in Ag metal (2.883 Å), there exist possibly weak Ag–Ag interactions.

The coexistence of S^{2-} and S_2^{2-} ligands suggests a possible reductive decomposition reaction with respect to BaS_3 . Figure 2 shows that the disulfide unit, consisting of atoms

S(4) and S(5), sits vertically above two adjacent C-shaped units. The observed S–S bond distance is 2.146(6) Å, which is comparable to 2.126(9) Å of barium disulfide, BaS_2 .^[18] This homonuclear dianion behaves as a ligand to the $[\text{Ag}_8\text{S}_5]$ unit. We speculate that a partial reduction [Eq. (1)] takes place in the BaS_3 /ethylenediamine solution. Preliminary studies employing a higher voltage (3 V) result in a pure sulfide phase, $\text{Ba}_2\text{Ag}_{10}\text{S}_7$.^[19] Detailed studies with respect to controlled reduction are underway.



The intercolumn interaction in $\text{Ba}_2\text{Ag}_8\text{S}_7$ is primarily characterized by the Ba–S bonds, and the Ba^{2+} cation coordinates to a total of eight sulfur atoms in a bicapped trigonal prism. The Ba–S bond distances range from 3.15 to 3.35 Å, which are comparable to 3.26 Å, the sum of the Shannon crystal radii of Ba^{2+} (1.56 Å for coordination number 8) and S^{2-} (1.70 Å).^[16] Judging from the long intercolumn Ag–S distance (3.184(4) Å), this interaction is too weak to hold the framework together.

The optical spectra reveal that $\text{Ba}_2\text{Ag}_8\text{S}_7$ is an indirect band-gap semiconductor^[13a] exhibiting a steep absorption edge. Figure 3 shows the UV/Vis spectrum; the optical band gap

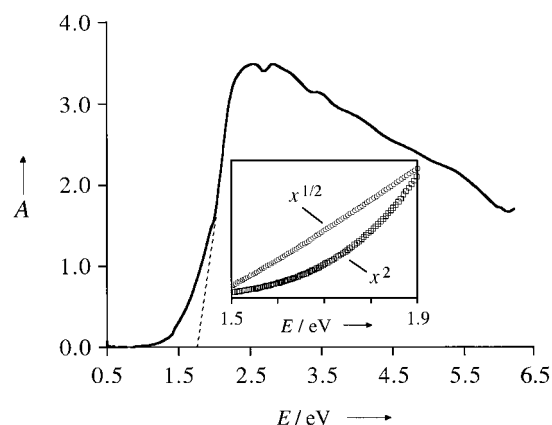


Figure 3. UV/Vis spectrum of $\text{Ba}_2\text{Ag}_8\text{S}_7$. Inset: the analyses based on functions $f(R)^{1/2}$ and $f(R)^2$.

obtained by extrapolation of a linear portion of the band edge is about 1.80 eV. Further fitting of the data with $f(R)^{1/2}$ and $f(R)^2$ functions confirm that $\text{Ba}_2\text{Ag}_8\text{S}_7$ is an indirect band-gap semiconductor, as the former gives a linear correlation with energy (see inset of Figure 3). In any event, the observed band gap is consistent with the red-orange color of the compound as well as the experimental observation of the existence of disulfide units. These results lead to an electron-precise formulation, $(\text{Ba}^{2+})_2(\text{Ag}^+)_8(\text{S}^{2-})_5(\text{S}_2^{2-})$.

In summary, by employing electrochemical methods, crystals of a novel quasi-one-dimensional barium silver(I) sulfide, $\text{Ba}_2\text{Ag}_8\text{S}_7$, have been grown. Upon applying a higher voltage, a new sulfide phase $\text{Ba}_2\text{Ag}_{10}\text{S}_7$ was synthesized. These preliminary results further illustrate the utility of the electrochemical method for controlled synthesis of reduced polychalcogenide phases. The extended framework exhibits an interesting stingray pattern, and the disulfide unit behaves as a ligand

that governs the packing of the $^1[\text{Ag}_8\text{S}_5]$ chain. Systematic studies of such materials allow for the possibility of exploiting the redox chemistry of solids containing polychalcogenide Q_x^{2-} ligands at the atomic level (e.g., reduction of S–S bonds).

Experimental Section

BaS₃: A typical batch of BaS₃ was prepared by mixing barium (5.0 g, 36.4 mmol; 99.9%, Strem) and sulfur (3.56 g, 109.2 mmol; 99.99%, Aldrich) in liquid ammonia. The solvated form of barium is $\text{Ba}^{2+}(2\text{e}^-)(\text{NH}_3)_6^{[19]}$ and gives rise to a dark blue solution. The solution was stirred with a magnetic stirrer and allowed to warm to room temperature over 24 h. A steady flow of dry nitrogen gas was maintained throughout the reaction. The product was obtained as a yellow precipitate, and the powder X-ray diffraction analysis showed that it was amorphous. Heating the amorphous product in a fused silica ampoule at 550 °C under vacuum resulted in mixed crystalline polysulfides—that is, BaS₂ (ca. 70 %) and BaS₃ (ca. 30 %)—according to powder X-ray diffraction.

Ba₂Ag₈S₇: Crystals of Ba₂Ag₈S₇ were grown in a two-electrode chemical cell. In a typical reaction BaS₃ (0.50 g, used as prepared) was loaded into a 100-mL round-bottom flask in a nitrogen-purged dry box. A rubber septum was used to cap the flask to protect the system from air, and a steady flow of dry nitrogen was maintained throughout the course of the reaction. Ethylenediamine (50 mL; 99 %, Aldrich, distilled over CaH₂) was injected into the reaction flask. The resulting solution was preheated in a sand bath to 110 °C for 2 h to ensure that all of the electrolytes were dissolved. The reaction temperature was maintained at 110 °C during the course of study. Two parallel electrode plates (1.0 × 1.5 cm²) made from silver foil (0.28 mm thick; 99.9 %, Alfa/Aesar) were then immersed in the solution and connected to a constant voltage source. The applied voltage was 1.0 V. The temperature of the electrochemical cell was controlled by a Gemini-2 Temperature Controller (J-KEM Scientific). Crystals of diffraction quality were grown on the anode in about 3 d. The products were dried on a Schlenk line. Two new phases, Ba₂Ag₈S₇ (red-orange columns, 95 %) and Ba₂Ag₁₀S₇ (black thin needles, 5 %),^[20] were identified by single-crystal X-ray diffraction methods.

Received: February 2, 1999 [Z 12985 IE]

German version: *Angew. Chem.* **1999**, *111*, 3253–3256

Keywords: barium • electrochemistry • polychalcogenides • silver • solid-state structures • sulfur

- [1] Examples of molten salt electrolysis (MSE) for single-crystal growth of bronzes: a) H. R. Shanks, *J. Cryst. Growth* **1972**, *13/14*, 433–437, and references therein; of LaB₆; b) I. V. Zubek, R. S. Feigelson, R. A. Huggins, P. A. Pettit, *J. Cryst. Growth* **1976**, *34*, 85–91.
- [2] a) H. Li, R. Mackay, S.-J. Hwu, Y.-K. Kuo, M. J. Skove, Y. Yokota, T. Ohtani, *Chem. Mater.* **1998**, *10*, 3172–3183; b) W. H. McCarroll, K. V. Ramanujachary, M. Greenblatt, F. Cosandey, *J. Solid State Chem.* **1998**, *136*, 322–327; c) A. Nemudry, M. Weiss, I. Gainutdinov, V. Boldyrev, R. Schöllhorn, *Chem. Mater.* **1998**, *10*, 2403–2411; d) X. Wang, L. Liu, R. Bontchev, A. Jacobson, *Chem. Commun.* **1998**, 1009–1010; e) C. J. Warren, R. C. Haushalter, A. B. Bocarsly, *J. Alloys Compd.* **1995**, *229*, 175–205; f) L. Z. Zhao, *Solid State Commun.* **1995**, *94*, 857–859; g) G. L. Roberts, S. M. Kauzlarich, R. S. Glass, J. C. Estill, *Chem. Mater.* **1993**, *5*, 1645–1650; h) T. N. Nguyen, D. M. Giaquinta, W. M. Davis, H. C. zur Loye, *Chem. Mater.* **1993**, *5*, 1273–1276; i) V. C. Korthius, R. D. Hoffman, A. W. Sleight, *Mater. Res. Bull.* **1992**, *27*, 1379–1384; j) M. L. Norton, H. Y. Tang, *Chem. Mater.* **1991**, *3*, 431–434; k) M. D. Ward in *Electroanalytical Chemistry, A Series of Advances* (Ed.: A. J. Bard), Marcel Dekker, New York, **1989**, pp. 181–312, and references therein.
- [3] a) S.-J. Hwu, H. Li, R. Mackay, Y.-K. Kuo, M. J. Skove, M. Mahapatro, C. K. Bucher, J. P. Halladay, M. W. Hayes, *Chem. Mater.* **1998**, *10*, 6–9; b) Y.-K. Kuo, M. J. Skove, D. T. Verebelyi, H. Li, R. Mackay, S.-J. Hwu, M.-H. Whangbo, J. W. Brill, *Phys. Rev. B* **1998**, *57*, 3315–3325; c) K.-S. Lee, D.-K. Seo, M.-H. Whangbo, H. Li, R. Mackay, S.-J. Hwu, *J. Solid State Chem.* **1997**, *134*, 5–9.
- [4] a) J. C. Tedennac, B. Gardes, G. Burn, E. Philippot, M. Maurin, *J. Solid State Chem.* **1980**, *33*, 429–433; b) K. Klepp, *Monatsh. Chem.* **1980**, *111*, 1433–1436.
- [5] W. Bronger, C. Burschka, *Z. Anorg. Allg. Chem.* **1976**, *425*, 109–116.
- [6] a) C. Burschka, W. Bronger, *Z. Anorg. Allg. Chem.* **1977**, *430*, 61–65; b) K. O. Klepp, *J. Less-Common Met.* **1985**, *107*, 139–146.
- [7] P. T. Wood, W. T. Pennington, J. W. Kolis, *J. Chem. Soc. Chem. Commun.* **1993**, 235–236.
- [8] a) M. Emirdag, G. L. Schimek, J. W. Kolis, *Acta Crystallogr. Sect. C* **1998**, *54*, 1376–1378; b) P. T. Wood, W. T. Pennington, J. W. Kolis, *Inorg. Chem.* **1994**, *33*, 1556–1558; c) J. Huster, *J. Alloys Compd.* **1992**, *183*, 377–384.
- [9] K. O. Klepp, W. Bronger, *J. Less-Common Met.* **1985**, *106*, 91–101.
- [10] K. O. Klepp, *Z. Kristallogr.* **1983**, *162*, 136.
- [11] a) A. Mueller, M. Roemer, H. Boegge, E. Krickemeyer, F. W. Baumann, K. Schmitz, *Inorg. Chim. Acta* **1984**, *89*(1), L7–L8; b) A. Mueller, J. Schimanski, M. Roemer, H. Boegge, F. W. Baumann, W. Eltzner, E. Krickemeyer, U. Billerbeck, *Chimia* **1985**, *39*(1), 25–27; c) R. M. Herath Banda, D. C. Craig, I. G. Dance, M. L. Scudder, *Polyhedron* **1989**, *8*, 2379–2383.
- [12] a) Crystal data of Ba₂Ag₈S₇: red-orange column crystal (0.05 × 0.05 × 0.3 mm³), *M_r* = 1363.8, orthorhombic, space group *Pmmn* (no. 59), *a* = 15.643(3), *b* = 4.407(2), *c* = 10.869(2) Å, *V* = 749.3(4) Å³, *Z* = 2, $\rho_{\text{calcd}} = 6.044 \text{ g cm}^{-3}$, $\mu = 163.29 \text{ cm}^{-1}$. Data collection: Nicolet R3mV diffractometer, ω mode, MoK α radiation ($\lambda = 0.71073 \text{ Å}$), *T* = 295 K. Of 1014 unique reflections measured, 851 (*F* > 6 σ (*F*)) were used for the calculation. Lorentz-polarization and empirical absorption corrections based on three azimuthal scans ($2\theta = 14.43^\circ, 19.31^\circ, 23.93^\circ$) were applied to the intensity data (transmission factors: 0.5892–0.7068). The TEXSAN software package^[12c,d] was used for crystal structure solution and refinement. The atomic coordinates of fully occupied atoms were determined using the SHELXS-86 program.^[12e] Those of disordered S and partially occupied Ag atoms were resolved using a difference Fourier map with the SHELXS-93 program.^[12f] Final *R* = 0.034, *R_w* = 0.055, GOF = 1.44 for 65 parameters; min./max. residual electron density –4.69/ +3.65 e Å^{–3}; b) Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de) on quoting the depository number CSD-410642; c) TEXSAN: Single Crystal Structure Analysis Software, Version 1.6b, Molecular Structure Corp., The Woodlands, TX, **1993**; d) “Scattering Factors for Non-hydrogen Atoms”: D. T. Cromer, J. T. Waber, *International Tables for X-ray Crystallography, Vol. IV*, Kynoch, Birmingham, UK, **1974**, Table 22A, pp. 71–98; e) G. M. Sheldrick in *Crystallographic Computing 3* (Eds.: G. M. Sheldrick, C. Krüger, R. Goddard), Oxford University Press, London, **1985**, pp. 175–189; f) G. M. Sheldrick, SHELXS-93, Göttingen, Germany, **1993**.
- [13] Optical absorption spectra were obtained from a PC-controlled SHIMADZU UV-3100 UV/vis/near-IR spectrometer equipped with an integrating sphere (standard equipment for diffuse reflectance). BaSO₄ was used as a reflectance standard. Data were collected in the reflectance mode (*R* [%]) and manually converted into arbitrary absorption units (*a/s*) (*a*: absorption coefficient, *s*: scattering coefficient) with Equation (2): a) J. I. Pankove, *Optical Processes in Semiconductors*, Dover Publications, New York, **1971**, pp. 34–42; b) P. Kubelka, F. Z. Munk, *Tech. Phys. USSR* **1931**, *12*, 593; c) P. Kubelka, *J. Opt. Soc. Am.* **1948**, *38*, 448–457.

$$A = f(R) = a/s = (1 - R)^2/2R \quad (2)$$

- [14] The atoms Ag(5) and Ag(6) were first refined independently to result in values of 0.58(1) and 0.431(9), respectively, which are summed together nearly to one. These two atoms were then refined with a constrained total occupancy of one to give the value of *x* denoted in the formula (0.576(7)).
- [15] R. J. Cava, F. Reidinger, B. J. Wuensch, *J. Solid State Chem.* **1980**, *31*, 69–80.
- [16] R. D. Shannon, *Acta Crystallogr. Sect. A* **1976**, *32*, 751–767.

- [17] M. Jansen, *Angew. Chem.* **1987**, *99*, 1136–1148; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1098–1110.
 [18] a) H. G. von Schnering, N.-K. Goh, *Naturwissenschaften* **1974**, *61*, 272; b) I. Kawada, K. Kato, S. Yamaoka, *Acta Crystallogr. Sect. B* **1975**, *31*, 2905–2906.
 [19] a) W. E. Ferneliuss, G. W. Watt, *Chem. Rev.* **1937**, *20*, 195–258; b) Mentrel, *Bull. Soc. Chim.* **1903**, *29*, 493–503; c) S. Yamaoka, J. T. Lemley, J. M. Jenks, H. Steinfink, *Inorg. Chem.* **1975**, *14*, 129–131.
 [20] Crystal data of $\text{Ba}_2\text{Ag}_{10}\text{S}_7$: black needle crystal, monoclinic, space group $C2/m$ (no. 12), $a = 14.460(3)$, $b = 4.295(2)$, $c = 13.467(3)$ Å, $\beta = 103.88(3)^\circ$, $V = 812.1(5)$ Å³, $Z = 2$.

NMR Spectroscopic Structural Determination of Organozinc Reagents: Evidence for “Highly Coordinated” Zincates**

T. Andrew Mobley and Stefan Berger*

In an interesting series of papers from the laboratories of Uchiyama and Sakamoto,^[1] differences in the reactivity between stoichiometrically formulated $[\text{Me}_3\text{Zn}]\text{Li}$ and $[\text{Me}_4\text{Zn}]\text{Li}_2$ led the authors to postulate the existence of a tetracoordinated zinc complex in solution. ^1H NMR studies indicate that only one type of methyl resonance exists in these species, even at very low temperatures. However, as noted by the authors the NMR spectra observed could be the result of a rapid equilibrium of different complexes. Based upon our recent success in using fully ^{13}C -labeled material to identify the number of methyl groups bound to the central copper atom in analogous cuprate complexes,^[2] we undertook a structural investigation of the above mentioned organozincates.

The use of fully ^{13}C -labeled material results, in the absence of ^1H -decoupling irradiation, in magnetic inequivalence of chemically equivalent carbon atoms. This result is a consequence of the difference in the C_H coupling between a carbon atom and those protons directly attached and those protons attached to another ^{13}C -labeled methyl group in the same molecule. Since the magnetic inequivalence of the carbon atoms allows the observation of the carbon–carbon coupling constant over two bonds, analysis of the spectra provides an easy method of counting the number of labeled methyl groups attached to the metal center.

As a base compound, the neutral $(^{13}\text{CH}_3)_2\text{Zn}$ species (**1**) was synthesized by heating $^{13}\text{CH}_3\text{I}$ and Zn powder in the presence of a small amount of Cu catalyst in a sealed glass system.^[3]

Vacuum transfer of the volatile material from the solid residue to a liquid-nitrogen cooled flask resulted in the isolation of **1** contaminated by a small amount of $^{13}\text{CH}_3\text{I}$ starting material. A small amount of **1** was dissolved in $[\text{D}_8]\text{THF}$ or $[\text{D}_{14}]\text{hexane}$ and the ^1H and ^1H -coupled ^{13}C NMR spectra were obtained at 400 and 600 MHz, respectively. Expansions of the methyl regions of the ^{13}C NMR spectra are shown for **1** in hexane and **1** in $[\text{D}_8]\text{THF}$ (Figure 1a and 1b, respectively). For compar-

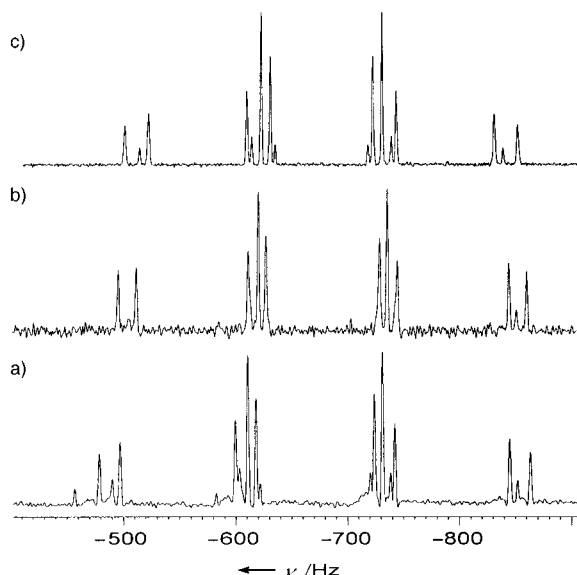


Figure 1. ^1H coupled ^{13}C NMR spectra at -80°C : a) **1** (0.08 M) in hexane; b) **1** (0.35 M) in $[\text{D}_8]\text{THF}$; c) **2** (0.26 M) in $[\text{D}_8]\text{THF}$.

ison the spectrum of the analogous compound $[(^{13}\text{CH}_3)_2\text{Cu}]\text{Li}$ (**2**) in $[\text{D}_8]\text{THF}$ is also shown (Figure 1c). All three spectra show a similar coupling pattern with only slight changes in the coupling constants. The spectra were modeled on the basis of the higher-order coupling pattern of an $\text{A}_3\text{XX}'\text{A}_3'$ system and the calculated coupling constants are summarized in Table 1. Dimethylzinc synthesized by treatment of ZnI_2 with two equivalents of $^{13}\text{CH}_3\text{Li}$ resulted in identical spectra when the concentration of the zinc species was low.

The species $[(^{13}\text{CH}_3)_3\text{Zn}]\text{Li}$ (**3**) could be synthesized by treatment of $(^{13}\text{CH}_3)_2\text{Zn}$ with one equivalent of $^{13}\text{CH}_3\text{Li}$. In practice a suitable excess of $^{13}\text{CH}_3\text{Li}$ was used to account for the presence of the $^{13}\text{CH}_3\text{I}$ contaminant. The ^1H and ^{13}C NMR spectra of this sample also show a higher order coupling pattern; however, the coupling pattern differs substantially from that of dimethylzinc (Figure 2a). These spectra could be modeled successfully with a $\text{A}_3\text{XA}_3'\text{X}'\text{A}_3''\text{X}''$ system (Figure 3).^[4] The resulting calculated spectrum is shown for comparison in Figure 2b and the calculated coupling constants are summarized in Table 1.

Addition of one additional equivalent of $^{13}\text{CH}_3\text{Li}$ results in the formation of $[(^{13}\text{CH}_3)_4\text{Zn}]\text{Li}_2$ (**4**). The ^1H and ^{13}C spectra indicate that the bulk of the zinc-containing material is identical to **3**. However, in addition to one equivalent of $^{13}\text{CH}_3\text{Li}$ in its tetrahedral tetrameric form, a broad, weak resonance is observed at $\delta = -12$ (Figure 4). Furthermore, after an overnight ^{13}C NMR acquisition at high field

[*] Prof. Dr. S. Berger, Dr. T. A. Mobley
 Institut für Analytische Chemie
 Fakultät für Chemie und Mineralogie der Universität
 Linnéstrasse 3, D-04103 Leipzig (Germany)
 Fax: (+49) 341-9736115
 E-mail: stberger@rz.uni-leipzig.de

[**] This work was supported by the Fonds der Chemischen Industrie.

Table 1. Calculated coupling constants for organocuprate and organozincate compounds.

Compound	Spin system	$^1J_{AX}$ [Hz]	$^2J_{XX'}$ [Hz]	$^3J_{AX'}$ [Hz]	$^4J_{AA'}$ [Hz]
Me ₂ Zn (1) in Hexan	A ₃ XA ₃ X'	121.7	18.4	−1.0	−0.4
Me ₂ Zn (1) in [D ₈]THF	A ₃ XA ₃ X'	116.0	15.9	−0.6	0.4
[Me ₃ Zn]Li (3) in [D ₈]THF	A ₃ XA ₃ X'A ₃ X''	110.9	14.0	0.6	0.4
[Me ₄ Zn]Li ₂ (4) in [D ₈]THF	A ₃ XA ₃ X'A ₃ X''A ₃ X'''	112.0	12.2	0.4	0.4
[Me ₂ Cu]Li (2) in [D ₈]THF	A ₃ XA ₃ X'	109.5	21.0	−0.8	−

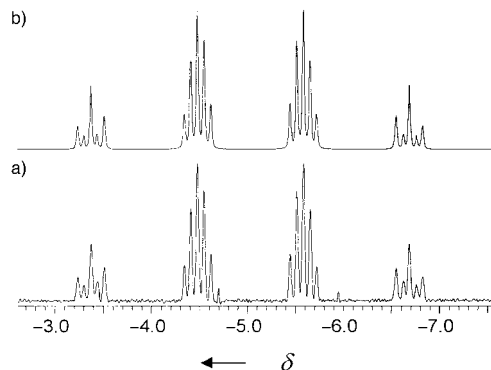


Figure 2. a) ^1H coupled ^{13}C NMR spectrum of **3** (0.08 M) in [D₈]THF at -80°C ; b) calculated spectrum for an A₃XA₃X'A₃X'' spin system (coupling constants are summarized in Table 1).

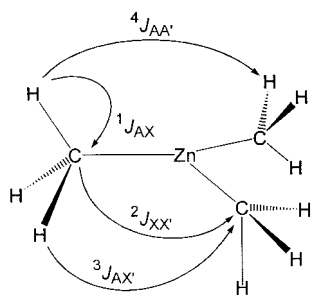


Figure 3. Trimethylzincate structure with spin couplings used in the calculation of the A₃XA₃X'A₃X'' spin system.

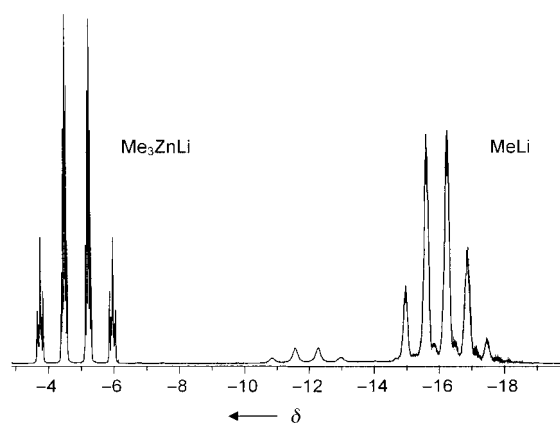


Figure 4. ^1H coupled ^{13}C NMR spectra of **4** (0.08 M) in [D₈]THF at -80°C .

(600 MHz) with this fully labeled material, a very weak set of resonances upfield is observed whose multiplicity corresponds to **4**. An expansion with significant magnification is shown in Figure 5. A simulation based upon an A₃XA₃X'A₃X''A₃X''' system confirms that identification of these resonances as [(¹³CH₃)₄Zn]Li₂ is reasonable (Figure 5b).

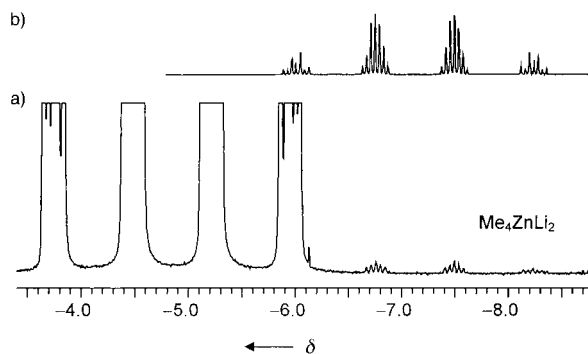


Figure 5. a) Expansion of the ^1H coupled ^{13}C NMR spectra of **4** (0.08 M) in [D₈]THF at -80°C showing the very weak set of resonances attributed to the tetramethylzincate species; b) calculated spectrum for the A₃XA₃X'A₃X''A₃X''' spin system (coupling constants are summarized in Table 1).

Unrefined coupling constants for the species are summarized in Table 1; however, no iterative fitting of the data was possible because of limitations in the large spin system.

Compounds **3** and **4** were synthesized by a method similar to that of Uchiyama and Sakamoto et al.^[1] The NMR spectra taken of concentrated samples (0.1 M) obtained by treatment of ZnCl₂ with three equivalents of ¹³CH₃Li result in spectra similar to those obtained by Uchiyama and Sakamoto et al. However, spectra obtained of highly cooled (-80°C) and highly dilute (0.005 M) samples show much more complicated spectra consisting of a mixture of [(¹³CH₃)₃Zn]Li, (¹³CH₃)₂Zn, (¹³CH₃)ZnCl, and (¹³CH₃)Li. These differences are consistent with a slowing of the fast exchange processes that are present in the concentrated samples.

We interpret our results in the following way. The addition of MeLi to Me₂Zn readily occurs to form a [Me₃Zn]Li species in which all three methyl groups are bound to the zinc center. All three methyl groups are chemically equivalent on the NMR timescale. This may be the result of the formation of a highly symmetrical structure (for example, C_{3v} or D_{3h}) or a rapid exchange of methyl groups in a lower symmetry structure (for example, C_{2v}). At higher temperatures intermolecular exchange of methyl groups occurs, which leads to a loss of the higher order coupling pattern. Upon addition of a second equivalent of MeLi an equilibrium with the [Me₄Zn]-Li₂ species can be observed. However, this equilibrium lies far to the left in Equation (1).



These results are consistent with the results obtained in the analogous copper system and are explained by a simple coulombic repulsion model. It is easy to form the mono-anionic species [Me₃Zn][−] or [Me₂Cu][−], but the addition of a

second negative group to the metal center to form $[\text{Me}_4\text{Zn}]^{2-}$ or $[\text{Me}_3\text{Cu}]^{2-}$, respectively, results in too great a coulombic repulsion and the reaction is thermodynamically unfavored. In the solid state, however, it appears that this coulombic repulsion may be overcome; $[\text{Me}_4\text{Zn}]\text{Li}_2$ has been isolated and structurally characterized by X-ray diffraction techniques.^[5] The identity of the broad resonance at $\delta = -12$ is at this time unknown. On the basis of its chemical shift and broad appearance it could be similar to MeLi in structure, with the broadness of the peaks arising from unresolved coupling between ^6Li and ^{13}C . Our results do not contrast those obtained in the chemical reactivity studies for these systems.^[1] Even though the ground-state structures of the "higher order" zincates and cuprates appear to be mono-anionic, the reactive species could of course be the higher energy tetracoordinated zincate and tricoordinated cuprate.

Further studies involving the nature of the interaction of the anion and the Li^+ counterion and studies examining the interaction of **1**, **3**, and **4** with reactive substrates are currently underway.

Received: May 27, 1999 [Z 134721E]

German version: *Angew. Chem.* **1999**, *111*, 3256–3258

Keywords: NMR spectroscopy • organometallic compounds • structure elucidation • zinc

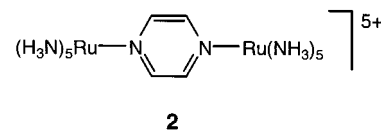
- [1] a) M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1996**, *118*, 8733–8734; b) M. Uchiyama, M. Koike, M. Kameda, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1996**, *118*, 8733–8734.
[2] T. A. Mobley, F. Müller, S. Berger, *J. Am. Chem. Soc.* **1998**, *120*, 1333–1334.
[3] N. K. Hota, C. J. Willis, *J. Organomet. Chem.* **1967**, *9*, 169–170.
[4] The ^{13}C NMR spectra were simulated using the WIN-DAISY simulation program (Bruker-Franzen Analytik GmbH, version 4.0)
[5] E. Weiss, R. Wolfrum, *Chem. Ber.* **1968**, *101*, 35–40.

An Exceedingly Stable Diiron(II,III) Complex Ion $[(\text{tz})\{\text{Fe}(\text{CN})_5\}_2]^{5-}$ with Comproportionation Constants between 10^8 (in H_2O) and 10^{19} (in CH_3CN)

Markus Glöckle and Wolfgang Kaim*

Prussian Blue, formulated as cyanoiron compound $[\text{Fe}_4^{\text{III}}\{\text{Fe}^{\text{II}}(\text{CN})_6\}_3]$ (**1**),^[1] and the heterocycle-bridged Creutz–Taube ion $[(\text{H}_3\text{N})_5\text{Ru}(\mu\text{-pz})\text{Ru}(\text{NH}_3)_5]^{5+}$ (**2**, pz = pyrazine) are textbook cases for mixed-valent compounds in coordination chemistry.^[2] The equilibrium constant K_c for comproportionation, which measures the stability towards

disproportionation [Eqs. (1), (2)] and thus specifies the range of existence of the mixed-valent state, is about 10^{12} for **1** in water^[1b] and between $10^{6.8}$ and $10^{7.3}$ for **2**, depending on the solvent.^[3]



$$\text{M}^{n+} + \text{M}^{(n-2)+} \rightleftharpoons 2\text{M}^{(n-1)+} \quad (1)$$

$$K_c = \frac{[\text{M}^{(n-1)+}]^2}{[\text{M}^{n+}][\text{M}^{(n-2)+}]} = e^{\Delta E F / RT} \quad (2)$$

ΔE : redox potential difference

It was therefore disappointing when the bis(pentacyanoiron) complex $[(\mu\text{-pz})\{\text{Fe}(\text{CN})_5\}_2]^{5-}$ (**3**⁵⁻) with bridging pyrazine was found to exhibit only a small K_c value of $10^{1.9}$ in water, signifying very little metal–metal interaction in **3**⁵⁻.^[4] Recent experiments in aprotic polar media, however, showed that this value for **3**⁵⁻ can increase up to $10^{6.5}$,^[5] illustrating the crucial role of the environment for the metal–metal coupling in such highly charged systems. Using the hitherto rather neglected^[6] unsubstituted 1,2,4,5-tetrazine (tz) as an excellently π -accepting bridging ligand, we have now been able to extend the stability range of such simple diiron(II,III) systems to $10^{7.9}$ in water and to $10^{19.0}$ in acetonitrile, allowing for the isolation of the corresponding ion $[(\mu\text{-tz})\{\text{Fe}(\text{CN})_5\}_2]^{5-}$ (**4**⁵⁻) as a stable pentakis(tetraethylammonium) salt.^[7b]

Compounds $(\text{NEt}_4)_6(\text{4})$ ($\text{Fe}^{\text{II}}(\text{tz})\text{Fe}^{\text{II}}$) and $(\text{NEt}_4)_5(\text{4})$ ($\text{Fe}^{2.5}(\text{tz})\text{Fe}^{2.5}$) were isolated^[7a,b] and characterized spectroscopically and electrochemically (Figure 1, Table 1). The neighbor-

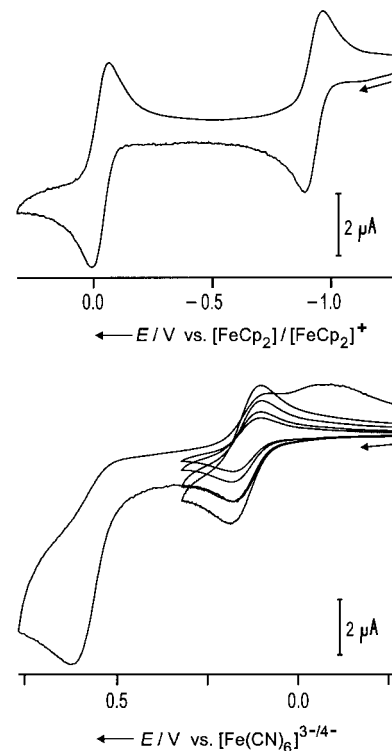


Figure 1. Cyclic voltammograms of $(\text{NEt}_4)_6(\text{4}) \cdot 2\text{H}_2\text{O}$ in $\text{CH}_3\text{CN}/0.1\text{M}$ NBu_4PF_6 at -35°C (50 mV s^{-1} ; top) and in $\text{H}_2\text{O}/0.25\text{M}$ Na_2SO_4 at room temperature (50 mV s^{-1} for full-scale voltammogram and 100, 50, 25, and 15 mV s^{-1} for the first oxidation wave; bottom).

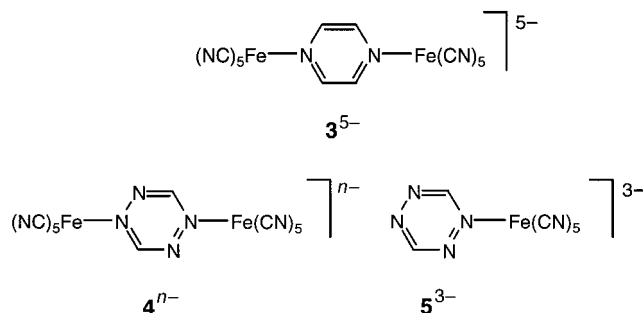
[*] Prof. Dr. W. Kaim, Dipl.-Chem. M. Glöckle
Institut für Anorganische Chemie der Universität
Pfaffenwaldring 55, D-70550 Stuttgart (Germany)
Fax: (+49) 711-685-4165
E-mail: kaim@iac.uni-stuttgart.de

Table 1. Electrochemical and spectroscopic data of pentacyanoiron complexes

Complex	$E_{\text{ox2}}^{[a]}$	$E_{\text{ox1}}^{[a]}$	K_c	$\lambda_{\text{IVCT}}(\epsilon)^{[b]}$	$\lambda(\epsilon)^{[b]}$	$\tilde{\nu}_{\text{CN}}^{[c]}$	Solvent ^[d]	Temp. ^[e]
3⁶⁻	0.62 ^[f]	0.51 ^[f]	10 ^{1.9}	—	505 (13 180)	n.o.	H ₂ O	298 ^[4c]
3⁶⁻	—0.60	—0.92	10 ^{6.5}	—	599 (17 400), 406 (3400)	n.o.	CH ₃ CN	248 ^[5]
3⁵⁻	—	—	—	1205 (2200) $\Delta\tilde{\nu}_{1/2}$ 4800 cm ⁻¹	n.o.	n.o.	H ₂ O	298 ^[4]
3⁵⁻	—	—	—	2475 (3900) $\Delta\tilde{\nu}_{1/2}$ 1500 cm ⁻¹	745 (8000), 599 (7300), 406 (4400)	2070 br, 2112 w	CH ₃ CN	—/298/298 ^[5]
4⁶⁻	0.64 ^[g, h]	0.14 ^[h]	10 ^{7.9}	—	848 (22 000), 452 (1300), 395 sh	n.o.	H ₂ O	293/298/—
4⁶⁻	0.00	—0.85	10 ^{17.8}	—	1014 ^[i]	n.o.	CH ₂ Cl ₂	233/240/—
4⁶⁻	—0.03	—0.93	10 ^{19.0}	—	1021 (21 670), 543 sh, 520 (1620), 353	2087 sh, 2067 vs	CH ₃ CN	238/233/242
4⁵⁻	—	—	—	2250(2820) $\Delta\tilde{\nu}_{1/2}$ 970 cm ⁻¹	744 (15 060), 439 sh, 402 (1420)	n.o.	D ₂ O	298
4⁵⁻	—	—	—	2520 (1150) $\Delta\tilde{\nu}_{1/2}$ 860 cm ⁻¹	678 (13 070), 345 (3710)	2110s, 2101s	CH ₃ CN	298
4⁴⁻	—	—	—	—	630 (6190), 414 (2020)	2123 sh, 2117 w	CH ₃ CN	—/238/242
5	—	0.37 ^h	—	—	685 (7830), 423 (1050)	n.o.	H ₂ O	293/298/—
5	—	—0.32	—	—	690 (7180)	2106 sh, 2097 m, 2082 s	CH ₃ CN	243/298/298

[a] Potentials in V vs. ferrocene^{+/0} (aprotic media) from cyclic voltammetry at 50 mV s⁻¹ scan rate (30 mV s⁻¹ in CH₂Cl₂). Values from aqueous solution were measured vs. [Fe(CN)₆]^{3-/4-}. [b] Wavelengths in nm, molar extinction coefficients in M⁻¹ cm⁻¹. n.o. = not observed. [c] CN stretching frequencies in cm⁻¹ (solution studies). [d] Electrolyte solutions for cyclic voltammetry: H₂O/0.25 M Na₂SO₄, CH₃CN/0.1 M Bu₄NPF₆, CH₂Cl₂/0.2 M Bu₄NPF₆. [e] In K, for cyclic voltammetry/absorption spectroscopy/IR spectroscopy. [f] Values vs. NHE in H₂O/1 M KCl, from ref. [4c]. [g] Anodic peak potential (irreversible wave due to adsorption); K_c calculated from peak potential difference. [h] Potentials vs. [Fe(CN)₆]^{3-/4-}. $E_{1/2}(\text{[Fe(CN)}_6\text{]}^{3-/4-}) = 0.17$ V vs. SCE; $E_{1/2}(\text{ferrocene}^{+/0}) = 0.16$ V vs. SCE. [i] Poor solubility in electrolyte-free CH₂Cl₂.

ing, more labile oxidation state **4⁴⁻** (Fe^{III}(tz)Fe^{III}) was studied after chemical oxidation.^[7c] For comparison the mononuclear complex (NEt₄)₃[(tz)Fe(CN)₅] (**5**) was also prepared and characterized.^[8]



The first remarkable result of these studies is the chemical stability of the mixed-valent complex (NEt₄)₅(**4**) in comparison to both the Fe^{II}(tz)Fe^{II} form (labile in aprotic media^[7a]) and the Fe^{III}(tz)Fe^{III} form. The facile synthesis, high stability, and easy handling correlate with the enormous increase in K_c on going from the pz- to the tz-bridged system, that is, from 10^{1.9} to 10^{7.9} in water and from 10^{6.5} to 10^{19.0} in acetonitrile. Both the absolute values for K_c and the solvent dependence of K_c are extraordinary (Table 1); apparently, the presence of electrophilic (protic) components in corresponding solvents attenuates the capability of the strong π acceptor 1,2,4,5-tetrazine to mediate the iron–iron interaction over a distance of about 6.8 Å.^[9] Hydrogen bonding to the “free” nitrogen atoms of the tetrazine and of the cyanide ligands is presumably responsible for this unusually strong effect. The additional factor of 10⁵ in comparison to bis(tetracyanoiron) complexes of bis(chelating) tetrazine ligands^[5, 10] is attributed to the lower charge and restricted orientation of the cyanometal moieties in the latter systems.

In the absorption spectra the iron(II)-containing tetrazine complexes exhibit intense metal-to-ligand charge transfer (MLCT) bands in the long-wavelength region. The intervalence charge transfer (IVCT) feature expected for a mixed-valent state occurs in the near IR range at 2520 nm in acetonitrile and at 2250 nm in aqueous solution (Figure 2).

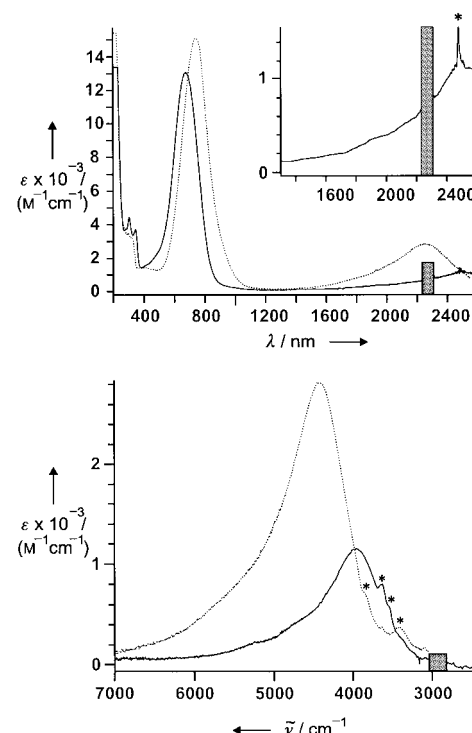


Figure 2. Absorption spectra of (NEt₄)₅(**4**)·2H₂O in CH₃CN (—) and in D₂O (····). Solvent absorptions are marked (* and bars).

Remarkably, the intensity of the IVCT band is more than twice as large in D₂O (Table 1), while the bandwidth at half height remains virtually unchanged at about 900 cm⁻¹. This value is thus well below that of approximately 3200 cm⁻¹ calculated by the Hush formula^[11a,b] for weakly coupled mixed-valent centers. In other words, **4⁵⁻** is a strongly coupled mixed-valent system belonging to class III according to the classification of Robin and Day;^[11c] the electronic interaction constant V_{AB} may thus be estimated^[11b] at $\nu_{\text{IVCT}}/2 = 2220$ (D₂O) or 1980 cm⁻¹ (CH₃CN).

The IR spectra exhibit only a limited number of discernible cyanide stretching features because of band overlap.^[4, 5] The high-energy shift from **4⁶⁻** via **4⁵⁻** to **4⁴⁻** is as expected; the

resolved band splitting of 9 cm^{-1} for the mixed-valent system does not signify valence localization but occurs similarly for the mononuclear iron(II) complex **5** (Table 1). Most importantly, there is no specific aromatic ring vibration band visible in the IR spectrum between 1500 and 1700 cm^{-1} for the mixed-valent state. This would indicate loss of inversion symmetry (nonzero dipole moment) and thus (partial) valence localization, as has been observed for pyrazine-bridged analogues.^[5, 12]

The g factor component pattern of $(\text{NEt}_4)_5(\mathbf{4})$ in the EPR spectrum at $g = 2.531$, 2.422 , and 1.794 is similar to the results observed for other $\text{Fe}^{\text{II}}(\text{L})\text{Fe}^{\text{III}}$ systems.^[5, 10, 13] This supports the formulation of a mixed-valent diiron complex with little direct participation of the ligands in the spin distribution.

By using 1,2,4,5-tetrazine as a superior π -acceptor bridging ligand, we have been able to obtain an unprecedentedly stable new cyanodiiron(2.5) coordination compound with an extraordinary solvent dependence^[14]—a link between the numerous well-known ammineruthenium complexes^[11b] and Prussian Blue.^[1]

Received: May 11, 1999 [Z13405 IE]

German version: *Angew. Chem.* **1999**, *111*, 3262–3264

Keywords: iron • mixed-valent compounds • N ligands • oxidation states

- [1] a) F. Herren, P. Fischer, A. Ludi, W. Halg, *Inorg. Chem.* **1980**, *19*, 956; b) K. Itaya, I. Uchida, V. D. Neff, *Acc. Chem. Res.* **1986**, *19*, 162.
- [2] a) D. F. Shriver, P. W. Atkins, C. H. Langford, *Inorganic Chemistry*, 2nd ed., Oxford University Press, Oxford, **1994**, p. 611; b) F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochmann, *Advanced Inorganic Chemistry*, 6th ed., Wiley, New York, **1999**, pp. 791 and 1017.
- [3] C. Creutz, M. H. Chou, *Inorg. Chem.* **1987**, *26*, 2995.
- [4] a) F. Felix, A. Ludi, *Inorg. Chem.* **1978**, *17*, 1782; b) F. Felix, U. Hauser, H. Siegenthaler, F. Wenk, A. Ludi, *Inorg. Chim. Acta* **1975**, *15*, L7; c) K. J. Moore, L. Lee, G. A. Mabbott, J. D. Petersen, *Inorg. Chem.* **1983**, *22*, 1108.
- [5] M. Ketterle, W. Kaim, J. A. Olabe, A. R. Parise, J. Fiedler, *Inorg. Chim. Acta* **1999**, *291*, 66.
- [6] a) M. Herberhold, M. Suss-Fink, *Z. Naturforsch. B* **1976**, *31*, 1489; b) W. Kaim, S. Kohlmann, *Inorg. Chem.* **1986**, *25*, 3442.
- [7] All synthetic operations were carried out under argon. a) $(\text{NEt}_4)_6(\mathbf{4}) \cdot 2\text{H}_2\text{O}$: An aqueous solution of $\text{Na}_3[\text{Fe}(\text{NH}_3)(\text{CN})_5] \cdot 3\text{H}_2\text{O}$ (536 mg, 1.64 mmol) was passed through a Dowex W50 column charged with NEt_4Cl . The eluate (ca. 100 mL) was added to a solution of 1,2,4,5-tetrazine (94 mg, 1.15 mmol) in water (30 mL). After 10 h at ambient temperature the solvent was removed and the residue purified by repeated chromatography (Sephadex LH 20, H_2O). The dark green solid obtained after removal of water was treated with acetone (25 mL) for 5 min in an ultrasonic bath. The undissolved solid was collected and dried under vacuum (230 mg, 18% $(\text{NEt}_4)_6(\mathbf{4}) \cdot 2\text{H}_2\text{O}$). Elemental analysis calcd for $\text{C}_{60}\text{H}_{126}\text{Fe}_2\text{N}_{20}\text{O}_2$ (1271.51 g mol^{-1}): C 56.68, H 9.99, N 22.03; found: C 56.74, H 10.01, N 21.95%. The complex is stable in water but dissociates above -25°C in CH_3CN or CH_2Cl_2 . ^1H NMR (D_2O): $\delta = 9.55$ (s); b) $(\text{NEt}_4)_5(\mathbf{4}) \cdot 2\text{H}_2\text{O}$: $(\text{NEt}_4)_6(\mathbf{4}) \cdot 2\text{H}_2\text{O}$ (50 mg, 0.039 mmol) was dissolved at -36°C in acetonitrile (50 mL). A solution of p -(N,N -dimethylamino)benzenediazonium hexafluorophosphate (12.7 mg, 0.043 mmol) in cold acetonitrile (-30°C , 20 mL) was added, and the resulting mixture stirred for 15 min at -36°C . After removal of the solvent the residue was treated with acetone (20 mL) in an ultrasonic bath at room temperature. The solid residue was treated once more with acetone (20 mL) to yield a colorless solution and a dark blue residue, which was collected and dried under vacuum (40 mg, 90% $(\text{NEt}_4)_5(\mathbf{4}) \cdot 2\text{H}_2\text{O}$). Elemental analysis calcd for $\text{C}_{52}\text{H}_{106}\text{Fe}_2\text{N}_{19}\text{O}_2$ (1141.25 g mol^{-1}): C 54.73, H 9.36, N 23.32; found: C 54.33, H 9.22, N 23.13%. The complex is stable in air as a solid and in solution, both in water and aprotic solvents. EPR (CH_3CN , 4 K): $g_1 = 2.531$, $g_2 = 2.422$, $g_3 = 1.794$. c) $(\text{NEt}_4)_4(\mathbf{4}) \cdot 2\text{H}_2\text{O}$: $(\text{NEt}_4)_6(\mathbf{4}) \cdot 2\text{H}_2\text{O}$ (6.1 mg, 4.8 μmol) was dissolved at -36°C in acetonitrile (5 mL). A solution of p -fluorobenzenediazonium hexafluorophosphate (3.6 mg, 13.4 μmol) in cold acetonitrile (-30°C , 1.1 mL) was added. This mixture was then rapidly transferred to a cooled (-42°C) cuvette for spectroscopic measurement. Temperatures higher than -30°C resulted in dissociation with formation of free tetrazine.
- [8] $(\text{NEt}_4)_5(\mathbf{5}) \cdot 2\text{H}_2\text{O}$: $(\text{NEt}_4)_6(\mathbf{4}) \cdot 2\text{H}_2\text{O}$ (50 mg, 0.039 mmol) dissolved under dissociation in acetonitrile (60 mL). Addition of solid NEt_4CN (10 mg, 0.064 mmol), removal of the solvent, and repeated chromatography on Sephadex LH20 in water yielded a dark blue powder which was treated with acetone (10 mL) in an ultrasonic bath at room temperature. The solid residue was dried under vacuum (8 mg, 30% $(\text{NEt}_4)_5(\mathbf{5}) \cdot 2\text{H}_2\text{O}$). Elemental analysis calcd for $\text{C}_{31}\text{H}_{66}\text{FeN}_{12}\text{O}_2$ (694.80 g mol^{-1}): C 53.59, H 9.58, N 24.19; found: C 53.28, H 9.28, N 23.04%. The complex is stable in air as a solid and in solution, both in water and aprotic solvents. ^1H NMR (D_2O): $\delta = 10.25$ (d, 1H), 9.18 (d, 1H); $J = 2.6\text{ Hz}$.
- [9] For structural data of substituted tetrazine complexes, see M. Schwach, H.-D. Hausen, W. Kaim, *Inorg. Chem.* **1999**, *38*, 2242.
- [10] Large K_c values of about 10^{14} have been reported for octacyanodiron(II,III) complexes with 3,6-disubstituted 1,2,4,5-tetrazine bis(chelate)ligands in aprotic media: M. Ketterle, J. Fiedler, W. Kaim, *Chem. Commun.* **1998**, 1701; M. Glockle, J. Fiedler, N. E. Katz, M. Garcia Posse, E. Cutin, W. Kaim, *Inorg. Chem.* **1999**, *38*, 3270.
- [11] a) G. C. Allen, N. S. Hush, *Prog. Inorg. Chem.* **1967**, *8*, 357; b) C. Creutz, *Prog. Inorg. Chem.* **1983**, *30*, 1; c) M. B. Robin, P. Day, *Adv. Inorg. Chem. Radiochem.* **1967**, *10*, 247.
- [12] F. Hornung, F. Baumann, W. Kaim, J. A. Olabe, L. D. Slep, J. Fiedler, *Inorg. Chem.* **1998**, *37*, 311 and 5402.
- [13] T. Glaser, F. Kesting, T. Beissel, E. Bill, T. Weyhermuller, W. Meyer-Klaucke, K. Wieghardt, *Inorg. Chem.* **1999**, *38*, 722.
- [14] The strong effect of the environment on the physical properties of mixed-valent complexes has been known for both dissolved and solid species: P. Chen, T. J. Meyer, *Chem. Rev.* **1998**, *98*, 1439; C.-C. Wu, H. G. Jang, A. L. Rheingold, P. Gutlich, D. N. Hendrickson, *Inorg. Chem.* **1996**, *35*, 4137.

Conversion of Molecular Oxygen into a Hydroperoxo Species by Ring-Opening Protonation of a Cyclic η^2 -Peroxo Intermediate: Characterization of the η^2 -Peroxo and Hydroperoxo Complexes**

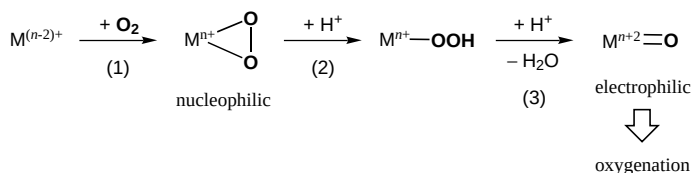
Yoshiaki Takahashi, Mariko Hashimoto, Shiro Hikichi, Munetaka Akita,* and Yoshihiko Moro-oka*

Transition metal–dioxygen species are key intermediates in catalytic oxygenation reactions such as synthetic and metabolic transformations.^[1] Since the oxygen atoms of cyclic

[*] Prof. Dr. M. Akita, Prof. Dr. Y. Moro-oka, Dr. Y. Takahashi, M. Hashimoto, Dr. S. Hikichi
Research Laboratory of Resources Utilization
Tokyo Institute of Technology, 4259 Nagatsuta
Midori-ku, Yokohama 226-8503 (Japan)
Fax: (+81)45-924-5226
E-mail: makita@res.titech.ac.jp

[**] We are grateful to the Ministry of Education, Science, Sports, and Culture of the Japanese Government for financial support of this research (Grant-in Aid for Scientific Research).

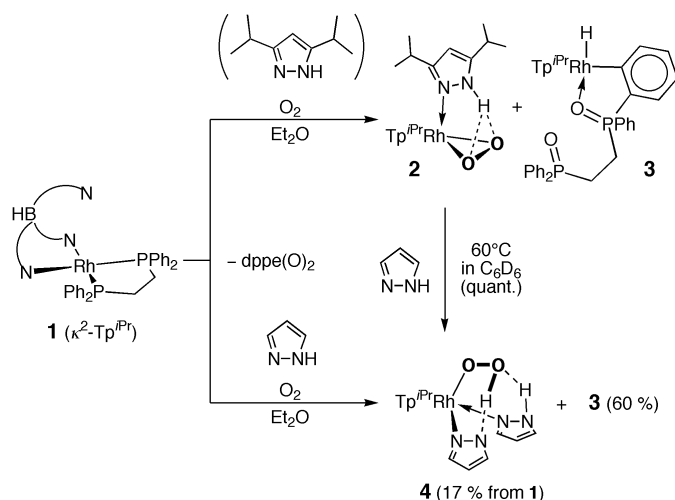
η^2 -peroxo intermediates, which are formed by the oxidative addition of a dioxygen molecule to a low valent metal species (step 1 in Scheme 1), are normally nucleophilic, such inter-



Scheme 1. Activation of molecular oxygen by a transition metal species.

mediates do not show remarkable oxygenation activity. Therefore the η^2 -peroxo intermediates need to be activated in some way prior to oxygenation. In the well-studied cytochrome P-450 system it is proposed that protonation of the η^2 -peroxo intermediate gives the η^1 -hydroperoxo species (step 2), which is further converted into the high valent, highly electrophilic oxo intermediate by protonation followed by the elimination of water (step 3).^[2] However, no concrete structural evidence for these steps has been reported so far.^[3] During the course of the systematic synthetic study on dioxygen complexes based on the Tp^{R} systems^[4,5] we have found that molecular oxygen can be converted into a hydroperoxo species, that is: 1) oxygenation of a Rh^{I} precursor affords the Rh^{III} -peroxo and -hydroperoxo species, and 2) the formation of the latter species involves a ring-opening protonation of the former η^2 -peroxo intermediate, which corresponds to step 2.

Stirring an ethereal solution of the square-planar Rh^{I} -dppe complex $[(\text{Tp}^{\text{R}})\text{Rh}(\text{dppe})]$ (**1**)^[5,6] under an O_2 atmosphere afforded a mixture of products, from which the O_2 adduct **2** was isolated as yellow crystals in a low yield (1.4 %) together with dppe dioxide and the cyclometalated hydride complex **3** (52 %; Scheme 2). Complex **2** contained the 3,5-di-2-propylpyrazole (pz^{RPrH}) ligand from the partial decomposition of the Tp^{RPr} ligand, and oxygenation of **1** in the presence of pz^{RPrH} improved the yield of **2** up to 23 %, while that of **3** remained virtually unaffected (51 %).



Scheme 2. Oxygenation of $[(\text{Tp}^{\text{RPr}})\text{Rh}(\text{dppe})]$ (**1**) to give η^2 -peroxo and hydroperoxo complexes (**2** and **4**, respectively).

Coordination of an O_2 molecule in **2** is evidenced by the O-O vibration observed at 848 cm^{-1} in the IR spectrum and the FD-MS data ($m/z = 752$ [$M^+ = 1 + \text{O}_2 + \text{pz}^{\text{RPrH}} - \text{dppe}$]) (FD = field desorption). The ^1H NMR spectrum of **2** contains three sets of pyrazolyl signals in a 1:1:2 ratio, which suggests a structure with mirror symmetry as well as the incorporation of one molecule of pz^{RPrH} . The B-H vibration appearing at 2540 cm^{-1} in the IR spectrum indicates a κ^3 -coordination of the Tp^{RPr} ligand.^[7] The octahedral hexacoordinated structure suggested by the spectral data has been confirmed by X-ray crystallographic analysis (Figure 1 a).^[8] The O-O ($1.467(5)\text{ \AA}$)

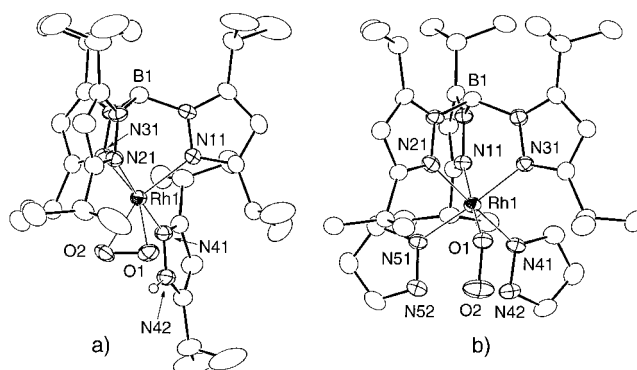
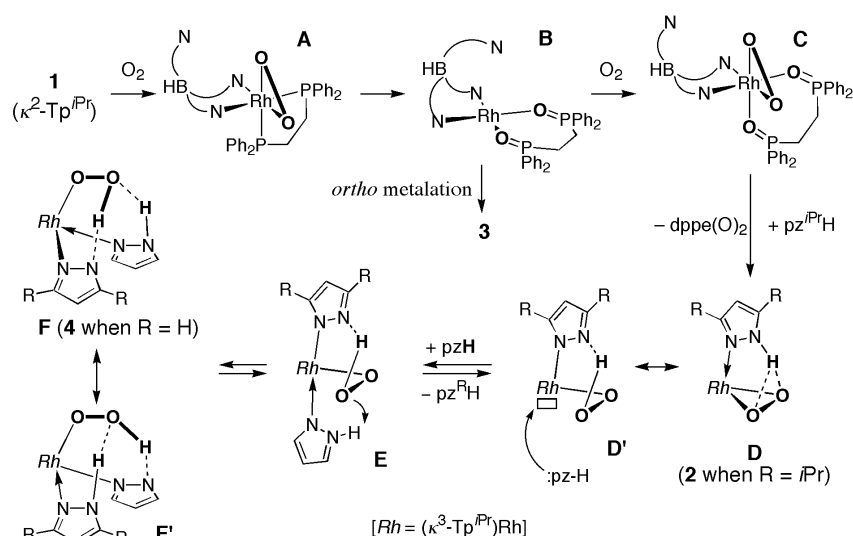


Figure 1. Molecular structures of **2** a) and **4** b) drawn at the 30 % probability level.

and Rh-O bond lengths ($2.013(3)$ and $2.001(4)\text{ \AA}$) are comparable to those of the previously reported octahedral $[\text{Rh}(\eta^2\text{-O}_2)]$ complexes^[9] and clearly indicate that the coordinated O_2 is present as a peroxo ligand (O_2^{2-}). The $\text{N}\cdots\text{O}$ distances ($\text{O1}\cdots\text{N42}$: $2.681(6)\text{ \AA}$, $\text{O2}\cdots\text{N42}$: $2.733(6)\text{ \AA}$) and the orientation of the pyrazole ring lead to the conclusion that a hydrogen-bonding interaction is present between the peroxo oxygen atoms and the pyrazole nitrogen atom (N42). The NH hydrogen atom, which was refined isotropically, is actually located in the middle of the three atoms (O1, O2, and N42). The deshielded NH signal ($\delta = 12.42$) in the ^1H NMR spectrum and the obscured NH vibration in the IR spectrum are in accord with this structural description. In the isostructural Mn complex $[(\text{Tp}^{\text{RPr}})\text{Mn}(\text{pz}^{\text{RPrH}})(\text{O}_2)]$ (**5**, O-O: $1.43(1)$, Mn-O: $1.841(9)$, $1.878(8)$, $\text{N}\cdots\text{O}$: $2.82(2)$, $2.99(2)\text{ \AA}$)^[10] however, the hydrogen-bonding interaction is unsymmetrical and weaker than that in **2**. The pz^{RPrH} moiety in the Mn complex **5** becomes dissociated from the metal center upon dissolution, whereas the Rh complex **2** retains the structure in solution. The strong interaction in **2** is probably a result of the highly basic O_2 ligand, which arises from the effective back-donation from the Rh center.

The cyclometalated complex **3** was characterized by the $\delta(\text{Rh-H})$ and $\nu(\text{Rh-H})$ absorptions in the NMR and IR spectra, respectively, and X-ray crystallographic analysis.^[8] Formation of **3** suggests that another Rh^{I} intermediate, namely $[(\text{Tp}^{\text{RPr}})\text{Rh}(\text{dppe}(\text{O}_2))]$ (**B** in Scheme 3), is the direct precursor to **2**.

Since an external pz^{RPrH} molecule was incorporated into the O_2 complex **2** (Scheme 2), the additive effect of another donor was examined. Oxygenation of **1** in the presence of the



Scheme 3. Plausible mechanism for the formation of **2** and **4**.

unsubstituted pyrazole afforded yellow crystals of **4** (17% yield) and the metallacycle **3** (Scheme 2). The FD-MS data ($m/z = 736$) of **4** suggested another peroxo complex that was formulated as $[(\text{Tp}^{\text{Pr}})\text{Rh}(\text{pzH})_2(\text{O}_2)]$. However, X-ray crystallographic analysis (Figure 1b) revealed the structure was actually the hydroperoxo complex $[(\text{Tp}^{\text{Pr}})\text{Rh}(\text{OOH})(\text{pz})(\text{pzH})]$.^[8] Examples of structurally characterized hydroperoxo complexes are still very rare,^[11] and complex **4** is only the second hydroperoxorhodium complex following the mixed metal Ir–Rh complex $[(\eta^5\text{-C}_5\text{Me}_5)\text{Ir}(\mu\text{-pz})_2\text{Rh}(\text{OOH})(\text{dppe})]$ (**6**, Rh–O: 2.021(5), O–O: 1.432(8) Å).^[11a] The O–O distance in **4** (1.413(8) Å) falls in the typical range of those reported for peroxo and hydroperoxo complexes including **2** and **6**,^[1, 11] though the Rh–O bond (1.994(4) Å) is slightly shorter than that in **2** and **6**. In this case, too, the N...O and N...N distances (O2–N42: 2.851(1) Å; O2–N52: 2.857(8) Å; N42–N52: 2.78(1) Å) and the orientation of the O₂ and pz groups indicate the presence of hydrogen-bonding interactions between the O₂, N42, and N52 atoms. Although the positions of the hydrogen atoms cannot be determined by X-ray crystallography,^[12] they should be located between the O₂ and N42 atoms and between the O₂ and N52 atoms as suggested by their ¹H NMR data and the obscured O–H and N–H vibrations. The ¹H NMR chemical shift ($\delta = 12.03$ (2H)) is comparable to the $\delta(\text{NH})$ value for **2** with the NH...O hydrogen bond, and the two hydrogen atoms remain equivalent even at –90 °C. The symmetry observed in the NMR spectrum and crystallographic features suggest the contribution of the two canonical structures **F** and **F'** (Scheme 3) to both the solution and solid-state structures.

The results reported in this communication can be interpreted in terms of the mechanism summarized in Scheme 3. Oxygenation of **1** should initially produce the simple O₂ adduct $[(\text{Tp}^{\text{Pr}})\text{Rh}(\eta^2\text{-O}_2)(\text{dppe})]$ (**A**), which is readily converted into **B** by oxygenation of the coordinated dppe ligand. In contrast to other $[(\text{Tp}^{\text{Pr}})\text{Rh}(\text{L}_2)]$ -type complexes ($\text{L}_2 = \text{diene}, (\text{olefin})_2, (\text{CO})_2$), which are inert toward O₂,^[6, 7] complex **1** with the electron-donating dppe ligand is readily

susceptible to O₂ oxidative addition. Subsequent orthometalation of the phosphane oxide ligand in **B** gives **3**,^[13] while some of **B** further reacts with an O₂ molecule ($\rightarrow$ **C**) to furnish the isolable O₂ adduct **D** (**2**) after elimination of $\text{dppe}(\text{O})_2$ and coordination of $\text{pz}^{\text{Pr}}\text{H}$. In the case of the 3,5-di-2-propyl derivative ($\text{R} = i\text{Pr}$), only one $\text{pz}^{\text{Pr}}\text{H}$ molecule can be coordinated to the Rh center as a consequence of the steric hindrance of the bulky 2-propyl substituents and, therefore, the reaction is terminated at this stage. The coordinatively unsaturated resonance structure **D'** should contribute to the final structure. A less bulky substrate such as pyrazole ($\text{R} = \text{H}$) can be further coordinated to the vacant site in **D'** to give the bis-pz adduct **E**, which is converted into the final product **F** (**4** when $\text{R} = \text{H}$) after reorganization of the

hydrogen-bonding interactions. Since the octahedral $[(\text{Tp}^{\text{Pr}})\text{Rh}]$ complexes are usually inert with respect to the ligand displacement,^[6] the hydrogen-bonding interaction must assist the incorporation of the second $\text{pz}^{\text{R}}\text{H}$ molecule.

In accord with this mechanism, heating a $[\text{D}_6]$ benzene solution of **2** with an excess of pyrazole at 60 °C resulted in the quantitative formation of **4** (Scheme 2); the bulky $\text{pz}^{\text{Pr}}\text{H}$ ligand in **2** is replaced by pzH , and **4** should be formed through incorporation of a second pzH molecule followed by a reorganization. The replacement of the $\text{pz}^{\text{Pr}}\text{H}$ ligand reveals that the incorporation of $\text{pz}^{\text{R}}\text{H}$ is a reversible process. It is remarkable that, as a result of the hydrogen-bonding interaction, both of the complexes **2** and **4** presented herein are sufficiently stable to survive chromatographic purification on silica gel.

In conclusion, we reveal that 1) oxygenation of the Rh^I precursor **1** produces the Rh^{III}-peroxo and -hydroperoxo complexes **2** and **4**, respectively, and 2) the OOH functional group in **4** results from ring-opening protonation of the O₂ ligand in **2**. These transformations can be viewed as the first structural evidence for the key steps of the O₂ activation by a transition metal species and conversion of molecular oxygen into a hydroperoxo species (steps 1 and 2 in Scheme 1). It should also be noted that the hydrogen-bonding interactions play pivotal roles in the formation and stabilization of **2** and **4** and similar assistance may be viable in the O₂ activation by metalloproteins.

Experimental Section

2 and **3**: A solution of **1**·0.5Et₂O (458 mg, 0.456 mmol) and 3,5-di-2-propylpyrazole (66 mg, 0.434 mmol) in diethyl ether (20 mL) was stirred under an O₂ atmosphere (1 atm) for 18 h. After removal of the precipitated colorless solid (dppe dioxide) by filtration through a celite pad the volatiles were removed under reduced pressure. The resulting residue was subjected to chromatography on silica gel. Elution with diethyl ether gave **3** (80 mg, 23%) as a pale yellow solid and subsequent elution with THF gave **2** (232 mg, 51%) as a yellow solid. **2**: ¹H NMR (selected data, 200 MHz, CDCl₃, 25 °C): $\delta = 12.42$ (brs, 1H; NH), 5.88 (s, 2H; 4- pz^{Pr} in Tp^{Pr}), 5.75 (d, ³J(H,H) = 2.4 Hz, 1H; 4- pz^{Pr} in additional $\text{pz}^{\text{Pr}}\text{H}$), 5.66 (s, 1H; 4- pz^{Pr} in

Tp^{Pr}); IR (KBr): $\tilde{\nu}$ = 2540 (BH), 848 cm⁻¹ (OO); FD-MS: m/z : 752 [M^+]. **3**: ¹H NMR δ = 5.70, 5.68, 5.67 (s $\times$ 3, 1H $\times$ 3; 4-pz^{Pr} in Tp^{Pr}), -16.86 (d, ¹J(Rh,H) = 17.5 Hz, 1H; RhH); ³¹P NMR (162 MHz, CDCl₃, 25 °C): δ = 57.5, 31.8 (d $\times$ 2, ³J(P,P) = 48 Hz). IR $\tilde{\nu}$ = 2534 (BH), 2082 cm⁻¹ (RhH); FD-MS: m/z : 998 [M^+].

4: A solution of **1** $\cdot$ 0.5 Et₂O (490 mg, 0.485 mmol) and pyrazole (67 mg, 0.984 mmol) in diethyl ether (15 mL) was stirred under an O₂ atmosphere (1 atm) for 17 h. After removal of the precipitated colorless solid (dppe dioxide) by filtration through a celite pad the volatiles were removed under reduced pressure and the residue was separated by column chromatography on silica gel. Elution with diethyl ether and THF gave **4** as a yellow solid (62 mg, 17%) and **3** (291 mg, 60%), respectively. **4**: ¹H NMR: δ = 12.03 (brs, 2H; N-H-O), 7.77, 6.89 (d $\times$ 2, ³J(H,H) = 2.0 Hz, 2H $\times$ 2; 3,5-pz), 6.20 (t, 2H, ³J(H,H) = 2.0 Hz; 4-pz), 5.88 (s, 2H; 4-pz^{Pr}), 5.79 (s, 1H; 4-pz^{Pr}); IR (KBr): $\tilde{\nu}$ = 2539 cm⁻¹ (BH); FAB-MS: m/z : 736 [M^+].

Received: April 19, 1999 [Z 13297 IE]

German version: *Angew. Chem.* **1999**, *111*, 3259–3262

Keywords: dioxygen complexes • hydroperoxo complexes • oxygenations • protonations • rhodium

- [1] a) R. A. Sheldon, J. K. Kochi, *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, New York, **1981**; b) *The chemistry of peroxides* (Ed.: S. Patai), Wiley, Chichester, **1983**; c) *Oxygen Complexes and Oxygen Activation by Transition Metals* (Eds.: A. E. Martell, D. T. Sawyer), Plenum, New York, **1988**; d) *Organic Peroxides* (Ed.: W. Ando), Wiley, Chichester, **1992**; e) special issue "Metal–Dioxygen Complexes": *Chem. Rev.* **1994**, *94*, 567–856; f) G. Strukul, *Angew. Chem.* **1998**, *110*, 1256–1267; *Angew. Chem. Int. Ed.* **1998**, *37*, 1198–1209; g) S. Murahashi, *Angew. Chem.* **1995**, *107*, 2670–2693; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2443–2465.
- [2] a) *Cytochrome P-450* (Eds.: R. Sato, T. Omura), Kodansha, Tokyo, **1978**; b) P. R. O. de Montellano, *Cytochrome P-450: Structure, Mechanism and Biochemistry*, Plenum, New York, **1986**; c) Y. Watanabe, J. T. Groves in *The Enzymes* (Ed.: B. Sigman), Academic, Orlando, **1992**; d) M. Sono, M. P. Roach, E. D. Coulter, J. H. Dawson, *Chem. Rev.* **1996**, *96*, 2625–2657.
- [3] Previously we reported a related protonation reaction of the peroxorhodium complex [RhCl(η^2 -O₂)(PPh₃)₃] with acetylacetone (acacH) that gave [RhCl(acac)(OOH)(PPh₃)₂]. The hydroperoxo complex was characterized by spectroscopic methods but conclusive structural evidence has not been obtained. a) H. Suzuki, S. Matsuura, Y. Moro-oka, T. Ikawa, *Chem. Lett.* **1982**, 1011–1014; b) H. Suzuki, S. Matsuura, Y. Moro-oka, T. Ikawa, *J. Organomet. Chem.* **1985**, *286*, 247–258; see also c) S. Muto, H. Ogata, Y. Kamiya, *Chem. Lett.* **1975**, 809–812; d) F. Igersheim, H. Mimoun, *Nouv. J. Chim.* **1980**, *4*, 711–713.
- [4] Pd-O₂: a) M. Akita, T. Miyaji, S. Hikichi, Y. Moro-oka, *Chem. Commun.* **1998**, 1005–1006; Co-OOR: b) S. Hikichi, H. Komatsuzaki, M. Akita, Y. Moro-oka, *J. Am. Chem. Soc.* **1998**, *120*, 4699–4710; Co, Ni-oxo: c) S. Hikichi, M. Yoshizawa, Y. Sasakura, M. Akita, Y. Moro-oka, *J. Am. Chem. Soc.* **1998**, *120*, 10567–10568; Mn-OO(R): d) H. Komatsuzaki, Y. Nagasu, K. Suzuki, T. Shibasaki, M. Satoh, F. Ebina, S. Hikichi, M. Akita, Y. Moro-oka, *J. Chem. Soc. Dalton Trans.* **1998**, 511–512; e) H. Komatsuzaki, S. Ichikawa, S. Hikichi, M. Akita, Y. Moro-oka, *Inorg. Chem.* **1998**, *37*, 3652–3656; f) H. Komatsuzaki, N. Sakamoto, M. Satoh, S. Hikichi, M. Akita, Y. Moro-oka, *Inorg. Chem.* **1998**, *37*, 6554–6555; V-O₂: g) M. Kosugi, S. Hikichi, M. Akita, Y. Moro-oka, *J. Chem. Soc. Dalton Trans.* **1999**, 1369–1372.
- [5] Abbreviations used in this communication: Tp^{Pr} = hydrotris(3,5-di-2-propylpyrazolyl)borate; Tp^R = hydrotris(substituted-pyrazolyl)-borate; pz = pyrazolyl, pz^{Pr} = 3,5-di-2-propylpyrazolyl; dppe = ethane-1,2-diylbis(diphenylphosphan).
- [6] K. Ohta, Y. Takahashi, M. Hashimoto, S. Hikichi, M. Akita, Y. Moro-oka, *Organometallics* **1999**, *18*, 3234–3240.
- [7] M. Akita, K. Ohta, Y. Takahashi, S. Hikichi, Y. Moro-oka, *Organometallics* **1997**, *16*, 4121–4128.
- [8] X-ray diffraction measurements were made on a Rigaku RAXIS IV imaging plate area detector with graphite-monochromated MoK α radiation at -60 °C. The structures were solved by a combination of the direct methods (SHELXS 86) and DIRDIF. Least-squares refinements were carried out using SHELXL 93 linked to teXsan (single crystal structure analysis software, version 1.9, Molecular Structure Corporation, The Woodlands, TX, **1985** and **1992**). Crystal data for **2**: C₃₆H₆₂N₈O₂BRh, M_r = 752.7, monoclinic, space group $P2_1/a$, a = 19.834(3), b = 9.719(1), c = 21.68(1) Å, β = 106.81(3)°, V = 4000(2) Å³, Z = 4, ρ_{calcd} = 1.25 g cm⁻³, μ = 4.7 cm⁻¹, $R1$ = 0.0676 (on F^2) for the 6317 unique data ($wR2$ = 0.1887 for all 6810 data) with $F > 4\sigma(F)$ and 453 parameters. Crystal data for **3** $\cdot$ 2toluene: C₆₇H₈₆N₆O₂BP₂Rh, M_r = 1183.12, triclinic, space group $P\bar{1}$, a = 15.095(5), b = 16.875(5), c = 12.649(3) Å, α = 91.71(3), β = 97.66(3), γ = 89.66(2)°, V = 3191(1) Å³, Z = 2, ρ_{calcd} = 1.23 g cm⁻³, μ = 3.6 cm⁻¹, $R1$ = 0.096 (on F^2) for the 8866 unique data with $F > 4\sigma(F)$ ($wR2$ = 0.2360 for all 10380 data) and 672 parameters. Crystal data for **4** $\cdot$ 0.5OEt₂ $\cdot$ 2MeCN: C₃₉H₆₅N₁₂O_{2.5}BRh, M_r = 855.7, triclinic, space group $P\bar{1}$, a = 13.542(6), b = 14.107(2), c = 12.859(6) Å, α = 113.09(3), β = 98.39(4), γ = 81.46(3)°, V = 2224(1) Å³, Z = 2, ρ_{calcd} = 1.28 g cm⁻³, μ = 4.3 cm⁻¹, $R1$ = 0.0725 (on F^2) for the 7578 unique data with $F > 4\sigma(F)$ ($wR2$ = 0.2063 for all 8068 data) and 525 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-118496 (**2**), -118497 (**3**), -118498 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] a) A. Vigalok, L. J. W. Simon, D. Milstein, *Chem. Commun.* **1996**, 1673–1674; b) K. Osakada, K. Hataya, T. Yamamoto, *Inorg. Chem.* **1993**, *32*, 2360–2365; c) E. Lindner, Q. Wang, H. A. Meyer, R. Fawzi, M. Steimann, *J. Organomet. Chem.* **1993**, *453*, 289–293; d) M. J. Bennett, P. B. Donaldson, *Inorg. Chem.* **1977**, *16*, 1581–1585; M. J. Bennett, P. B. Donaldson, *Inorg. Chem.* **1977**, *16*, 1585–1589; e) C. Busetto, A. D'Alfonso, F. Maspero, G. Perego, A. Zazzetta, *J. Chem. Soc. Dalton Trans.* **1977**, 1828–1834.
- [10] N. Kitajima, H. Komatsuzaki, S. Hikichi, M. Osawa, Y. Moro-oka, *J. Am. Chem. Soc.* **1994**, *116*, 11596–11597.
- [11] Rh: a) D. Carmona, M. P. Lamata, J. Ferrer, J. Modrego, M. Perales, F. J. Lahoz, R. Atencio, L. A. Oro, *J. Chem. Soc. Chem. Commun.* **1994**, 575–576; Co: b) U. Thewalt, R. Marsh, *J. Am. Chem. Soc.* **1967**, *89*, 6364–6365; Mo: c) J.-M. Le Carpentier, A. Mitschler, R. Weiss, *Acta. Crystallogr. Sect. B* **1972**, *28*, 1288–1290; d) A hydroperoxo-copper complex containing the hydrogen-bonding interaction between the OOH α -oxygen atom and an amido hydrogen atom in the ligand substituent was recently reported: A. Wada, M. Harata, K. Hasegawa, K. Jitsukawa, H. Masuda, M. Mukai, T. Kitagawa, H. Einaga, *Angew. Chem.* **1998**, *110*, 874–875; *Angew. Chem. Int. Ed.* **1998**, *37*, 798–799.
- [12] Because X-ray crystallography suggested intermolecular hydrogen-bonding interactions (O2 $\cdots$ N42*: 2.978(9) Å, O2 $\cdots$ N52*: 2.92(1) Å), location of the hydrogen atoms would be disordered among the O and N atoms. Another possible structure with mirror symmetry contains one hydrogen atom in the middle of the O2, N42, and N52 atoms and the other bonded only to the O2 atom, but apparently it is not consistent with the spectral data.
- [13] The formation of **3** is an irreversible process.

Macroscopic, Hierarchical, Two-Dimensional Self-Assembly**

Insung S. Choi, Ned Bowden, and
George M. Whitesides*

Herein we demonstrate the operation of a hierarchy of interactions in the two-dimensional self-assembly of hexagonal poly(dimethylsiloxane) (PDMS) plates at a fluid–fluid (perfluorodecalin (PFD)/water) interface.^[1–3] The work uses molecular chemistry at surfaces to control menisci and hence interactions: the work has a strong chemical component, but extends from molecular interactions to interactions at surfaces and between materials and then to meso-scale objects. These objects interact through capillarity, that is, by minimizing the surface area of the PFD/H₂O interface.^[4] We controlled the faces of the objects that are attracted to one another by patterning them to be hydrophobic or hydrophilic. Lateral capillary interactions can hold millimeter-sized objects through contacts that are sufficiently strong to withstand modest shear.^[1–3, 5] The hydrophobic faces have large, positive^[6] menisci (the maximum height of the menisci is approximately the height of the faces for the objects used) and these faces are strongly attracted to one another. The hydrophilic faces have small, negative^[6] menisci (the maximum height of the menisci is < 40 % of the height of the faces) and these faces are weakly attracted to one another.^[7] Faces having positive menisci are repelled by faces having negative menisci. We have called the attractive interactions between menisci having the same sense (positive or negative) relative to the interface “capillary bonds”, in loose analogy to chemical bonds.^[1]

In previous work we assembled objects with flat faces into arrays by means of a single type of interaction. Herein we demonstrate the operation of a hierarchy of capillary interactions between concave and convex faces of different shapes that enables the assembly of complex structures. This “hierarchical self-assembly” illustrates a new type of control in meso-scale self-assembly.

Hierarchical self-assembly is the formation of an ordered structure through a set of interactions that decreases in strength—that is, through a hierarchy of interactions.^[8] Hierarchical interactions are ubiquitous in biological systems. The assembly of a viral capsid,^[9] for example, involves three steps: a) the synthesis of polypeptide chains through covalent bonds; b) the folding of these polypeptide chains into proteins with well-defined tertiary structures through largely noncovalent intramolecular interactions (van der Waals interactions, hydrogen bonds, and electrostatic interactions); and c) the assembly of these folded proteins into the viral capsid through noncovalent intermolecular interactions (Figure 1 a).

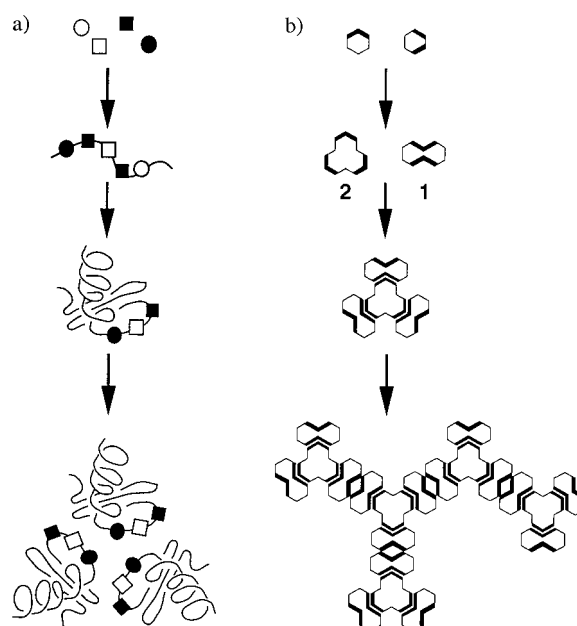


Figure 1. a) Schematic representation of the hierarchical self-assembly of a viral capsid. The squares and circles indicate amino acids that are covalently joined to form a polypeptide. The polypeptide folds into an ordered protein (a form of self-assembly). The proteins aggregate into the viral capsid; b) An example of hierarchical self-assembly of meso-scale polymeric objects. The hexagons represent the hexagonal plates of PDMS used in the experiments, and the thick lines indicate the hydrophobic faces that are involved in the attractive capillary interactions. Appropriately patterned hexagons were glued together to form C₃ (trefoil) or C₂ structures. The C₃ trefoil structure interacts through capillarity with three complementary plates to form an ordered [1 + 3] structure. These [1 + 3] structures aggregate into an ordered larger structure by interaction between the hydrophobic faces of the C₂ pieces.

Our hierarchy of interactions between the individual components—hexagonal PDMS plates with the faces patterned to be either hydrophobic or hydrophilic—was achieved in three steps (Figure 1 b): a) the strongest connections were permanent, and were formed by gluing hexagonal plates together; b) the strongest capillary interactions occurred between concave and convex hydrophobic faces with complementary shapes and large hydrophobic areas; c) the weakest interactions occurred between two concave hydrophobic faces (Figure 2). In the last two steps a number of different arrays could assemble from the components, so we designed the components to assemble preferentially into only one array. The meso-scale self-assembly illustrated in Figure 1 b is not analogous in any detailed sense to the biological self-assembly sketched in Figure 1 a other than that both involve a hierarchy of interactions, some irreversible and some reversible under the conditions of assembly. Nonetheless, the fundamental concept of “hierarchy” threads through both, and the biological details provide stimuli for future nonbiological studies.

We carried out the experiments that yielded the systems shown schematically in Figure 1 b in three steps. First, we assembled the structures 1 and 2 separately to demonstrate the various arrays that could assemble. Second, we allowed structures 2 and 3 to self-assemble into ordered arrays. Third, we assembled a more complex array from structures 1 and 2.

[*] Prof. Dr. G. M. Whitesides, I. S. Choi, N. Bowden
Department of Chemistry and Chemical Biology
Harvard University, 12 Oxford Street
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-9857
E-mail: gwhitesides@gmwhgroup.harvard.edu

[**] This work was supported by DARPA/ONR. N.B. acknowledges a predoctoral fellowship from the Department of Defense.

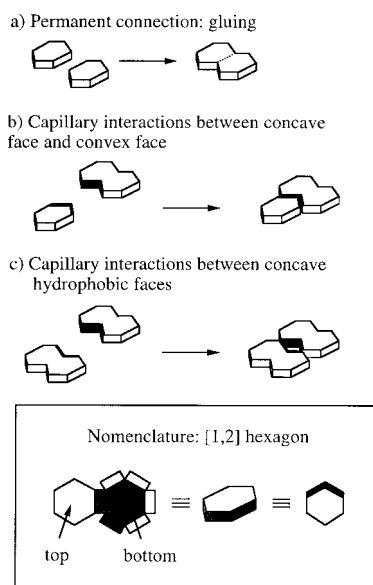


Figure 2. The strength of connections between hexagonal plates can be segregated into an ordered set by using three strategies: a) connecting the plates irreversibly by gluing them together; b) utilizing the capillary interactions between convex and concave faces; c) utilizing the capillary interactions between concave hydrophobic faces. The hexagons used in the work had a face width of 2.7 mm. The thick lines indicate hydrophobic faces and the thin lines indicate hydrophilic faces. In all of the experiments described here the bottom face of the plates was hydrophobic and the top was hydrophilic. The relative disposition of the hydrophobic sides is indicated by $[x,y,\dots]$; thus a $[1,2]$ hexagon is a hexagon with two adjacent sides (and the bottom) hydrophobic, and all other sides (and the top) hydrophilic.

The difference in the arrays that assemble from **1** and **2** separately and the arrays that assemble from a mixture of **1** and **2** demonstrates the control in the hierarchy of capillary-bond strength. We designed **1** and **2** to favor one array among the many that could form.

We fabricated individual structures by using the gluing technique to provide strong, permanent connections. Structure **1** was fabricated by gluing together two $[1,3]$ hexagonal plates,^[10] structure **2** by gluing together three $[1,2]$ hexagonal plates, and structure **3** by gluing together two $[1]$ hexagonal plates. The plates were fabricated as follows: PDMS was cured in a hexagonal mold and then removed. The hexagonal rod of PDMS was dyed blue or red by soaking it in either a solution of crystal violet in CH_2Cl_2 or Sudan red B in hexane/EtOH (1/1), respectively.^[1] The rod was dried to remove solvent. The faces that were to remain hydrophobic were covered with tape, while others that were to become hydrophilic were left exposed. The rods were cut into pieces and oxidized in a plasma cleaner (Harrick PDC-23G apparatus operating at the medium setting for 5 min). The tape was removed and the plates were cut and placed at the PFD/ H_2O interface with tweezers (for a more complete description, see reference [1]). The hexagons, with a thickness of about 1 mm and a diameter of 5.4 mm, were easily manipulated by hand. The two-plane liquid–liquid system (200 mL of PFD and 200 mL of H_2O) was contained in a Petri dish 14.5 cm in diameter, and swirled on an orbital shaker at a frequency ω between 0.6 and 1.8 s^{-1} . The assemblies were complete in 3–

5 h. We performed each experiment at least five times and in many cases more.

Figure 3a and b show the arrays that formed when objects **1** and **2** were allowed to self-assemble separately. We agitated the objects at $\omega = 0.6 \text{ s}^{-1}$ (Figure 3a) or $\omega = 1.5 \text{ s}^{-1}$ (Fig-

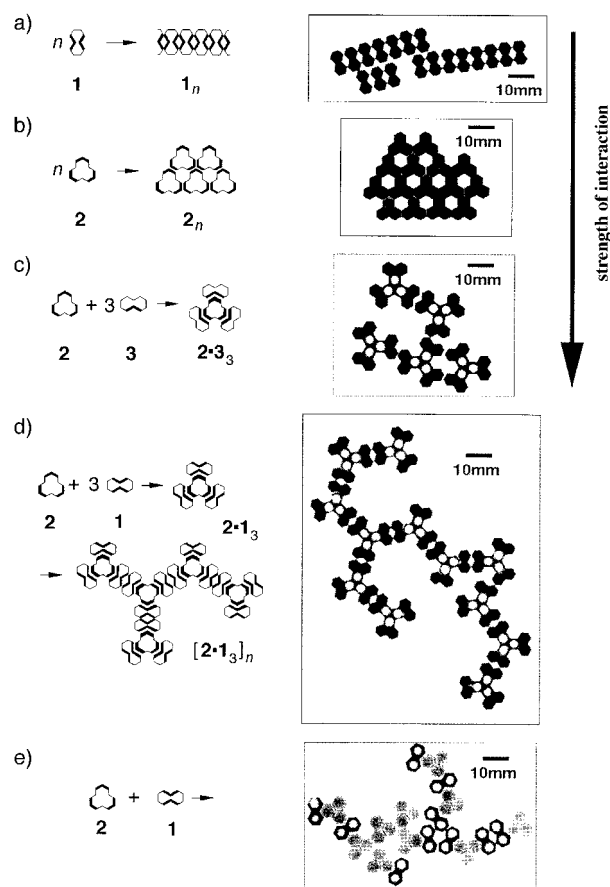


Figure 3. a) Formation of an extended linear array 1_n from **1** by interactions of menisci at concave hydrophobic sides. The optical micrograph also suggests weak attractive interactions between hydrophilic sides. In this system, where the density of PDMS is approximately equal to the density of H_2O , the menisci of water at hydrophilic sides (negative menisci) are small, and capillary interactions between these menisci are substantially weaker than those between menisci of PFD at hydrophobic sides; b) Self-assembled structure 2_n based on the oligomerization of hydrophobic faces of **2**; c) Structure $2 \cdot 3_3$ assembled from three objects of **3** and one of **2**. The further interaction of these structures through menisci at the hydrophilic faces was weak. Structure **3** was dyed a uniform color and structure **2** was dyed with three clear circles in the center of each hexagon; d) An extended hierarchical array $[2 \cdot 1_3]_n$ of twelve $[1+3]$ aggregates derived from **1** and **2**; e) Disordered, self-assembled aggregate formed from a 1:1 mixture of **1** and **2**.

ure 3b). In these assemblies we used 1.4-mm-thick objects of **1** and **2**. These optical micrographs establish that self-assembly yields ordered arrays, but give no indication of the relative strength of the two interactions that hold each aggregate together. We believe that the interaction between the plates in Figure 3a is weaker than that in Figure 3b since the aggregate 1_n broke apart under milder agitation ($\omega > 0.6 \text{ s}^{-1}$) than 2_n ($\omega > 1.5 \text{ s}^{-1}$).

To demonstrate the level of control over the final assembly that can be designed into this system, we allowed **2** and **3** to

self-assemble (Figure 3c). Here we used 0.9-mm-thick objects of **2** and 1.4-mm-thick objects of **3**.^[11] The frequency of agitation was periodically changed between 1.5 and 1.8 s⁻¹.^[12] A variety of structures could, in principle, form on self-assembly: **2_n**, **3·3**, **2·3₁**, **2·3₂**, and **2·3₃**. If the interactions between **2** and **3** were equal in strength we would expect a nearly statistical distribution of these structures. In fact, the structure **2·3₃** formed in approximately 70% yield.^[13] We designed the interaction between **2** and **3** to be the strongest interaction, and this interaction was observed most frequently. The interaction between **3** and **3** was weaker than that between **2** and **3** because the two concave faces of **3** were not complementary in shape.

We also examined the influence of the thickness of **3** on the self-assembly of **2** and **3** (Figure 4). We demonstrated previously that the capillary interactions between thick, flat

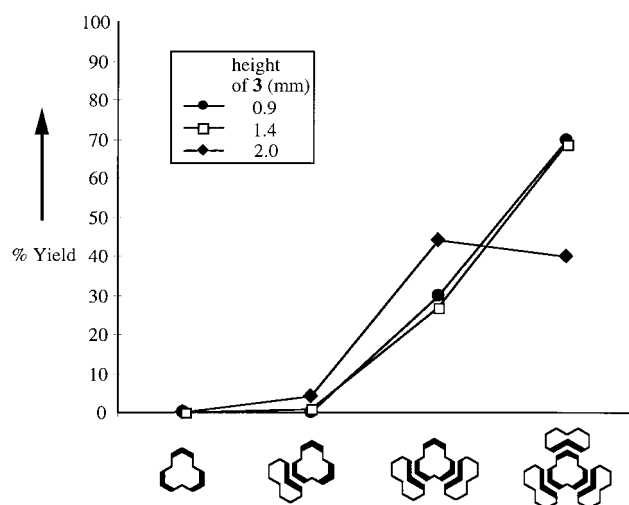


Figure 4. The yield for each of the possible arrays that assembled from **2** and **3** as a function of the height of **3** (for a constant height of **2** of 0.9 mm). The inset shows the symbols corresponding to the various thicknesses of **3**. We calculated the yields based on **2**. We repeated the experiment five or six times with six objects of **2** and eighteen of **3**. We agitated the objects for 1 h. The graph indicates that going to a thickness of **3** of less than 0.9 mm may result in a higher yield for **2·3₃**. We were limited by the method of fabrication and could not fabricate plates thinner than 0.9 mm.

objects are stronger than those between thin, flat objects of the same lateral dimensions.^[3] The assembly with 0.9-mm-thick objects of **3** gave a yield similar to that with 1.4-mm-thick **3**. When we allowed **2** and 2.0-mm-thick objects of **3** to assemble we obtained the desired structure **2·3₃** in a lower yield (40%). In this case, we believe that we had a lower yield because the interaction between the concave faces in **3·3** was strong.^[14] We conclude that the height of **3** made only a small contribution to the formation of the assembly.

To build more complex structures we introduced a further weak interaction: the interaction between menisci at concave faces (Figure 2c). We first allowed 36 objects of **1** (1.8-mm thick) and 12 of **2** (0.9-mm thick) to assemble at a rotation frequency of 1.5 s⁻¹ (the rate of agitation was periodically cycled between 1.5 and 1.8 s⁻¹ to accelerate annealing and to break up weakly associated structures) into the structure **2·1₃** (Figure 3d).^[15] The strongest capillary interaction between

complementary hydrophobic faces caused assembly of **2·1₃**. A weaker capillary interaction between two concave hydrophobic faces enabled **2·1₃** to assemble into larger aggregates, when the agitation was decreased to a frequency of 0.6 s⁻¹. We did not observe a cyclic array of **[2·1₃]_n** under any conditions.

Figure 3e shows the aggregate that forms on self-assembly of a 1:1 mixture of **1** and **2**. These objects, in this stoichiometry, could, in principle, assemble into a hexagonal lattice, but we did not observe this array experimentally. The aggregates consist of a partially assembled structure of **1** and **2** (**2·1₂** and **2·1₁**) and **2_n**. Aggregates of **2** as well as **2·1₂** and **2·1₁** (and sometimes **2·1₃**) were observed under agitation. We could not adjust the agitation in a way that generated a hexagonal lattice.

This demonstration illustrates the operation of a hierarchy of interactions of different strengths. The strategy of hierarchical self-assembly is one that was motivated by systems of biological molecules, but exists also in many other systems.^[16, 17] Although these initial assemblies are far from biological systems in terms of complexity, we believe that their formation, and the principles of design on which they are based, point the way to new strategies for assembling complex meso-scale aggregates.

Received: March 26, 1999 [Z13218IE]
German version: *Angew. Chem.* **1999**, *111*, 3265–3268

Keywords: capillarity • interfaces • noncovalent interactions • self-assembly • surface chemistry

- [1] N. Bowden, I. S. Choi, B. A. Grzybowski, G. M. Whitesides, *J. Am. Chem. Soc.* **1999**, *121*, 5373–5391.
- [2] I. S. Choi, N. Bowden, G. M. Whitesides, *J. Am. Chem. Soc.* **1999**, *121*, 1754–1755.
- [3] N. Bowden, A. Terfort, J. Carbeck, G. M. Whitesides, *Science* **1997**, *276*, 233–235.
- [4] There is also a gravitational term in the capillary forces, which results from the lowering of the liquid in the menisci to the level of the interface. The gravitational term is, in general, smaller than the energy associated with the change in the surface area.
- [5] a) V. N. Paunov, P. A. Kralchevsky, N. D. Denkov, K. Nagayama, *J. Colloid Interface Sci.* **1993**, *157*, 100–112; b) P. A. Kralchevsky, V. N. Paunov, N. D. Denkov, I. B. Ivanov, K. Nagayama, *J. Colloid Interface Sci.* **1993**, *155*, 420–437.
- [6] We call the menisci on the hydrophobic faces that form when PFD wets these faces “positive” menisci (menisci rising above the x,y plane of the interface) and those on the hydrophilic faces that form when H₂O wets these faces “negative” menisci (menisci sinking below the x,y plane of the interface).
- [7] Objects with an asymmetric pattern of hydrophobic faces tend to tilt and raise a hydrophilic face above the PFD/H₂O interface. Small, positive menisci form on the hydrophilic faces tilted out of the interface as a consequence of the PFD that wets the bottom, hydrophobic face. These positive menisci are often small and only weakly attracted to other positive menisci.
- [8] “Hierarchy” is defined in *The American Heritage College Dictionary*, 3rd ed., as a series in which each element is graded or ranked.
- [9] a) D. Chang, C.-Y. Fung, W.-C. Ou, P.-C. Chao, S.-Y. Li, M. Wang, Y.-L. Huang, T.-Y. Tzeng, R.-T. Tsai, *J. Gen. Virol.* **1997**, *78*, 1435–1439; b) W. Yang, J. Guo, Z. Ying, S. Hua, W. Dong, H. Chen, *J. Virol.* **1994**, *68*, 338–345; c) S. B. Larson, S. Koszelak, J. Day, A. Greenwood, J. A. Dodds, A. McPherson, *Nature* **1993**, *361*, 179–182; d) R. C. Liddington, Y. Yan, J. Moulai, R. Sahli, T. L. Benjamin, S. C. Harrison, *Nature* **1991**, *354*, 278–284; e) F. Birnbaum, M. Nassal, *J. Virol.* **1990**, *64*, 3319–3330.

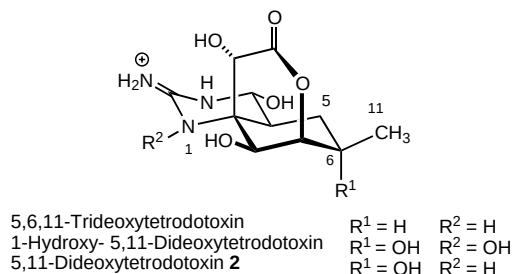
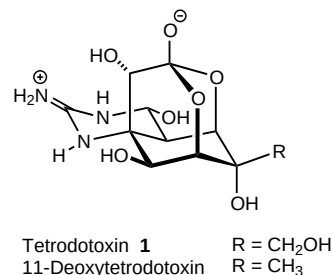
- [10] For the nomenclature used to describe hexagonal plates, see Figure 2 and Reference [1].
- [11] The thickness of the plates was controlled by cutting the oxidized hexagonal rod with a razor blade. The thickness is an average value since the hexagons vary slightly in their thickness (± 0.1 mm).
- [12] We periodically changed the rate of agitation to 1.8 s^{-1} to accelerate collisions, to break up weak structures, and to stimulate annealing.
- [13] We repeated the experiment six times. The yield was calculated by counting the number of times structure $2 \cdot 3_3$ was formed, relative to the incomplete structures $2 \cdot 3_2$ and $2 \cdot 3_1$. For example, in the assembly of 1.4-mm-thick objects of **3** and 0.9-mm-thick **2** we counted 21 arrays of $2 \cdot 3_3$, 3 arrays of $2 \cdot 3_2$, and 6 arrays of $2 \cdot 3_1$. The yield of $2 \cdot 3_3$ was 21/30 or 70%.
- [14] The structure $2 \cdot 3_3$ was not stable at $\omega = 1.5\text{ s}^{-1}$, but was stable at $\omega = 1.2\text{ s}^{-1}$. We agitated the objects at $\omega = 1.2\text{ s}^{-1}$ and periodically changed the frequency of agitation to 1.8 s^{-1} .
- [15] We repeated the experiment five times with six objects of **2** and eighteen of **1** to get statistics for this self-assembly. We agitated the plates for one hour. The yields of the assembly of $2 \cdot 1_3$ were 67%, 100%, 83%, 67%, and 67%. The micrograph shown in Figure 3 d is the most complete assembly (the highest yield) that we observed.
- [16] S. A. Jenekhe, X. L. Chen, *Science* **1999**, 283, 372–375.
- [17] D. E. Ingber, *Sci. Am.* **1998**, 278(1), 48–57.

Stereocontrolled Synthesis of (–)-5,11-Dideoxytetrodotoxin**

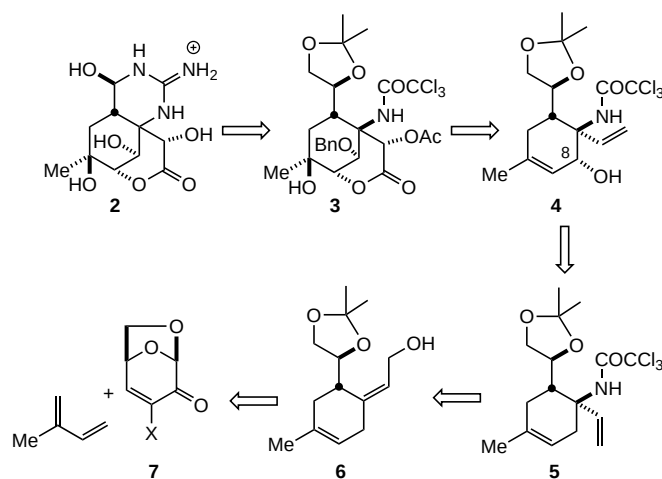
Toshio Nishikawa, Masanori Asai, Norio Ohyabu, Noboru Yamamoto, and Minoru Isobe*

Tetrodotoxin (**1**)^[1] is a well-known marine natural product that is the toxic principle of puffer fish poisoning. Due to its highly selective inhibition of voltage-dependent sodium channels, tetrodotoxin has served widely as an important biochemical tool in neurophysiological studies.^[2] Recently, tetrodotoxin analogues have been isolated from many kinds of animals.^[3] These studies brought to light a number of new interesting problems associated with tetrodotoxin,^[4] for example its biosynthesis, mechanisms of accumulation, detoxification, and binding to the sodium channel protein,^[5] and its actual biological function.^[6] In order to examine such new problems on a molecular level, suitably labeled tetrodotoxins are desirable. Such labeled compounds, however, are difficult to prepare from naturally occurring tetrodotoxin.^[7] The complex structure, which has a variety of functional groups and unique chemical properties, has thwarted recent attempts

at its total synthesis. In spite of many efforts,^[8] no total synthesis of tetrodotoxin has been reported since the total synthesis of the racemate by Kishi, Goto, and co-workers in 1972.^[9] During the course of our synthetic studies on tetrodotoxin, we have developed a stereocontrolled synthesis of polyhydroxylated cyclohexane,^[10] the introduction of a nitrogen functionality by the Overman rearrangement,^[11, 12] and a novel guanidine synthesis.^[13] Here we describe the stereocontrolled synthesis of enantiomerically pure 5,11-dideoxytetrodotoxin (**2**), a tetrodotoxin analogue not yet found in natural sources.



Our retrosynthetic plan for 5,11-dideoxytetrodotoxin (**2**) is shown in Scheme 1. The guanidine part of **2** is introduced at the latest stage of the synthesis because of the instability and low solubility of the intermediates. Lactone intermediate **3**



Scheme 1. Retrosynthetic plan for 5,11-dideoxytetrodotoxin (**2**).

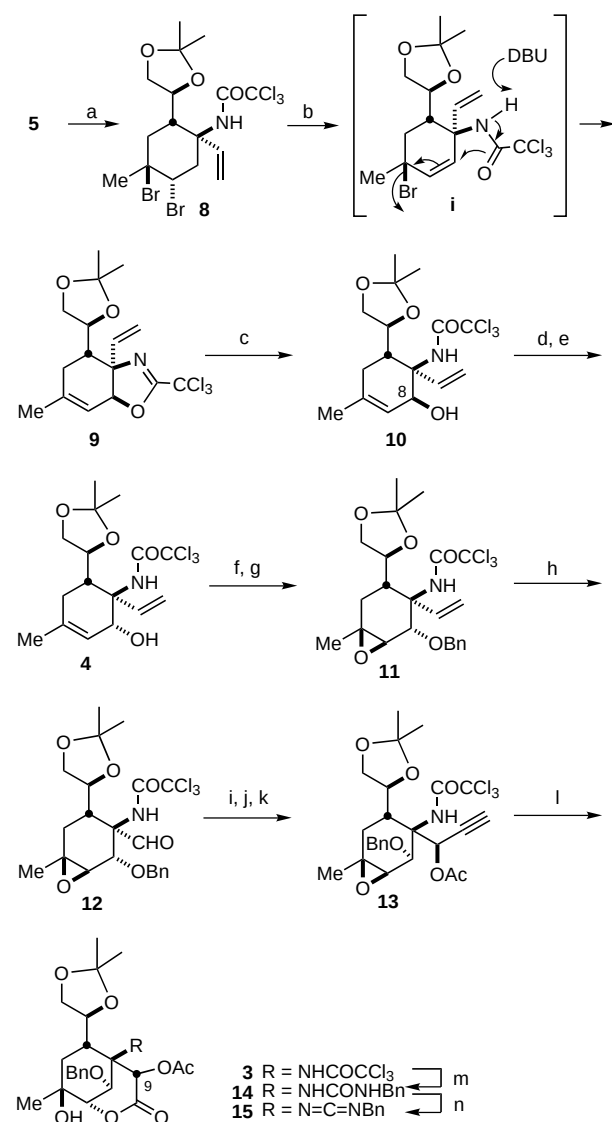
was envisioned to be synthesized from trichloroacetamide diene **5** via diene alcohol **4** in a stereoselective manner. Compound **5** has already been synthesized from levoglucosone **7** (X = H) as a chiral starting material^[14] by means of a

[*] Prof. M. Isobe, Dr. T. Nishikawa, M. Asai, N. Ohyabu, N. Yamamoto
Laboratory of Organic Chemistry
School of Bioagricultural Sciences
Nagoya University
Chikusa, Nagoya 464–8601 (Japan)
Fax: (+81) 52-789-4111
E-mail: isobem@agr.nagoya-u.ac.jp

[**] We are grateful to Prof. T. Yasumoto and Dr. M. Yotsu-Yamashita (Tohoku University) for fruitful discussions. We also acknowledge the valuable contributions of Y. Fukuda and Dr. S. Pikul to the early stages of this work. This work was financially supported by JSPS-RFTF, a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan, and Iyakushigen Zaidan (the Fujisawa foundation).

nine-step sequence that included the Diels–Alder reaction of bromolevogluconone **7** (X = Br) with isoprene and a highly stereoselective introduction of the amino group by the Overman rearrangement of the *exo*-allylic alcohol **6**^[12, 15] as key steps.

Stereoselective α -hydroxylation at the C8 position of the key intermediate **5** was critical because the hydroxy group has this configuration in all of the naturally occurring tetrodotoxin analogues. Bromination of **5** with pyridinium bromide perbromide gave dibromide **8**, which was treated with DBU in DMF to give oxazoline **9** in a high yield (Scheme 2;

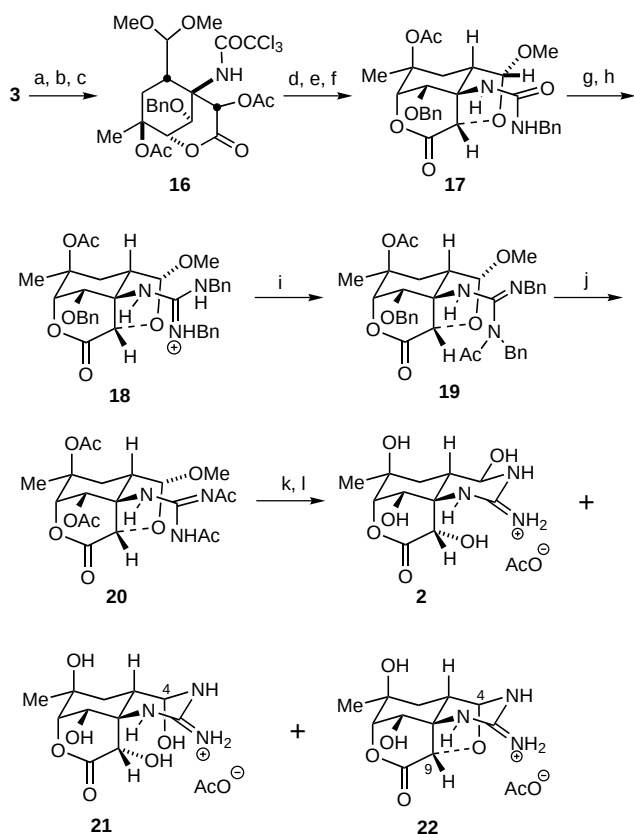


Scheme 2. Synthesis of lactone **15**. a) Pyridinium bromide perbromide, K_2CO_3 , CH_2Cl_2 , $10^\circ C$, 3 h, 87%; b) DBU, DMF, rt, 6 h; c) *p*TsOH, pyridine– H_2O , $70^\circ C$, 1.5 h, 71% over two steps; d) PCC, MS 4 Å, CH_2Cl_2 , rt, 11 h; e) $NaBH_4$, $CeCl_3(H_2O)_7$, $EtOH-CH_2Cl_2$, $0^\circ C$, 2 h, $\rightarrow$ rt, 30 min, 75% over two steps; f) MCPBA, CH_2Cl_2 , rt, 24 h; g) NaH, BnBr, THF, DMF, rt, 22 h, 86% over two steps; h) O_3 , MeOH, $-78^\circ C$, 70 min, Me_2S , 96%; i) $Me_3SiC\equiv CMgBr$, THF, rt, 2 h; j) *n*Bu₄NF, THF, rt, 2.5 h; k) Ac_2O , pyridine, rt, 5.5 h, 86% over three steps; l) $RuO_2(H_2O)_m$, $NaIO_4$, $CCl_4-CH_3CN-H_2O$, rt, 4.5 h, 75%; m) BnNH₂, Na_2CO_3 , DMF, $125^\circ C$, 30 min; n) Ph_3P , CBR_4 , Et₃N, CH_2Cl_2 , rt, 7 h, 87% over two steps. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = dimethylformamide, rt = room temperature, *p*TsOH = 4-toluenesulfonic acid, PCC = pyridinium chlorochromate, MCPBA = *meta*-chloroperbenzoic acid.

abbreviations are defined in the legend). This reaction involves regioselective dehydrobromination of the dibromide **8** and subsequent S_N2' reaction of the resulting allylic bromide **i** with the neighboring trichloroacetamide group in a stereospecific manner. The product **9** was hydrolyzed with *p*TsOH in aqueous pyridine^[16] to give trichloroacetamide **10** having an 8*S* hydroxy group without further hydrolysis. The hydroxy group of **10** was inverted by oxidation with PCC and highly stereoselective reduction with $NaBH_4/CeCl_3$ to afford largely the desired 8*R* alcohol **4** (20:1).^[17] This high stereoselectivity is attributed to the steric hindrance of the axially oriented vinyl group of the cyclohexene ring, whose conformation is fixed by the bulky equatorial trichloroacetamide group.

Prior to the transformation of the terminal olefinic bond into a hydroxycarboxylic acid function, the trisubstituted C=C bond of **4** was epoxidized with MCPBA to give a β -epoxide as a sole product,^[18] whose hydroxy group was protected as benzyl ether **11** in a high yield. In accord with our model studies,^[19] the vinyl group of **11** was strongly shielded by the bulky trichloroacetamide group and therefore was extremely inert toward a variety of reagents. This C=C bond was, however, cleaved by ozonolysis to afford the aldehyde **12**, which was transformed into the hydroxycarboxylic acid by the addition of a carboxylic acid equivalent. Vinylmagnesium bromide, which we had employed previously,^[19] did not react with the aldehyde **12**. On the other hand, a smaller *sp* nucleophile, an alkynylmagnesium bromide, added in a highly stereoselective manner to give a propargylic alcohol as a single stereoisomer. The resulting unstable product was immediately transformed into **13** by successive desilylation and acetylation in high yield. The acetylenic moiety was cleaved with ruthenium oxide^[20] to give a carboxylic acid, which spontaneously opened the epoxide to furnish six-membered lactone **3**^[21] in moderate yield.

With the key intermediate **3** in our hands, we were ready for the crucial construction of the guanidine moiety. The trichloroacetamide group of **3** was difficult to deprotect to the amine, because the hydroxy group at the C9 position was easily epimerized even under mild basic conditions such as K_2CO_3 in MeOH. Consequently, we could not synthesize the guanidine unit in the usual way, from a nonprotected amine with one of a variety of guanylation reagents. To overcome this difficulty, we developed a novel guanidine synthesis from the trichloroacetamide group proceeding through a dibenzylguanidine.^[13] This new route did not proceed through the corresponding free amine as an intermediate. First, we applied this route to the intermediate **3**, which was transformed into benzylurea **14** with benzylamine and Na_2CO_3 in DMF,^[13, 22] and the resulting urea was dehydrated with Ph_3P and CBR_4 to give benzylcarbodiimide **15** (Scheme 2). However, extensive examination under a variety of conditions revealed that the addition of an amine to carbodiimide **15** to obtain the corresponding dibenzylguanidine was very difficult because of the labile C9 acetoxy group.^[23] Second, we planned an alternative route going through a stable tricyclic intermediate **17**, which could survive the guanidine synthesis. The synthesis of **17** is shown in Scheme 3. Oxidative cleavage of the ketal^[24] in **3** was followed by protection of the resulting aldehyde and tertiary alcohol to give the dimethylacetal **16**, which was



Scheme 3. Synthesis of 5,11-dideoxytetrodotoxin (**2**). a) H_5IO_6 , AcOEt , rt, 24 h; b) CSA, $\text{CH}(\text{OMe})_3$, MeOH, rt, 10 h; c) Ac_2O , pyridine, DMAP, rt, 24 h, 78 % over three steps; d) BnNH_2 , Na_2CO_3 , DMF, 140°C , 15 min; e) KCN, EtOH, rt, 1 h; f) CSA, acetone, rt, 2 h, 70 % over three steps; g) Ph_3P , CBr_4 , Et_3N , CH_2Cl_2 , rt, 4 h; h) $\text{BnNH}_2 \cdot \text{HCl}$, pyridine, reflux, 5.5 h; i) Ac_2O , pyridine, Et_3N , rt, 4.5 h, 85 % over three steps; j) H_2 (1 atm), $\text{Pd}(\text{OH})_2/\text{C}$, Ac_2O , rt, 14 d, 81 %; k) aq. NH_3 , MeOH– H_2O , rt, 20 h; l) TFA, H_2O , rt, 34 h, 81 % over two steps. CSA = 10-camphorsulfonic acid, DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid.

transformed into the acetal urea under the above-mentioned conditions. Mild deacetylation with potassium cyanide in ethanol,^[25] and partial hydrolysis of the acetal gave the urea **17** (as a 5:1 diastereomeric mixture at the acetal carbon) as the precursor to the guanidine installation. The major isomer **17** was separated and dehydrated with Ph_3P and CBr_4 to afford the carbodiimide, which was further treated with benzylamine hydrochloride in pyridine^[26] to furnish the dibenzylguanidine **18** in a high yield. Our model studies revealed that the benzyl group of benzylguanidinium salts was difficult to remove under hydrogenolytic conditions, while the benzyl group of acetylbenzylguanidine could be easily removed under the same conditions.^[12b] In the event, the corresponding acetylbenzylguanidine **19** was hydrogenolyzed in acetic anhydride under one atmosphere of hydrogen to give diacetylguanidine **20** in a good yield.^[27] Under the reaction conditions, the benzyl ether in **19** was also converted to an acetyl group. At this stage, all the protective groups were unified to acetyl groups except for the acetal.

To complete the synthesis of 5,11-dideoxytetrodotoxin (**2**), two steps of deprotection were carried out. Thus, hydrolysis of the acetyl groups with ammonium hydroxide and then acid hydrolysis of the acetal with aqueous TFA was performed.

The crude product was separated by HPLC with an ion-exchange resin (Hitachi gel 3013c)^[3] to afford 5,11-dideoxytetrodotoxin (**2**), 4-*epi*-5,11-dideoxytetrodotoxin (**21**), and 4,9-anhydro-*epi*-5,11-dideoxytetrodotoxin (**22**)^[28] in yields of 29, 16, and 36 %, respectively. These structures were confirmed by full characterization by the NMR techniques COSY, HMBC, and HSQC, and by FAB mass spectrometry.

We have achieved a highly stereocontrolled synthesis of (–)-5,11-dideoxytetrodotoxin and its isomer. This is the first asymmetric synthesis of tetrodotoxin analogues and provides a practical route accessible to the labeled compounds for biochemical studies. Further studies toward naturally occurring tetrodotoxin (**1**) and other analogues are in progress in our laboratory.

Received: April 15, 1999 [Z13284IE]

German version: *Angew. Chem.* **1999**, *111*, 3268–3271

Keywords: asymmetric synthesis • natural products • synthetic methods • tetrodotoxins

- [1] For the structure: a) T. Goto, Y. Kishi, S. Takahashi, Y. Hirata, *Tetrahedron* **1965**, *21*, 2059–2088; b) K. Tsuda, S. Ikuma, M. Kawamura, K. Tachikawa, K. Sakai, C. Tamura, O. Akamatsu, *Chem. Pharm. Bull.* **1964**, *12*, 1357–1374; c) R. B. Woodward, *Pure Appl. Chem.* **1964**, *9*, 49–74.
- [2] T. Narahashi, *Physiol. Rev.* **1974**, *54*, 813–889.
- [3] a) 5,6,11-Trideoxytetrodotoxin: M. Yotsu-Yamashita, Y. Yamagishi, T. Yasumoto, *Tetrahedron Lett.* **1995**, *51*, 9329–9332; b) 1-hydroxy-5,11-dideoxytetrodotoxin: Y. Kotaki, Y. Shimizu, *J. Am. Chem. Soc.* **1993**, *115*, 827–830; c) 6-*epi*- and 11-deoxytetrodotoxin: T. Yasumoto, M. Yotsu, M. Murata, H. Naoki, *J. Am. Chem. Soc.* **1988**, *110*, 2344–2345.
- [4] “Tetrodotoxin, Saxitoxin, and the Molecular Biology of the Sodium Channel”: *Ann. N.Y. Acad. Sci.* **1986**, 479 (review series).
- [5] a) H. Nakayama, Y. Hatanaka, M. Takai, E. Yoshida, Y. Kanaoka, *Ann. N.Y. Acad. Sci.* **1993**, 707, 349; b) G. M. Lipkind, H. A. Fozzard, *Biophys. J.* **1994**, *66*, 1–33.
- [6] Tetrodotoxin was identified as a pheromonelike substance among the puffer fish. K. Matsumura, *Nature* **1995**, 378, 563.
- [7] For examples of some labeled tetrodotoxin derivatives, see: a) M. Balerna, A. Lombet, R. Chicheportiche, G. Romey, M. Lazdunski, *Biochim. Biophys. Acta* **1981**, *644*, 219–225; b) J. Bontemps, R. Cantineau, C. Grandfils, P. Leprince, G. Dandridge, E. Schoffeniels, *Anal. Biochem.* **1984**, *139*, 149–157; c) B. Q. Wu, L. Yang, C. Y. Kao, S. R. Levinson, M. Yotsu-Yamashita, T. Yasumoto, *Toxicol.* **1996**, *34*, 407–416.
- [8] Recent reports: a) B. Noya, R. Alonso, *Tetrahedron Lett.* **1997**, *38*, 2745–2748; b) C. S. Burgey, R. Vollerthun, B. Fraser-Reid, *J. Org. Chem.* **1996**, *61*, 1609–1618; c) K. Sato, Y. Kajihara, Y. Nakamura, J. Yoshimura, *Chem. Lett.* **1991**, 1559–1562; d) J. F. W. Keana, J. S. Bland, P. J. Boyle, M. Erion, R. Hartling, J. R. Husman, R. B. Roman, G. Ferguson, M. Parvez, *J. Org. Chem.* **1983**, *48*, 3627–3631; J. F. W. Keana, P. J. Boyle, M. Erion, R. Hartling, J. R. Husman, J. E. Richman, R. M. Wah, *J. Org. Chem.* **1983**, *48*, 3621–3626.
- [9] a) Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, H. Kakoi, *J. Am. Chem. Soc.* **1972**, *94*, 9217–9219; b) Y. Kishi, T. Fukuyama, M. Aratani, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, H. Kakoi, *J. Am. Chem. Soc.* **1972**, *94*, 9219–9221; c) Y. Kishi, F. Nakatsubo, M. Aratani, T. Goto, S. Inoue, H. Kakoi, S. Sugiura, *Tetrahedron Lett.* **1970**, 5127–5128; d) Y. Kishi, F. Nakatsubo, M. Aratani, T. Goto, S. Inoue, H. Kakoi, *Tetrahedron Lett.* **1970**, 5129–5132.
- [10] M. Isobe, T. Nishikawa, S. Pikul, T. Goto, *Tetrahedron Lett.* **1987**, *28*, 6485–6488.
- [11] Reviews: a) L. E. Overman, *Acc. Chem. Res.* **1980**, *13*, 218–224; b) K. Ritter in *Stereoselective Synthesis (Houben-Weyl) Vol. 21/9 E21, Vol. 9* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1996**, pp. 5677–5699.

- [12] M. Isobe, F. Fukuda, T. Nishikawa, P. Chabert, T. Kawai, T. Goto, *Tetrahedron Lett.* **1990**, 31, 3327–3330.
- [13] a) N. Yamamoto, M. Isobe, *Chem. Lett.* **1994**, 2299–2302; b) T. Nishikawa, N. Ohyaibu, N. Yamamoto, M. Isobe, *Tetrahedron* **1999**, 55, 4325–4340.
- [14] M. Isobe, N. Yamamoto, T. Nishikawa in *Levogluconone and Levogluconans, Chemistry and Applications* (Ed.: Z. J. Wiczak), ATL Press, **1994**, pp. 99–118.
- [15] T. Nishikawa, M. Asai, N. Ohyaibu, M. Isobe, *J. Org. Chem.* **1998**, 63, 188–192.
- [16] H. W. Pauls, B. Fraser-Reid, *Carbohydr. Res.* **1986**, 150, 111–119.
- [17] The original conditions described by Luche and Gamal using MeOH as a solvent gave a low yield of **4** and recovered starting material; J. L. Luche, A. L. Gamal, *J. Am. Chem. Soc.* **1979**, 101, 5848. On the other hand, the reduction with the solvent system (EtOH–CH₂Cl₂) reported by Danishefsky et al. gave our desired product **4** in better yield and with higher selectivity; S. J. Danishefsky, H. G. Selnick, R. E. Zelle, M. P. DeNinno, *J. Am. Chem. Soc.* **1988**, 110, 4368–4378.
- [18] The stereochemistry was controlled by a steric factor rather than an orientation of the neighboring hydroxy group; see ref. [9d].
- [19] N. Yamamoto, T. Nishikawa, M. Isobe, *Synlett* **1995**, 505–506.
- [20] P. H. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, 46, 3936–3938.
- [21] Determination of the configuration at the C9 position is included in the Supporting Information.
- [22] J. Petrov, I. Atanassova, A. Balabanova, N. Mollov, *Izv. Khim.* **1990**, 23, 53–57.
- [23] Detailed analysis of the crude product revealed that one of the products lacked H9, indicating that an oxidation occurred at the C9 position. Kishi et al. reported on the lability of the acetoxy group at the C9 position in their total synthesis of tetrodotoxin. See: a) ref. [9b]; b) H. Tanino, S. Inoue, M. Aratani, Y. Kishi, *Tetrahedron Lett.* **1974**, 335–338.
- [24] M. Xie, D. A. Berges, M. J. Robins, *J. Org. Chem.* **1996**, 61, 5178–5179.
- [25] K. Mori, M. Tominaga, T. Takigawa, M. Matsui, *Synthesis* **1973**, 790–791.
- [26] Pyridine was indispensable in this addition, while we used DMF in our model studies.^[13b]
- [27] In this specific case, acetic anhydride was an indispensable solvent. This reaction was much slower or unreproducible when a mixture of acetic anhydride and triethylamine was employed as in our previous (successful) model studies.^[13b]
- [28] 4-*epi*- and 4,9-Anhydrotetrodotoxins have been found as minor constituents with tetrodotoxins from natural sources.^[1, 3a, 3c] For example, 5,6,11-trideoxytetrodotoxin was also isolated with 4-*epi*-trideoxytetrodotoxin in the ratio (ca. 1:1.2).^[3a] Compound **22** is the first example of 4,9-anhydrotetrodotoxin among a series of 5-deoxy-tetrodotoxin analogues.

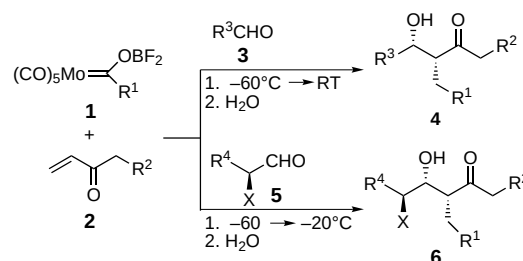
Regio- and Diastereoselective Aldol Products through Three-Component Coupling Reactions of Difluoroboroxy Fischer Carbene Molybdenum Complexes**

José Barluenga,* Félix Rodríguez,
Francisco J. Fañanás, and Eduardo Rubio

The formation of a large number of carbon–carbon bonds with high efficiency in the minimal number of chemical steps is the requirement of modern synthetic design.^[1] In this context, radical and carbanion chemistry has become a valuable tool in organic synthesis. However, both reactive intermediates can be used in a complementary manner and sequential reactions have been devised to prepare complex molecules.^[2, 3] On the other hand, despite the importance of Fischer carbene complexes for the development of novel organic transformations^[4] there is only a very limited number of examples in which these complexes have been used as precursors of radicals. Thus, tetramethylammonium acyl chromate complexes are adequate precursors for alkyl and acyl radicals, which are formed by oxidation with manganese(III)^[5] and copper(II)^[6] salts.

In 1997 we reported a simple method for generating acyl radicals from difluoroboroxy Fischer carbene molybdenum complexes in very mild reaction conditions and in the absence of an oxidant.^[7] Herein we describe a sequential radical-anionic three-component coupling reaction of difluoroboroxy Fischer carbene molybdenum complexes, vinyl ketones, and aldehydes to give *syn*- β -hydroxyketones diastereoselectively. This process is amenable for synthesizing enantiomerically pure compounds.

The treatment of pentacarbonyl(difluoroboroxycarbene)-molybdenum complexes **1** (formed by reaction of lithium pentacarbonyl acyl molybdate and boron trifluoride diethyl ether complex)^[7] with vinyl ketones **2** and aldehydes **3** in diethyl ether at temperatures from –60 to 20 °C led to β -hydroxyketones **4**. According to the NMR studies the *syn* products were formed exclusively (Scheme 1 and Table 1).^[3a, 8]



Scheme 1. Reaction of difluoroboroxycarbene-molybdenum complexes with vinyl ketones and aldehydes—Formation of *syn*- β -hydroxyketones **4** or **6**.

[*] Prof. Dr. J. Barluenga, Dr. F. Rodríguez,
Dr. F. J. Fañanás, Dr. E. Rubio
Instituto Universitario de Química
Organometálica “Enrique Moles”
Unidad Asociada al CSIC, Universidad de Oviedo
Julian Clavería 8, E-33071-Oviedo (Spain)
Fax: (+349) 8-510-34-50.
E-mail: barluenga@sauron.quimica.uniovi.es

[**] This work was supported by DGICYT (Grant PB97–1271).

Table 1. Synthesis of *syn*- β -hydroxyketones **4** and **6** from carbene complexes **1**, vinyl ketones **2**, and aldehydes **3** and **5**, respectively.

carbene complex	R ¹	vinyl ketone R ²	aldehyde R ³	R ⁴	X	Product	Yield [%] ^[a]	de [%] ^[b]
1a	<i>c</i> -C ₅ H ₉	2a H	3a Pr	–	–	4a	48	–
1a	<i>c</i> -C ₅ H ₉	2a H	3c 2-Fu ^[c]	–	–	4b	50	–
1b	<i>i</i> Pr	2a H	3a Pr	–	–	4c	54	–
1b	<i>i</i> Pr	2a H	3b Ph	–	–	4d	49	–
1b	<i>i</i> Pr	2a H	3c 2-Fu	–	–	4e	51	–
1b	<i>i</i> Pr	2b Bu	3c 2-Fu	–	–	4f	44	–
1c	Bu	2a H	3a Pr	–	–	4g	32 ^[d]	–
1b	<i>i</i> Pr	2a H	5a –	Me	OBn	6a ^[e]	43	78
1b	<i>i</i> Pr	2a H	5b –	Me	NBn ₂	6b	42	> 99
1b	<i>i</i> Pr	2b Bu	5b –	Me	NBn ₂	6c	37	> 99
1b	<i>i</i> Pr	2b Bu	5c –	Bn	NBn ₂	6d	36	> 99
1a	<i>c</i> -C ₅ H ₉	2a H	5c –	Bn	NBn ₂	6e	34	> 99

[a] Based on [Mo(CO)₆]. [b] Determined by ¹H NMR spectroscopy of the crude product. [c] 2-Fu = 2-furyl. [d] Nonane-2,5-dione (25 %) was also isolated. [e] Both diastereoisomers have been isolated.

As a consequence of the complete *syn* diastereoselectivity observed for **4** in all the cases examined we carried out a set of experiments using chiral aldehydes **5** to study the diastereofacial selectivity of this process. Thus, the reagents were mixed at –60 °C, and then the reaction mixture allowed to warm up to –20 °C, and kept at this temperature for 72 hours (Scheme 1 and Table 1). From this procedure we found diastereoselectivities above 99 % in most cases. A lower selectivity was observed only for **6a**. In this case, the absolute configuration of the new stereogenic centers in the major diastereoisomer of **6a** was determined from the $\Delta\delta$ values ($\delta_{S-MTPA} - \delta_{R-MTPA}$) obtained for the MTPA esters **7** (Figure 1).^[9] The configura-

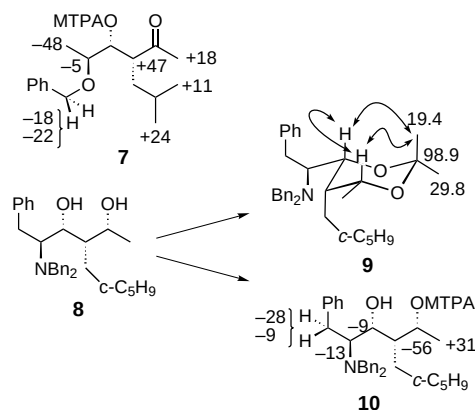
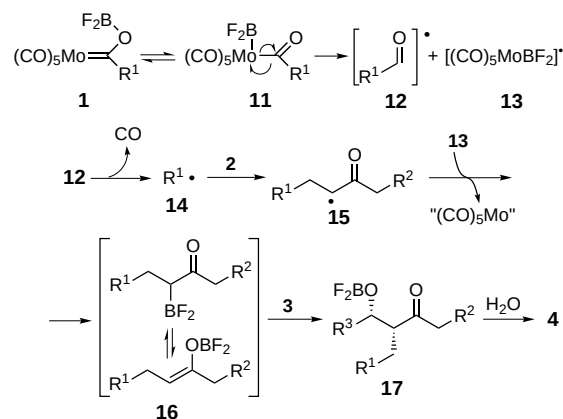


Figure 1. Diagnostic NMR data for **9** and $\Delta\delta$ values ($\delta_S - \delta_R$) for the (*S*) and (*R*)-MTPA esters of **7** (at 300 MHz) and **10** (at 400 MHz). Selected NOEs observed are indicated by arrows. Bn = benzyl; MTPA = α -methoxy- α -(trifluoromethyl)phenylacetic acid.

tional assignment for compounds **6b–e** was made on the basis of the following transformations on **6e**. First, we prepared diol **8** by reduction with lithium aluminium hydride. The relative configuration of C(2)–C(4) was clear from NMR studies on the corresponding acetonide **9** (prepared by treatment of **8** with 2,2-dimethoxypropane and pyridinium-*p*-toluene sulfonate (PPTS) as catalyst). Thus, the high difference in chemical shift between the C(2) methyl groups ($\Delta\delta = 10.4$), the chemical shift of the acetal carbon atom ($\delta = 98.9$), together with the observed NOEs between H(4) and H(6) and the upfield C(2) methyl group correspond to a chair conformation with a 1,3-*syn* disposition of H(4) and H(6) (Figure 1).^[10, 11]

Finally, the absolute configuration of diol **8** was established as above through the $\Delta\delta$ values of the mono-MTPA esters **10** (Figure 1).^[9, 11]

A plausible mechanism that explains the formation of β -hydroxyketones **4** is outlined in Scheme 2. Thus, the equilibrium between the tautomeric species **1** and **11** is shifted



Scheme 2. Mechanism proposed for the formation of *syn*- β -hydroxyketones **4** and **6**.

towards **11**, presumably as a consequence of a favorable interaction between the boron and the molybdenum atoms,^[7, 12] which leads to the acyl radicals **12** and the radical species **13** after the homolytic scission of the carbon–molybdenum bond. These acyl radicals **12** surprisingly undergo decarbonylation^[13] to generate the alkyl radicals **14**,^[14] which then add to vinyl ketones **2** to generate the radical intermediates **15**. Further electron transfer from **13** to intermediate **15** with loss of the Mo(CO)₅ fragment produces boron enolates **16**, which afford the adducts **17** on addition to aldehydes **3**. Finally, hydrolysis of **17** leads to the β -hydroxyketone derivatives **4**. An explanation of the 1,2-*syn* induction in the aldol reaction is possible on the basis of the well known Zimmermann–Traxler chairlike transition state model^[15] if the geometry of the formed enolate is assumed to be exclusively *Z*. In our case, the small size of the fluorine atoms would favor the formation of the *Z* isomer.^[8b, 16]

The preference for the Felkin-type products (3,4-*anti*) when chiral aldehydes **5** were used can be accounted for by

assuming a nonchelated transition state,^[17] as observed in similar reactions.^[18] These results reflect a very high degree of substrate control in the aldol addition of achiral boron enolates to chiral aldehydes.^[18]

It is worth pointing out that the three-component coupling reaction described here represents an interesting alternative to the aldol reaction where the main problem of the lack of regioselectivity for nearly symmetrical ketones is solved (Figure 2). Further studies on the mechanism and synthetic applications of this novel transformation will be reported in due course.

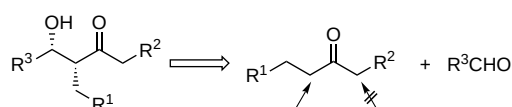


Figure 2. Regio and diastereoselective aldol reaction.

Experimental Section.

Preparation of **4** and **6**: $\text{BF}_3 \cdot \text{OEt}_2$ (0.36 mL, 3 mmol) was slowly added at -60°C to a solution of **1**, generated by reaction of hexacarbonylmolybdenum (3 mmol) and the corresponding organolithium compound (3 mmol), in diethyl ether (30 mL), and the mixture stirred for 10 min. The vinyl ketone **2** and the aldehyde **3** or **5** were then added dropwise at the same temperature. Stirring was continued while the temperature reached room temperature (compounds **4**) or -20°C (compounds **6**). The mixture was hydrolyzed with water (30 mL), extracted with diethyl ether (3 $\times$ 10 mL), and the organic layer dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the crude product purified by column chromatography (silica gel, hexane/ethyl acetate 40/1). All compounds gave satisfactory analytical data, including elemental analysis, mass and NMR spectra.

Received: May 17, 1999 [Z134251E]

German version: *Angew. Chem.* **1999**, *111*, 3272–3274

Keywords: carbene complexes • C-C coupling • molybdenum • radical reactions • synthetic methods

- [1] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) T.-L. Ho, *Tandem Reactions in Organic Synthesis*, Wiley, New York, **1992**; c) L. F. Tietze, *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131; d) N. Hall, *Science* **1994**, *226*, 32.
- [2] For some reviews of representative examples of serial processes with different intermediates, see a) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223; b) M. Malacria, *Chem. Rev.* **1996**, *96*, 289; c) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307; d) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339.
- [3] For some representative examples, see a) K. Nozaki, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403; b) D. P. Curran, M. J. Totleben, *J. Am. Chem. Soc.* **1992**, *114*, 6050; c) D. P. Curran, T. L. Fevig, C. P. Jasperse, M. J. Totleben, *Synlett.* **1992**, 943; d) B. S. Bronk, S. J. Lippard, R. L. Danheiser, *Organometallics* **1993**, *12*, 3340; e) G. A. Molander, J. A. McKie, *J. Org. Chem.* **1995**, *60*, 872; f) K. Takai, T. Ueda, N. Ikeda, T. Moriwake, *J. Org. Chem.* **1996**, *61*, 7990; g) K. Takai, N. Matsukawa, A. Takahashi, T. Fujii, *Angew. Chem.* **1998**, *110*, 160; *Angew. Chem. Int. Ed.* **1998**, *37*, 152.
- [4] a) K. H. Dötz, *Angew. Chem.* **1984**, *96*, 573; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 587; b) K. H. Dötz in *Organometallics in Organic Synthesis: Aspects of a Modern Interdisciplinary Field* (Eds.: H. tom Dieck, A. de Meijere), Springer, Berlin, **1988**; c) W. D. Wulff in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, New York, **1991**, p. 1065; d) M. P. Doyle in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, p. 387; e) W. D. Wulff in *Comprehensive Organometallic Chemistry II*,

Vol. 12 (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, p. 469; f) L. S. Hegedus in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, p. 549.

- [5] K. Narasaka, H. Sakurai, *Chem. Lett.* **1993**, 1269.
- [6] H. Sakurai, K. Narasaka, *Chem. Lett.* **1994**, 2017.
- [7] J. Barluenga, F. Rodríguez, F. J. Fañanás, *Organometallics* **1997**, *16*, 5384.
- [8] The relative stereochemistry of **4** was assigned from the reported coupling constant (ca. 6 Hz). See a) C. H. Heathcock, C. T. Buse, N. A. Kleschick, M. C. Pirrung, J. E. Sohn, J. Lampe, *J. Org. Chem.* **1980**, *45*, 1066; b) D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099.
- [9] I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.
- [10] S. D. Rychnovsky, B. Rogers, G. Yang, *J. Org. Chem.* **1993**, *58*, 3511.
- [11] K. Kouda, T. Ooi, T. Kusumi, *Tetrahedron Lett.* **1999**, *40*, 3005.
- [12] J. Barluenga, F. Rodríguez, J. Vadeкарd, M. Bendix, F. J. Fañanás, F. López-Ortiz, *J. Am. Chem. Soc.* **1996**, *118*, 6090.
- [13] I. Ryu, N. Sonoda, *Angew. Chem.* **1996**, *108*, 1140; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1050.
- [14] This decarbonylation process is highly dependent on the structure of the radicals formed; thus for primary radicals ($\text{R}^1 = \text{Bu}$, carbene **1c** in Table 1) decarbonylation is a slower process and the trapping of **12** with **2** competes with the formation of **14**.
- [15] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920.
- [16] D. A. Evans, E. Vogel, J. V. Nelson, *J. Am. Chem. Soc.* **1979**, *101*, 6120.
- [17] a) M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556; b) M. T. Reetz, *Angew. Chem.* **1991**, *103*, 1559; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531.
- [18] a) C. Genari, A. Bernardi, S. Cardani, C. Scolastico, *Tetrahedron* **1984**, *40*, 4059; b) M. T. Reetz, E. Rivadeneira, C. Niemeyer, *Tetrahedron Lett.* **1990**, *31*, 3863; c) C. Genari, D. Moresca, A. Vulpetti, G. Pain, *Tetrahedron Lett.* **1994**, *35*, 4623; d) C. Genari, G. Pain, D. Moresca, *J. Org. Chem.* **1995**, *60*, 6248; e) M. T. Reetz, *Chem. Rev.* **1999**, *99*, 1121.

High-Yielding Enantioselective Synthesis of the Macrolactam Aglycon of Sch 38516 from Two Units of (2R)-2-Ethyl-4-penten-1-ol**

Manuel Martín, Gemma Mas, Fèlix Urpí,* and Jaume Vilarrasa*

Dedicated to Professor Elias J. Corey and in memory of Felix Serratosa

The tridecanelactam antifungal agents Sch 38516, Sch 38518, and Sch 39185 isolated by researchers at Schering–Plough^[1] from *Actinomyces vulgaris*, shown to be active

[*] Prof. F. Urpí, Prof. J. Vilarrasa, M. Martín, G. Mas
Departament de Química Orgànica
Facultat de Química, Av. Diagonal 647
Universitat de Barcelona
E-08028 Barcelona (Spain)
Fax: (+349) 3-339-7878
E-mail: vilarrasa@gsaa1.qo.ub.es

[**] Financial support from the Ministerio de Educación y Ciencia (grants SAF93-0201 and PM95-0061, and doctorate studentship to M.M. from 1994 to 1997) and from the Generalitat de Catalunya (GRQ93-1096 and 1996SGR0102) is acknowledged. Preliminary studies by D. García (1992), with the collaboration of Dr. M. Bartra as supervisor, deserve to be mentioned as well. Thanks are also due to Dr. L. González for obtaining a sample of iodo derivative **9** and to Dr. A. González for the preparation of **11**.

against *Candida* sp. and dermatophytes, and the 14-membered lactams fluvirucins A₁, A₂, B₁, B₂, B₃, B₄, and B₅ isolated by scientists at Bristol–Myers Squibb^[2] from different strains of actinomycetes, shown to be active against influenza A virus, belong to the same family of compounds.^[1, 2] Fluvirucin B₂ was also isolated from *Streptomyces* sp. MJ677-72F5 and found to inhibit phosphatidylinositol-specific phospholipase C (among ca. 3000 samples screened).^[3] Most fluvirucin aglycons (called fluvirucinins) have structures similar to the representative examples shown in Figure 1.^[4]

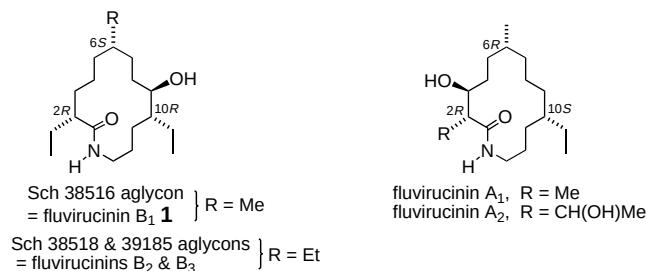
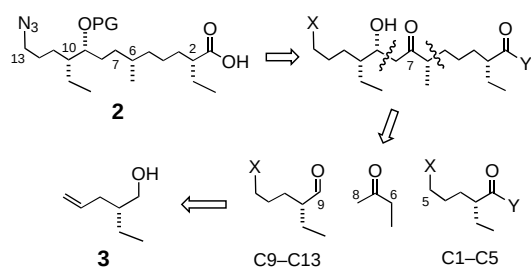


Figure 1. Schematic representations of various fluvirucinins.

The novelty of these macrolactams, which are not strictly macrolide-like antibiotics,^[1, 2, 5] their variety of biological roles, and the difficulty of controlling the creation of the distant stereocenters during total synthesis drew the attention of several research groups. So far, two brilliant syntheses of **1** (Figure 1) have been reported, the first one by Hoveyda et al.^[6] and the second one by Trost et al.^[7] Both syntheses are primarily based on the application of transition metal mediated C–C bond formations. By contrast, our synthesis of **1** relies upon the direct macrolactamization reaction of a 13-azidotridecanoic acid derivative and a peculiar asymmetric aldol-like reaction as key steps.

Our retrosynthetic analysis began with the disconnection of the amide bond to **2** (Scheme 1). Formal introduction of an oxo group at C7 and disconnection of the ketone between C5

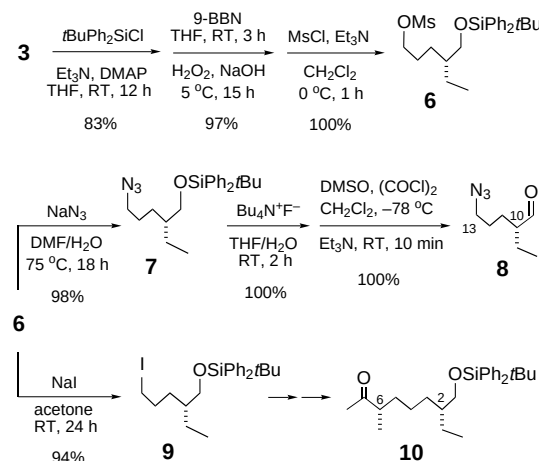


Scheme 1. The retrosynthetic analysis for the synthesis of **1**. PG = protecting group.

and C6 and between C8 and C9 led to synthetically equivalent fragments C1–C5 and C9–C13. Both fragments could be readily prepared from enantiopure (2*R*)-2-ethyl-4-penten-1-ol (**3**) or its carboxyl or carbonyl derivatives. The essential points were to form the C5–C6 bond by a stereoselective alkylation and the C8–C9 bond by a stereoselective aldol reaction. The versatility of this simple strategy is remarkable since, for example, use of 2-pentanone derivatives instead of

butanone-related derivatives should afford an entry to fluvirucinins B₂–B₅. However, the “state of the art” of synthetic methodology does not yet permit such flexible and straightforward manipulations in a controlled fashion.

The synthesis of **1** started from the phenylalanine-derived oxazolidinone (**20** g) of Evans et al., which was converted as reported into enantiopure **3** in excellent overall yield.^[8] Protection of the hydroxyl group of **3**, hydroboration with 9-BBN followed by oxidation, and reaction with methanesulfonyl chloride afforded **6**, also in excellent overall yield (Scheme 2). A fraction of **6** was converted into azide **7**,



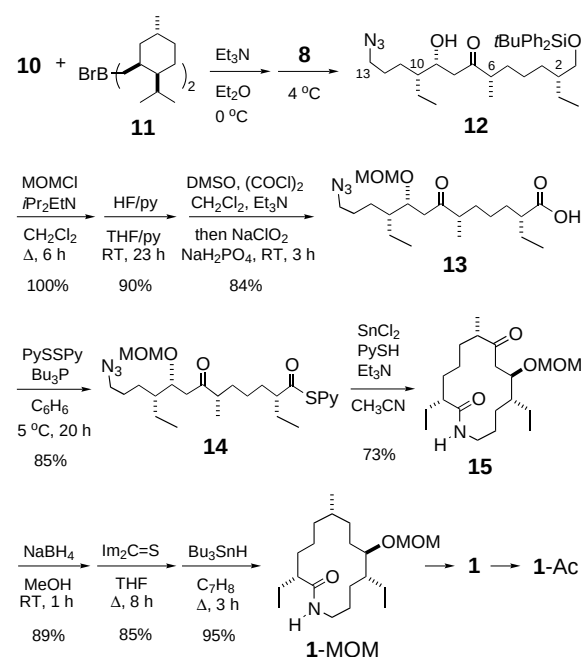
Scheme 2. Synthesis of ketone **10** from **3**. 9-BBN = 9-borabicyclo[3.3.1]nonane, DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl.

deprotected with tetrabutylammonium fluoride, and oxidized to aldehyde **8**. The other portion of **6** was transformed to iodo derivative **9** by reaction with NaI in acetone. After careful optimization of all steps, **8** and **9** were obtained in about 60 % overall yield each from the oxazolidinone.

The challenge at this stage was the diastereoselective alkylation of Aux^{*}-CO-Et (Aux^{*} = chiral auxiliary) with **9** to establish the C5–C6 bond.^[9] Myers et al. have demonstrated that enolates from pseudoephedrine-derived amides react efficiently with alkyl iodides and that removal of the auxiliary is feasible.^[10] Therefore, we treated the *N*-propanoyl derivative of (–)-pseudoephedrine with lithium diisopropylamide (LDA, 2.25 equiv) and LiCl (6 equiv) and then with **9** (0.5 equiv) to give the alkylation product in 87 % yield; addition of MeLi (3.0 equiv) afforded the desired methyl ketone **10** (only one stereoisomer by 500-MHz ¹H NMR) in 92 % yield. To summarize, **10** was available in three high-yielding steps from **6**.

We anticipated difficulties in the aldol-like reaction between **8** and **10**, since the two C α substituents of aldehyde **8** are sterically very similar. Moreover, it was presumed that the C α methyl group of **10** would not be sufficient to discriminate the two faces of its enolate. A series of experiments with lithium, sodium, or titanium(IV) enolates of **10** under different conditions afforded, as expected, almost equimolar mixtures of the “Felkin” (*syn* OH and Et groups) and “anti-Felkin” aldols (*anti*). So, we had to rely on a “triple asymmetric approach”.

Boron enolates of **10**—generated by using either (–)-Ipc₂BCl, (+)-Ipc₂BCl, (–)-Ipc₂BBr, (–)-Ipc₂BOTf^[11] (Ipc = isopinocampheyl), or the menthone-derived boryl bromide of Gennari et al.^[12] (**11**)—were allowed to react under different conditions with equimolar amounts of **8** (Scheme 3). The



Scheme 3. Synthesis of **1**. Im = imidazole, MOM = methoxymethyl, py = pyridine, Py = 2-pyridyl.

best results were 1) 61 % conversion with a 6.6:1 *syn:anti* ratio by using (–)-Ipc₂BCl and *i*Pr₂EtN in Et₂O for after 4 d at 4 °C, and 2) 79 % conversion with a 20.6:1 *syn:anti* ratio by using **11** and Et₃N in Et₂O for 4 d at 4 °C. Pure *syn* aldol **12**^[13] could be isolated by flash column chromatography (in 40–45 % yield), and unchanged starting materials (**8** and **10**) were easily recovered in the first eluted fractions.

Protection of the hydroxyl group of **12** was accomplished in quantitative yield with methoxymethyl chloride and *i*Pr₂EtN in refluxing CH₂Cl₂. Deprotection of the hydroxyl group at C1 with HF/pyridine and oxidation of the primary alcohol afforded the carboxylic acid **13**. Thus, in 75 % overall yield from **12**, we obtained an ω -azido acid amenable to the cyclization, which is in principle the last key step of our synthetic strategy. The carboxylic acid moiety was activated as its *S*-2-pyridyl ester (**14**) in 85 % yield.^[14] Cyclization of **14** by slow addition (over 6 h) to a large volume of refluxing acetonitrile containing SnCl₂ (20 equiv), Et₃N (80 equiv), and 2-thiopyridone^[15] (80 equiv) afforded the desired macrolactam **15** in 73 % yield. The ketone functionality of **15** was removed by reduction to the corresponding alcohol, followed by reaction with 1,1'-thiocarbonyldiimidazole and radical reduction with Bu₃SnH,^[16] to yield the desired MOM-protected **1** (**1-MOM**). A very small amount of **1-MOM** was hydrolyzed with aqueous HCl (MOM removal), and the evaporation residue (**1**), after confirmation of its structure by NMR spectroscopy and FAB-MS, was heated in the presence

of excess acetic anhydride and pyridine; the spectroscopic data of the resulting product were identical to those previously reported for the *O*-acetyl derivative of **1** (**1-Ac**).^[6]

In summary, a simple and efficient strategy to reach the aglycon of Sch 38516/fluvirucin B₁ (i.e., fluvirucin B₁, **1**), which is readily amenable to the synthesis of related targets, has been demonstrated. The challenging acetate aldol reaction to form the C8–C9 bond has been achieved with a conversion of 79 % and a diastereomeric ratio of 20:1 by using the chiral boron derivative of Gennari et al. Another key step, macrolactamization, proceed in a gratifying 73 % yield from a *S*-2-pyridyl 13-azidothioester by reduction (with Sn^{II}–PySH complexes) and cyclization *in situ*.

Experimental Section

12: To a solution of **11** in CH₂Cl₂ (432 μ L, 0.4 M solution, 0.177 mmol), at 0 °C and under N₂, were added by means of a syringe Et₃N (24 μ L, 0.173 mmol) and a solution of ketone **10** (44 mg, 0.104 mmol) in Et₂O (1 mL). The reaction mixture was stirred for 5 h. Aldehyde **8** (16 mg, 0.103 mmol) in Et₂O (1 mL) was then added dropwise. After stirring for 4 d at 4 °C, the reaction was quenched with phosphate buffer (pH 7, 10 mL), and the mixture extracted with Et₂O (3 $\times$ 10 mL). The volatile components were removed *in vacuo*, and the crude product was diluted with MeOH (2 mL), phosphate buffer (0.5 mL), and 30 % aqueous H₂O₂ (0.5 mL). The resulting mixture was stirred at 0 °C for 1.5 h, diluted with H₂O (15 mL), and extracted with CH₂Cl₂ (3 $\times$ 15 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (15 mL) and brine (15 mL), and then dried over Na₂SO₄. Analysis by HPLC (hexanes/EtOAc 95/5, Tracer Spherisorb S3W column, 4.6 mm $\times$ 25 cm, 9 mL min^{–1}) of the product indicated a 20.6:1 ratio of the stereoisomers **5R** (*t*_r = 17.1 min) and **5S** (*t*_r = 12.2 min). Separation by flash chromatography on silica gel (CH₂Cl₂) afforded first **10** (20 mg) and finally ketone **12** (26 mg, 44 %, 79 % based on recovered starting material) as a colorless oil: *R*_f = 0.33 (hexanes/EtOAc 85/15); [α]_D²⁰ = +25.43 (*c* = 0.98 in CHCl₃); IR (film): $\tilde{\nu}$ = 3600–3200, 3100–2800, 2100, 1700, 1450 cm^{–1}; ¹H NMR (CDCl₃, 500 MHz): δ = 7.7–7.6 (m, 4H; ArH), 7.4–7.3 (m, 6H; ArH), 4.1–4.0 (m, 1H; CHOH), 3.51 (d, *J* = 2.5 Hz, 2H; CH₂OSi), 3.3–3.2 (m, 2H; CH₂N₃), 3.0 (d, *J* = 4.0 Hz, 1H; CHOH), 2.52 (d, *J* = 9.5 Hz, 2H; COCH₂), 2.47 (h, *J* = 7.0 Hz, 1H; CH₃CH), 1.7–1.1 (m, 16H), 1.04 (d, *J* = 7.0 Hz, 3H; CH₃CH), 1.03 (s, 9H; *t*Bu), 0.89 (t, *J* = 7.2 Hz, 3H; CH₃), 0.79 (t, *J* = 7.2, 3H; CH₃); ¹³C NMR (CDCl₃, 50.3 MHz): δ = 216.6, 135.6, 133.9, 129.5, 127.5, 68.5, 65.6, 51.7, 47.0, 44.0, 43.7, 41.8, 33.1, 30.6, 26.8, 26.4, 26.0, 24.5, 23.5, 22.0, 19.3, 16.0, 11.7, 11.2; MS (FAB): 602 [*M*+Na]; HPLC analysis of the Mosher ester of **12**: *t*_r = 5.9 min (hexanes/EtOAc 95/5).

15: To a stirred mixture of SnCl₂ (120 mg, 0.62 mmol), PySH (277 mg, 2.44 mmol), and Et₃N (340 μ L, 2.45 mmol) in acetonitrile (20 mL), heated at 80 °C under argon atmosphere, was added by means of a syringe pump over 3 h a solution of **14** (15.0 mg, 0.030 mmol) in toluene (20 mL). Heating was maintained for one further hour, and the flask was then cooled externally. The solvent was evaporated *in vacuo*. The residue was treated with CH₂Cl₂/MeOH (95/5, 40 mL) and washed with aqueous KOH (2 M, 2 $\times$ 40 mL). The aqueous layers were extracted with CH₂Cl₂ (2 $\times$ 40 mL). The combined organic extracts were washed with saturated aqueous NaCl (100 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The resulting colorless oil was dissolved in Et₂O (20 mL) and extracted twice with 1 M HCl (20 mL). The aqueous phase was extracted with Et₂O (3 $\times$ 20 mL). The extracts were dried (MgSO₄) and purified by chromatography on silica gel (CH₂Cl₂, CH₂Cl₂/EtOAc 3/1 $\rightarrow$ 1/1) to give lactam **15** (8.0 mg, 73 %) as a white foam: *R*_f = 0.29 (CH₂Cl₂/EtOAc 3/1); [α]_D²⁰ = +6.8 (*c* = 0.6 in CHCl₃); IR (film): $\tilde{\nu}$ = 2850, 1710, 1640, 1560, 1460, 1420 cm^{–1}; ¹H NMR (CDCl₃, 500 MHz): δ = 5.4–5.3 (brs, 1H; NH), 4.64 (d, *J* = 6.5 Hz, 1H; OCH₂H₂O), 4.59 (d, *J* = 6.5 Hz, 1H; OCH₂H₂O), 3.89 (dt, *J* = 9.0 Hz, *J* = 4.5 Hz, 1H; CHO), 3.8–3.6 (m, 1H; CH₂H₂NH), 3.30 (s, 3H; CH₃O), 3.0–2.9 (m, 1H; CH₂H₂NH), 2.77 (d, *J* = 4.5 Hz, 2H; CH₂CO), 2.6–2.4 (m, 1H; CH₃CH), 1.9–1.8 (m, 1H; CHCONH), 1.7–1.1 (m, 15H), 1.02 (d, *J* = 7.0 Hz, 3H; CH₃CH), 0.85 (t, *J* = 7.2 Hz, 3H; CH₃CH₂), 0.84 (t, *J* = 7.5 Hz, 3H; CH₃CH₂); ¹³C NMR (CDCl₃, 75.4 MHz): δ = 212.7, 175.2, 97.0, 74.6, 55.9,

50.6, 48.7, 46.6, 43.7, 38.9, 34.4, 33.0, 29.7, 26.7, 26.1, 25.4, 21.2, 17.3, 12.2, 9.6; MS (CI, NH₃): 356 [M+1], 373 [M+18]; HR-MS (CI, CH₄) calcd for C₂₀H₃₇NO₄ [M+H]: 355.2723, found: 355.2715.

Received: April 1, 1999 [Z132381E]
German version: *Angew. Chem.* **1999**, *111*, 3274–3277

Keywords: aldol reactions • antifungal agents • asymmetric synthesis • macrocycles • total synthesis

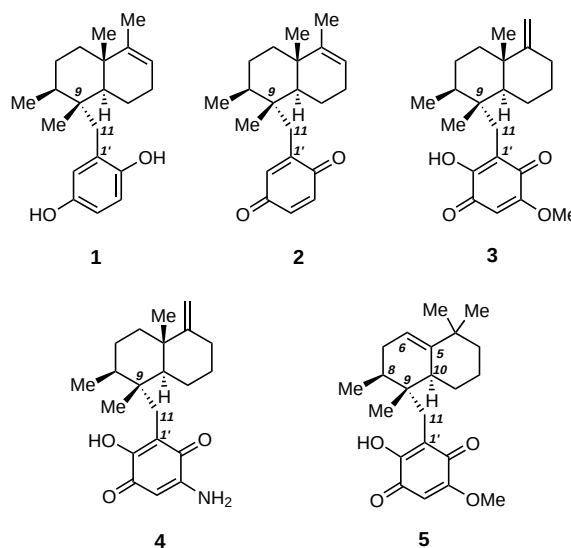
- [1] a) V. R. Hegde, M. G. Patel, V. P. Gullo, A. K. Ganguly, O. Sarre, M. S. Puar, A. T. McPhail, *J. Am. Chem. Soc.* **1990**, *112*, 6403–6405; b) V. R. Hegde, M. G. Patel, V. P. Gullo, M. S. Puar, *J. Chem. Soc. Chem. Commun.* **1991**, 810–812.
- [2] a) N. Naruse, O. Tenmyo, K. Kawano, K. Tomita, N. Ohgusa, T. Miyaki, M. Konishi, T. Oki, *J. Antibiot.* **1991**, *44*, 733–740; b) K. Tomita, N. Oda, Y. Hoshino, N. Ohkusa, H. Chikazawa, *J. Antibiot.* **1991**, *44*, 940–948, and references therein.
- [3] H. Ui, M. Imoto, K. Umezawa, *J. Antibiot.* **1995**, *48*, 387–390.
- [4] Apart from the substituents on the macrolactam ring, the congeners differ in the aminosaccharide that is linked to the hydroxyl group: Sch 38516, Sch 39185, and fluvirucin A₁ contain 3-amino-3,6-dideoxy- α -L-talopyranose; Sch 38518 is a mycosamine glycoside; etc.^[1,2]
- [5] a) *Antibiotics and Antiviral Compounds* (Eds.: K. Krohn, H. A. Kirst, H. Maag), VCH, Weinheim, **1993**; b) M. Bartra, F. Urpí, J. Vilarrasa in *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products, Vol. 2* (Ed.: G. Lukacs), Springer, Berlin, **1993**, pp. 1–65.
- [6] a) A. F. Hourí, Z. Xu, D. A. Cogan, A. H. Hoveyda, *J. Am. Chem. Soc.* **1995**, *117*, 2943–2944; b) Z. Xu, C. W. Johannes, A. F. Hourí, D. S. La, D. A. Cogan, G. E. Hofilena, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316.
- [7] B. M. Trost, M. A. Ceschi, B. König, *Angew. Chem.* **1997**, *109*, 1562–1564; *Angew. Chem. Int. Ed.* **1997**, *36*, 1486–1489.
- [8] D. A. Evans, D. L. Rieger, T. K. Jones, S. W. Kaldor, *J. Org. Chem.* **1990**, *55*, 6260–6268.
- [9] The auxiliaries of Evans et al. do not work with nonactivated substrates such as **9**. The camphorsultam-derived auxiliary (W. Oppolzer, *Tetrahedron* **1987**, *43*, 1969–2004) afforded the desired alkylation product in only 39% yield, and, moreover, cleavage of the chiral auxiliary turned out to be troublesome.
- [10] A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511, and references therein.
- [11] For leading references on chiral boron enolates, see a) P. V. Ramachandran, W. Xu, H. C. Brown, *Tetrahedron Lett.* **1996**, *37*, 4911–4914; b) I. Paterson, K. R. Gibson, R. M. Oballa, *Tetrahedron Lett.* **1996**, *37*, 8584–8588.
- [12] a) C. Gennari, C. T. Hewkin, F. Molinari, A. Bernardi, A. Comotti, J. M. Goodman, I. Paterson, *J. Org. Chem.* **1992**, *57*, 5173–5177; b) C. Gennari, D. Moresca, S. Vieth, A. Vulpetti, *Angew. Chem.* **1993**, *105*, 1717–1719; *Angew. Chem. Int. Ed.* **1993**, *32*, 1618–1621; c) A. González, J. Aiguadé, F. Urpí, J. Vilarrasa, *Tetrahedron Lett.* **1996**, *37*, 8949–8952.
- [13] The absolute configuration of **12** (and that of its epimer) was established by ¹H NMR spectroscopy (cf. W. R. Roush, T. D. Bannister, M. D. Wendt, *Tetrahedron Lett.* **1993**, *34*, 8387–8390) and was confirmed by comparing the $\Delta\delta(^1\text{H})$ values of the diastereomeric Mosher esters arising from (*R*)- and (*S*)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (cf. I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096).
- [14] For leading references on the preparation of thiopyridyl esters, see a) T. Mukaiyama, R. Matsueda, M. Suzuki, *Tetrahedron Lett.* **1970**, 1901–1904; b) E. J. Corey, D. A. Clark, *Tetrahedron Lett.* **1979**, 2875–2878.
- [15] For the reduction of azides with tin(II)–thiolate complexes, see a) M. Bartra, F. Urpí, J. Vilarrasa, *Tetrahedron Lett.* **1987**, *28*, 5941–5944; b) M. Bartra, P. Romea, F. Urpí, J. Vilarrasa, *Tetrahedron* **1990**, *46*, 587–594.
- [16] a) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585; b) H. Ishiwata, H. Sone, H. Kigoshi, K. Yamada, *Tetrahedron* **1994**, *50*, 12853–12882.

Enantioselective Total Synthesis of Avarol and Avarone**

Taotao Ling, Alan X. Xiang, and
Emmanuel A. Theodorakis*

In memory of Sir Derek H. R. Barton

Quinone and hydroquinone subunits are featured in a variety of natural products,^[1] including a family of marine metabolites represented by avarol (**1**),^[2] avarone (**2**),^[2] ili-maquinone (**3**),^[3] smenospongine (**4**),^[4] and mamanuthaquinone (**5**).^[5] Among the exciting and diverse biological properties exhibited by all members of this family, the antimitotic, antileukemic, and antiviral effects reported for **1** and **2** are particularly noteworthy.^[6] Although the chemical origins of



these biological properties remain obscure, the redox properties of the hydroquinone–quinone system present in **1** and **2** may be held accountable for such a profile.^[7]

The combination of attractive structure and biological activity displayed by the above family has spurred the development of multiple syntheses for some of these compounds.^[8,9] A common element in all reported strategies is the early assembly of the entire skeleton of the natural products

[*] Prof. Dr. E. A. Theodorakis, T. Ling, A. X. Xiang
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive #0358, La Jolla, CA 92093–0358 (USA)
Fax: (+1) 858-822-0386
E-mail: etheodor@ucsd.edu

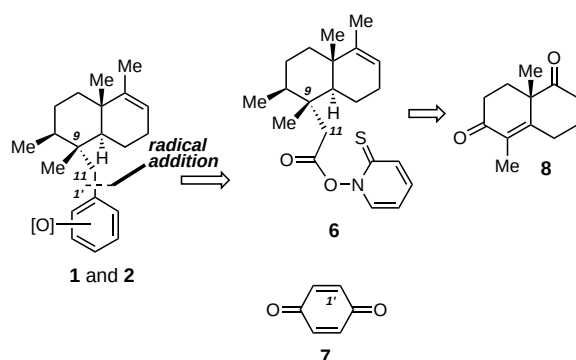
[**] Dedicated with respect and appreciation to the memory of Professor Sir Derek H. R. Barton. Financial support from the Cancer Research Coordinating Committee, the American Cancer Society (RPG CDD-9922901), the NSF (Shared Instrumentation Grant CHE-9709183), and the Hellman Foundation (Faculty Research Fellowship to E.A.T.) is gratefully acknowledged. We also thank Professor D. John Faulkner (Scripps Institute of Oceanography) for a sample of natural avarol and avarone and for critical suggestions.



Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

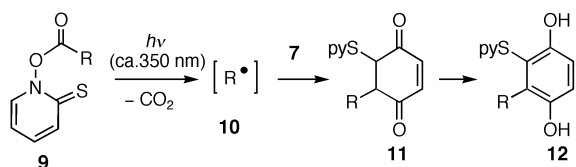
by constructing the C9–C11 bond. This is generally achieved by allowing the C9 enolate (formed by in situ reduction of enone **8**, see Scheme 1) to react with a suitably substituted benzyl bromide.^[10] While this regime has allowed the synthesis of the natural products, it consistently suffers from low yields during the final deprotection of the masked quinone.

In considering the above observations, we sought to develop a method for constructing the entire framework by forming the C11–C1' carbon–carbon bond (Scheme 1). If



Scheme 1. Strategy for the synthesis of avarol (**1**) and avarone (**2**).

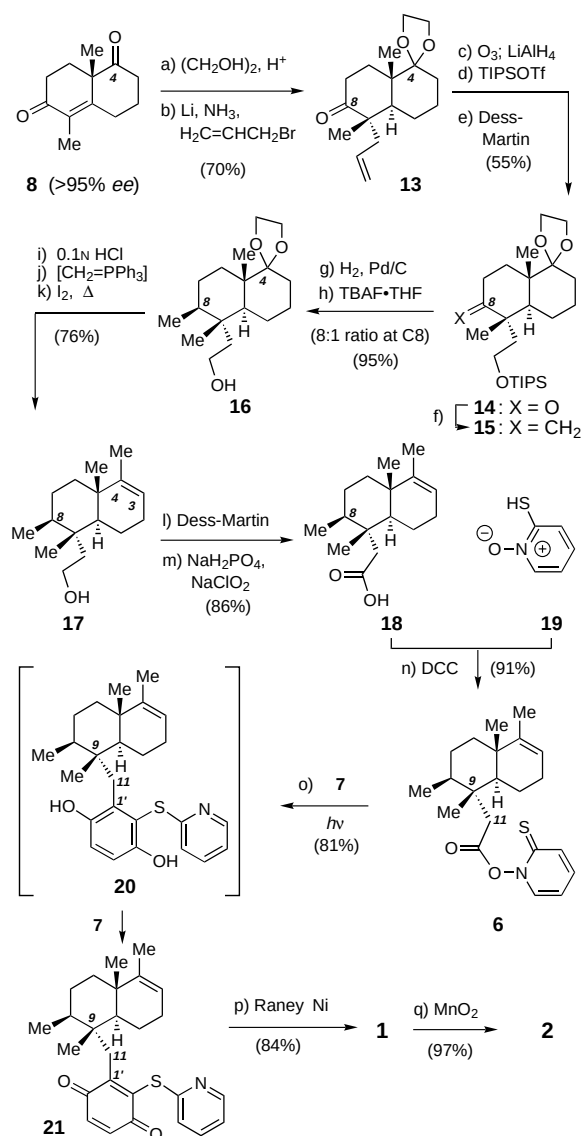
successful, this strategy could allow for the rapid construction of several analogues of **1** and **2** differing only in the quinone moiety, which could be used to address the significance of the redox chemistry of these molecules during a biological event. In addition, this strategy could circumvent the low-yielding deprotection steps toward **1** or **2**. To this end, application of Barton's radical decarboxylation and quinone addition appeared to be the best reaction candidate (Scheme 2).^[11]



Scheme 2. Use of Barton's radical decarboxylation and addition to quinones for the synthesis of **12**. py = 2-pyridyl.

Conceptually, this reaction involves photochemical activation of a thiohydroxamic ester **9** and in situ trapping of the generated carbon-centered radical **10** with a quinone radicalophile (such as benzoquinone (**7**)).^[12] In accordance with a radical chain mechanism, this conjugate-type addition was expected to furnish initially the 1,2 substituted quinone **11**, which could rapidly tautomerize to hydroquinone **12**. Further manipulation of **12** could produce avarol (**1**) and avarone (**2**). Execution of this strategy is shown in Scheme 3.^[13]

Our synthetic approach began with optically pure enone **8**, which was readily available through an L-phenylalanine-mediated asymmetric Robinson annulation (60–65% yield, >95% *ee*).^[14] Selective protection of the C4 ketone group followed by reductive alkylation with allyl bromide afforded ketone **13** in 70% overall yield. Transformation of alkene **13** to silyl ether **14** was accomplished in 64% combined yield by ozonolysis, reduction, and silylation of the resulting alcohol. The C8 ketone functionality that also suffered reduction



Scheme 3. Synthesis of avarol (**1**) and avarone (**2**). a) $(\text{CH}_2\text{OH})_2$ (1.0 equiv), TsOH (0.1 equiv), 80 °C, benzene, 12 h, 90%; b) Li (5.0 equiv), NH_3 , $-80 \rightarrow -30^\circ\text{C}$, H_2O (1.0 equiv), $\text{CH}_2=\text{CHCH}_2\text{Br}$ (5.0 equiv), $-80 \rightarrow -30^\circ\text{C}$, 5 h, 78%; c) O_3 , CH_2Cl_2 , -78°C , then LiAlH₄ (3.0 equiv), Et₂O, $0 \rightarrow 25^\circ\text{C}$, 1 h, 65%; d) TIPSOTf (1.0 equiv), 2,6-lutidine (1.3 equiv), CH_2Cl_2 , -80°C , 0.5 h, 98%; e) Dess–Martin periodinane (1.6 equiv), CH_2Cl_2 , 1 h, 25 °C, 87%; f) $\text{CH}_3\text{PPh}_3\text{Br}$ (3.0 equiv), NaHMDS (2.5 equiv), THF, 65 °C, 10 h, 89%; g) Pd/C (10%, 0.1 equiv by weight), H_2 , $\text{CH}_3\text{CO}_2\text{Et}$, 25 °C, 12 h, 95%; h) TBAF·THF (1N, 1.3 equiv), THF, 25 °C, 0.5 h, 100%; i) 0.1N HCl, THF, 3 h, 25 °C, 93%; j) $\text{CH}_3\text{PPh}_3\text{Br}$ (3.0 equiv), NaHMDS (2.5 equiv), THF, 65 °C, 10 h, 92%; k) I_2 (0.01 equiv), xylenes, 150 °C, 12 h, 89%; l) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2 , 1 h, 25 °C, 96%; m) NaClO_2 (2.0 equiv), NaH_2PO_4 (2.0 equiv), $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)_2$ (2.0 equiv), *t*BuOH/ H_2O (2/1), 25 °C, 1 h, 90%; n) **19** (1.0 equiv), **18** (1.0 equiv), DCC (1.0 equiv), CH_2Cl_2 , 12 h, 25 °C, dark, 91%; o) **7** (3.0 equiv), CH_2Cl_2 , $h\nu$ (300 W), 2 h, 0 °C, 81%; p) Raney nickel (excess), CH_2Cl_2 , 45 °C, 10 min, 84%; q) MnO_2 (5.0 equiv), Et₂O, 25 °C, 0.5 h, 97%. DCC = dicyclohexylcarbodiimide, HMDS = hexamethyldisilamide, TBAF = tetrabutylammonium fluoride, TIPSOTf = triisopropylsilyl trifluoromethanesulfonate, TsOH = *p*-toluenesulfonic acid.

during the above procedure was subsequently restored upon treatment with Dess–Martin periodinane (87% yield). Manipulation of the C8 stereocenter was attained by Wittig olefination of the C8 ketone followed by a Pd-catalyzed

hydrogenation of the exocyclic methylene unit. This procedure installed the methyl group at the C8 carbon atom in 85 % combined yield, as an unseparable mixture of stereoisomers (8:1 in favor of the desired β epimer). The stereoisomers were easily separated after a fluoride-induced deprotection of the primary silyl ether, and alcohol **16** was furnished in 75 % overall yield (starting from **14**). Acid-catalyzed deprotection of the C4 ketal of **16** followed by a second Wittig methylation provided the *exo*-alkene, which was isomerized to the C3–C4 endocyclic olefin **17** upon treatment with iodine (76 % yield over three steps).

The stage was now set for the attachment of the aromatic residue on the avarol core. This was accomplished by a two-step oxidation of primary alcohol **17** to carboxylic acid **18** with Dess–Martin periodinane and sodium chlorite (86 % overall yield). DCC-induced esterification of **18** with commercially available 2-sulfanylpipridine *N*-oxide (**19**) furnished the photolabile ester **6** (91 % yield).^[12] Light-induced decarboxylation (350 nm) of **6** in the presence of benzoquinone (**7**, 3.0 equiv) produced the substituted quinone **21** in 81 % yield. The structure of **21** can be mechanistically rationalized by considering an initial formation of the hydroquinone adduct **20**, which is further oxidized in situ with excess **7**.^[12, 15, 16] An additional remarkable feature of this radical addition is its efficiency, especially when considering the presumed steric hindrance of the intermediate neopentyl carbon-centered radical at C11.

For the transformation of **21** to **1** a reductive desulfurization procedure was sought. To this end, brief treatment of **20** with Raney nickel produced synthetic avarol (**1**) in high yield. Avarone (**2**) was produced from **1** in 97 % yield by heterogeneous oxidation with MnO₂.

In conclusion, we have developed an enantioselective synthesis of avarol (**1**) and avarone (**2**) that departs from the readily available Wieland–Miescher-type enone **8** and proceeds in 16 steps and 12 % overall yield.^[17] Essential to our strategy is the application of Barton's radical decarboxylation and quinone addition reaction employed to install the quinone nucleus during the last steps of the synthesis. Our strategy provides the first application of the above methodology to natural products synthesis and clearly demonstrates its power and versatility. Our strategy also paves the way for the construction of designed analogues of **1** and/or **2** that could be used to address biologically relevant issues.

Received: April 29, 1999 [Z13347IE]

German version: *Angew. Chem.* **1999**, *111*, 3277–3279

Keywords: natural products • quinones • radical reactions • synthetic methods • total synthesis

- [1] Recent reviews: a) *The Chemistry of the Quinonoid Compounds*, Vol. 1, 2 (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1988**; b) *Naturally Occurring Quinones IV: Recent Advances* (Ed.: R. H. Thomson), 4th ed., Blackie Academic & Professional, London, **1997**.
- [2] a) L. Minale, R. Riccio, G. Sodano, *Tetrahedron Lett.* **1974**, 3401–3404; b) R. Puliti, S. De Rosa, C. A. Mattia, *Acta Crystallogr. Sect. C* **1994**, *50*, 830–833.
- [3] a) R. T. Luijbrand, T. R. Erdman, J. J. Vollmer, P. J. Scheuer, J. Finer, J. C. Clardy, *Tetrahedron* **1979**, *35*, 609–612; b) R. J. Capon, J. K. MacLeod, *J. Org. Chem.* **1987**, *52*, 5059–5060.
- [4] M. L. Kondracki, M. Guyot, *Tetrahedron* **1989**, *45*, 1995–2004.
- [5] J. C. Swersey, L. R. Barrows, C. M. Ireland, *Tetrahedron Lett.* **1991**, 6687–6690.
- [6] a) W. E. G. Müller, D. Sladic, R. K. Zahn, K. H. Bässler, N. Dogovic, H. Gerner, M. J. Gasic, H. C. Schröder, *Cancer Res.* **1987**, *47*, 6565–6571; b) M. L. Ferrandiz, M. J. Sanz, G. Bustos, M. Paya, M. J. Alcaraz, S. de Rosa, *Eur. J. Pharmacol.* **1994**, *253*, 75–82; c) S. Loya, A. Hizi, *FEBS Lett.* **1990**, *269*, 131–134; d) H. C. Schröder, M. E. Begin, R. Klocking, E. Matthes, A. S. Sarma, M. Gasic, W. E. G. Müller, *Virus Res.* **1991**, *21*, 213–223.
- [7] M. A. Belisario, M. Maturo, R. Pecce, S. de Rosa, G. R. D. Villani, *Toxicology*, **1992**, *72*, 221–233.
- [8] Three different syntheses of **1** and **2** have been reported to date: a) A. S. Sarma, P. Chattopadhyay, *J. Org. Chem.* **1982**, *47*, 1727–1731; b) E. P. Locke, S. M. Hecht, *Chem. Commun.* **1996**, 2717–2718; c) J. An, D. F. Wiemer, *J. Org. Chem.* **1996**, *61*, 8775–8779.
- [9] For syntheses of **3**, see a) S. D. Bruner, H. S. Radeke, J. A. Tallarico, M. L. Snapper, *J. Org. Chem.* **1995**, *60*, 1114–1115; b) H. S. Radeke, C. A. Digits, S. D. Bruner, M. L. Snapper, *J. Org. Chem.* **1997**, *62*, 2823–2831; c) S. Poigny, M. Guyot, M. Samadi, *J. Org. Chem.* **1998**, *63*, 5890–5894.
- [10] A noteworthy exception to this strategy is the *exo*-Diels–Alder approach employed to the synthesis of **5**: T. Yoon, S. J. Danishefsky, S. de Gala, *Angew. Chem.* **1994**, *106*, 923–925; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 853–855.
- [11] Selected reviews: a) D. Crich, *Aldrichimica Acta* **1987**, *20*, 35–49; b) D. Crich, L. Quintero, *Chem. Rev.* **1989**, *89*, 1413–1432; c) D. H. R. Barton, *Tetrahedron* **1992**, *48*, 2529–2544.
- [12] a) D. H. R. Barton, D. Bridon, S. Z. Zard, *Tetrahedron* **1987**, *43*, 5307–5314; b) D. H. R. Barton, W. Sas, *Tetrahedron* **1990**, *46*, 3419–3430.
- [13] All new compounds exhibited satisfactory spectroscopic and analytical data (see the Supporting Information). Yields refer to spectroscopically and chromatographically homogeneous materials.
- [14] H. Hagiwara, H. Uda, *J. Org. Chem.* **1988**, *53*, 2308–2311.
- [15] Alkyl-substituted quinones have lower oxidation potentials than the unsubstituted counterparts. See reference [1a] for more precise data.
- [16] Compound **20** was independently produced by reduction of **21** with Na₂S₂O₄ and was quantitatively reoxidized to **21** upon treatment with benzoquinone (**7**).
- [17] For a recent application of **8** to natural products synthesis, see A. X. Xiang, D. A. Watson, T. Ling, E. A. Theodorakis, *J. Org. Chem.* **1998**, *63*, 6774–6775.