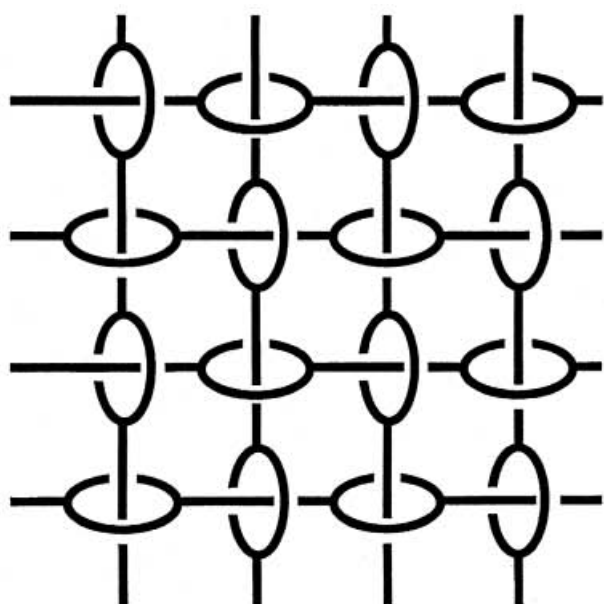
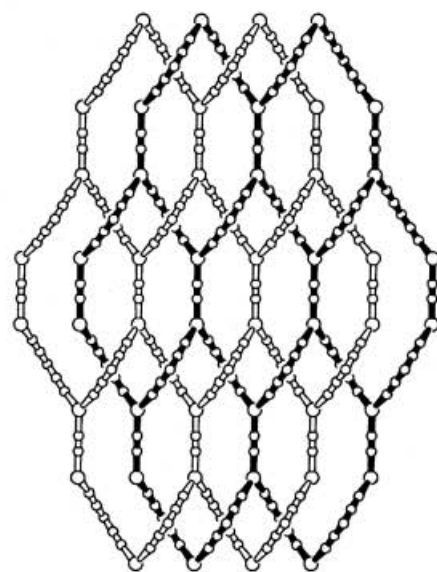
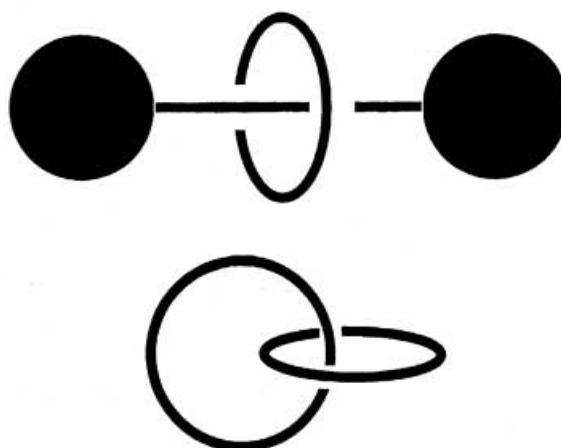




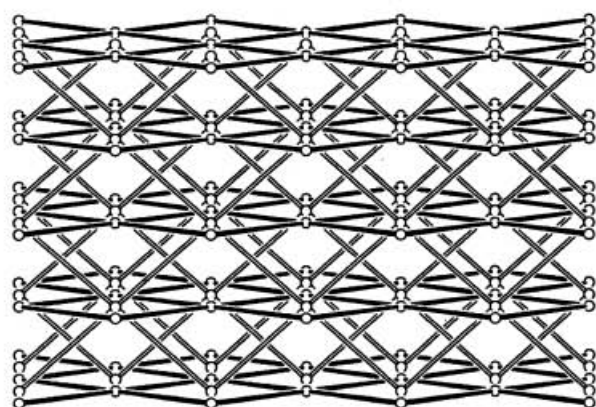
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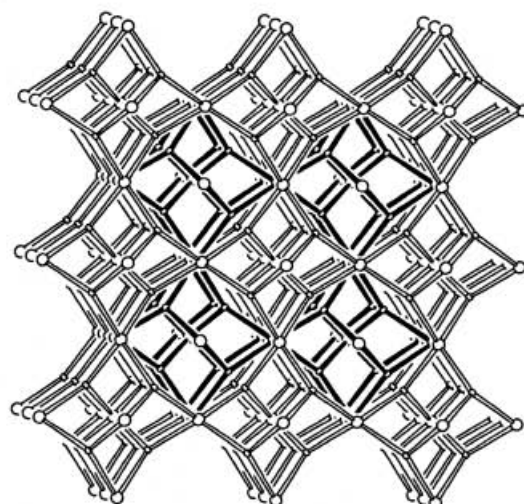
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Interpenetrating Nets: Ordered, Periodic Entanglement

Stuart R. Batten and Richard Robson*

Taking inspiration from the examples biology provides for the organization of simple units into a vast range of intricate and beautiful structures with complex and wonderfully efficient functions, many chemists have been turning their attention to the deliberate design of self-assembling aggregates of molecular building blocks with some specific structural or functional purpose in mind. This is supramolecular chemistry. It embraces systems ranging upwards in size and complexity to include infinite solid arrays. Molecular entanglement is common in biology. Entanglement that is inextricable, in the sense that disentanglement can be achieved only by breaking internal connections, has been one of the major themes of supramolecular chemistry. Such inextricable entanglements—as seen in catenanes, rotaxanes, and mo-

lecular knots—have provided a long-standing fascination for chemists, and many beautiful examples of ingenious design have been constructed. In the area of solids, the deliberate control of structure, and therefore properties and function, is a long-term objective being vigorously pursued by numerous groups. Increasingly, solid structures are being invented and created rather than discovered. The potential for technologically useful electronic, optical, electrochemical, and catalytic applications is an obvious driving force for much of this work, but the area is also of great fundamental structural interest and importance. Framework solids, which are often accessible by self-assembly under exceedingly mild conditions, are particularly attractive in this context because of their chemical and structural diversity and aes-

thetic appeal and because of the control potentially achievable in their construction. One aspect of framework solids which becomes increasingly apparent as more of them are discovered or invented is their tendency to form entangled structures in which two or more independent infinite networks interpenetrate each other. Polycatenane or polyrotaxane associations are an inherent feature of these structures. Examples of interpenetration were relatively rare until recently, but they are now being reported with increasing frequency. This is an opportune time to review this expanding area.

Keywords: coordination polymers • interpenetrating structures • crystal engineering • hydrogen bonds • supramolecular chemistry

1. Introduction

1.1. Framework Structures

The synthesis and characterization of infinite two- and three-dimensional networks has been an area of rapid growth in recent years.^[1–3] The motivation behind much of this activity has been provided by the prospect of generating, by deliberate design, a wide range of purpose-built materials with predetermined structures and useful properties, for example electronic, magnetic, optical, and catalytic. Implicit or explicit

in much of this work has been the idea of *self-assembly of specifically designed building blocks*. There is still a long way to go in the development of this field before it will be possible to say that these ambitious objectives have been fully realized. Nevertheless, great opportunities for exciting advances are provided by the enormous sweep of chemistry embracing coordination, organic, and main group chemistry, which is at our disposal for creative use in the planned construction of frameworks.

1.2. The Net-Based Approach to Framework Construction

One conceptual approach to building frameworks is based on the idea of a net. In essence, nets are abstract mathematical entities consisting of a collection of points or nodes with some clearly defined connectivity or topology. A very useful catalogue of nets of relevance to chemistry was compiled by

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Wells over twenty years ago.^[4] Examples of simple, infinite 2D nets are those given the symbols (6,3) and (4,4) shown in Figures 1 and 2, respectively. One way to represent the

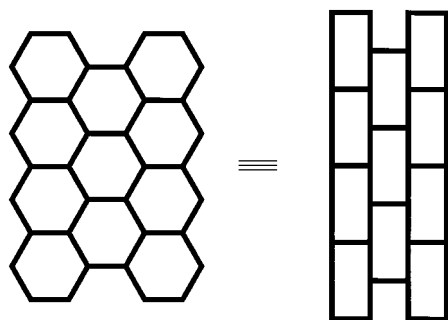


Figure 1. Two geometrically different forms of the (6,3) net.

topology or connectivity of a given net is in terms of the general symbol (n,p) , where p is the number of connections to neighboring nodes that radiate from any center or node, and n is the number of nodes in the smallest closed circuits in the net. Thus, the number 6 in the symbol (6,3) indicates that the smallest complete circuits in the net are hexagons, and the number 3 indicates that each node is connected to three other nodes. The (n,p) notation applies strictly only to nets in which all $p(p-1)/2$ shortest circuits originating from any node are n -gons; otherwise the more complete Schläfli notation $n^{p(p-1)/2}$ should be used. Two of the six shortest circuits around any node in the net shown in Figure 2, whose representation as (4,4) is not strictly correct, in fact involve six nodes, and the complete Schläfli notation should be $4^6 6^2$; this was simplified by Wells to 4^4 or (4,4) by arbitrarily excluding circuits involving colinear connections.

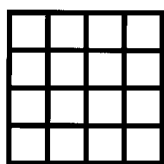


Figure 2. The (4,4) net.

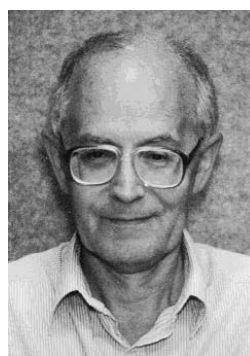
Figure 1 shows two versions of the (6,3) net which are geometrically different but topologically identical. This example illus-

trates the general point that nets may be geometrically deformed to any extent and yet, provided no connections are broken, the topology is considered to remain unchanged. Some examples of simple, infinite 3D nets are

- the α -polonium (or NaCl) net with six-connected, octahedral nodes,
- the diamond, lonsdalite, quartz, feldspar-related, and zeolite-related nets, all of which have four-connected, essentially tetrahedral nodes,
- the NbO net, which has square-planar nodes with a 90° twist along every connection,^[5]
- a variety of intriguing and little-known three-connected nets described by Wells,^[4]
- a number of nets containing more than one type of node, such as the PtS net which contains equal numbers of tetrahedral and square-planar nodes, the rutile net containing octahedral and trigonal nodes, the "Pt₃O₄" net with square-planar and trigonal nodes, and the Ge₃N₄ net with tetrahedral and trigonal nodes. All of these nets provide realistic targets for crystal engineers.

One approach to building frameworks is based on the expectation that if molecular building blocks with a chemical functionality and a stereochemistry appropriate to one of the above target nets can be devised, then simply allowing these specifically organized components to react together in the correct proportions may lead to the spontaneous assembly of the intended network.^[1, 6] Thus, for the sake of illustration, if we had set our sights on a Ge₃N₄-type net, we would require building blocks with tetrahedral and trigonal dispositions of complementary functional groups. This approach has met with some success—for example, in generating diamond,^[6–8] PtS,^[9, 10] and α -polonium^[11, 12] nets by design—but outcomes of such attempts to build frameworks are often determined by a very fine balance of complex and subtle effects. Predicting such outcomes simply on the basis of the reactants present in the reaction mixture constitutes a major challenge for the theoretician. In the meantime, the empirical, experimental

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R. Robson



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Stuart Batten was born and raised in Moyhu. After school he obtained a B.Sc. (Hons) (1990) and a Ph.D. (1996) in chemistry at the University of Melbourne. His Ph.D. research was performed under the supervision of Richard Robson and Bernard Hoskins, and involved the synthesis and characterization by X-ray crystallography of coordination polymers, with a view to predetermining their topology by judicious choice of ligand and metal ion. Particular attention was paid to the trigonal ligands tcm and tpt. Following postdoctoral positions at both the University of Bristol and Monash University, he is currently employed in Richard Robson's group on work related to his Ph.D. research.

approach, based largely on sensible design and chemical intuition, has a great deal to offer. It has already revealed much new chemistry, including several unprecedented structural types, and there is every indication that it will continue to do so.

The idea of *topological equivalence* is useful in describing networks. For example the 2D network formed when large numbers of benzene-1,3,5-tricarboxylic acid (trimesic acid) molecules associate through hydrogen bonds of the type seen for acetic acid dimers (Figure 3) is said to be topologically

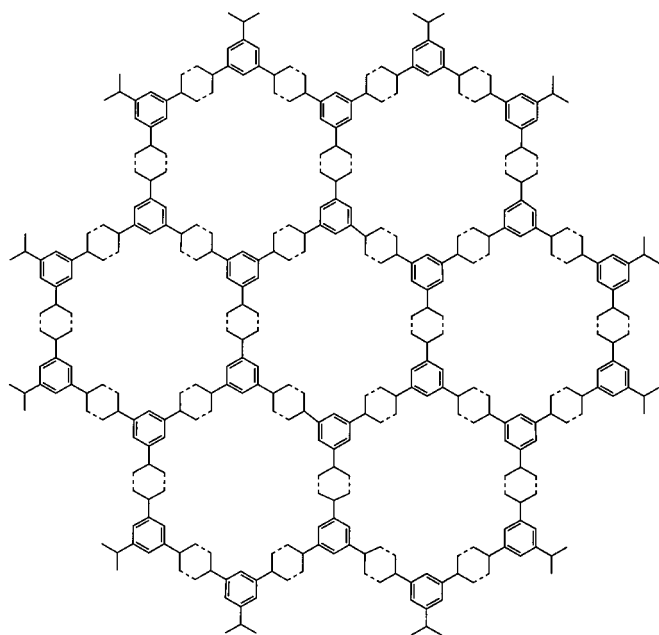


Figure 3. A hydrogen-bonded sheet of trimesic acid molecules with the (6,3) topology.

equivalent to or to have the topology of the (6,3) net.^[13] Nodes within a net do not necessarily have to coincide with a particular atom, and in the trimesic acid sheets they are located at the centers of the benzene rings. The imaginary process of reducing a real chemical structure to the essence of its connectivity is useful for clarifying this fundamental aspect of its nature: It is particularly useful in understanding and interrelating modes of interpenetration, as we shall see below.

1.3. Voids, Interpenetration, and the Scope of This Review

Examination of models of a range of framework structures constructed from molecular building blocks that might realistically be employed in practice leads to the realization that, for many simple nets, connecting units with rodlike character need not be very long to provide structures with relatively large channels, cavities, and windows. In recent years large numbers of framework solids have been structurally characterized; the vast majority make use of either hydrogen bonding^[3] or ligand-to-metal coordinative bonding^[2] to link the individual components. In some cases the

frameworks do generate spacious voids, cavities, and channels, which may account for more than half the volume of the crystal.^[6, 7, 10, 14] These large spaces are usually occupied by highly disordered, essentially liquid solvent. In other cases remarkable interpenetrating structures are formed in which the voids associated with one framework are occupied by one or more independent frameworks; an inherent feature of such entangled structures is that they can be disentangled only by breaking internal connections.

These interpenetrating framework structures are the subject of this article; until recently examples were rare,^[15] but they are now being reported with ever increasing frequency. We have restricted the scope of this review to interpenetrating structures in which the building blocks within the individual infinite networks or chains are linked together through either metal-to-ligand bonds or hydrogen bonds. A further restriction is that only ordered, structurally regular, and crystallographically characterized systems will be covered. The interpenetrating polymer networks (IPNs),^[16] which are noncrystalline materials with rubberlike and plastic properties, are therefore not included.

1.4. Molecular Entanglement

Infinite interpenetrating structures constitute a subgroup within a broader class of entangled systems, which are the subject of intensive current research.^[17] A familiar example is provided by the entangled strands in the DNA double helix. This and other helical biological molecules have provided the inspiration for a rapidly expanding range of double- and triple-helical coordination compounds.^[18] Dendrimers are another class of tangled compounds of great current interest.^[19] Catenanes, rotaxanes, and molecular knots,^[20] however, occupy positions of special importance in the area of molecular entanglement, because they can be disentangled only by breaking connections (in contrast, for example, to the DNA double helix, for which it is not necessary to disrupt the individual strands in order to disentangle them). Catenanes consist of independent rings that are locked together (Figure 4a) In rotaxanes a ring component encircles the shank of an

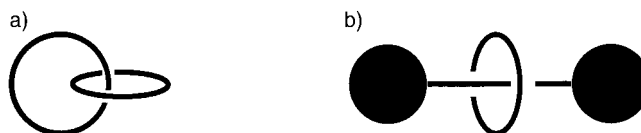


Figure 4. Schematic representation of a) a catenane and b) a rotaxane.

independent dumbbell-like component (Figure 4b). The two “stops” at the ends of the dumbbell-like component prevent the ring from escaping. In pseudorotaxanes one or more rings are threaded onto a molecular “string”, but the stops present in true rotaxanes are lacking. Molecular knots are characterized by self-entanglement.

1.5. Some General Points about Interpenetration

Some general points about interpenetrating networks can be illustrated by considering the example of zinc cyanide, whose structure was determined over half a century ago.^[6, 21, 22] It consists of two independent infinite frameworks, each with diamondlike topology. The point symbol for the diamond net is 6^6 -a; the superscript indicates the number of different pairs of connections radiating from one node to its neighbors (i.e., $(4 \times 3)/2$). The smallest circuits in which each pair participates are hexagons, which is indicated by the main, nonsuperscripted symbol. The -a indicates that this is the most symmetrical of a number of different possible 6^6 nets. In $[\text{Zn}(\text{CN})_2]$ the metal centers provide the tetrahedral nodes, and the cyanide groups act as linear bridges between the metal atoms. A characteristic structural motif within the diamond net is the “adamantane unit” (Figure 5a). The two independent networks interpenetrate in such a way that every

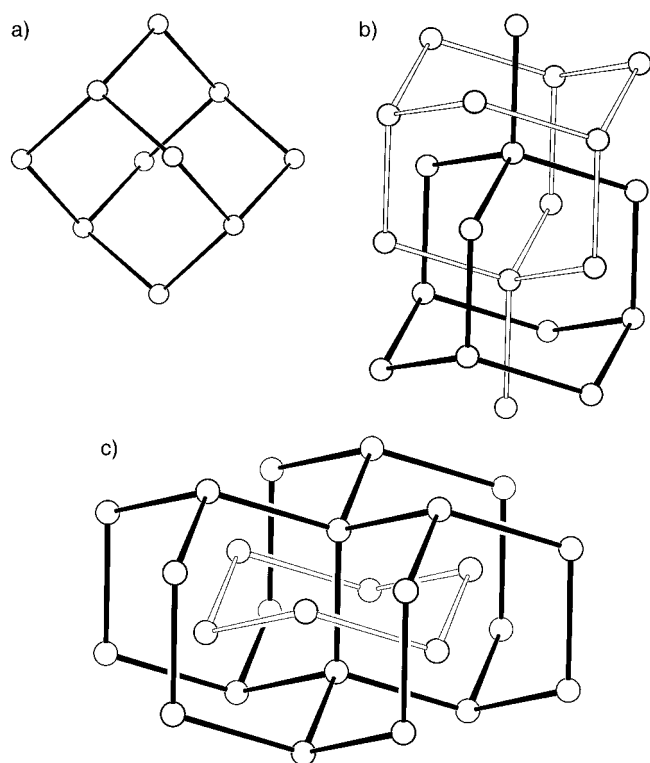


Figure 5. a) An adamantane unit of a diamondlike net. b) Interlocked adamantane units of two independent diamondlike nets. c) A cyclohexane-like ring of one net with a rod of the other passing through it; the rod is part of six different hexagons.

tetrahedral node is found at the center of an adamantane unit of the other framework, and the four connections to nearest neighbors project through the four cyclohexane-like windows of the surrounding adamantane unit (Figure 5b). We shall refer to connections between nodes within nets in general as rods. Each rod in $[\text{Zn}(\text{CN})_2]$ forms part of six distinguishable cyclohexane-like rings and is exclusively associated with one particular cyclohexane-like ring of the other framework through which it passes (Figure 5c). This is catenation on the grand scale. Clearly, the two frameworks can be disen-

tangled only by wholesale breaking of connections. The regions of closest contact between the two independent frameworks are at the midpoint of every cyanide unit, and the closest parts of the other framework are the midpoints of the six equivalent cyanide units that surround it.

In this review we shall use the term *n*-fold interpenetration to describe systems with *n* independent nets; for example, $[\text{Zn}(\text{CN})_2]$ displays twofold interpenetration.

All interpenetrating network structures can be regarded as infinite, ordered polycatenanes or polyrotaxanes. One of their characteristic features is the repeated, orderly appearance of rings belonging to one framework or chain, through which independent components are inextricably entangled. The very interesting possibility, presently unrealized, in which the individual rings in an infinite polycatenane are themselves finite and molecular would not fall in the category of interpenetrating frameworks as we define it here because the units participating in interpenetration are not infinite.

Another example of a structure involving infinite entanglement which nevertheless does not fall in the category of an interpenetrating structure is the material of composition $[\text{IAuP}(\text{C}_6\text{H}_5)_2(\text{CH}_2)_6\text{P}(\text{C}_6\text{H}_5)_2\text{AuI}]_n$. This contains 1D zigzag polymeric chains in which neutral digold monomers are linked together through weak gold–gold interactions.^[23] These chains are then interwoven like warp and weft to generate a clothlike 2D sheet in which every chain passes alternately over and then under an infinite number of other chains (Figure 6). This interesting structure is not interpenetrating in the sense we have reserved for the term because it is

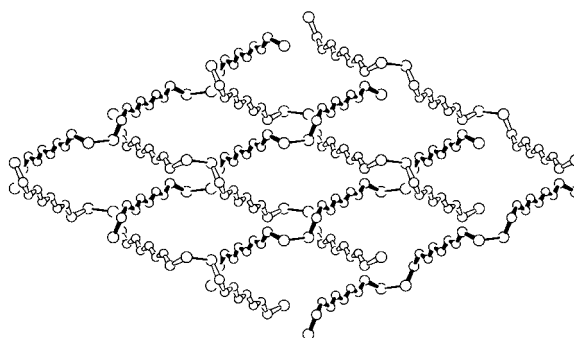
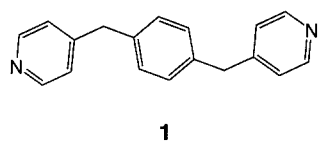


Figure 6. Warp-and-weft structure of $[\text{IAuP}(\text{C}_6\text{H}_5)_2(\text{CH}_2)_6\text{P}(\text{C}_6\text{H}_5)_2\text{AuI}]_n$. The circles represent in order of decreasing size Au, P, and C atoms. Phenyl groups and iodine atoms have been omitted for clarity.

not necessary, in principle, to break any links within the independent chains in order to disentangle them, nor do the components contain rings through which other components can project and become entangled. For similar reasons we exclude from the general class of interpenetrating frameworks microporous structures with linear polymers trapped in their channels.

2. Interpenetrating One-Dimensional Polymers

We know of only two examples that can be assigned to this category. Ligand **1** affords a coordination polymer of compo-



type three-connected center; its seven-coordinate environment is completed by two bidentate nitrate ligands which are pendant, that is, not an essential part of the connectivity of the network. Each ladderlike chain contains an infinite number of rings, all equivalent, defined by two ladder “rungs” and segments of two ladder “uprights”. In the interpenetration shown in Figure 7 the uprights of four separate ladders pass through each such ring.

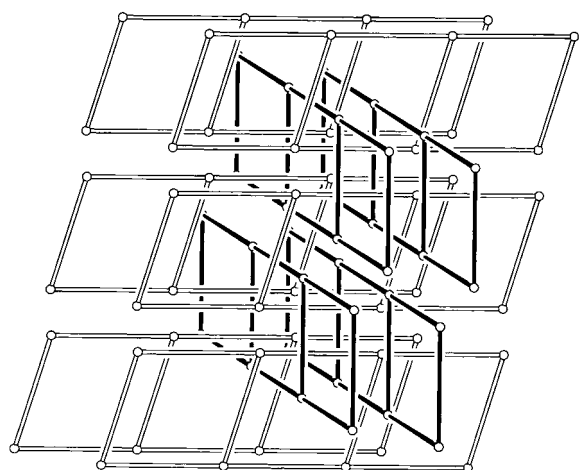
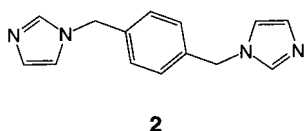


Figure 7. Interpenetrating ladderlike chains in $[\text{Cd}_2(\mathbf{1})_3](\text{NO}_3)_4$. The T-type three-connected centers represent Cd atoms. Every ring has the uprights of four separate ladders passing through it.

Ligand **2** gives a coordination polymer of composition $[\text{Ag}_2(\mathbf{2})_3](\text{NO}_3)_2$ which contains 1D chains of the type shown



in Figure 8.^[25] We shall later encounter examples of interpenetrating structures which can correctly be described either as polyrotaxanes or as polycatenanes; deciding which is the better description is not easy. The mode of interpenetration in $[\text{Ag}_2(\mathbf{2})_3](\text{NO}_3)_2$ (shown schematically in Figure 8c), however, is unquestionably of the polyrotaxane type, and catenane associations are simply not present. Each individual chain is interlocked with an infinite number of others by multiple rotaxane associations in which every one of its rodlike segments passes through a ring of another chain and every one of its rings encircles a rod of another chain (Figure 8c).

In the first example, $[\text{Cd}_2(\mathbf{1})_3](\text{NO}_3)_4$, the interpenetration produces a 3D interlocked structure, whereas in $[\text{Ag}_2(\mathbf{2})_3](\text{NO}_3)_2$ a 2D interlocked structure results.

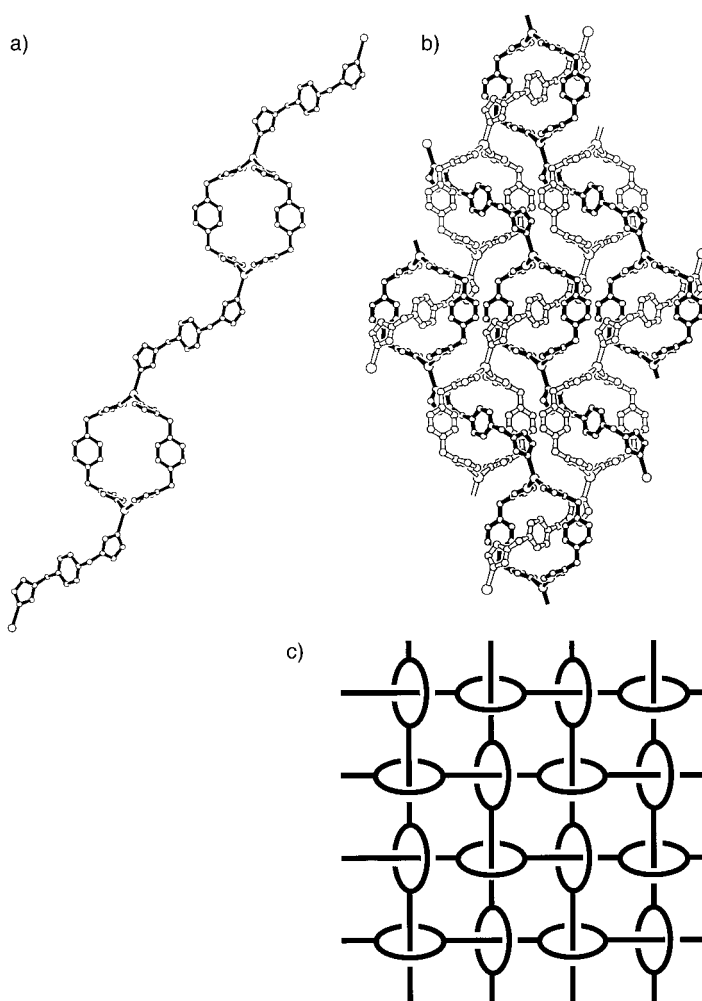


Figure 8. a) A single chain in $[\text{Ag}_2(\mathbf{2})_3](\text{NO}_3)_2$. The large circles represent Ag atoms, and the smaller circles C and N atoms. b) A polyrotaxane sheet in $[\text{Ag}_2(\mathbf{2})_3](\text{NO}_3)_2$. c) Schematic representation of the multiple rotaxane associations.

3. Interpenetrating Two-Dimensional Networks

Two major categories of interpenetrating 2D networks can be discerned: One we shall call “parallel interpenetration” and the other “inclined interpenetration”.

For parallel interpenetration to be possible, the individual 2D networks must be corrugated or possess some appropriate element of undulation. Usually two such undulating sheets, but occasionally more, are arranged with their average planes parallel—this is indeed the case in all presently known examples—so that each is able to pass through the other an infinite number of times (shown schematically in Figure 9).

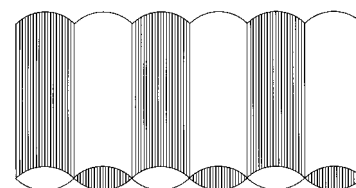


Figure 9. Parallel interpenetration of undulating sheets.

The composite structure resulting from this form of interpenetration is itself two-dimensional, and these composite sheets are then stacked one on top of another.

In inclined interpenetration there are two stacks of sheets, one stack inclined, often perpendicular, to the other (Figure 10). Any particular 2D network layer then has an infinite

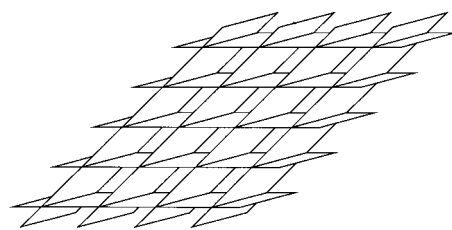


Figure 10. Inclined interpenetration of sheets.

number of inclined layers passing through it. In contrast to parallel interpenetration, each sheet passes through an inclined one just once along a line of intersection of the two planes. Also in contrast to parallel interpenetration, the product of inclined interpenetration is a 3D interlocked structure. With only one exception the individual networks involved in 2D interpenetration, whether of the parallel or inclined types, are based on either the (4,4) or the (6,3) topology.

3.1. Parallel Interpenetration of Two-Dimensional Frameworks

3.1.1. Two Parallel, Interpenetrating Nets Based on the (6,3) Topology

Four topologically different modes of (6,3) parallel interpenetration which are crystallographically regular and within which all rings are equivalent are shown in Figure 11. By topologically different we mean that one could be transformed into another only by breaking connections and making new ones. If we relax the restriction that all rings be equivalent (e.g., if we allow some rings to have no part of the other net passing through them) then clearly an infinite number of modes of interpenetration become possible.

[Ag(tcm)] (tcm[−] = tricyanomethanide, C(CN)₃[−]) contains (6,3) nets whose three-connected nodes are provided by alternating central carbon atoms of the tcm ions and three-coordinate Ag^I centers.^[26, 27] The two independent and identical (6,3) networks are corrugated so that each is able to pass through the other an infinite number of times (Figure 12). This is topologically identical to the interpenetration mode shown in Figure 11a. The corrugations in the sheets which make the interpenetration possible arise from a combination of a distinctly nonplanar, pyramidal geometry at the silver centers and a significant bending at the nitrogen centers.

It is possible to make derivatives of [Ag(tcm)] which retain the parallel, interpenetrating, double-sheet structure. [Ag(tcm)(CH₃CN)] has basically the same composite layer structure as [Ag(tcm)], but the acetonitrile molecule is now

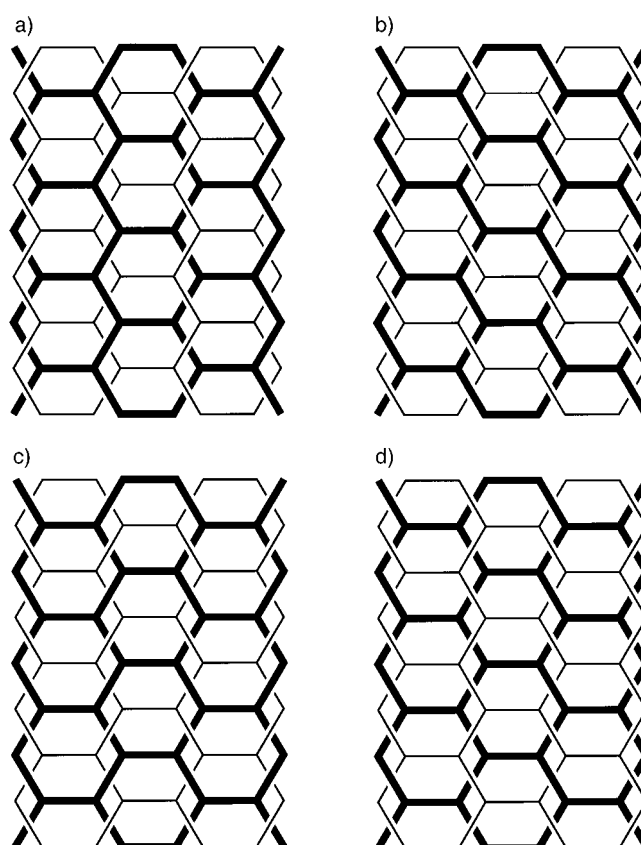


Figure 11. a)–d) Four topologically different modes of parallel interpenetration of (6,3) nets.

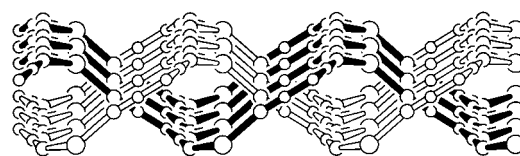


Figure 12. Interpenetrating undulating (6,3) nets in the structure of [Ag(tcm)]. The circles represent in order of decreasing size Ag, N, and C atoms.

coordinated to the metal, which acquires thereby a tetrahedral geometry.^[28] The acetonitrile methyl groups are directed generally away from the center of the composite sheet and towards the neighboring sheets, causing an increase in the separation between composite layers. In [Ag(tcm)(L)_{1/2}] (L = phenazine) almost the same double-interpenetrating [Ag(tcm)] layers are present, but they are now connected together through phenazine molecules that bridge silver atoms in one composite sheet to those in a neighboring composite sheet.^[27] Two independent but interpenetrating 3D networks are thus formed.

Two examples that involve the interpenetration of 3D nets are described at this point because of the close structural relationship, elaborated below, to the tcm compounds above. [Ag{C(CN)₂NO}] contains (6,3) nets in the form of undulating sheets, closely analogous to those in [Ag(tcm)], in which the two nitrile nitrogen atoms and the nitroso oxygen atom of each ligand form dative bonds to the silver atom.^[29] These undulating sheets participate in twofold parallel interpenetration in a fashion almost identical to that seen in [Ag(tcm)].

Dative bonds between the nitroso nitrogen atoms in one composite sheet and silver atoms in an adjacent composite sheet then produce two interpenetrating 3D networks (Figure 13).

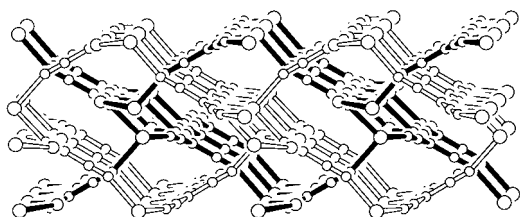


Figure 13. Structure of $[\text{Ag}\{\text{C}(\text{CN})_2\text{NO}\}]$ in which parallel interpenetrating (6,3) nets are joined together into a 3D structure through bonds between Ag atoms in one sheet and the nitroso N atoms of another. The circles represent in order of decreasing size Ag, O, and C/N atoms.

The series of compounds with variable composition $[\text{Cu}(\text{NH}_3)(\text{py})\text{Ag}_{3-x}\text{Cu}_x(\text{CN})_5] \cdot \text{py}$ (py = pyridine) form layers of two (6,3) sheets that interpenetrate in the fashion shown in Figure 11 a.^[30] The three-connected nodes of the sheets are formed by alternating Cu^{II} centers (which also coordinate to pendant pyridine and ammonia groups to give a five-coordinate center) and Ag^{I} centers, and are connected through CN^- and $\text{Ag}(\text{CN})_2^-$ bridges. The three-connected Ag^{I} atoms and the Ag^{I} atom in one of the two crystallographically independent $\text{Ag}(\text{CN})_2^-$ links are partially substituted by Cu^{I} . Again, there are links between the layers. Each set made up of a trigonally coordinated $\text{Ag}^{\text{I}}/\text{Cu}^{\text{I}}$ atom and a carbon atom connected to it has a centrosymmetric dimeric partnership with a corresponding pair of atoms in an adjoining layer. The tetrahedral coordination geometry of the metal atom is completed by a carbon atom in the adjoining layer; short metal–metal contacts are seen (2.641(1) and 2.791(3) Å in the two phases studied). These interactions produce two interpenetrating 3D nets with a similar topology to that seen in $[\text{Ag}(\text{tcm})(\text{L})_{1/2}]$ (L = phenazine).

$[\text{Ag}\{\text{CH}_3\text{COCH}_2\text{C}(\text{CN})_2\text{C}(\text{CN})_2\}]$, produced by the unexpected reaction of tetracyanoethylene with $[\text{Ag}(\text{CF}_3\text{SO}_3)]$ in $\text{H}_2\text{O}/\text{Me}_2\text{CO}$, has layers of two interpenetrating (6,3) nets in which each ligand is coordinated through three of the nitrile nitrogen atoms to three-connected silver atoms.^[31] The interpenetration of the sheets is topologically identical to that shown in Figure 11 a.

The semiconductor $\theta\text{-(BEDT-TTF)}_2[\text{Cu}_2(\text{CN})\{\text{N}(\text{CN})_2\}_2]$ (BEDT-TTF = bis(ethylenedithio)tetrathiafulvalene) contains anionic $[\text{Cu}_2^{\text{I}}(\text{CN})\{\text{N}(\text{CN})_2\}_2]^-$ layers with intercalated $[(\text{BEDT-TTF})_2]^+$ ions.^[32] The anionic layers consist of two independent and interpenetrating (6,3) nets in which Cu^{I} provides the three-connected nodes and CN^- and $\text{N}(\text{CN})_2^-$ act as two-connectors. A pronounced bend at the central nitrogen atom in $\text{N}(\text{CN})_2^-$ provides the undulating character to each individual sheet that makes the interpenetration possible (Figure 14). This mode of interpenetration is topologically identical to that represented schematically in Figure 11 b, and is intrinsically different from that observed in the previous examples.

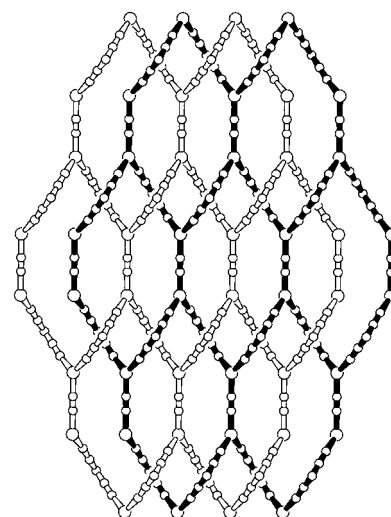


Figure 14. The parallel interpenetration of (6,3) nets in the $[\text{Cu}_2(\text{CN})\{\text{N}(\text{CN})_2\}_2]^-$ polyanion, which is topologically identical to that shown in Figure 11 b. The large circles represent Cu atoms, and small circles C and N atoms.

The bis(imidazole) ligand **2** combines with zinc nitrate to give a coordination polymer of composition $[\text{Zn}(\mathbf{2})_2](\text{NO}_3)_2 \cdot 4.5\text{H}_2\text{O}$, which contains layers comprising two independent 2D nets that interpenetrate in the parallel manner;^[33] the individual nets, represented schematically in Figure 15 a, are

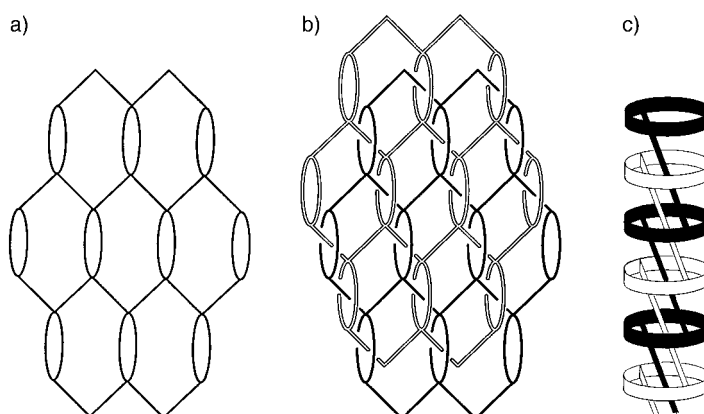


Figure 15. a) Schematic representation of a single 2D net in $[\text{Zn}(\mathbf{2})_2](\text{NO}_3)_2 \cdot 4.5\text{H}_2\text{O}$. Zn atoms provide the four-connected nodes, and molecules of **2** the connections between nodes. b) Schematic representation of the two interpenetrating nets in $[\text{Zn}(\mathbf{2})_2](\text{NO}_3)_2 \cdot 4.5\text{H}_2\text{O}$. c) Schematic representation of the polyrotaxane columns.

based on the (6,3) topology, but a second bridging ligand is present within certain pairs of zinc nodes. The zinc atoms thus become four-coordinate. Two such nets then interpenetrate in the manner represented schematically in Figure 15 b to generate polyrotaxane columns (Figure 15 c). This structure is closely related to that of $[\text{Ag}_2(\mathbf{2})_3](\text{NO}_3)_2$ (Figure 8), which unquestionably is a polyrotaxane. However, $[\text{Zn}(\mathbf{2})_2](\text{NO}_3)_2 \cdot 4.5\text{H}_2\text{O}$ could equally well be considered as a polycatenane, because the smallest rings of one net are involved in catenane associations with the second-smallest rings (Zn_6) of the other net. There is little to be gained by argument as to which

description should take precedence; the structure has both polyrotaxane and polycatenane character.

3.1.2. Two Parallel Interpenetrating Nets Based on the (4,4) Topology

A close analogue of the mode of interpenetration seen in [Ag(tcm)] is provided by [Cd(4-pic)₂{Ag(CN)₂}₂](4-pic) (4-pic = 4-methylpyridine), which involves two corrugated (4,4) nets (Figure 16) rather than the two (6,3) nets in [Ag(tcm)]

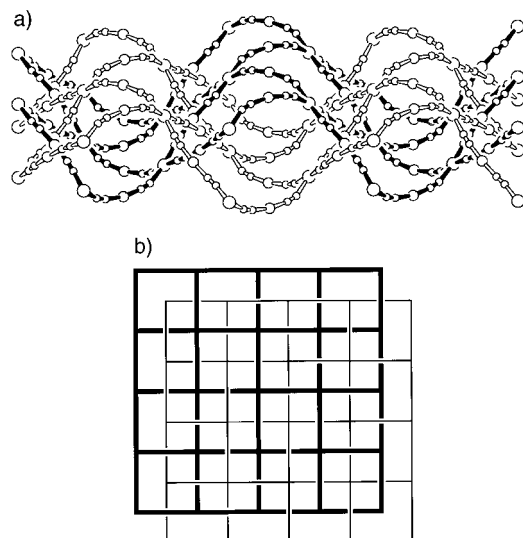


Figure 16. a) Parallel interpenetrating (4,4) nets in the structure of [Cd(4-pic)₂{Ag(CN)₂}₂](4-pic) (4-pic = 4-methylpyridine). The pendant 4-pic molecule is omitted. Therefore, the six-coordinate Cd atoms appear to be four-connected. Each Cd atom is connected to four others through bridging Ag(CN)₂[−] units. The circles represent in order of decreasing size Cd, Ag, and C/N atoms. b) Schematic representation of the mode of interpenetration.

(Figure 12).^[34] The cadmium centers, all of which are equivalent, are four-connected nodes; they are coordinated by two mutually *trans* picoline molecules, which can be regarded as mere appendages to the 2D net, and by a roughly square-planar set of nitrogen atoms from four two-connected Ag(CN)₂[−] units. Each (4,4) net is corrugated with its troughs and crests parallel with one diagonal of the Cd₄ rhombuses within the net. Two nets then interpenetrate as shown in Figure 16.

A topologically different mode of parallel interpenetration of two (4,4) nets is found in [Cu(tcm)(bipy)] (bipy = 4,4'-bipyridine), in which the tcm ligands act as bent two-connected units (Figure 17).^[28]

Clusters of composition [Re₄(CO)₁₂(OH)₄], which have a cubanelike arrangement of four Re(CO)₃ units and four μ₃-OH groups at alternating cube corners, cocrystallize with 4,4'-bipyridine to yield crystals of composition Z · 2bipy · 2MeOH (Z = [Re₄(CO)₁₂(OH)₄]) containing hydrogen-bonded (4,4) nets.^[35] The four-connected nodes of the net are provided by Z units, which are connected to one another through their OH groups by the hydrogen-bonded system Z(OH)/CH₃OH/bipy/(HO)Z. Two such (4,4) nets interpenetrate in the manner shown schematically in Figure 18. This mode of interpenetra-

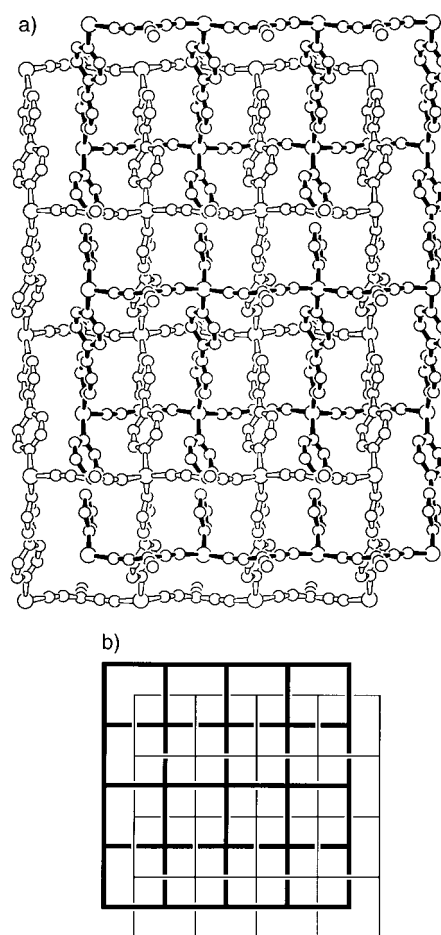


Figure 17. a) Two parallel interpenetrating (4,4) nets in the structure of [Cu(tcm)(bipy)]. The large circles represent Cu atoms, and the small circles C and N atoms. b) Schematic representation of the mode of interpenetration.

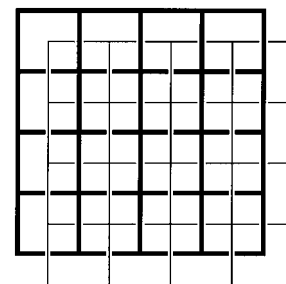


Figure 18. Schematic representation of the two parallel interpenetrating hydrogen-bonded (4,4) nets in the structure of [Re₄(CO)₁₂(OH)₄] · 2bipy · 2MeOH. The four-connected nodes shown represent the centers of the Re₄ clusters.

tion is topologically different from that in [Cd(4-pic)₂{Ag(CN)₂}₂](4-pic) and [Cu(tcm)(bipy)], as can be appreciated by comparison of Figure 18 with Figures 16b and 17b; in all of these Figures the structure has been reduced to its topological essence. Answers to questions concerning the number of different ways two (4,4) nets could theoretically interpenetrate in the parallel fashion must await systematic mathematical treatment of the topology of interpenetration. Such an investigation is highly desirable, not only with regard to (4,4) nets, but in general.

4,4'-Sulfonyldiphenol crystallizes to give hydrogen-bonded (4,4) nets that interpenetrate in the parallel manner shown in Figure 19.^[36] This mode of interpenetration is topologically identical to that in $[\text{Cu}(\text{tcm})(\text{bipy})]$ (Figure 17).

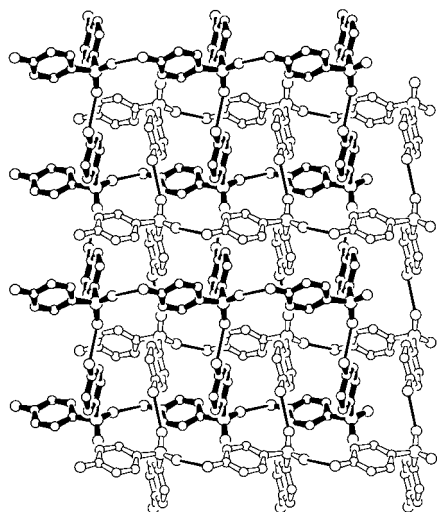
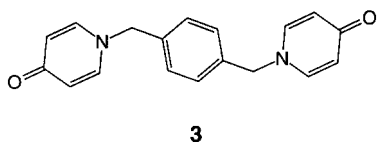


Figure 19. Two parallel interpenetrating hydrogen-bonded (4,4) nets in the structure of 4,4'-sulfonyldiphenol. The circles represent in order of decreasing size S, O, and C atoms. The thin lines represent hydrogen bonds.

The coordination polymer formed by the ligand *N,N'*-*p*-phenylenedimethylenebis(pyridin-4-one) (**3**) of composition $[\text{Mn}(\mathbf{3})_3](\text{ClO}_4)_2$ consists of two (4,4)-based nets that interpenetrate in the parallel fashion.^[37] As in the case of



$[\text{Zn}(\mathbf{2})_2](\text{NO}_3)_2 \cdot 4.5 \text{H}_2\text{O}$ considered in Section 3.1.1, a second bridging ligand is present between certain Mn nodes, whereby $\text{Mn}_2(\mathbf{3})_2$ rings are formed and the metal centers become six-connected. A schematic representation of the polyrotaxane/polycatenane fashion in which they interpenetrate is shown in Figure 20. Compounds $[\text{Ag}_2(\mathbf{2})_3](\text{NO}_3)_2$, $[\text{Zn}(\mathbf{2})](\text{NO}_3)_2 \cdot$

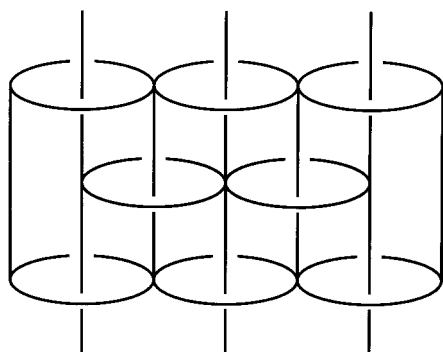


Figure 20. Schematic representation of the two parallel interpenetrating (4,4) nets in $[\text{Mn}(\mathbf{3})_3](\text{ClO}_4)_2$ showing the polyrotaxane/polycatenane associations. Six-connected nodes are provided by six-coordinate Mn, and connections between the nodes by ligand **3**.

$4.5 \text{H}_2\text{O}$, and $[\text{Mn}(\mathbf{3})_3](\text{ClO}_4)_2$ can be considered as members of a progression in which the connectivity of the metal center increases from three to four to six; in all cases $(\text{metal})_2(\text{ligand})_2$ rings participate in rotaxane interactions.

3.1.3. Two Interpenetrating Two-Dimensional 8^210 Nets: Hittorf's Phosphorus

The allotrope of phosphorus known as Hittorf's phosphorus is the only example of 2D parallel interpenetration involving nets other than those based on (6,3) and (4,4) topologies. Two 2D 8^210 nets interpenetrate in the manner represented schematically in Figure 21 a.^[38] The three-connected nodes of the net

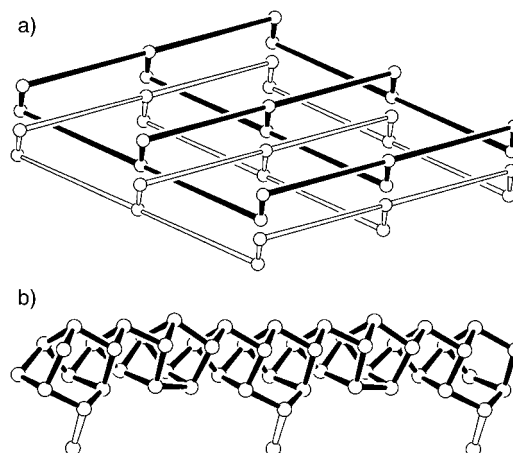


Figure 21. a) Schematic representation of the interpenetration of two 2D 8^210 nets in Hittorf's phosphorus. b) Representation of the columnar rods which constitute the long connections between three-connected phosphorus nodes in a). The open bonds in b) represent direct P–P covalent bonds between the three-connected phosphorus nodes of the rod shown to three adjoining rods running at right angles.

are located at particular phosphorus atoms. All such nodes are equivalent, and each is connected to one other node through a direct P–P bond (the short node-to-node connections in Figure 21 a) and to two other nodes through columnar rods with a roughly pentagonal cross-section (Figure 21 b).

3.1.4. Three Parallel Interpenetrating Two-Dimensional Nets

There is of course no reason why parallel interpenetration should be restricted to two independent nets. A number of examples of threefold parallel interpenetration are known at present, all of which involve (6,3) nets.

Trimesic acid cocrystallizes with 4,4'-bipyridine to form hydrogen-bonded (6,3) networks with voids so large that three identical but independent networks of this type form a structure with parallel interpenetration (Figure 22).^[39] This mode of threefold interpenetration is closely related to the hypothetical mode of twofold interpenetration shown in Figure 11c. This can be imagined by removing any one of the three nets in Figure 22, which leaves a twofold interpenetrating system topologically identical to that in Figure 11c.

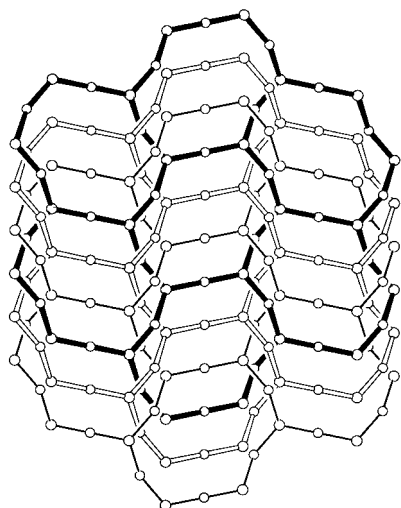


Figure 22. Schematic representation of the threefold parallel interpenetration of (6,3) nets in the cocrystal of trimesic acid and bipy. Three-connected nodes represent the centers of trimesic acid molecules, while the two-connected nodes represent the midpoints of the bipy ligands.

$[\text{Cd}_2(\mathbf{4})_3(\text{NO}_3)_4]$ contains three independent (6,3) nets in which the three-connected nodes are provided by cadmium atoms that are bridged by ligand **4**.^[24] Every $\text{Cd}_6(\mathbf{4})_6$ ring has a rod from each of the other two nets passing through it (Figure 23). This interpenetration mode is a very close analogue of the twofold interpenetration shown by $[\text{Ag}(\text{tcm})]$, as comparison of Figure 23 with Figures 12 and 11a will reveal. Indeed, removal of any one of the three nets in

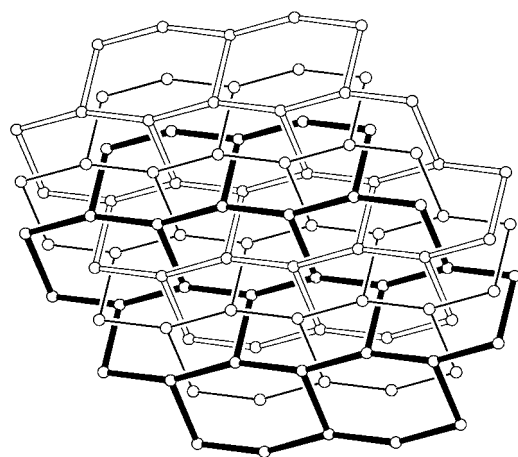
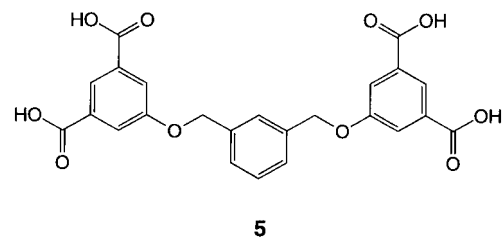


Figure 23. Three parallel interpenetrating (6,3) nets in the structure of $[\text{Cd}_2(\mathbf{4})_3(\text{NO}_3)_4]$. The three-connected nodes are provided by Cd atoms, and ligand **4** forms the connections between the nodes.

Figure 23 leaves a twofold interpenetrated system topologically identical to that in Figures 12 and 11a.

The crystal structure of **5** contains three interpenetrating (6,3) nets; the nodes of the nets are the centers of the two

isophthalic acid groups in each molecule.^[40] One of the links from any three-connected node represents the covalent



spacer between the two isophthalic acid groups of each molecule, and the other two links represent hydrogen-bonding associations with adjacent molecules. The interpenetration is shown schematically in Figure 24; a comparison of Figures 23 and 24 shows that the mode of interpenetration is identical to that in $[\text{Cd}_2(\mathbf{4})_3(\text{NO}_3)_4]$.

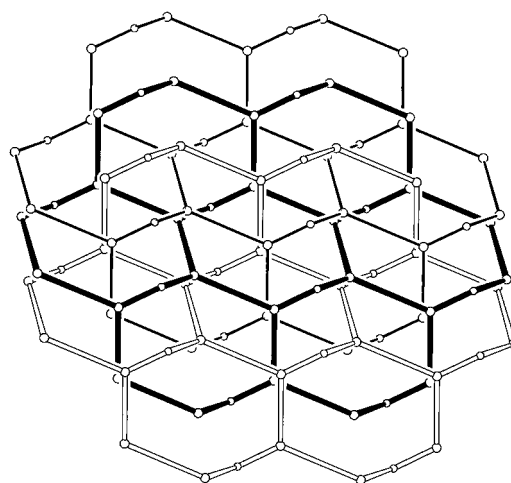
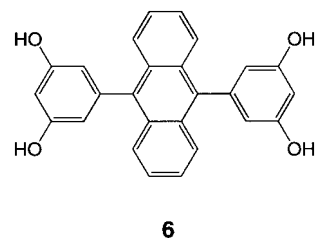


Figure 24. Schematic representation of the three parallel interpenetrating (6,3) nets in the crystal structure of **5**. The three-connected centers represent the centers of the isophthalic acid groups of **5**, while the smaller two-connected centers represent the midpoint of the central C_6 ring of **5**.

Similarly, $\mathbf{6} \cdot 2\text{L}$ ($\text{L} = 1,4\text{-benzoquinone}$) has three interpenetrating (6,3) sheets in which the three-connected nodes are the centers of the resorcinol groups of the ligand.^[41] One link from each node represents the covalent bridging of the resorcinol groups through the anthracene unit, and the other two links represent hydrogen-bonding interactions in which resorcinol groups of two different molecules are bridged by bifunctional 1,4-benzoquinone molecules. This interpenetration is shown schematically in Figure 25. Removal of any one net would leave a system of two interpenetrating nets topologically identical to that shown in Figure 11c.



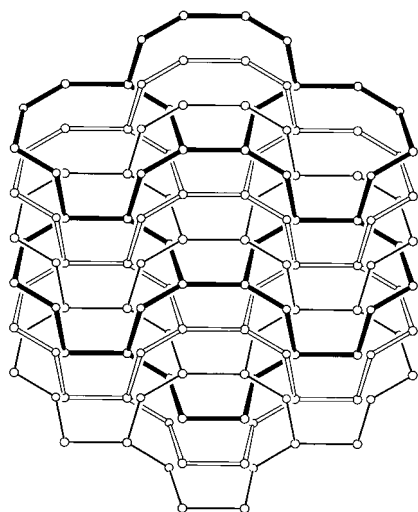
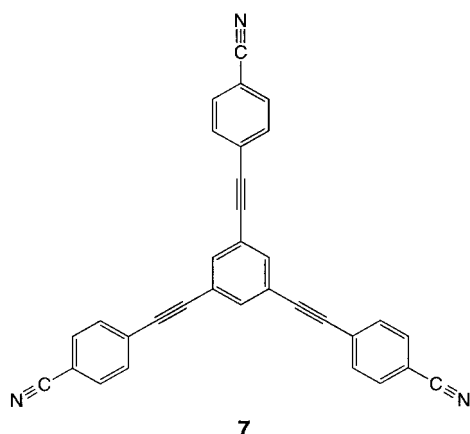


Figure 25. Schematic representation of the three parallel interpenetrating (6,3) nets in the crystal structure of $6 \cdot 2L$ ($L = 1,4$ -benzoquinone). The larger three-connected circles represent the resorcinol groups on **6**, and smaller two-connected circles represent the midpoints of the 1,4-benzoquinone molecules.

3.1.5. Six Parallel Interpenetrating Two-Dimensional Nets

Six parallel interpenetrating (6,3) sheets are seen in the structure of solvated $[\text{Ag}(\text{teb})\text{CF}_3\text{SO}_3]$ (teb = 1,3,5-tris(4-ethynylbenzonitrile)benzene, **7**).^[42] The three-connected nodes are defined by alternating ligand and silver centers. The



silver atoms are also coordinated to pendant triflate ions, and hence have tetrahedral geometry. The nets interpenetrate such that any two nets have the same topological relationship as that shown in Figure 11 a.

3.2. Inclined Interpenetration of Two-Dimensional Frameworks

In the inclined mode of interpenetration of 2D frameworks any one sheet has an infinite number of others passing through it (see Figure 10). As mentioned earlier, inclined interpenetration of 2D sheets produces an interlocked 3D structure; this is in contrast to parallel interpenetration, which yields a composite 2D product. Any pair of inclined sheets

pierce each other only along the line of intersection of the two planes. In some cases each ring of a sheet has only one rod of an inclined sheet passing through it, but there are examples in which the rings are large enough and the rods slim enough to allow more than one sheet to pass through each ring. All known cases of inclined interpenetration of 2D sheets involve either (4,4) or (6,3) nets.

3.2.1. Inclined Interpenetration of (4,4) Nets

Crystalline compounds of composition $[\text{M}(\text{bipy})_2(\text{H}_2\text{O})_2](\text{SiF}_6)$ ($\text{M} = \text{Zn}, \text{Cd}, \text{Cu}$) and $[\text{Cd}(\text{bipy})_2(\text{H}_2\text{O})(\text{OH})](\text{PF}_6)$ have the interlocked, perpendicular, square-grid structure shown in Figure 26.^[43, 44] The bridging bipy ligands are

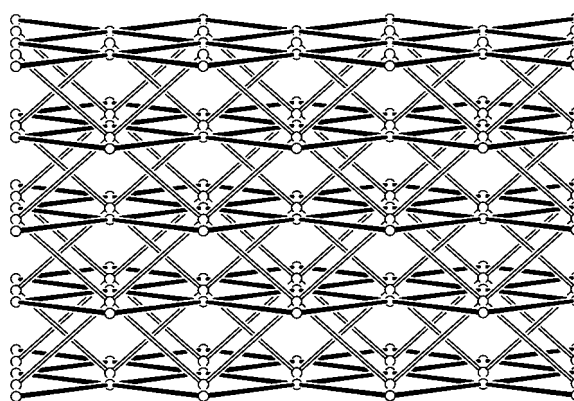


Figure 26. Inclined interpenetration (actually perpendicular) of two (4,4) nets in $[\text{M}(\text{bipy})_2(\text{H}_2\text{O})_2](\text{SiF}_6)$. Four-connected nodes are provided by M atoms, which have two pendant *trans* H_2O ligands not shown here.

arranged around the metal atom in a square-planar fashion, and two water ligands (or, in the Cd/PF_6 case, one water and one hydroxide ligand) on opposite sides of that plane complete an octahedral coordination environment. The $\text{Cd}(\text{PF}_6)_2/\text{bipy}$ system is interesting in that the use of solvent mixtures only slightly different from those used to obtain the interpenetrating $[\text{Cd}(\text{bipy})_2(\text{H}_2\text{O})(\text{OH})](\text{PF}_6)$ structure yields noninterpenetrating $[\text{Cd}(\text{bipy})_2(\text{H}_2\text{O})_2](\text{PF}_6)_2 \cdot 4\text{H}_2\text{O} \cdot 2\text{bipy}$,^[44] which contains very similar square-grid sheets in which each corallike ring encloses two uncoordinated bipy molecules. This example demonstrates how fine a balance may dictate whether an interpenetrating structure is formed or not.

$[\text{Fe}(\text{bpe})_2(\text{NCS})_2] \cdot \text{CH}_3\text{OH}$ (bpe is the “extended” bipy analogue *trans*-1,2-di-(4-pyridyl)ethene) has a structure that is geometrically very similar and topologically identical to that in Figure 26; bipy has been replaced by bpe, and the two *trans* water ligands have been replaced by thiocyanate ligands.^[45]

A bipy analogue that is even more extended than bpe, 1,4-bis(4-pyridyl)butadiyne (bpb), gives crystals of the composition $[\text{M}_2(\text{OH})(\text{bpb})_4](\text{BF}_4)_3 \cdot \text{H}_2\text{O} \cdot \text{EtOH}$ ($\text{M} = \text{Cd}, \text{Cu}$) containing “doubled-up” square-grid sheets which interpenetrate each other (Figure 27). The manner of interpenetration is closely analogous, and in fact topologically identical, to that represented in Figure 26.^[46]

$[\text{Cd}(\text{NH}_3)_2\{\text{Ag}(\text{CN})_2\}_2]$ also has an interpenetrating sheet structure which is topologically identical to that in Figure 26;

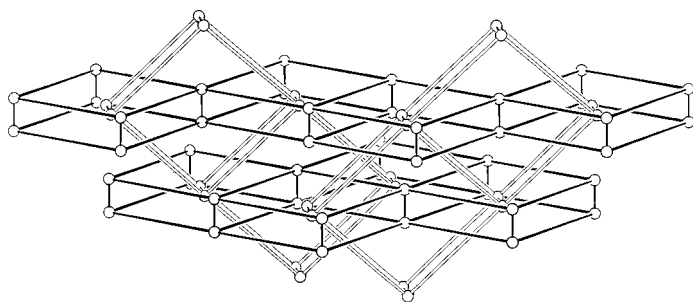


Figure 27. Inclined interpenetrating doubled-up sheets in the structure of $[M_2(OH)(bpb)_4](BF_4)_3 \cdot H_2O \cdot EtOH$ ($bpb = 1,4\text{-bis(4-pyridyl)butadiyne}$). The circles represent M atoms. "Short" connections here are provided by $\mu_2\text{-OH}^-$ and "long" connections by $\mu_2\text{-bpb}$ ligands. The overall topology of the doubled-up sheets is (4,4), and the nodes are located at the midpoints of the short connections.

there are $Ag(CN)_2^-$ bridging ligands in place of bipy and two *trans* amine ligands in place of the two water ligands.^[47]

A second, chemically realistic way in which two inclined (4,4) nets could be imagined to interpenetrate is shown in Figure 28. The only example of this mode of interpenetration

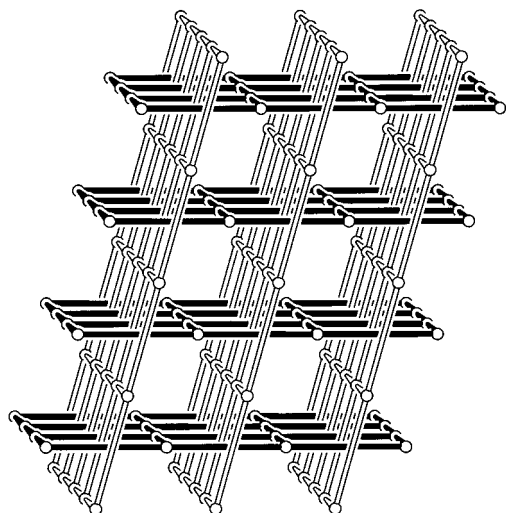


Figure 28. An alternative mode of inclined interpenetration of two (4,4) nets.

exists in the structure of $[Cd(4\text{-ampy})_2[Ag(CN)_2]_2] \cdot [Cd(me a)(4\text{-ampy})\{Ag(CN)_2\}_2]_2$ (4-ampy = 4-aminopyridine, mea = 2-aminoethanol).^[48] This structure contains (4,4) 2D sheets that are composed of octahedrally coordinated cadmium atoms bound to terminal 4-ampy ligands and bridged by linear $Ag(CN)_2^-$ moieties. A second type of sheet exists in the structure which contains linear chains of cadmium atoms bridged by $Ag(CN)_2^-$ groups. These chains are linked to one another through hydrogen bonds between the uncoordinated nitrogen atoms of monodentate $Ag(CN)_2^-$ ligands, which are also bound to the cadmium atoms, and the oxygen atoms of the mea ligands, which are coordinated to cadmium atoms of adjacent chains (Figure 29).

A particularly interesting feature of this structure is that the windows of the two types of sheets have different numbers of

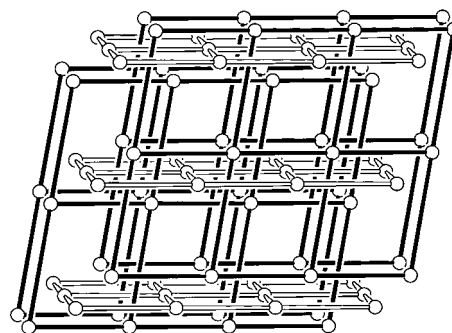


Figure 29. Schematic representation of the 2D inclined interpenetration of (4,4) sheets in the structure of $[Cd(4\text{-ampy})_2[Ag(CN)_2]_2] \cdot [Cd(me a)(4\text{-ampy})\{Ag(CN)_2\}_2]_2$ (4-ampy = 4-aminopyridine, mea = 2-aminoethanol). The open bonds represent the coordination polymer nets of composition $[Cd(4\text{-ampy})_2[Ag(CN)_2]_2]$, while the black bonds represent the sheets formed by cross-linking of coordination polymer chains of composition $[Cd(me a)(4\text{-ampy})\{Ag(CN)_2\}_2]$ through hydrogen bonds. The hydrogen bonds are represented by the almost vertical black bonds. The circles represent Cd atoms.

nets passing through them. In the first type of net two sheets of the second type pass through any given window, while in the second type only one net of the first type passes through any given window.

The structure of solvated $[Cd(py)_2[Ag(CN)_2]_2]$ (py = pyridine) contains (4,4) sheets composed of octahedrally coordinated cadmiums which are bound to pendant pyridine ligands and bridged by linear $Ag(CN)_2^-$ units.^[49] Every ring of any sheet contains parts of two others passing through it (Figure 30). The mode of interpenetration is unrelated to the two previous modes discussed for (4,4) nets (Figures 26 and 28).

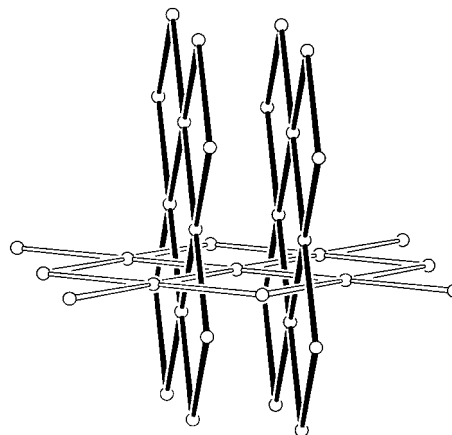


Figure 30. Schematic representation of the 2D inclined interpenetration of (4,4) sheets in the structure of $[Cd(py)_2[Ag(CN)_2]_2]$ (py = pyridine). Each window of each sheet, all of which are equivalent, has parts of two other sheets passing through it. The circles represent Cd atoms.

In principle, inclined interpenetration of (4,4) nets in three mutually perpendicular planes is possible (Figure 31), but no examples of this are known at present.

3.2.2. Inclined Interpenetration of (6,3) Nets

Two topologically different ways in which two inclined (6,3) nets can interpenetrate are shown in Figure 32. $[Cu_2(pz)_3]^-$

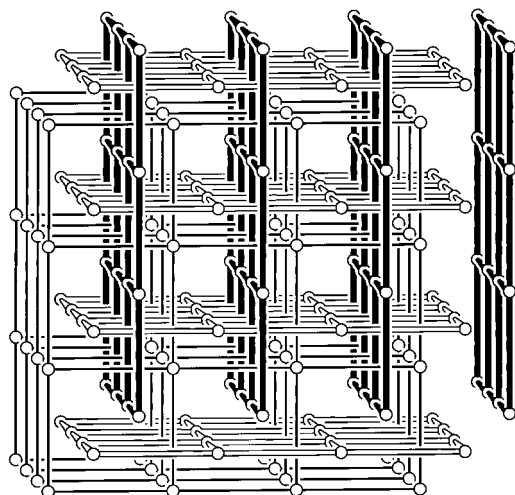


Figure 31. Hypothetical mode of interpenetration of (4,4) nets in three mutually perpendicular planes.

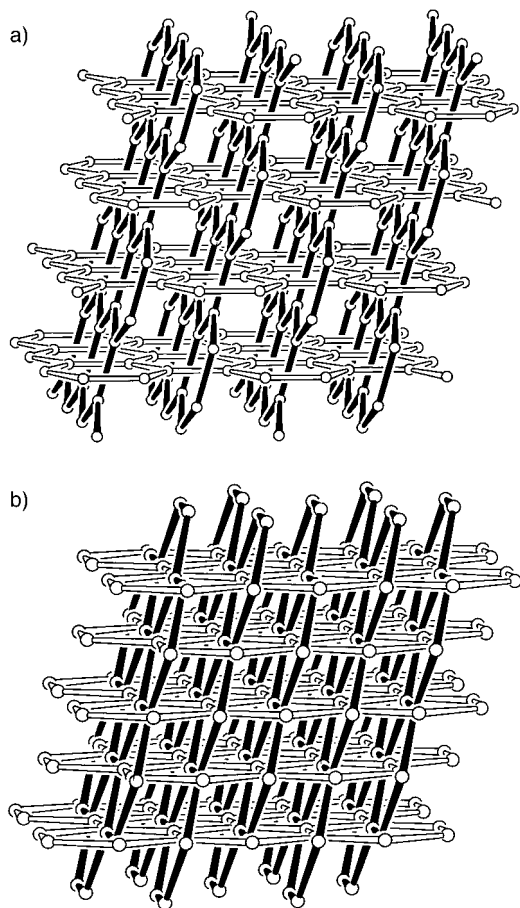


Figure 32. Two topologically different ways inclined (6,3) nets may interpenetrate.

(SiF₆) (pz = pyrazine) contains (6,3) nets in which the three-connected nodes are provided by Cu^I centers, which are each connected to three neighboring Cu^I centers through pyrazine bridges. The mode of interpenetration, shown in Figure 33, is topologically identical to that represented schematically in Figure 32 a.^[50]

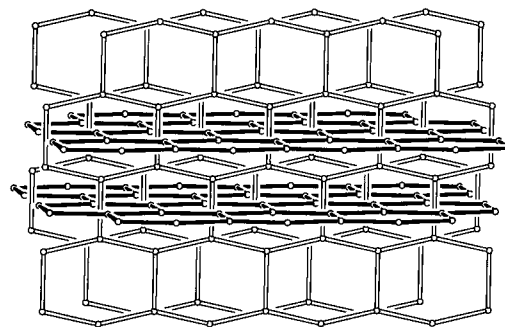
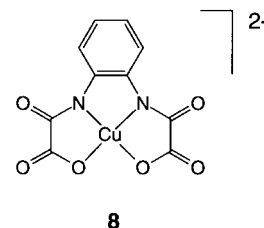
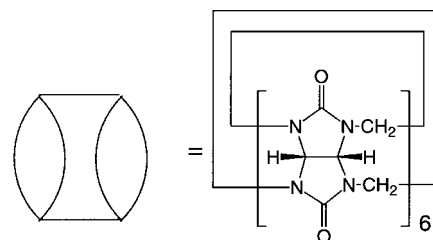
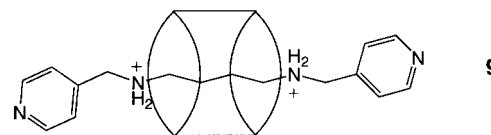


Figure 33. Inclined interpenetration of (6,3) nets in the structure of [Cu₂(pz)₃](SiF₆) (pz = pyrazine). The circles represent Cu atoms.

The anionic complex [Cu^{II}(opba)]²⁻ (**8**, opba = *o*-phenylenebis(oxamate)) can itself act as a bridging unit. With Mn^{II} ions this yields a (6,3) net of composition [Mn₂^{II}(**8**)₃]²⁻ in which the triply chelated Mn^{II} center acts as the three-connected node. The negative charge on the 2D network is counterbalanced by the organic radical cation 2-(4-*N*-methylpyridinium)-4,4,5,5-tetramethylimidazolin-1-oxyl-3-oxide. Each (6,3) net has an infinite number of identical sheets passing through it, inclined at 72.7°, with one rod from an inclined sheet passing through every hexagon: The essential nature of the interpenetration is that represented schematically in Figure 32 a. The radical cations play an important role in the overall structure, since they provide weak “axial” dative bonds through their oxygen atoms to copper centers in independent inclined sheets and thus act as weak bridging agents between sheets. There are three different paramagnetic centers present, namely, the radical cation, the copper ions, and the manganese ions; the couplings are such that the material acts as a magnet below 22.5 K.^[51]



One example was reported recently in which every ring has components of two independent inclined (6,3) nets passing through it;^[52] in this case the three-connected nodes are provided by Ag^I ions which are linked by units of **9**. This beautiful structure is an example of a 2D polyrotaxane in



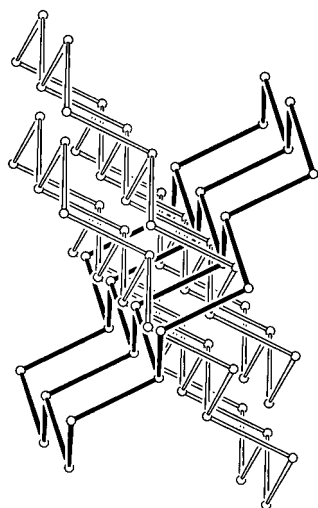


Figure 34. Representation of the interpenetration in the network of composition $[\text{Ag}_2^{\text{I}}(\mathbf{9})_3]$. Every hexagon has components of *two* inclined (6,3) nets passing through it. The circles represent Ag atoms.

inclined sheets passing through it.^[13] The essential character of the interpenetration, which is related to that in Figure 32a, is represented in Figure 35.

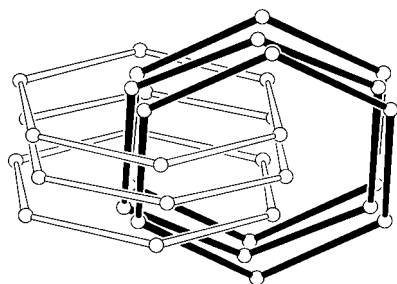


Figure 35. Schematic representation of the mode of inclined (6,3) interpenetration seen in various derivatives of trimesic acid. Every hexagon has components of three inclined independent nets passing through it in the manner shown in Figure 32a. The circles represent the midpoints of the central C_6 rings of the trimesic acid molecules.

Another example of inclined (6,3) interpenetration in which every ring has components of three independent inclined sheets passing through it is $[\text{Cu}(\text{bipy})\text{X}]$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$).^[53, 54] Binuclear halide-bridged $(\text{CuX})_2$ units play the role of the three-connected nodes; each is connected to a neighboring $(\text{CuX})_2$ node by two side-by-side bipy ligands and to two other neighbors through single bipy units (Figure 36, the connections consisting of side-by-side bipy units are represented by two parallel lines). This example is of particular interest from the topological point of view because one of the three independent sheets, the central one, passing through any one ring adopts the interpenetration mode represented in Figure 32b, whilst the other two, which are equivalent, adopt a different mode.

which the beadlike component encircling the diprotonated diamine in **9** in rotaxane fashion is furnished by cucurbituril (Figure 34). All rings are equivalent, and every ring has a rod from each of two inclined sheets passing through it.

Various forms and derivatives of benzene-1,3,5-tricarboxylic acid (trimesic acid) contain hydrogen-bonded (6,3) nets of the type shown in Figure 3, which interpenetrate so that every hexagonal ring has components of three inclined sheets passing through it.

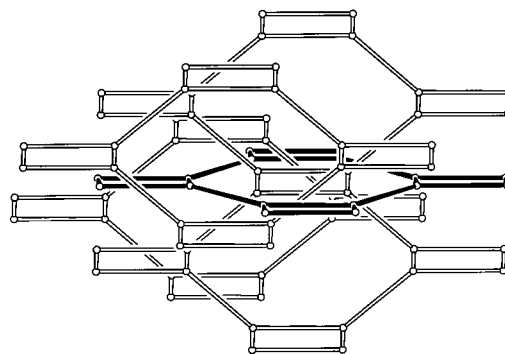


Figure 36. Structure of $[\text{Cu}(\text{bipy})\text{X}]$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$). The circles represent Cu atoms. Each “short” connection shown here is provided by two $\mu_2\text{-X}^-$ bridges. “Long” connections are provided by bipy ligands, some of which are present in close side-by-side pairs. The three-connected nodes of the (6,3) net are located at the midpoints of the $\text{Cu}(\text{X})_2\text{Cu}$ rectangles (i.e., at the midpoints of the “short” connections shown here).

4. Interpenetrating Three-Dimensional Nets

An infinite number of different 3D nets are theoretically possible. Nevertheless, the individual 3D nets involved in interpenetration, as far as is presently known, belong to a restricted number of topological classes with only a few exceptions. This situation may of course change radically in the near future. The diamond net is by far the most common type currently known to participate in interpenetration. We classify the modes of 3D interpenetration below in terms of the topologies of the individual nets.

4.1. Interpenetrating Three-Connected Three-Dimensional Nets

All known examples of interpenetrating three-connected 3D nets are of either the (10,3)-a type or the (10,3)-b type; there is one exception of the (8,3)-c type. In view of the large number of three-connected 3D nets that are possible—no fewer than thirty topologically uniform examples were listed by Wells^[4]—it is surprising that so few types are represented in real cases. However these are early days in the generation of framework structures, and perhaps this situation will change as a result of further work in the area.

4.1.1. Interpenetrating (10,3)-a Nets

Figure 37 shows a representation of the (10,3)-a net (sometimes referred to as the SrSi_2 -related net) in its most regular form possible. It should be recalled that any net, however much it may be geometrically distorted, is considered to retain its topological identity provided connections are not broken. The net is shown in Figure 37 in its geometrically most symmetrical form (cubic), and every node shows a trigonal-planar environment with 120° angles. A characteristic feature of the (10,3)-a net is the presence of fourfold helices, all of the same handedness, running parallel with the three cubic axes (Figure 37). The net as a whole is therefore chiral. In the discussion that follows we shall refer to (10,3)-a nets contain-

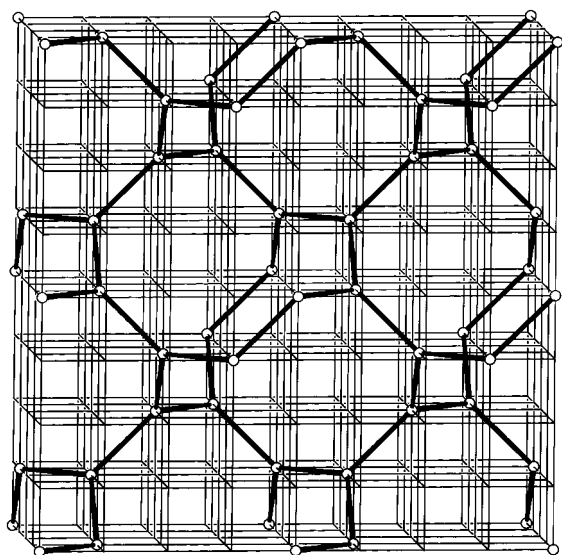


Figure 37. The (10,3)-a net in its most symmetrical form, cubic, displayed on a cubic grid.

ing right-handed fourfold helices simply as “right-handed nets”.

Showing remarkable insight, Wells suggested,^[4] well before real examples were discovered, that the (10,3)-a net is in principle capable of interpenetrating not only an identical net of the same handedness, but also a net of the opposite handedness. In the latter case “a three-dimensional racemate”, as he referred to it, is generated that at the time was purely hypothetical. The crystal structure of cyanamide NH_2CN (Figure 38) can be regarded, because of the simplicity

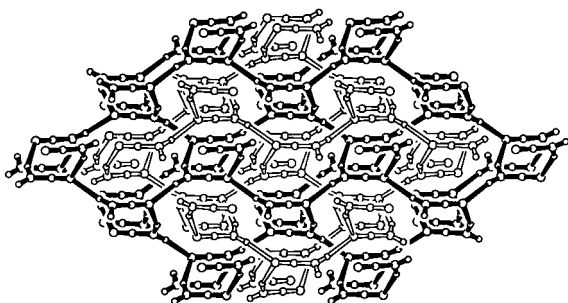
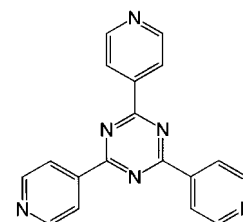


Figure 38. Two enantiomorphic interpenetrating (10,3)-a nets in the crystal structure of cyanamide NH_2CN . The circles represent in order of decreasing size N, C, and H atoms.

of its components, as the prototype for this sort of racemic interpenetration.^[55] The two types of nitrogen centers provide the three-connected nodes for the hydrogen-bonded (10,3)-a net. Two such nets of opposite handedness then interpenetrate in the manner shown in Figure 38. $[\text{Ag}_2(2,3\text{-Me}_2\text{pz})_3](\text{SbF}_6)_2$, in which the silver atoms provide the three-connected nodes, is topologically identical.^[56]

Both modes of interpenetration proposed by Wells, interpenetration of a given (10,3)-a net by nets of the same handedness and by nets of the opposite handedness, are simultaneously displayed in cubic crystals of composition $[\text{Zn}(\text{tpt})_{2/3}(\text{SiF}_6)(\text{H}_2\text{O})_2(\text{CH}_3\text{OH})]$ ($\text{tpt} = 2,4,6\text{-tris}(4\text{-pyridyl})\text{-}$

1,3,5-triazine, **10**).^[57] The three-connected nodes are provided by triazine molecules. The zinc centers—with a coordination environment consisting of two *trans* tpt-pyridine donors, one SiF_6^{2-} ion bound through one F atom, two water ligands, and one methanol ligand—effectively act as linear two-connected units. Figure 39a shows one of the eight (10,3)-a nets that are present. Inspection will reveal that this is left-handed; also present are three other left-handed and four right-handed nets. Any net is related to the three others of the same handedness by half-cell translations parallel to the three cubic axes. Helices consequently appear in pairs sharing the same helical axis, an example of which is shown in Figure 39b. Each double helix makes multiple close triazine–triazine π contacts with four double helices of the opposite handedness, all with their helical axes parallel; a pair of double helices connected by such π interactions is shown in Figure 39c. The tpt units appear in close, centrosymmetrically related pairs (indicated in Figure 39c by arrows).



10

The mineral eglestonite of composition $[(\text{Hg}_2)_3\text{O}_2\text{H}]\text{Cl}_3$ has been described as consisting of four $[(\text{Hg}_2)_3\text{O}_2^{2+}]_n$ nets with the (10,3)-a topology.^[58, 59] The oxide centers act as the three-connected nodes, and the mercurous units act as two-connected nodes that link one oxide to another. The $\text{O} \cdots \text{O} \cdots \text{O}$ angles of 102.1° are close to the tetrahedral angle. This observation led us to the realization that it is possible to construct strain-free (10,3)-a nets using pyramidal three-connected nodes, provided these retain a threefold axis of symmetry, which, like the “parent” (10,3)-a net with trigonal nodes, also have cubic symmetry (indeed, the structure of H_2O_2 can be described in terms of a (10,3)-a topology with pseudo-tetrahedral centers, and SrSi_2 itself displays slight pyramidal distortion at each three-connected node).^[4] Such a net consisting of pyramidal nodes with tetrahedral angles of 109.45° is shown in Figure 40. For ease of description, (10,3)-a nets comprising trigonal or pyramidal nodes will be referred below to as “trigonal” and “pyramidal nets”, respectively. As can be seen by comparing Figures 37 and 40, the trigonal and pyramidal (10,3)-a nets differ considerably in appearance and geometry. One consequence of substituting the planar-trigonal centers by pyramidal ones is that the fourfold helices become markedly flattened. Some of these flattened helices can be seen in Figure 40; their axes are roughly perpendicular to the plane of the page, and, since the structure has cubic symmetry, equivalent flattened helices also run from left to right and from top to bottom. The (10,3)-a nets present in eglestonite, two right-handed and two left-handed (Figure 41), are very similar to the idealized net shown in Figure 40. The flattened helices of two nets of the same handedness share a common axis, and they can be related by a translation along this shared axis of half the helical period combined with a 90° rotation (Figure 41). Two pyramidal nets of the same handedness can be derived from a single trigonal net of the same handedness by distorting each individual node into a pyramidal geometry in the appropriate direction along

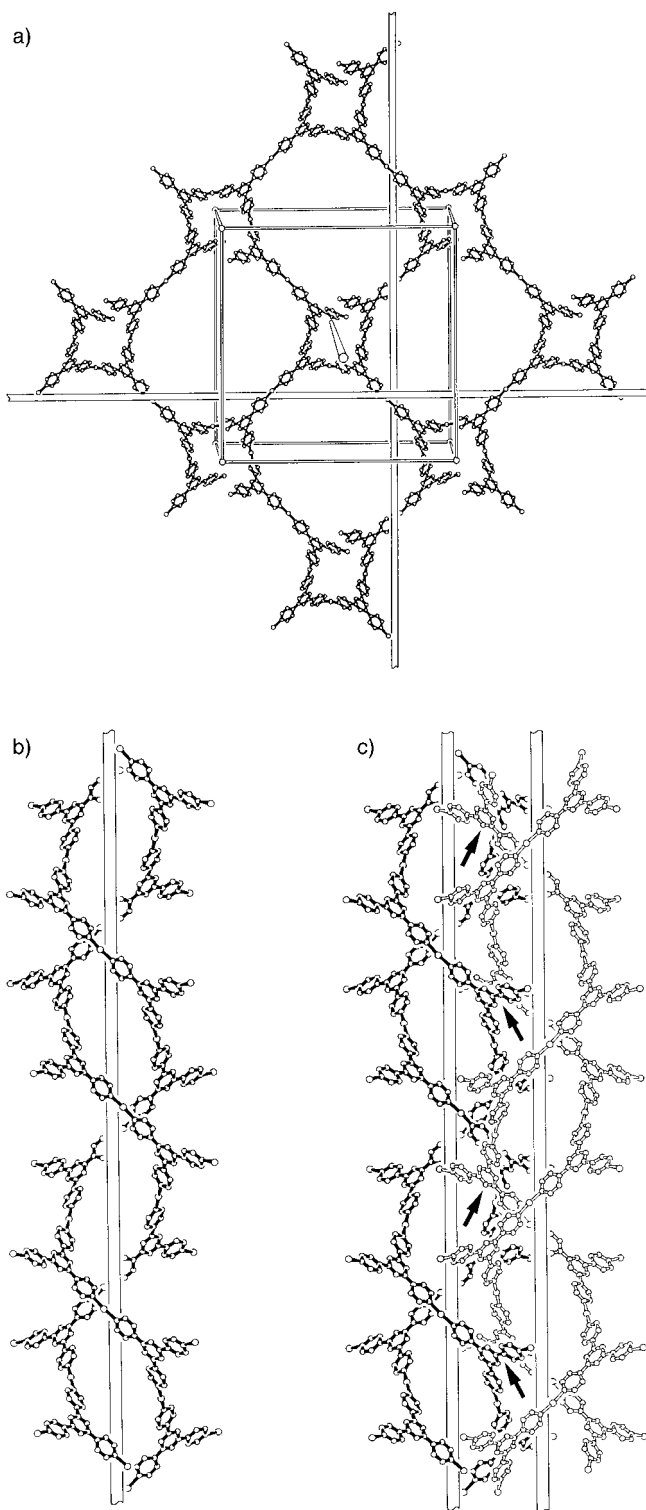


Figure 39. a) One of the eight (10,3)-a nets present in $[\text{Zn}(\text{tpt})_{2/3}(\text{SiF}_6)(\text{H}_2\text{O})_2(\text{CH}_3\text{OH})]$ ($\text{tpt} = \mathbf{10}$). The larger circles represent Zn atoms, and the smaller circles C and N atoms. b) A double helix. c) A π -contacting pair of double helices of opposite handedness. The arrows indicate centrosymmetrically related π -contacting pairs.

the normal to the trigonal plane (Figure 42); two directions of distortion are possible, hence the existence of two derived pyramidal nets. Conversely, the trigonal net can be derived from the two pyramidal nets by placing a trigonal node at the

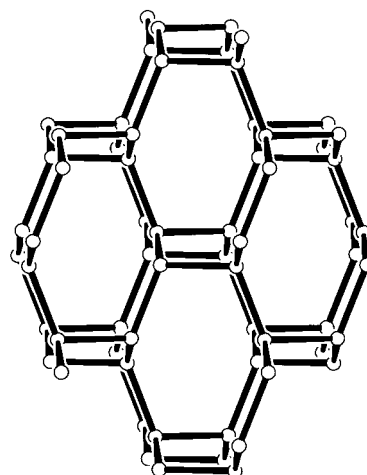


Figure 40. A (10,3)-a net constructed from pyramidal nodes with tetrahedral angles.

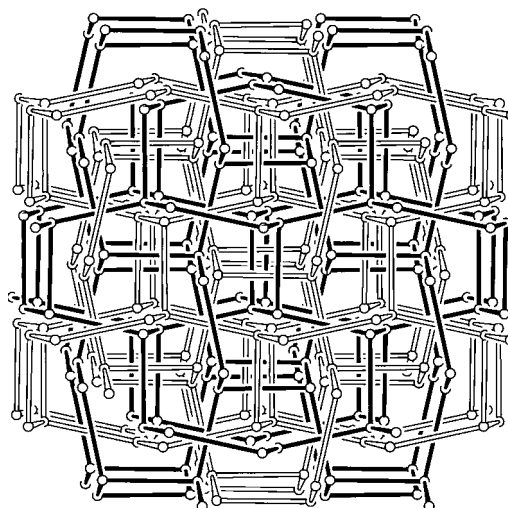


Figure 41. Four "pyramidal" (10,3)-a nets, two right-handed and two left-handed, in eglestonite. The circles represent O atoms.

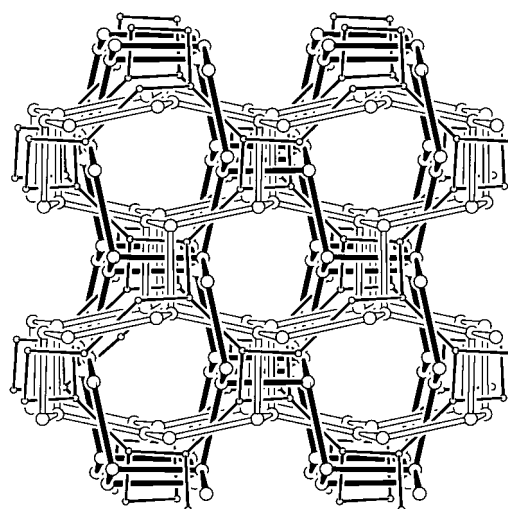


Figure 42. Relationship between a "trigonal" (10,3)-a net and the two possible derived "pyramidal" (10,3)-a nets.

midpoint between two directly neighboring pyramidal nodes of independent nets that share the same threefold axis, as can also be seen in Figure 42. In eglestonite the helices of the second pair of nets with handedness opposite to that of the first pair are then located in the channels generated by the first pair (Figure 41).

In many of the structures discussed here it is debatable how independent the various nets are. It is convenient to describe the structure of eglestonite in terms of four “independent” (10,3)-a nets, as we have done above (and as others have done previously, although not in the detail presented here). However, the fact is that the pyramidal oxygen centers from adjacent nets form short hydrogen bonds ($\text{O}\cdots\text{O} \approx 2.5 \text{ \AA}$;[58] note the presence of one proton per two oxides in the composition).

In cubic RhBi_4 all Rh centers are equivalent and provide the nodes for a four-connected 3D net.[60] Bi_2 units connect Rh atoms, and every Rh is immediately surrounded by four Bi_2 pairs. The four-connected net thus formed has previously and correctly been described as possessing the $3^2 \cdot 10^4$ topology, which in fact is chiral. In RhBi_4 two such nets of opposite handedness interpenetrate, as shown in Figure 43. The units

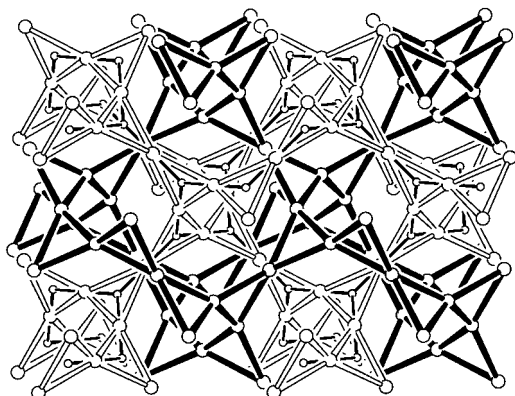


Figure 43. Two interpenetrating $3^2 \cdot 10^4$ nets of opposite handedness in the structure of RhBi_4 . The circles represent Rh atoms. The midpoints of the Rh_3 triangles within a particular $3^2 \cdot 10^4$ net form a (10,3)-a net. The (10,3)-a net derived from the $3^2 \cdot 10^4$ net represented here by “open” connections is indicated by fine lines and smaller circles. For clarity the (10,3)-a net derived from the other net is omitted.

linked together are triangular Rh_3 groups; each triangle is linked to three others through shared Rh vertices. It is helpful to conceptually simplify these nets to the (10,3)-a form in which the midpoints of the Rh_3 triangles now provide the three-connected nodes (Figure 43). RhBi_4 , which has the same space group as eglestonite ($Ia3d$), can thus be seen as yet another example of the type of 3D racemate predicted by Wells.

4.1.2. Interpenetrating (10,3)-b Nets

The (10,3)-b net (sometimes referred to as the ThSi_2 -related net) is tetragonal in its most symmetrical form (Figure 44). As in (10,3)-a nets, the nodes have 120° angles. Each node is connected to two neighbors in a 1D planar zigzag strip. The third connection at every node is to a node belonging to a

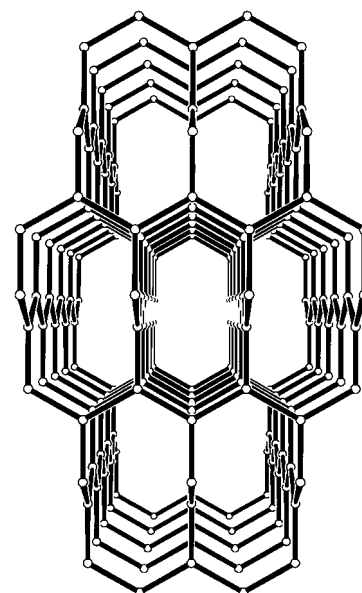


Figure 44. The (10,3)-b net in its most symmetrical form (tetragonal).

zigzag strip running perpendicular to the first. Alternate nodes within a strip are connected to a strip above it, then a strip below it, and so on. An interesting feature of this net is that it can be “collapsed” by concerted rotation around the strip–strip connections of all the strips in one direction relative to all those in the other direction. This collapse does not interfere with the trigonal geometry of the individual nodes; it merely reduces the angle between connected zigzag strips. This collapse is seen in real cases to extents that vary so as to achieve optimum packing.

A characteristic structural motif in the (10,3)-b net that parallels the adamantane motif in the diamond net is the cagelike unit shown in Figure 45a. Indeed, the (10,3)-b net

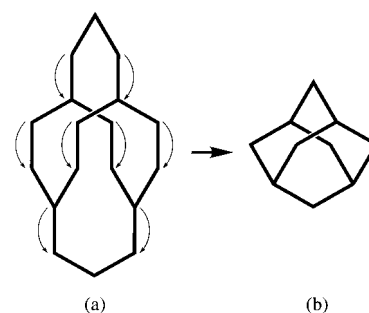


Figure 45. The imaginary contraction and fusion process relating a “(10,3)-b cage” (a) of the (10,3)-b net to an adamantane cage (b) of the diamondlike net.

and the diamond net are very closely related, in that the former can be converted into the latter by contraction of the links between the zigzag strips (i.e., the links aligned with the tetragonal axis in the most symmetrical form of the (10,3)-b net) to the point where the two three-connected nodes fuse together to become a single four-connected node. Figure 45 illustrates this imaginary conversion of a (10,3)-b cage into an adamantane cage. Just as the nature of the interpenetration of

diamond nets can most simply be understood by focussing on the way one adamantane unit is interpenetrated by others (as we saw in the example of $[\text{Zn}(\text{CN})_2]$ in Section 1.5 and as we shall see in more complicated examples in Section 4.2.1), the nature of the interpenetration of (10,3)-b nets can be best appreciated by looking at the way one (10,3)-b cage is interpenetrated by others.

Examples are known in which two, three, and six independent (10,3)-b nets interpenetrate. The mineral neptunite, $\text{M}_4^{\text{II}}\text{M}_2^{\text{I}}(\text{TiO})_2\text{Si}_8\text{O}_{22}$ ($\text{M}^{\text{II}} = \text{Fe}^{\text{II}}, \text{Mg}^{\text{II}}, \text{Mn}^{\text{II}}; \text{M}^{\text{I}} = \text{alkali metal}$), contains two infinite polysilicate (10,3)-b nets, one of which is shown in Figure 46a, that interpenetrate in the manner

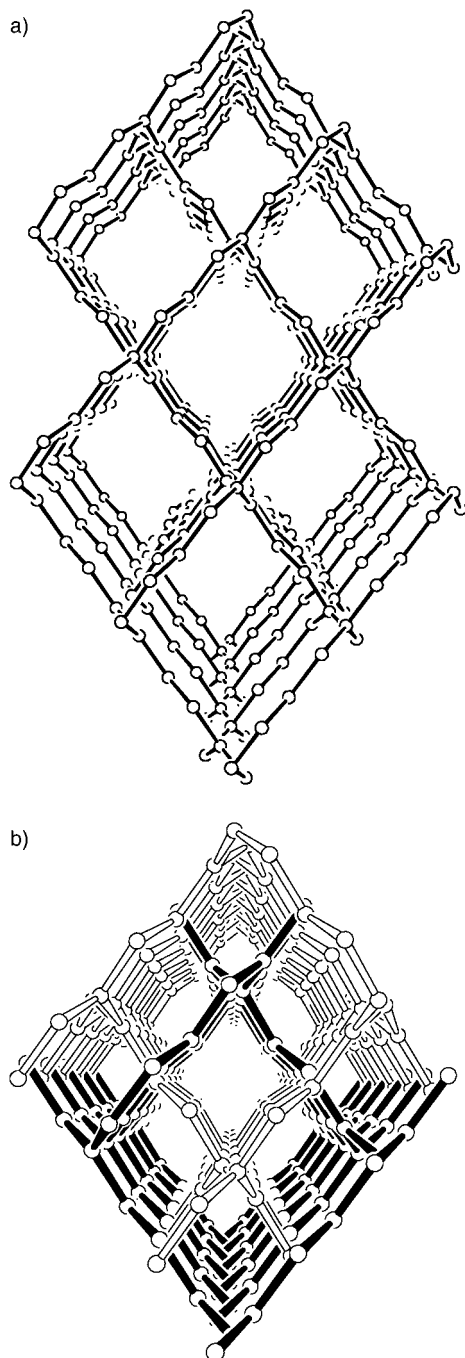


Figure 46. a) A single (10,3)-b net in neptunite. The circles represent Si atoms. b) Two interpenetrating nets in neptunite.

depicted in Figure 46b.^[61] The three-connected nodes are provided by SiO_4 tetrahedra that each carry one terminal, nonbridging SiO^- unit and are represented as Si^3 below. Present in equal numbers are two-connected SiO_4 tetrahedra, each carrying two terminal SiO^- groups (represented as Si^2 below). The zigzag planar strips that are characteristic of the (10,3)-b net consist in neptunite of alternating long and short bonds between three-connected nodes. The short bonds consist of direct connections between Si^3 centers, and the long bonds have two Si^2 centers interposed between Si^3 nodes to produce the sequence $\cdots \text{Si}^3\text{Si}^3\text{Si}^2\text{Si}^2\text{Si}^3\text{Si}^3\text{Si}^2\text{Si}^2\cdots$ within a strip (Figure 46a). Zigzag strips of this type run from top right to bottom left and also from top left to bottom right. Also apparent in Figure 46a are channels running perpendicular to the plane of the page, that is, parallel to what would have been the tetragonal axis if the net had not been deformed. The interpenetration is such that the connections between zigzag strips within one net are located along the centers of these channels in the other net (Figure 46b).

Two interpenetrating (10,3)-b nets are present in crystals of solvated $[(\text{ZnCl}_2)_3(\text{tpt})_2]$ ($\text{tpt} = \mathbf{10}$).^[28] The three-connected nodes are provided by the triazine molecules. The zinc centers have an approximately tetrahedral coordination environment consisting of two tpt-pyridine and two chloro ligands, and therefore act as angular two-connectors. As a consequence, the resulting (10,3)-b net (Figure 47a) is considerably distorted. Figure 47b shows the two interpenetrating (10,3)-b nets.

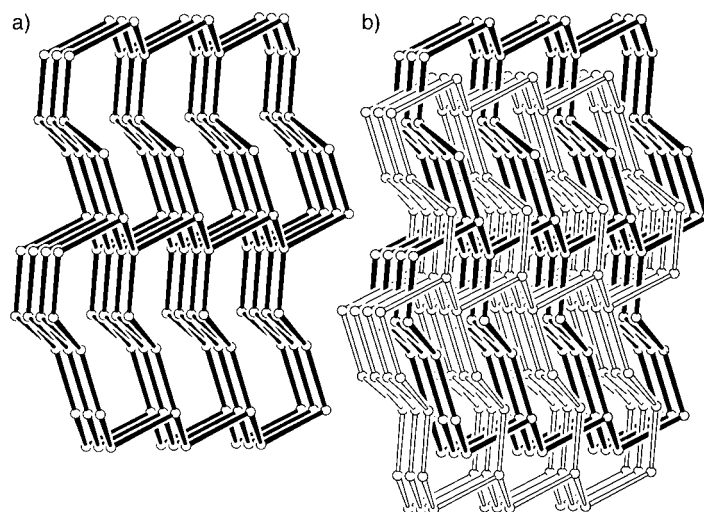


Figure 47. a) One of the two (10,3)-b nets in the structure of $[(\text{ZnCl}_2)_3(\text{tpt})_2]$ ($\text{tpt} = \mathbf{10}$). The circles represent the centers of triazine rings. b) Two interpenetrating (10,3)-b nets.

Three independent, identical, and interpenetrating (10,3)-b nets are seen in $[\text{Ag}_2(\text{pz})_3](\text{BF}_4)_2$.^[62] Silver atoms provide the three-connected nodes, which are linked together through bridging pyrazine units. The nets are collapsed, so that the angle between zigzag strips is 55.4° . Figure 48a shows three unit cells stacked along the a direction. One net can be generated from another by a $(1,0,0)$ translation; but a shorter translation $(1/2, 1/2, 0)$ also relates one net to another. Every decagon has one rod from each of the other two nets passing

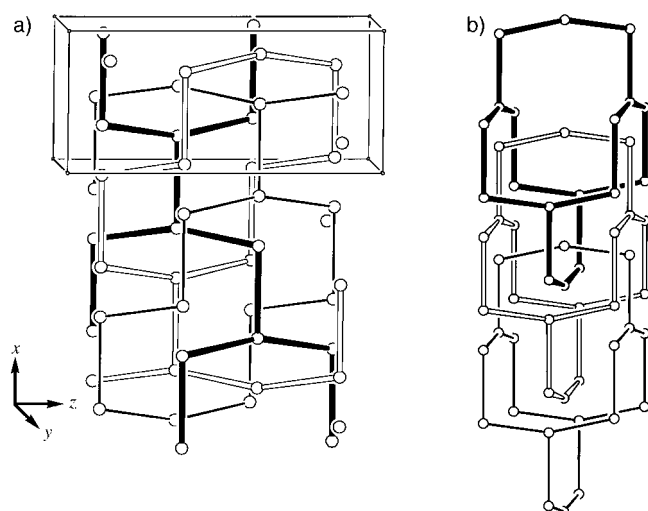


Figure 48. a) Three unit cells in the structure of $[\text{Ag}_2(\text{pz})_3](\text{BF}_4)_2$. The circles represent Ag atoms. b) Three interpenetrating “(10,3)-b cages” from separate nets.

through it. Three interpenetrating (10,3)-b cages from separate nets are shown in Figure 48b.

With regard to the general question concerning the circumstances under which an interpenetrating structure or a noninterpenetrating alternative form, it is interesting that out of the same reaction mixture a second type of crystal can be obtained with the same $[\text{Ag}_2(\text{pz})_3]^{2+}$ framework composition but with a different and noninterpenetrating structure: the 2D (6,3) net. This can be viewed as consisting of the same zigzag strips joined together in a coplanar fashion to give the 2D structure, rather than joined together at an angle to give the 3D (10,3)-b net.

A second example of threefold interpenetration of (10,3)-b nets is provided by a material of composition $[\text{CrP}_3\text{S}_{9+x}]$ ($x \approx 0.25$),^[63] which consists of Cr^{III} centers interconnected through bridging $\text{P}_2\text{S}_6^{2-}$ ligands (**11**), a small fraction of which (approximately 1 in 12) have been replaced by $\text{P}_2\text{S}_8^{2-}$ (**12**). Both ligands act as bidentate chelating agents at both ends. The Cr^{III} centers are therefore in a triply chelated pseudo-octahedral coordination environment of six sulfur

atoms and provide the three-connected, essentially trigonal nodes for the (10,3)-b nets. The three independent nets interpenetrate in a manner topologically identical to that described above for $[\text{Ag}_2(\text{pz})_3](\text{BF}_4)_2$.

Another system that has been described in terms of three interpenetrating three-connected nets, which we have noticed have the (10,3)-b topology, is $[\text{Ag}(\text{bipy})]\text{NO}_3$.^[64] Linear polymeric chains consisting of alternating bridging bipy units and linearly coordinated silver centers are cross-linked through Ag–Ag interactions at a distance of 2.977(1) Å to give the 3D (10,3)-b net in which the three-connected nodes are the T-shaped metal centers. Three such nets then interpenetrate (Figure 49a). Three (10,3)-b nets that interpenetrate in a manner topologically identical to that observed for $[\text{Ag}(\text{bipy})]\text{NO}_3$ are shown in their idealized, most symmet-

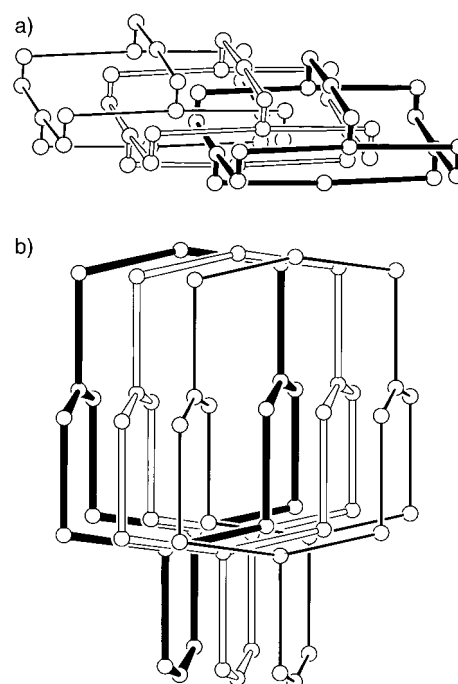


Figure 49. a) Three interpenetrating (10,3)-b nets with T-shaped three-connected nodes in the structure of $[\text{Ag}(\text{bipy})]\text{NO}_3$. The circles represent Ag atoms. “Long” connections represent bridging bipy units, and “short” connections are direct $\text{Ag} \cdots \text{Ag}$ interactions. b) An idealized version of the mode of interpenetration of three (10,3)-b nets, of the type seen in $[\text{Ag}(\text{bipy})]\text{NO}_3$.

rical form in Figure 49b. This figure was constructed to facilitate comparison with Figure 48b; the two modes of threefold interpenetration are clearly topologically different.

Two examples are known of six-fold (10,3)-b interpenetration. One of these is solvated $[\text{Ag}(\text{teb})]\text{CF}_3\text{SO}_3$ ($\text{teb} = 7$),^[65] which contains two types of three-connected nodes provided by alternating **7** and silver centers. Figure 50 shows a representation of the way in which (10,3)-b cages from five other independent nets interpenetrate a given (10,3)-b cage. The central C_6 rings of units of **7** from independent nets are stacked (with minor deviations) along the direction AB shown in Figure 50 (which corresponds to the crystallographic a axis). It is worth noting that this structure is a polymorph of an earlier structure discussed which has six parallel interpenetrating (6,3) 2D nets.

The second example of sixfold interpenetration of (10,3)-b nets, $[\text{Cu}_2(\text{bipy})_3](\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$,^[66] differs from the one just described in that all the three-connected nodes are of the same type: Cu^{I} ions. The topology of interpenetration is distinctly different, as can be seen in

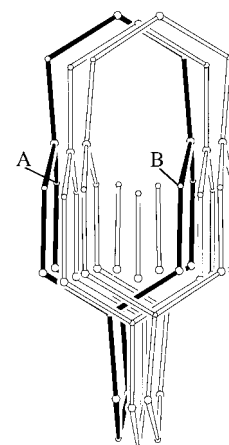


Figure 50. Representation of six independent interpenetrating (10,3)-b cages in $[\text{Ag}(\text{teb})]\text{CF}_3\text{SO}_3$ ($\text{teb} = 7$). The smaller circles represent centers of ligands **7**, and the larger circles represent Ag atoms. Analogous ligand nodes of independent nets are stacked (with minor deviations) along the line AB. For clarity only a single rod of three of the nets is shown.

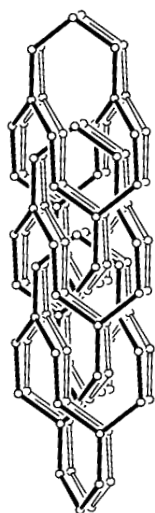


Figure 51. Six interpenetrating “(10,3)-b cages” from separate nets in the structure of $[\text{Cu}_2(\text{bipy})_3](\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$. The circles represent Cu atoms.

Figure 51, which shows (10,3)-b cages from six independent nets. The nets are present in closely spaced pairs, and each pair is interpenetrated by the two other pairs in much the same way as a single (10,3)-b cage was interpenetrated by two other single (10,3)-b cages in the examples of threefold interpenetration in Figure 48b. The comparison between sixfold interpenetration in $[\text{Cu}_2(\text{bipy})_3](\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$ and threefold interpenetration in $[\text{Ag}_2(\text{pz})_3](\text{BF}_4)_2$ is interesting, because both contain trigonal metal nodes that are linked through linear bridging ligands of very similar girth, but the longer bipy units allow a much greater degree of interpenetration.

4.1.3. Interpenetrating (8,3)-c Nets

Figure 52 shows a representation of the (8,3)-c net in its most symmetrical form, which has a hexagonal unit cell. All nodes, of which there are two types, have 120° angles. The plane of one type

of node is normal to the hexagonal axis, and the second type of node, of which there are three times as many, forms planar zigzag strips that run parallel with the hexagonal axis. It has previously not been appreciated that $\text{Na}[\text{Ti}_2(\text{PS}_4)_3]$ ^[67] contains

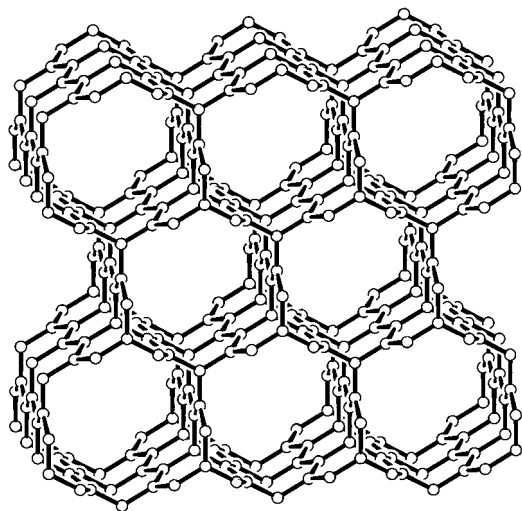


Figure 52. The (8,3)-c net in its geometrically most symmetrical form (hexagonal).

(8,3)-c nets. The Ti^{IV} centers are chelated by three bidentate PS_4^{3-} ligands, which in turn act as μ_2 ligands and bind two metals each by a bidentate interaction. The metal centers thus provide the trigonal nodes for the (8,3)-c net. Two nets of this type then interpenetrate as shown in Figure 53. An important feature is that the nodes normal to the hexagonal axis from the two nets are arranged in a colinear and equidistant fashion. If the nets were in their most symmetrical form, this interpenetration mode would lead to a clash between the

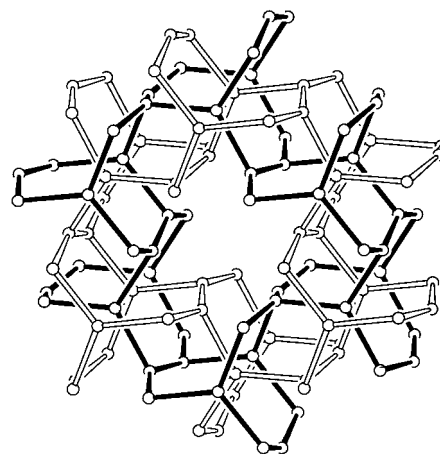


Figure 53. Two interpenetrating (8,3)-c nets in the structure of $\text{Na}[\text{Ti}_2(\text{PS}_4)_3]$. Three-connected nodes are located at the Ti centers, represented here by circles. PS_4^{3-} ions act as μ_2 -bis-bidentate bridging ligands connecting the Ti nodes.

zigzag strips from the two nets. Deformation of the nets depicted in Figure 53 allows the zigzag strips to avoid each other.

4.2. Interpenetrating Three-Dimensional Four-Connected Nets

4.2.1. Interpenetrating Diamondlike Nets

By far, the largest class of interpenetrating structures involves diamond-related nets. The twofold interpenetrating structure of $[\text{Zn}(\text{CN})_2]$ has already been described in Section 1.5.^[6, 21, 22] Examples are known of degrees of interpenetration ranging from two- to ninefold (Table 1). With, to the best of our knowledge, only one exception which is discussed below, the modes of interpenetration in all these examples are closely related. In an undeformed (cubic) diamondlike net each adamantane unit possesses three orthogonal twofold rotation axes aligned parallel with the cubic axes. One of these twofold axes running from top to bottom is shown in Figure 54. The common interpenetration mode is such that the nodes of independent nets are aligned and equally spaced along one of these twofold axes. To illustrate this common n -fold interpenetration mode, we show in Figure 55 a representation of a ninefold interpenetrating system in which the nodes of eight other nets are arranged equally spaced between the top-most and bottom-most extremities of an adamantane unit of the “first” net.^[68] As can be seen here, and as is often the case, the individual nets are distorted so as to elongate the adamantane units along the

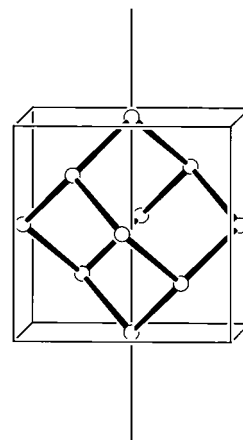


Figure 54. One of the twofold rotation axes in an adamantane component of a diamond-related net.

Table 1. Interpenetrating diamond-related nets; n = number of nets.

Compound ^[a]	n	Comments	Ref.
Various organic polymers	2 or 3		[81]
Two lipid – water phases	2		[82]
M ₂ O (M = Cu, Ag, Pb)	2		[59, 84, 85]
CaWO ₄ (scheelite) and related structures (e.g. [NH ₄][ReO ₄]), ZrSiO ₄ (zircon) and related structures	2	Diamond nets can be constructed.	[85–87]
MO · 2B ₂ O ₃ , (M = Li ₂ , Mg, Zn, Cd, Mn, Fe, Co, Ni, Hg), α-Na ₂ O · 3B ₂ O ₃ , MO · 4B ₂ O ₃ (M = Ag ₂ , Na ₂ , Ba), MO · 5B ₂ O ₃ (M = K ₂ (α and β forms), Rb ₂ , Tl ₂), Cs ₂ O · 9B ₂ O ₃	2	Diamond nets are constructed from borate frameworks, and the clusters within these frameworks act as the tetrahedral nodes. Intercalated M atoms link the nets through M–O interactions in many cases.	[88]
K ₂ [PdSe ₁₀]	2	Each net has a different composition.	[80]
Some high-pressure forms of ice (ice VII and VIII)	2	Ice VII is orientationally disordered, whereas ice VIII is not.	[89]
2,6-Dimethylideneadamantane-1,3,5,7-tetracarboxylic acid	2	Hydrogen-bonded; four structures with different guests.	[71]
[M ₂ (C ₆ H ₂ O ₄) ₃] · 24H ₂ O (M = lanthanide, Y)	2	Diamond net with one link being a hydrogen-bonded water cluster; hydrogen bonding between nets.	[79]
K ₂ [M{NC ₅ H ₃ (CO ₂) ₂ }] ₂ (M = Mn, Zn)	2		[78]
[HN(CH ₃) ₂] ₂ [Sn ₅ S ₉ O ₂]	2	Tetrahedral Sn ₁₀ S ₃₀ O ₄ clusters linked through S atoms.	[90]
[Si(NCN) ₂]	2		[91]
CBr ₄ · hmta	2	Nets containing N–Br interactions.	[92]
[Si(C ₆ H ₄ NO) ₄]	2	Hydrogen-bonded nets containing various guests.	[72, 73]
[M(CO) ₃ (μ ₃ -OH)] ₄ · 2L (M = Mn, Re; L = hydrogen-bonding, bridging ligand)	2, 3, or 4	Hydrogen bonds between tetrahedral clusters.	[8, 93]
[SCd ₈ {SCH(CH ₃)C ₂ H ₅ }] ₁₂ (CN) ₂]	2	Clusters form the nodes of the nets.	[94]
[Cd ₁₇ S ₄ (SCH ₂ CH ₂ OH) ₂₆]	2	Clusters form the nodes of the nets.	[95]
[M(CN) ₂] (M = Zn, Cd)	2		[6, 21, 22, 76]
[Cu(L) ₂](ClO ₄) (L = 4-cyanopyridine)	2		[96]
[Cd(en)Cd(CN) ₄]	2	Net with four-connected nodes, which can be related to a diamond net where the nodes are Cd(CN) ₄ squares.	[71, 97]
Li ₅ B ₇ S ₁₃ , Li ₉ B ₁₉ S ₃₃	2	Nodes are boron sulfide clusters.	[98]
Tetrasodium 1,3,5,7-adamantanetetracarboxylate tetrahydrate	3	Hydrogen-bonded.	[99]
2,6-Dioxoadamantane-1,3,5,7-tetracarboxylic acid (hydrate)	3	Hydrogen-bonded; contains acetic acid guests.	[70]
3,3-Bis(carboxymethyl) glutaric acid (“methanetetraacetic acid”)	3	Hydrogen-bonded.	[87]
All- <i>trans</i> -cyclobutane-1,2,3,4-tetracarboxylic acid	3	Hydrogen-bonded.	[71]
4,4',4'',4'''-Tetraphenylmethanecarboxylic acid	3	Hydrogen-bonded.	[100]
[Cu(CN)(L)] (L = 4-cyanopyridine)	3		[101]
[Ag ₂ {OOC(CH ₂) ₂ COO}]	3	Ag ₄ clusters bridged by chelating bridges.	[102]
[Cd(meal)(dahxn){Ni(CN) ₄ }] · H ₂ O	3		[103]
[Cu(dmtpn) ₂](X)(dmtpn)(THF) (X = BF ₄ , ClO ₄)	3		[104]
Disodium and dipotassium dihydrogen 1,3,5,7-adamantanetetracarboxylate	4	Hydrogen-bonded.	[99]
[Cu(Hcmp) ₄](X) (X = PF ₆ , CF ₃ SO ₃)	4	Nets with hydrogen bonding between CuL ₄ molecules.	[105]
[Cu(bipy) ₂](PF ₆)	4		[50, 106]
[M(bipy) ₂](CF ₃ SO ₃) (M = Ag, Cu)	4		[107]
[Ag(L) ₂](BF ₄) (L = 4-cyanopyridine)	4		[107]
Adamantane-1,3,5,7-tetracarboxylic acid	5	Hydrogen-bonded; different mode of interpenetration.	[69]
[Cu(L) ₂](BF ₄) (L = 1,4-dicyanobenzene)	5		[44]
[Cu(bpe) ₂](BF ₄)	5	CH ₃ CN or CH ₂ Cl ₂ guest molecules.	[54, 108]
[Zn(L) ₂](ClO ₄) ₂ (L = [−] O ₂ CCH ₂ CH ₂ N ⁺ (CH ₂ CH ₂) ₃ N ⁺ -CH ₂ CH ₂ CO ₂ [−])	6		[109]
[Cu{NC(CH ₂) ₄ CN}] ₂ (NO ₃)	6		[110]
[Cu(bpb) ₂](X) (X = ClO ₄ , BF ₄)	6		[46]
[Cu(R ¹ ,R ³ -dcnqi) ₂] and deuterated derivatives (R ¹ ,R ³ = CH ₃ , CH ₃ O, Cl, Br, I)	7	With Li or Ag in place of Cu: isomorphous; with Na, K, NH ₄ , Rb, or Tl in place of Cu: very closely related structures (but no longer separate, interpenetrating frameworks).	[83]
[C(C ₆ H ₅ CCC ₅ H ₄ NO) ₄]	7	Hydrogen-bonding nets containing various guests.	[73, 74]
[Si(C ₆ H ₅ CCC ₅ H ₄ NO) ₄] · 2G (G = valeric acid)	8	Hydrogen-bonded	[73, 75]
[Ag(4,4'-NCC ₆ H ₄ C ₆ H ₄ CN)](XF ₆) (X = P, As, Sb)	9		[68]

[a] Abbreviations used: hmta = hexamethylenetetramine; en = ethylenediamine; mea = 2-aminoethanol; dahxn = 1,6-diaminohexane; dmtpn = 2,3-dimethylterephthalonitrile; bipy = 4,4'-bipyridine; Hcmp = 3-cyano-6-methyl-2(1*H*)-pyridinone; bpe = *trans*-1,2-bis(4-pyridyl)ethene; bpb = 1,4-bis(4-pyridyl)-butadiyne; dcnqi = N,N'-dicyanoquinodimine.

shared twofold axis. In the general n -fold interpenetrating case, the translation of $1/n$ times the length of the adamantane unit along the direction of the shared twofold axis corresponds to one of the unit cell dimensions (generally the shortest).

The only exception to this general pattern is seen in the unusual fivefold mode of interpenetration shown by crystal-line adamantane-1,3,5,7-tetracarboxylic acid.^[69] The structure is contrasted in Figure 56 with that of the “normal” mode of fivefold interpenetration. In this exceptional case the inde-

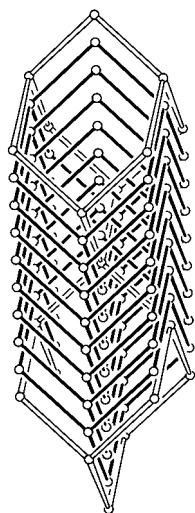


Figure 55. Representation of the structure of $[\text{Ag}(\text{L})_2](\text{PF}_6)$ ($\text{L} = 4,4'$ -biphenyldicarbonyl nitrile) consisting of nine interpenetrating diamondlike nets. The circles represent Ag atoms. The dinitrile ligand links Ag atoms to each other.

pendent nets are related not by the usual translation of $1/n$ (i.e., $1/5$) of the distance across an adamantane unit along a shared twofold axis (Figure 56a), but rather by the translation indicated in Figure 56b.

Interpenetration can be regarded as a space-filling device, but in some cases relatively large intraframework spaces remain even after "optimum" interpenetration has taken place; this is true of the normal mode of diamondlike interpenetration. Figure 57 shows an example of a normal fivefold interpenetrating system, the structure of $[\text{Cu}(\text{L})_2]\text{BF}_4$ ($\text{L} = 1,4$ -dicyanobenzene),^[44] viewed slightly displaced from the shared twofold axis. As can be seen, channels of rhombic cross-section running parallel with the twofold axis are generated. In $\text{Cu}[(\text{L})_2]\text{BF}_4$ ($\text{L} = 1,4$ -dicyanobenzene) these channels are occupied by the BF_4^- ions, but in cases where the networks are electrically neutral the channels may be occupied by significant quantities of solvent.^[70–75]

In many of the examples presented in Table 1 the four-connected nodes of the diamondlike nets are to be found at the midpoints of complex clusters of atoms. A detailed discussion is precluded here by space restrictions.

$[\text{Cd}(\text{CN})_2]$ derivatives, besides adopting a wide range of framework structures which are interesting in their own right, are important in the context of interpenetration because they demonstrate how interpenetration can be prevented by the

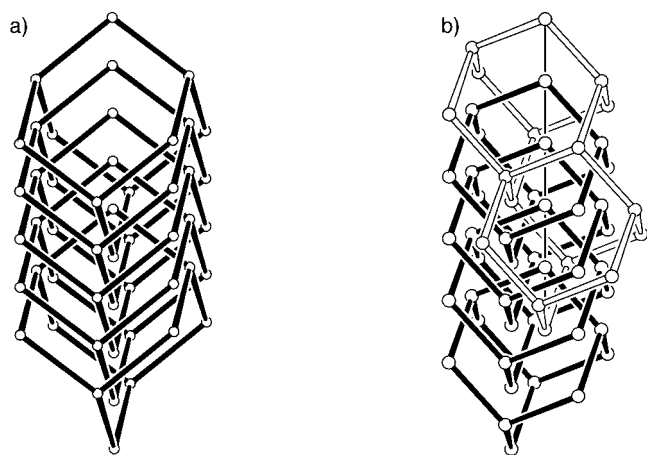


Figure 56. a) The "normal" mode of fivefold interpenetration of diamondlike nets, as seen in $[\text{Cu}(\text{L})_2]\text{BF}_4$ ($\text{L} = 1,4$ -dicyanobenzene). The circles represent Cu atoms. b) The "abnormal" mode of fivefold interpenetration, as seen in adamantane-1,3,5,7-tetracarboxylic acid, showing the translational relationship between independent nets. Two adamantane units of one of the nets fused together by one shared rod are represented here with open connections. Nodes of the remaining four nets are then equally spaced along the vector indicated here by a fine line joining the top-most node to the bottom-most node of the pair of adamantane units in the first net. The circles represent the centers of the molecules.

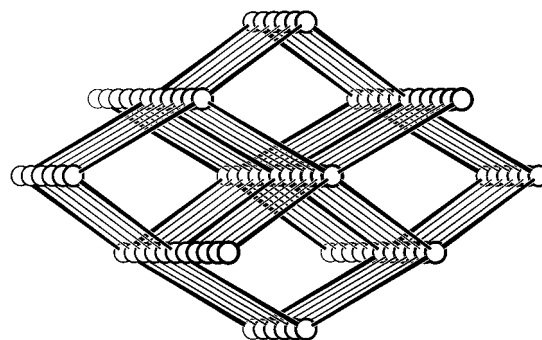


Figure 57. The fivefold interpenetrating diamondlike framework system in $[\text{Cu}(1,4\text{-dicyanobenzene})_2]\text{BF}_4$; the view is slightly displaced from the shared twofold axis. The circles represent Cu atoms.

inclusion of guests. $[\text{Cd}(\text{CN})_2]$ itself is isostructural with $[\text{Zn}(\text{CN})_2]$, consisting of two interpenetrating diamondlike nets.^[6, 22, 76] However, when it is crystallized in the presence of certain organic solvents, such as chlorinated solvents, the crystals contain a *single* diamondlike framework with guest solvent molecules occupying the spaces where the second network is found in the parent structure.^[22, 77] $[\text{Me}_4\text{N}][\text{CuZn}(\text{CN})_4]$, whose structure was truly crystal-engineered, contains a single diamond-related anionic $[\text{CuZn}(\text{CN})_4]^-$ network with NMe_4^+ counter cations occupying half the adamantane cavities thereby preventing interpenetration.^[6] In relation to the general question of whether interpenetration will or will not occur in a particular case, the example of heavily solvated $[\text{Cu}^I\{(4\text{-NCC}_6\text{H}_4)_4\text{C}\}](\text{BF}_4)$ is interesting: Despite the fact that the framework occupies only about a third of the volume of the crystal and that there is ample space for a second network to interpenetrate, this does not occur.^[6, 7]

Crystals of composition $\text{K}_2[\text{M}(\text{L})_2]$ ($\text{M} = \text{Zn}, \text{Mn}$; $\text{L} = \text{pyridine-2,3-dicarboxylate}$) are noteworthy because they contain two chiral interpenetrating diamondlike nets with opposite handedness.^[78] The ligands bridge between metal centers by chelating to one and binding to the second through the 3-carboxylate donor. Every metal center has a coordination environment consisting of two N,O chelating units and two monodentate carboxylate donors which are *cis* to each other. In one net all metals have the Δ configuration, whilst in the other net all are Λ .

The networks in most of the systems listed in Table 1 are formed with either hydrogen bonds or metal–ligand bonds. Both types of interactions are present in the two diamondlike networks in $[\text{Ce}^{\text{III}}(\text{dhbq})_3] \cdot 24\text{H}_2\text{O}$ ($\text{dhbq}^{2-} = \text{dianion of 2,5-dihydroxy-1,4-benzoquinone H}_2\text{dhbq}$).^[79] This is yet another example for which the degree of independence of the two nets is debatable, because there is evidence of hydrogen bonding between the nets.

$\text{K}_2[\text{PdSe}_{10}]$, which will be discussed in Section 4.5.1, is unusual in that it contains two *different* diamondlike nets that interpenetrate.^[80]

Two- and threefold interpenetrating diamondlike structures have been proposed for certain organic polymers,^[81] and a "structure" based on twofold interpenetration of diamond-related nets has been suggested for two lipid/water phases.^[82]

A series of compounds of composition $[\text{Cu}\{\text{R}^1, \text{R}^2\text{-dcnqi}\}_2]$ (dcnqi = *N,N'*-dicyanoquinonediimine; $\text{R}^1, \text{R}^2 = \text{CH}_3, \text{CH}_3\text{O}, \text{Cl}, \text{Br}, \text{I}$) consist of seven interpenetrating diamondlike nets.^[83] As a result of the interpenetration, the planar aromatic rings form infinite stacks showing close $\pi-\pi$ contacts, which are thought to be responsible for the metallike electrical conductivity. These are significant examples that point to the potential of interpenetration as a source of interesting or useful physical properties.

4.2.2. Interpenetrating Quartzlike Nets

The structures of $[\text{M}\{\text{Au}(\text{CN})_2\}_2]$ ($\text{M} = \text{Zn},^{[111]} \text{Co}^{[112]}$) consist of six interpenetrating 3D nets with the same connectivity as quartz, which, like the NbO net discussed below, has a 6^48^2 topology (Wells designates the NbO net as 6^48^2-a and the quartz net as 6^48^2-b). The structure of a single, chiral net is shown in Figure 58a, and the way the six nets, all of the same handedness, interpenetrate is shown in Figure 58b. The metal centers provide the four-connected pseudo-tetrahedral nodes, and the links between them are provided by approximately

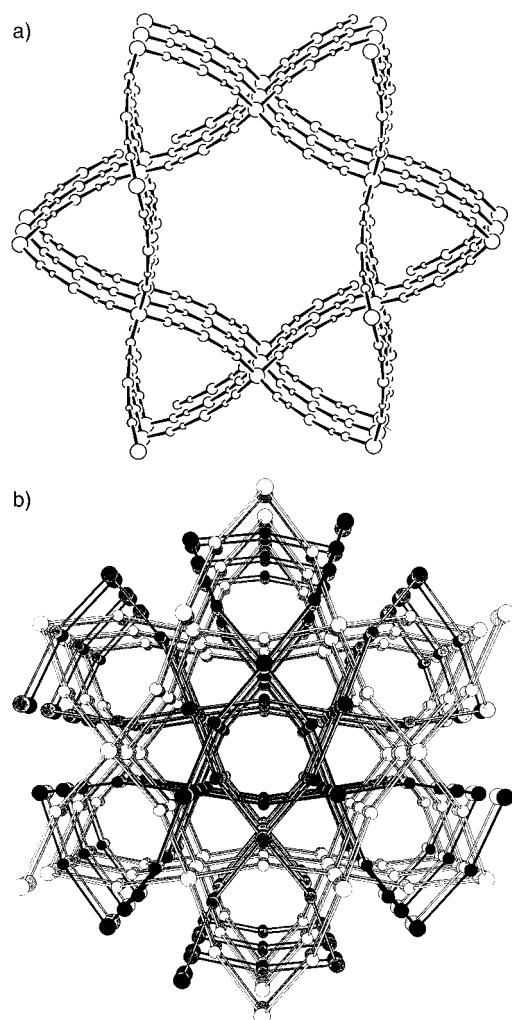


Figure 58. a) A single quartzlike net in the structure of $[\text{Zn}\{\text{Au}(\text{CN})_2\}_2]$. The circles represent in order of decreasing size Zn, Au, N, and C atoms. b) Six interpenetrating quartzlike nets in $[\text{Zn}\{\text{Au}(\text{CN})_2\}_2]$. Only Zn (large circles) and Au centers (small circles) are shown.

linear $\text{Au}(\text{CN})_2^-$ bridges whose considerable length combined with small girth make possible the relatively high degree of interpenetration. Based on the number of examples known at present, there is an apparent marked preference of interpenetrating four-connected nets with essentially tetrahedral nodes to adopt the topology of diamond rather than that of quartz. This may arise from the fact that the idealized quartz net with linear connecting rods requires considerable distortion from regular tetrahedral geometry at the four-connected nodes, whereas in the diamond case linear rods and regular tetrahedral nodes are exactly suited to each other. When the rods are appropriately bent this situation may be reversed; for example, the bent connecting rod provided by the angular two-connected oxygen atom in SiO_2 may be an important factor contributing to the preference for the quartz topology in this case at low temperature. The reason why the quartz topology is preferred in $[\text{M}\{\text{Au}(\text{CN})_2\}_2]$ is not known, but significant $\text{Au} \cdots \text{Au}$ interaction between nets may play a part.

4.2.3. Interpenetrating NbO-Like Nets

From the purely topological point of view, the NbO net (6^48^2-a) is fundamentally important for it is a very simple four-connected net. In its most symmetrical (cubic) form, it consists of square-planar nodes that are each connected to four equivalent neighbors with a 90° twist along every connection. It has received little attention from chemists for the good reason that few examples are known. We noticed that the structure reported for the 1:1 co-crystal formed by cyanuric acid (**13**) and biuret (**14**) consists of two hydrogen-bonded interpenetrating NbO-like nets.^[113] Every cyanuric acid molecule, all of which are equivalent, is hydrogen-bonded to four others either directly or through two-connected biuret molecules to generate a somewhat distorted NbO-like net. The nodes of the net are found at the centers of the cyanuric acid molecules. Two independent nets interpenetrate as shown in Figure 59.

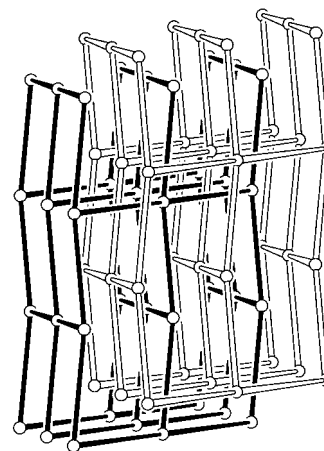
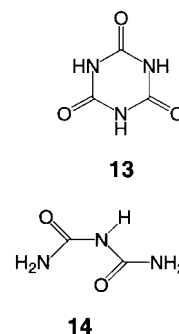


Figure 59. Two interpenetrating NbO-like nets in the hydrogen-bonded structure of cocrystals of cyanuric acid and biuret. The circles represent the four-connected nodes located at the centers of the cyanuric acid molecule.

4.2.4. Interpenetrating 4^28^4 Nets

A simple way in which equal numbers of tetrahedral and square-planar centers can be combined to give an infinite 3D net is shown by PtS, which thus provides a convenient label for the net. Every node is connected to four nodes of the other type, as can be seen in Figure 60, to give a 4^28^4 net which, in its most symmetrical form, has a tetragonal unit cell.

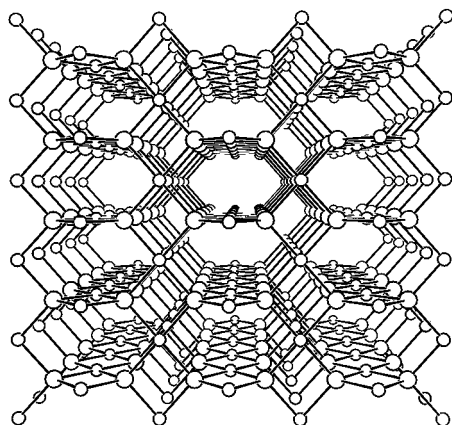
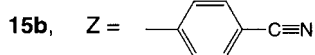
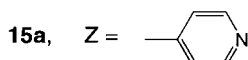
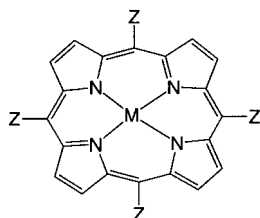


Figure 60. The PtS-like net.

When the porphyrin derivatives **15a** and **15b**, which were intended to play the role of the square-planar component of a PtS-like net, were allowed to react with Cu^I , which was intended to act as the tetrahedral component, PtS-like nets did indeed spontaneously assemble.^[10] In the case of the



pyridyl-substituted derivative **15a** a single, noninterpenetrating network is formed, whereas derivative **15b**, with somewhat longer 4-cyanophenyl substituents attached to the porphyrin, gives a twofold interpenetrating structure (Figure 61). Yet again, interactions between the nets are clearly present, and the porphyrin molecules appear in close centrosymmetrically related pairs, one from each net.

Large, solvent-filled intraframework spaces, accounting for well over 50% of the volume of the crystal, are present in the noninterpenetrating network formed by **15a**. However, even in the interpenetrating structure in Figure 61 the two independent nets hug each other so tightly that, despite the interpenetration, very large solvent-filled spaces still remain.

It has been noted^[114] that $[\text{Ag}(\text{tcnq})]$ (tcnq = tetracyanoquinodimethane)^[115] consists of two interpenetrating PtS-related nets.

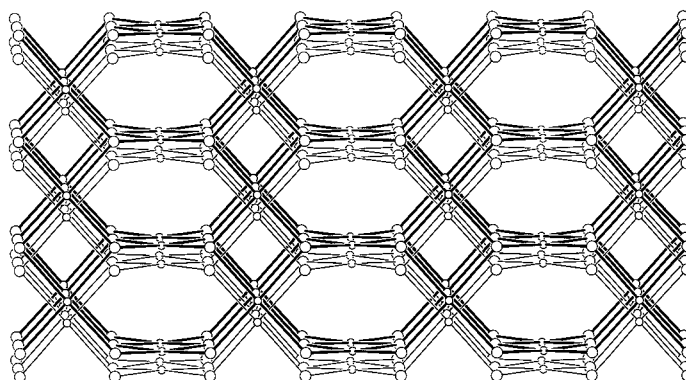


Figure 61. Two interpenetrating PtS-like nets in the structure of solvated $[\text{Cu}^I(\mathbf{15b})](\text{BF}_4)$. Tetrahedral centers represent Cu^I atoms, and square-planar centers represent the Cu^I atoms at the centers of the **15b** ligands ($M = \text{Cu}^I$).

The diol **16** gives on crystallization from benzene $(\mathbf{16})_4 \cdot \text{C}_6\text{H}_6$.^[116] The OH groups of four separate diols are hydrogen-bonded together to give $(\text{O}-\text{H} \cdots)_4$ rings. From the topological point of view, it is convenient to



16

consider these rings as providing four-connected nodes, the nodes being located at the centers of the rings. Molecule **16** therefore acts as a two-connect or that links nodes into the unusual four-connected net (Figure 62a). Like the PtS net,

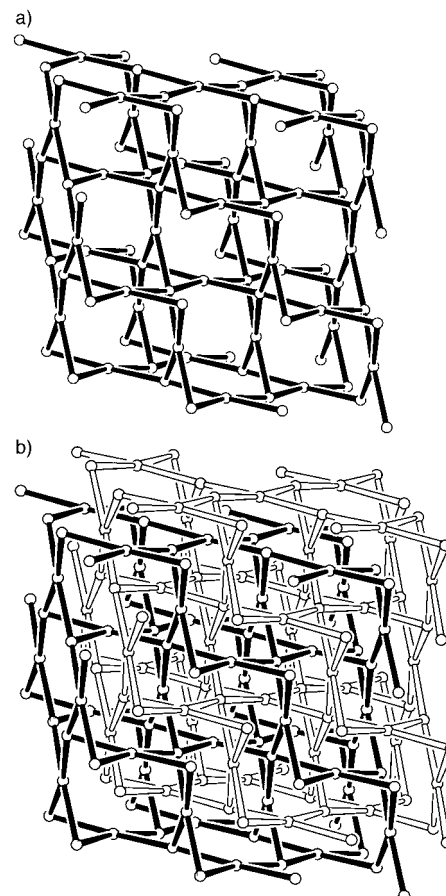


Figure 62. a) A single net of the unusual 4^28^4 type present in $(\mathbf{16})_4 \cdot \text{C}_6\text{H}_6$. The circles represent the four-connected nodes located at the centers of the $(\text{O}-\text{H} \cdots)_4$ rings. b) Two interpenetrating 4^28^4 nets in the structure of $(\mathbf{16})_4 \cdot \text{C}_6\text{H}_6$.

this net has the 4^28^4 point symbol, but is geometrically and topologically quite different. Two nets of this type that are related by an inversion center then interpenetrate as shown in Figure 62b. This structure has also been described in terms of interpenetrating diamond nets, where the nodes of the net represent the centers of the four-membered rings in Figure 62.^[70]

4.3. Interpenetrating Six-Connected Nets

All bar one of the known examples of interpenetrating six-connected nets are of the α -polonium-related ($4^{12}6^3$) topology. In its most symmetrical form this net consists of nodes with an octahedral geometry and has a primitive cubic unit cell, as in α -polonium itself.

4.3.1. Interpenetrating α -Polonium-Like Nets

Examples of two- and threefold interpenetrating α -polonium nets are known. Nb_6F_{15} contains Nb_6F_{12} clusters made up of niobium centers at the apices of a regular octahedron with angular μ_2 -bridging fluoride ions along the twelve edges of the octahedron.^[117] Each cluster is linked to six others by additional linear μ_2 -bridging fluoride ions to give an α -polonium network of composition $(\text{Nb}_6\text{F}_{12})(\mu_2\text{-F})_{6/2}$ (Figure 63a). The

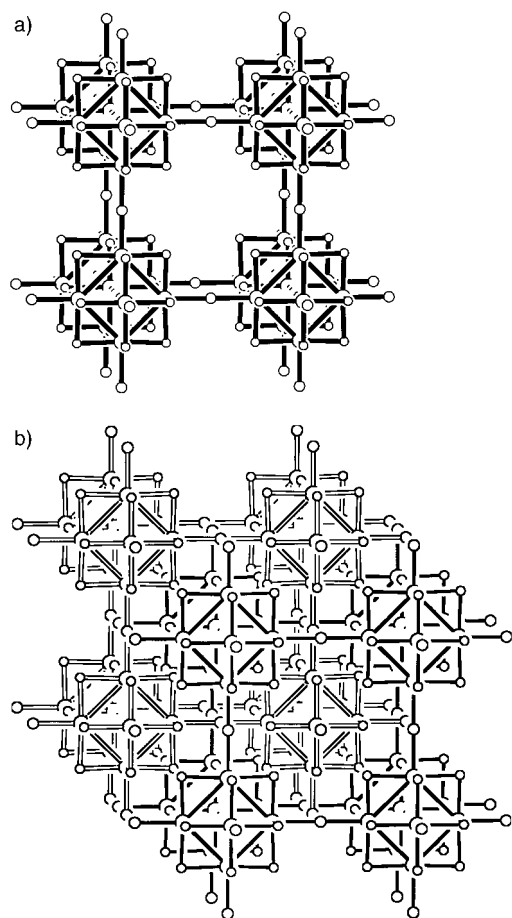


Figure 63. a) A single α -polonium-related net in the structure of Nb_6F_{15} . The circles represent in order of decreasing size Nb atoms, cluster-bridging F atoms, and other F atoms. b) Two interpenetrating nets in Nb_6F_{15} .

six-connected nodes are located at the centers of the Nb_6 octahedra. Two independent nets of this type then interpenetrate, as shown in Figure 63b, so that the nodes of one net are located at the centers of the cubes formed by the other net. The structures of $\text{Zr}_6\text{Cl}_{15}\text{M}$,^[118] ($\text{M} = \text{Li}_2\text{Mn}, \text{LiFe}, \text{Co}, \text{Ni}$) and $\text{Th}_6\text{Br}_{15}\text{M}$ ^[119] ($\text{M} = \text{H}_7$,^[120] $\text{Mn}, \text{Fe}, \text{Co}, \text{Ni}$) are essentially the same, with guest metal atoms trapped inside M_6X_{12} clusters.

Solvated $[\text{Cu}_3(\text{tpt})_4](\text{ClO}_4)_3$ ($\text{tpt} = \mathbf{10}$) has essentially the same twofold interpenetrating α -polonium net structure as Nb_6F_{15} despite its very different constitution.^[121] In this case cuprous centers are located at the apices of a regular octahedron, and μ_3 -bridging tpt ligands are found in alternate faces of the octahedron; the other faces are vacant. Every copper center is shared by two octahedra, and thus links them together (Figure 64a). In this way every $\text{Cu}_6(\text{tpt})_4$ octahedron

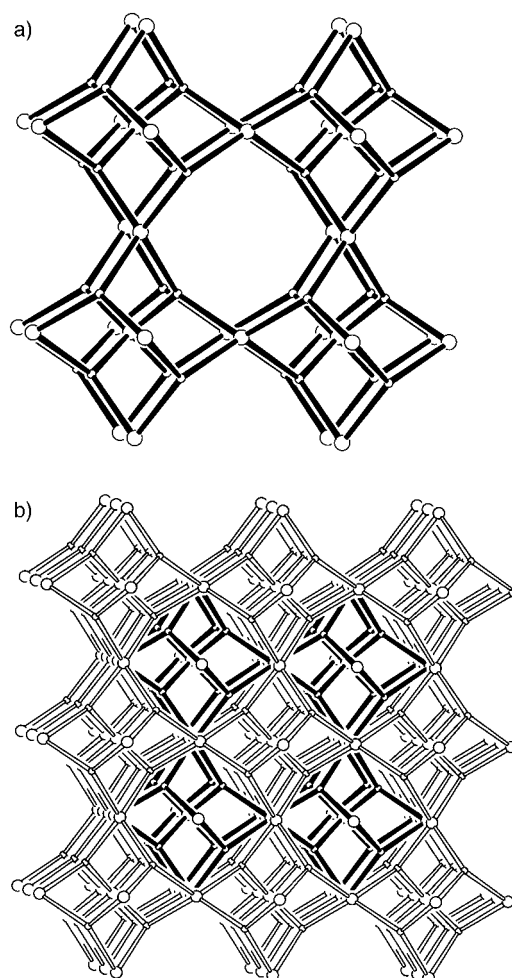


Figure 64. a) A single α -polonium-related net in the structure of solvated $[\text{Cu}_3(\text{tpt})_4](\text{ClO}_4)_3$ ($\text{tpt} = \mathbf{10}$). The larger circles represent Cu atoms, and the smaller circles represent the centers of the tpt ligands. b) Two interpenetrating nets.

is attached through shared copper apices to six others to generate an α -polonium net whose nodes are located at the centers of the octahedra. Two independent nets of this type then interpenetrate as shown in Figure 64b, which is essentially as in Nb_6F_{15} . An additional feature is that tpt units from independent nets are brought into close π contact in

centrosymmetrically related pairs. This is yet another example in which interactions between nets are probably decisive for the structure adopted.

Another highly symmetrical cubic coordination polymer of tpt that exhibits a mode of twofold interpenetration closely related to those described above is solvated $[\text{Zn}(\text{CN})(\text{NO}_3)(\text{tpt})_{2/3}]$.^[122] A single net of this compound is represented in Figure 65 a. This, as well as the aforementioned $[\text{Cu}_3(\text{tpt})_4](\text{ClO}_4)_3$, can be regarded as a net with three- and four-

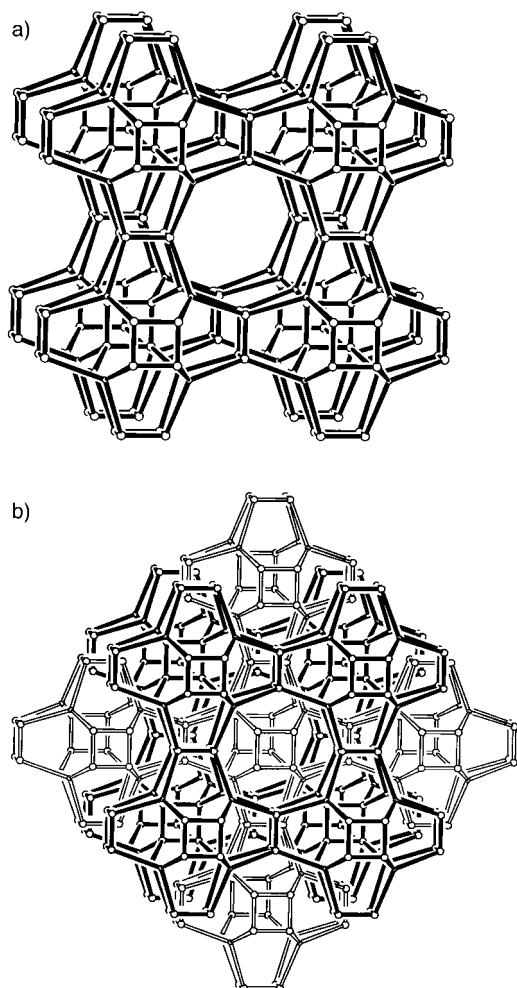


Figure 65. a) A single α -polonium-related net in the structure of solvated $[\text{Zn}(\text{CN})(\text{NO}_3)(\text{tpt})_{2/3}]$ ($\text{tpt} = \mathbf{10}$). The larger circles represent Zn atoms, and the smaller circles represent the centers of the tpt ligands. Short $\text{Zn} \cdots \text{Zn}$ connections represent ZnCNZn groups. b) Representation of two interpenetrating nets in $[\text{Zn}(\text{CN})(\text{NO}_3)(\text{tpt})_{2/3}]$. The chambers of the “white” net projecting through the front and back faces of the “black” net have been omitted for clarity.

connected nodes. However, when the focus is on the nature of the interpenetration, it is useful to reduce it conceptually to an α -polonium net in which the six-connected nodes are at the centers of the large cavities. The two nets viewed in these terms then interpenetrate in a manner topologically identical to that seen above in Nb_6F_{15} and solvated $[\text{Cu}_3(\text{tpt})_4](\text{ClO}_4)_3$ (Figure 65 b). The tpt units from independent nets thus make close π contact in centrosymmetrically related pairs similar to those seen in $[\text{Cu}_3(\text{tpt})_4](\text{ClO}_4)_3$.

One of the high-pressure forms of ice, ice VI,^[123] consists of two independent hydrogen-bonded networks that are usefully described as α -polonium-like nets interpenetrating in a manner closely analogous to that described above. Two sorts of four-connected oxygen centers are present; those of the first sort are connected to three other oxygen atoms in one cluster and to one oxygen atom in another, whereas those of the second sort are connected to two oxygen atoms in one cluster and to two oxygen atoms in another. As is apparent in Figure 66 the individual nets have tetragonal symmetry and have the same topology as the aluminosilicate net in the mineral edingtonite.^[59] If one considers the centers of each

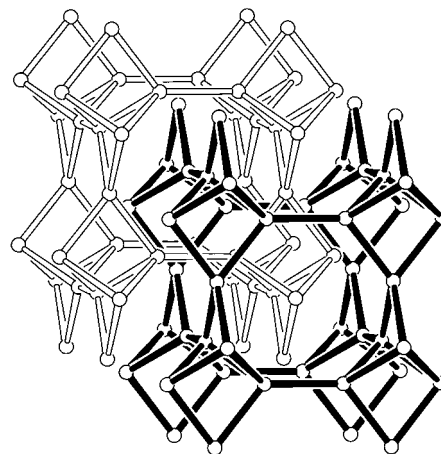


Figure 66. Two interpenetrating α -polonium-related nets in the structure of ice VI. The circles represent O atoms. The six-connected nodes of the net are located at the centers of the $(\text{H}_2\text{O})_6$ clusters.

$(\text{H}_2\text{O})_6$ cluster to constitute a six-connected node, the individual nets can then be regarded as tetragonally distorted α -polonium nets. At the center of each tetragonally distorted cube of one net is a six-connected node of the other net.

$[\text{Co}(\text{Hdcbpy})_3]$ (Hdcbpy^- = monoanion of 2,2'-bipyridyl-5,5'-dicarboxylic acid H_2dcbpy) forms a crystalline hydrate in which metal complex molecules are hydrogen-bonded into an α -polonium network; two such nets interpenetrate as in the preceding examples.^[124] The water of crystallization forms a third hydrogen-bonded network between the two nets.

Another example of the same type of twofold interpenetrating α -polonium-related nets is provided by the compound obtained from $\text{Mn}^{\text{II}}(\text{BF}_4)_2$ and the two-connected ligand N,N' -butylenebis(imidazole).^[125]

The structure of β -quinol, discovered by Powell almost half a century ago, is one of the classic examples of twofold interpenetration.^[126] The phenolic OH groups from six separate 1,4-dihydroxybenzene molecules are hydrogen-bonded to produce hexagonal $(\text{O}-\text{H} \cdots)_6$ rings (Figure 67 a). Every one of these rings is linked through C_6H_4 bridges to six others, three on one side and three on the other, in a pseudo-octahedral fashion to give an infinite 3D net which can be regarded as possessing the α -polonium topology; the centers of the rings constitute the six-connected nodes. Two such α -polonium nets then interpenetrate in the usual manner, with the nodes of one net located at the centers of the “cubes”

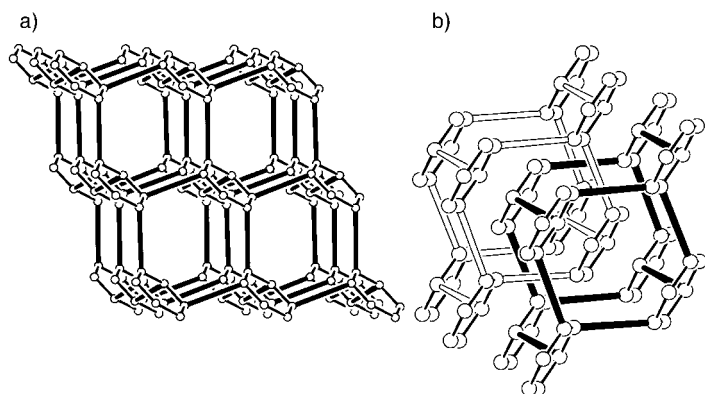


Figure 67. a) A single α -polonium-related net in the structure of β -quinol. The circles represent O atoms. The $\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds are represented by thin lines, and the $\text{OC}_6\text{H}_4\text{O}$ bridges are represented by thick lines. Six-connected nodes of the net are located at the centers of the $(\text{O})_6$ rings. b) The two interpenetrating nets.

(actually rhombohedra) formed by the nodes of the other (Figure 67b). Guest molecules are incorporated into the spaces formed between the $(\text{O}-\text{H}\cdots)_6$ rings of separate nets.

Several examples of threefold interpenetrating α -polonium nets are provided by cyanometallate derivatives of the types $[\text{A}_3\text{M}(\text{CN})_6]$ ($\text{A} = \text{Ag}$ and $\text{M} = \text{Co}^{\text{III}}$,^[127] Cr^{III} ,^[128] $\text{Cr}^{\text{III}}/\text{Co}^{\text{III}}$ ^[128] or $\text{A} = \text{H}$ and $\text{M} = \text{Co}^{\text{III}}$,^[127, 129] Fe^{III} ^[129]) and $\text{K}[\text{Co}\{\text{Au}(\text{CN})_2\}_3]$,^[130] $\text{Rb}[\text{Cd}\{\text{Ag}(\text{CN})_2\}_3]$,^[111] $\text{K}[\text{Cd}\{\text{Ag}(\text{CN})_2\}_3]$,^[114] and $\text{K}[\text{Cd}\{\text{Au}(\text{CN})_2\}_3]$.^[114] These nets comprise octahedral M centers linked together by essentially linear rods of the form $\text{M}-\text{NC}-\text{A}-\text{CN}-\text{M}$ or $\text{M}-\text{CN}-\text{H}-\text{NC}-\text{M}$, which are sufficiently long and thin to permit threefold interpenetration of the type shown in Figure 68. These systems are often distorted

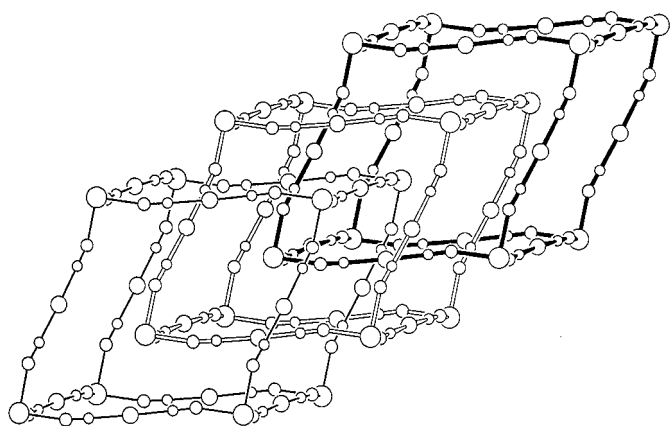


Figure 68. Threefold interpenetration of α -polonium-related nets in the structure of $\text{Rb}[\text{Cd}\{\text{Ag}(\text{CN})_2\}_3]$. The circles represent in order of decreasing size Cd, Ag, N, and C atoms. Intercalated Rb atoms are omitted for clarity.

so as to become rhombohedral, and the essence of the interpenetration is that nodes of the second and third nets are located, equally spaced, along the rhombohedral “solid diagonal” of a distorted cube of the first net. Each square or rhombic “window” has a rod from each of the other two nets passing through it. In the case of the alkali metal derivatives listed above, for which the octahedral metal center is in

oxidation state II, the alkali metal counterions occupy interframework void space. Related α -polonium-based nets belonging to the Prussian blue family, consisting of octahedral metal nodes linked through only cyanide ions, do not participate in the interpenetration. It is interesting that whilst six-membered rings of the $\text{M}_6(\text{CN})_6$ type found, for example, in $[\text{Zn}(\text{CN})_2]$ are large enough to allow a rod of an independent network to pass through, corresponding four-membered $\text{M}_4(\text{CN})_4$ rings of the type found in the Prussian blue family are not.

Combining the bis(imidazole) ligand **2** with cadmium perchlorate gives a cationic coordination polymer of composition $[\text{Cd}(\mathbf{2})_3]^{2+}$ in which the cadmium atom is octahedrally coordinated by imidazole donors from six separate bridging ligands generating an α -polonium-related network. Three of the ligands interpenetrate in a manner topologically identical to that described above for the cyanometallates.^[131]

$[\text{Cd}(\text{pz})\{\text{Ag}_2(\text{CN})_3\}\{\text{Ag}(\text{CN})_2\}]$ shows threefold interpenetration of α -polonium nets in which octahedral Cd^{II} centers are linked together by three different types of rods: pyrazine, $\text{Ag}(\text{CN})_2^-$, and $\text{Ag}_2(\text{CN})_3^-$.^[132]

4.3.2. Interpenetrating Six-Connected Nets Unrelated to α -Polonium

Just as six-connected nodes with octahedral geometry link in a natural, unstrained way to give the α -polonium net, six-connected centers with trigonal-prismatic geometry can be assembled in an unstrained manner to give a simple 3D net (Figure 69a); the threefold axes of the individual trigonal-prismatic centers are parallel. $[\text{Eu}\{\text{Ag}(\text{CN})_2\}_3(\text{H}_2\text{O})_3]$ ^[133] contains nine-coordinate Eu atoms around which three trigonally disposed water ligands occupy an “equatorial belt”. Three N donors from $\text{Ag}(\text{CN})_2^-$ bridging ligands above the belt and three others below it form the trigonal prism. What has not been previously recognized is that this structure involves threefold interpenetration (Figure 69b), and the individual nets have the connectivity shown in Figure 69a. Yet again, interaction between individual nets is apparent in the form of close $\text{Ag}\cdots\text{Ag}$ contacts.

4.4. Interpenetrating Nets Each Containing Two Types of Nodes with Different Connectivities

4.4.1. Interpenetrating Nets with Three- and Six-Connected Nodes

The series of isostructural “binary” metal–tcm compounds $[\text{M}(\text{tcm})_2]$ ($\text{tcm}^- = \text{C}(\text{CN})_3^-$; $\text{M} = \text{Cr}, \text{Mn}, \text{Co}, \text{Ni}, \text{Cu}, \text{Zn}, \text{Cd}, \text{Hg}$) consist of two rutile-related nets that interpenetrate in the manner shown in Figure 70.^[28, 44, 134]

$[\text{Cd}(\text{bipy})_2\{\text{Ag}(\text{CN})_2\}_2]$ consists of two interpenetrating three, six-connected 3D nets that can be visualized in terms of square-grid sheets made up of Cd^{II} centers interconnected through approximately linear bridging $\text{Ag}(\text{CN})_2^-$ ligands; bridging bipy ligands link the silver atoms of one sheet to the cadmium atoms of a neighboring sheet.^[132] There are twice as many silver atoms present as cadmium atoms, and each

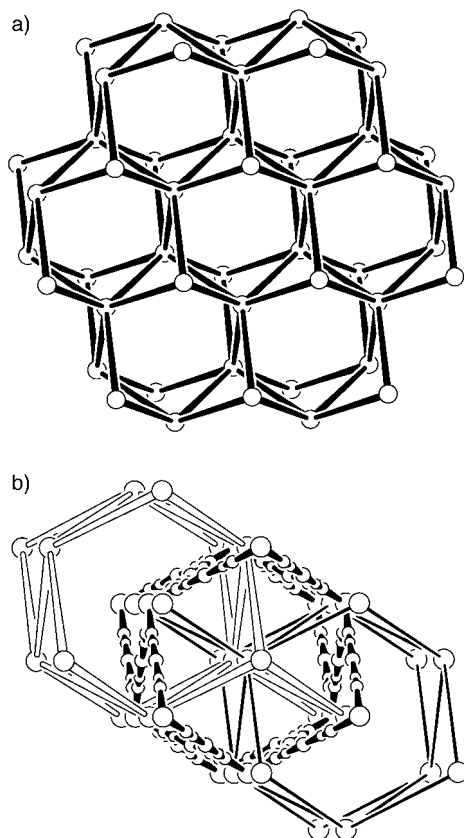


Figure 69. a) A simple six-connected 3D net formed by linking nodes with trigonal-prismatic geometry. The single nets in $[\text{Eu}\{\text{Ag}(\text{CN})_2\}_3(\text{H}_2\text{O})_3]$ have this topology. b) Three nets of the type shown in a) that interpenetrate in $[\text{Eu}\{\text{Ag}(\text{CN})_2\}_3(\text{H}_2\text{O})_3]$. The circles represent Eu atoms, and linear connections represent EuNCAgCNEu groups (shown in full in the central net).

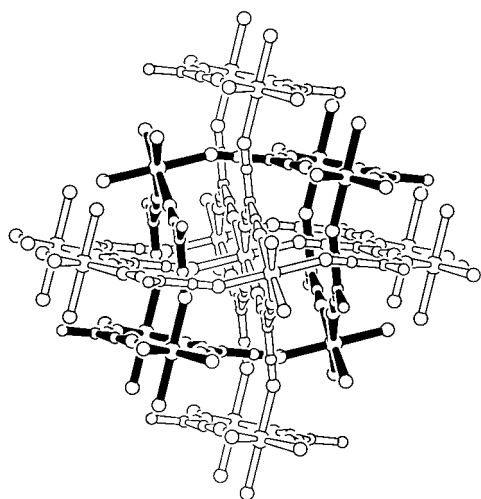


Figure 70. Two interpenetrating rutile-related nets in the structure of $[\text{Hg}\{\text{C}(\text{CN})_3\}_2]$. The circles represent in order of decreasing size Hg, N, and C atoms.

silver atom is attached to one bipy ligand whilst each cadmium atom is attached to two. The silver atoms thus become three-connected, and the cadmium atoms six-connected. Two 3D nets of this type then interpenetrate as shown in Figure 71.

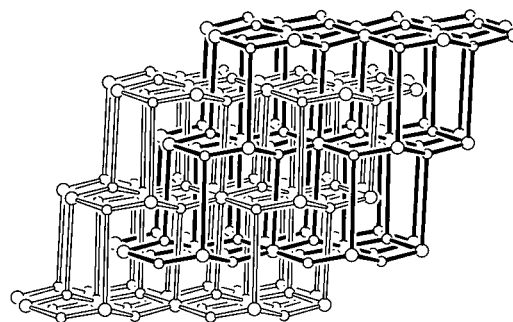


Figure 71. Two interpenetrating nets with three- and six-connected nodes in the structure of $[\text{Cd}(\text{bipy})_2][\text{Ag}(\text{CN})_2]_2$. The larger circles represent Cd atoms, and the smaller circles Ag atoms. The long $\text{Cd}\cdots\text{Ag}$ connections (vertex here) are through bipy ligands.

4.4.2. Interpenetrating Nets with Three- and Five-Connected Nodes

Compounds $[\text{Ag}(\text{tcm})(\text{L})]$ (L = pyrazine, 1,4-diazobicyclo-[2.2.2]octane (dabco), 4,4'-bipyridine) consist of planar hexagonal-grid $[\text{Ag}(\text{tcm})]$ sheets that are connected together into a 3D net through bridging ligands L that link silver atoms of adjacent sheets.^[27, 28] The silver centers thereby become five-connected, and the central carbon atoms of the tcm molecules remain three-connected. Two such nets with three- and five-connected nodes then interpenetrate in the manner shown in Figure 72 with the example of the dabco compound.

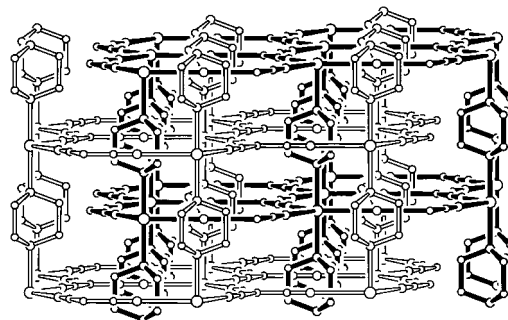


Figure 72. Two interpenetrating nets with three- and five-connected nodes in the structure of $[\text{Ag}(\text{tcm})(\text{dabco})]$. The circles represent in order of decreasing size Ag, N, and C atoms.

4.5. Interpenetrating Nets with Different Chemical Compositions

4.5.1. Interpenetrating Nets of the Same Topology

It is rather surprising that crystals will spontaneously assemble that consist of two independent and interpenetrating nets with the same topology and with exactly the same separation between nodes, but of different chemical composition. Nevertheless, examples do exist.

Crystals of composition $\text{K}_2[\text{PdSe}_{10}]$ consist of two interpenetrating diamond-related nets of different composition (Figure 73).^[80] In both nets the four-connected centers are provided by Pd^{II} atoms in an essentially square-planar coordination environment of four anionic Se donors. In one

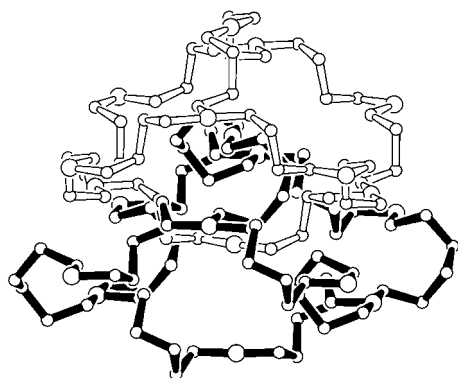


Figure 73. Two interpenetrating adamantane units from the two different diamond-related nets in the structure of $K_3[PdSe_{10}]$. In the net depicted in black, the Pd atoms are connected through Se_6^{2-} units. The large circles represent Pd atoms, and the small circles Se atoms.

net the metal centers are interconnected through Se_4^{2-} bridging ligands, and in the other the bridging ligands are Se_6^{2-} . Although the immediate coordination environment of the metal is square planar, the twisted character of the bridging ligands enables the metal centers to play the role of pseudo-tetrahedral four-connected node required for the diamond net. The same Pd...Pd separation within the two nets is achieved by the Se_6^{2-} ligand adopting a much more twisted conformation than the Se_4^{2-} ligand.

Some oxides of the pyrochlore type can be described in terms of two different interpenetrating diamondlike nets.^[59, 135] $Hg_2Nb_2O_7$, which we use here to illustrate the general features of this type of interpenetration, can be viewed in terms of separate $[Hg_2O^{2+}]_n$ and $[Nb_2O_6^{2-}]_n$ nets. The mercury-based diamond net, is relatively simple: The tetrahedral nodes are provided by oxides and are linked through two-coordinate linear metal centers, much as in Cu_2O . The basic tetrahedral units from which the diamondlike $[Nb_2O_6^{2-}]_n$ net is constructed are “ Nb_4O_6 ” cages of the sort shown in Figure 74a, which themselves are, interestingly, adamantane-like. Cages of this type are linked together

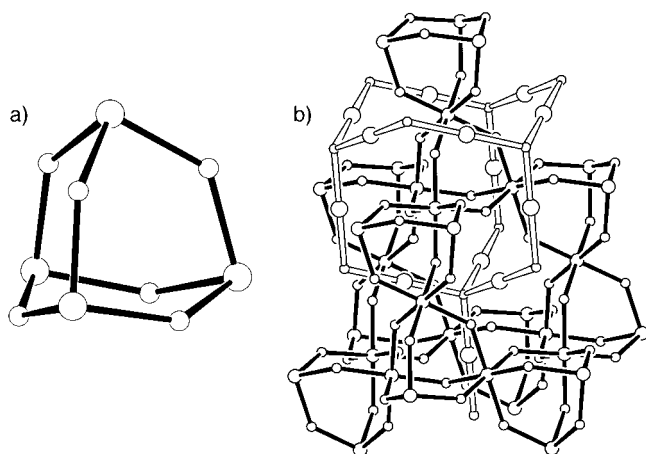


Figure 74. a) “ Nb_4O_6 ” cages present in the pyrochlore structure of $Hg_2Nb_2O_7$. The large circles represent Nb atoms, and the small circles O atoms. b) Interpenetrating adamantane units of the $[Nb_2O_6^{2-}]_n$ (filled bonds) and $[Hg_2O^{2+}]_n$ nets (open bonds) in pyrochlore. The circles represent in order of decreasing size Hg, Nb, and O atoms.

through shared niobium centers; hence the composition of each cage strictly is $[(Nb_{1/2})_4O_6]^{2-}$. Each niobium center is bonded in an octahedral fashion to three oxygen atoms in one cage and three in its neighboring cage. Every cage is thus connected tetrahedrally to four others, and in this way the diamond net is built up. Figure 74b shows an adamantane unit of this diamond net, the four-connected nodes of which are located at the centers of the “ Nb_4O_6 ” cages. The separation between these nodes is exactly the same as that between the oxide nodes of the $[Hg_2O^{2+}]_n$ net, which enables the two different nets to interpenetrate as shown in Figure 74b.

$[Ag(hmta)](PF_6)(H_2O)$ ($hmta$ = hexamethylenetetramine) contains two interpenetrating (10,3)-a nets.^[136] One is a Ag/ $hmta$ coordination polymer in which the three-connected nodes are provided in an alternating fashion by three-coordinate silver atoms and $hmta$ ligands which use only three of the four nitrogen atoms to form donor bonds to metal. The second (10,3)-a net, which is of the opposite handedness, consists of a hydrogen-bonded $PF_6^- \cdot H_2O$ system in which the PF_6^- ions act as the three-connected nodes.

As mentioned in Section 3.2.1, the structure of $[Cd(4-ampy)_2\{Ag(CN)_2\}_2] \cdot [Cd(me_a)(4-ampy)\{Ag(CN)_2\}_2]_2$ contains two sets of (4,4) 2D nets displaying inclined interpenetration.^[148] One set of sheets is a $[Cd(4-ampy)_2\{Ag(CN)_2\}_2]$ coordination polymer, and the other is composed of linear coordination polymer chains cross-linked by hydrogen bonds.

4.5.2. Interpenetrating Nets of Different Topology

Crystals of composition $[H_{31}O_{14}][CdCu_2(CN)_7]$ contain a crystallographically well-defined anionic coordination polymer of composition $[CdCu_2(CN)_7]^{3-}$ which has the pyrites topology.^[137] This is interpenetrated by a hydrogen-bonded network that is not as well defined of apparent composition $(H_3O^+)_3 + (H_2O)_{11}$ (some apparent O...O separations are unrealistically short, and thermal parameters are extremely large). Present in the coordination polymer net are $(CN)_3CuCNCu(CN)_3^{5-}$ units in which the $CuCNCu$ moiety is essentially linear. Encircling each of these linear units in a rotaxane fashion are $(H_2O)_{12}$ rings (Figure 75). These rings

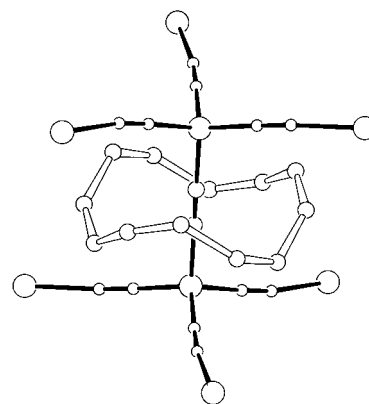
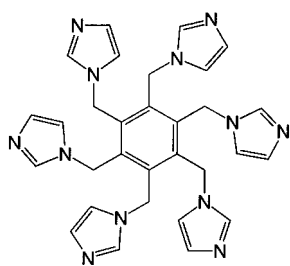


Figure 75. A $(H_2O)_{12}$ ring component of the $[H_{31}O_{14}]_n$ 3D network encircling a $(CN)_3CuCNCu(CN)_3^{5-}$ component of the pyrites-like $[CdCu_2(CN)_7]_n$ net in $[H_{31}O_{14}][CdCu(CN)_7]$. The circles represent in order of decreasing size Cd, O, and C/N atoms.

**17**

are hydrogen-bonded to others through intervening and ill-defined H_2O or H_3O^+ units to give a complicated 3D net.

Hexakis(imidazol-1-ylmethyl)benzene (**17**) reacts with cadmium fluoride to give heavily hydrated crystals of composition $[\text{Cd}(\textbf{17})\text{F}_2] \cdot 14\text{H}_2\text{O}$ which contain a single, rhombohedral α -polonium-related net (Figure 76a); the Cd^{II} centers are octahedrally coordinated by imidazole donors from six separate ligands **17**, and each ligand is bonded to six cadmium atoms.^[138] Two types of hydrogen-bonded sheets of (6,3) topology, one consisting entirely of

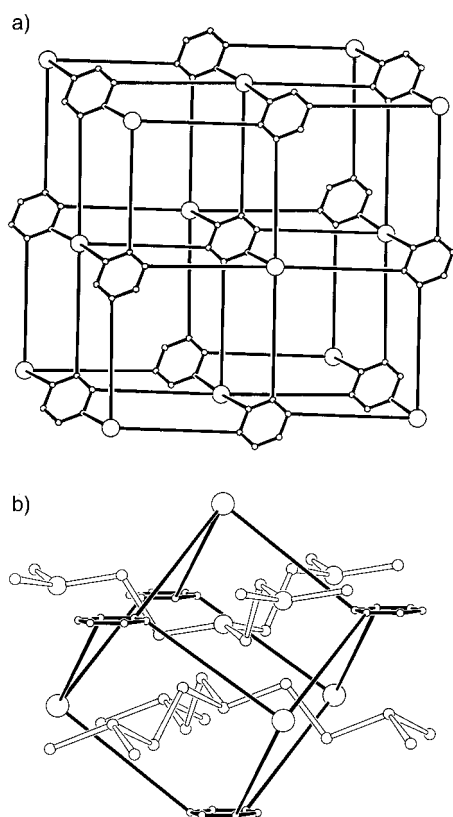


Figure 76. a) The rhombohedral $[\text{Cd}(\textbf{17})^{2+}]_n$ α -polonium-related net in $[\text{Cd}(\textbf{17})\text{F}_2] \cdot 14\text{H}_2\text{O}$. The small circles represent the C atoms of the central C_6 ring of **17**, and the large circles Cd atoms. Long connections between C and Cd are through the imidazolylmethyl arms of **17**. b) One rhombohedron of the $[\text{Cd}(\textbf{17})^{2+}]_n$ α -polonium net with two different hydrogen-bonded sheets interpenetrating it. The circles represent in order of decreasing size Cd, F, O, and C atoms. Connections drawn with open lines represent hydrogen bonds.

water molecules and the other of F^- ions and water molecules, interpenetrate the coordination polymer network (but not each other, because they are parallel) with their average planes perpendicular to the rhombohedral axis (Figure 76b).

The structure of $\text{Bi}_3\text{GaSb}_2\text{O}_{11}$ may be described in terms of three interpenetrating nets, one with NbO-like topology and two with diamondlike topology (Figure 77).^[139] The NbO-like

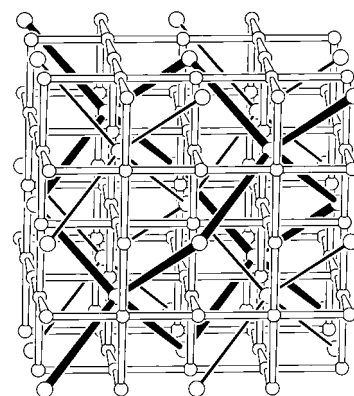


Figure 77. The three interpenetrating nets (one NbO-like and two diamond-related) in the structure of $\text{Bi}_3\text{GaSb}_2\text{O}_{11}$. One diamondlike net is shown with thick lines, and the other with thin lines. The NbO-like net is shown with open lines. The smaller circles represent the centers of $(\text{Ga}_{1/3}\text{Sb}_{2/3})_4\text{O}_6$ clusters, and the larger circles represent the centers of Bi_4O_4 clusters.

net consists of $(\text{Ga}_{1/3}\text{Sb}_{2/3})_4\text{O}_6$ clusters connected to each other through shared metal atoms. The four-connected node of the NbO net can thus be placed at the center of these clusters. The two diamondlike nets contain cubelike clusters of alternating bismuth and oxygen atoms of composition Bi_4O_4 . These clusters are connected to one another through two-connected bismuth atoms coordinating to the tetrahedral oxygen atoms of the clusters. The nodes of the diamond nets are consequently at the centers of the cubelike clusters. There are interactions between the two-connected bismuth atoms of the diamondlike nets and the oxygen atoms of the NbO net; however, these Bi–O distances are significantly longer than those within the nets.

5. Summary and Outlook

There can be no doubt that many new framework solids will be created in the near future and that new forms of interpenetration will soon need to be added to those considered here. Useful properties and applications arising directly from the phenomenon of interpenetration remain to be discovered, but we suspect the area is ripe for such discoveries. The ordered juxtapositioning of components from independent networks cries out for exploitation, for example with regard to electronic interactions or secondary chemical reactions such as polymerization. Hoffmann et al. have proposed that a possible way to obtain materials harder than diamond is to use interpenetrating frameworks,^[140] and a coordination polymer with metallike electrical conductivity consisting of seven interpenetrating diamondlike networks is thought to owe this property to the interpenetration.^[83] It is interesting that one of the more promising systems generated in the quest for new magnetic materials is, coincidentally, interpenetrating.^[51]

The degree to which nets we choose to regard as separate are truly independent is variable and debatable. Nevertheless, the approach adopted here of breaking down complicated interpenetrating structures into nets we choose to describe as “independent”, even though significant interaction between

nets is clearly evident in some cases, remains a useful, powerful, and simplifying aid to understanding the structures.

There is a need for radical new theoretical work in two separate areas associated with interpenetrating networks. Our inability to predict the structure of a crystal given the components in the medium from which the crystal grows was referred to, unjustifiably in our opinion, as the “scandal” of crystal engineering as long ago as 1988^[141] and remains as much a scandal today. This is a difficult problem, and, in the case of framework solids, simply predicting the connectivity of the net formed, which appears at present on purely empirical grounds to depend critically on moderately subtle and not easily modeled factors such as interactions with solvent molecules and the nature of counterions, seems almost intractable. Predicting the nature of interpenetration would appear to be even more difficult. We suspect that the empirical, experimental approach, provided it is based on sound chemical intuition and sensible design, will remain a very fruitful way forward for some considerable time to come.

The second area where theoretical input is required concerns the basic mathematical theory underlying the topology of 2D and 3D nets. Wells's compilation of nets^[4] is extremely useful for synthetic chemists such as ourselves, but he did not attempt to conceal the fact that his derivations were intuitive, nonrigorous, and probably incomplete. Constructing a comprehensive theory of the topology of nets would be challenging; a theory of the *topology of interpenetration* would, we suspect, be even more testing.^[142]

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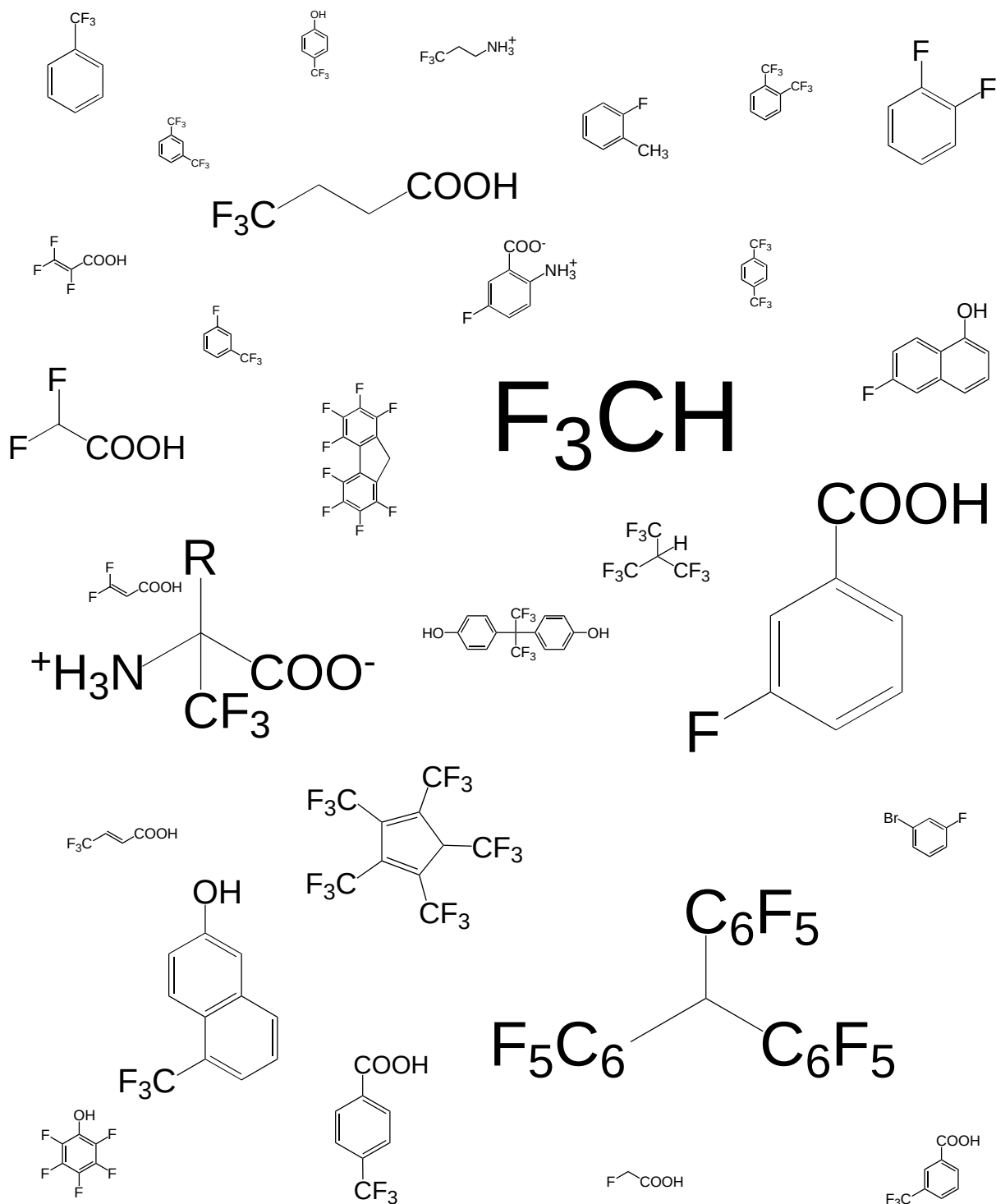
German version: *Angew. Chem.* **1998**, *110*, 1558–1595

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- [142] Since submission of this review we have become aware of a number of other very recent structures which contain interpenetrating nets: a) [Zn(H₂O)₄(bipy)](NO₃)₂·bipy: two interpenetrating hydrogen-bonded α-polonium nets (L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *Chem. Commun.* **1997**, 1801–1803); b) K₂[Cd(H₂O)-Cu₄(CN)₈]·1.5H₂O: two interpenetrating, enantiomeric 3D nets with three- and four-connected nodes (S. Nishikiori, *J. Coord. Chem.* **1996**, 37, 23–38); c) [Cd(1,3-bppn)₂][Ag(CN)₂]₂ (1,3-bppn = 1,3-bis(4-pyridyl)-propane): two interpenetrating 3D nets with a topology identical to that of the bipy analogue described in Section 4.4.1 (T. Soma, T. Iwamoto, *Acta Crystallogr. Sect. C* **1997**, 53, 1819–1821); d) [Ag(3,3'-dcpa)₂]₂XF₆ (X = P, As, Sb; 3,3'-dcpa = 3,3'-dicyanodiphenylacetylene): twofold parallel interpenetrating (4,4) sheets with a topology identical to that shown in Figure 18; [Ag(3,3'-dcpa)₂]₂ClO₄·H₂O: eight interpenetrating diamondlike nets (K. A. Hirsch, S. R. Wilson, J. S. Moore, *Inorg. Chem.* **1997**, 36, 2960–2968); e) (NH₄)[N(NO₂)₂]₂: two interpenetrating hydrogen-bonded 3D nets with three- and four-connected nodes (R. Gilardi, J. Flippen-Anderson, C. George, R. J. Butcher, *J. Am. Chem. Soc.* **1997**, 119, 9411–9416); f) MGa(CN)₄ (M = Li, Cu) (L. C. Brousseau, D. Williams, J. Kouvetakis, M. O'Keeffe, *J. Am. Chem. Soc.* **1997**, 119, 6292–6296) and Li[Co(CO)₄]₄ (P. Klufers, *Z. Kristallogr.* **1984**, 167, 275–286); these compounds are amorphous with Zn(CN)₂ (which has recently been examined with neutron diffraction: D. J. Williams, D. E. Partin, F. J. Lincoln, J. Kouvetakis, M. O'Keeffe, *J. Solid State Chem.* **1997**, 134, 164–169); g) [Cu(dmtpn)₂](X)(dmtpn)(THF) (dmtpn = 2,5-dimethylterephthalonitrile; X = BF₄⁻, ClO₄⁻): three interpenetrating diamondlike nets (T. Kuroda-Sowa, T. Horino, M. Yamamoto, Y. Ohno, M. Maekawa, M. Munakata, *Inorg. Chem.* **1997**, 36, 6382–6389); h) (Me₃Sn)₂Rh(SCN)₆: three interpenetrating α-polonium-related nets (E. Siebel, R. D. Fischer, *Chem. Eur. J.* **1997**, 3, 1987–1991); i) [Cu(3,3'-bipy)₂](X) (X = BF₄⁻, PF₆⁻): doubly interpenetrating diamond-like nets (S. Lopez, M. Kahraman, M. Harmata, S. W. Keller, *Inorg. Chem.* **1997**, 36, 6138–6140); j) [(CH₃)₂NH₂]₆[In₁₀S₁₈]: two interpenetrating diamond-like nets in which [In₁₀S₁₈]¹⁰⁻ clusters act as the tetrahedral nodes (C. L. Cahill, Y. Ko, J. B. Parise, *Chem. Mater.* **1998**, 10, 19–21); k) [Ni₃(btc)₂(py)₆(eg)₆]·x eg·y H₂O (btc = benzene-1,3,5-tricarboxylate, py = pyridine, eg = ethylene glycol): four interpenetrating (10,3)-a nets of the same handedness (C. J. Kepert, M. J. Rosseinsky, *Chem. Commun.* **1998**, 31–32); l) [Cu₂(MeCN)₂(L)₃](PF₆)₂ (L = 1,4-bis(4-pyridyl)butadiyne): 1D ladderlike chains which interpenetrate in a side-by-side fashion (which is topologically different to the examples of 1D interpenetration described in Section 2) to give 2D sheets (A. J. Blake, N. R. Champness, A. Khlobystov, D. A. Lemenovskii, W.-S. Li, M. Schroder, *Chem. Commun.* **1997**, 2027–2028); each ladder is interpenetrated by four others; m) The remarkable structure of [AgL₂][SbF₆] (L = 3-cyanophenyl 4-cyanobenzoate) displays both 2D inclined and parallel interpenetration simultaneously: layers of 2D parallel twofold interpenetrating (4,4) sheets interpenetrate each other in an inclined fashion (K. A. Hirsch, S. R. Wilson, J. S. Moore, *Chem. Commun.* **1998**, 13–14). n) The 1:1 adduct of hexamethylenetetramine and 1,1,1-tris(4-hydroxyphenyl)ethane contains hydrogen-bonded (6,3) nets which show twofold 2D parallel interpenetration analogous to that of [Ag(tcm)]; however, the nets are cross-linked through C–H...O bonds (P. J. Coupar, G. Ferguson, C. Glidewell, P. R. Meehan, *Acta Crystallogr. Sect. C* **1997**, 53, 1978–1980). When 1,1,1-tris(2-methyl-4-hydroxy-5-tert-butylphenyl)butane is used in place of 1,1,1-tris(4-hydroxyphenyl)ethane, the (6,3) sheets do not interpenetrate owing to the larger steric bulk (P. R. Meehan, R. M. Gregson, C. Glidewell, G. Ferguson, *Acta Crystallogr. Sect. C* **1997**, 53, 1637–1640). o) Fe(C₆H₄COC₆H₄OH)₂: hydrogen-bonded (6,3) sheets displaying 2D inclined interpenetration analogous to that shown in Figure 32a (A. C. Benyei, C. Glidewell, P. Lightfoot, B. J. L. Royle, D. M. Smith, *J. Organomet. Chem.* **1997**, 539, 177–186); p) Co(4,4'-dipyridyl sulfide)₂Cl₂: twofold 2D parallel interpenetrating (4,4) sheets of a motif unrelated to those discussed in the main text (O.-S. Jung, S. H. Park, D. C. Kim, K. M. Kim, *Inorg. Chem.* **1998**, 37, 610–611); q) [Ag₂Si(p-C₆H₄CN)₄](OTf)₂·2 C₆H₆ (Tf = CF₃SO₂): four interpenetrating 3D nets with three- and four-connected nodes (related to the individual nets of [Ag(tcm)(L)_{1/2}] (L = phenazine); see Section 3.1.1) which are cross-linked into a single, self-penetrating 3D net through close Ag–Ag interactions. [Ag₃{Si(p-C₆H₄CN)₄}]₂(PF₆)₃·1.6 THF·0.5 C₆H₆·CH₂Cl₂ contains 2D double layers displaying 2D parallel interpenetration. Each double layer is interpenetrated by four other double layers so that an overall 3D structure results, rather than the normal 2D structure. This is a result of average planes of the double layers being parallel but not coincident (F.-Q. Liu, T. D. Tilley, *Inorg. Chem.* **1997**, 36, 5090–5096). r) While we have tried to make this review as comprehensive as possible, either of the authors would appreciate hearing about any other interpenetrating structures known.



Not only a diverse range of possible substitution patterns, but also numerous, sometimes contradictory, effects the extent of which are seldom measurable, make it difficult to predict the acidity of fluoro compounds. A systematic comparison of the acidities in all relevant media provides a better insight into the influence of fluoro substituents.

Parametrization of Substituents: Effects of Fluorine and Other Heteroatoms on OH, NH, and CH Acidities

Manfred Schlosser*

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

Fluorine leaves nobody indifferent; it inflames emotions, be that affections or aversions. As a substituent it is rarely boring, always good for a surprise, but often completely unpredictable. It behaves nonconformingly even when fundamental properties such as ionic dissociation are under consideration. Although fluorine scores highest in the Pauling scale of electronegativity, its Hammett constants ($\sigma_m + 0.34$, $\sigma_p + 0.06$) are all but spectacular. Alanine and α -fluoroalanine have virtually the same pK_a values, whereas trifluoroalanine proves to be a fairly strong acid. Apparently, the smallest halogen emits different kinds of electronic effects which, depending on the given situation, may counterbalance or

amplify each other. To gain better insight, a new approach is undertaken. A comparison between thermodynamic acidity (proton dissociation in aqueous medium and in the gas phase) and kinetic proton mobility (rates of base-catalyzed hydrogen isotope exchange and stoichiometric hydrogen/metal interconversion processes) allows key issues to be addressed, in particular to identify medium effects on acidity and to probe the additivity of substituent effects. In this way fluorine, the heterosubstituent par excellence, which can have a stronger impact on the reactivity in its vicinity than any other element, may serve as a crucial test of any model concerning the origin and transmission of electronic effects. There are,

however, also practical implications. Organometallic compounds carrying one, two, or several fluorine atoms are versatile intermediates in organic synthesis; they allow access to a variety of pharmaceutically, agrochemically, or technically attractive products. For this reason, organofluorine chemistry surely must welcome any information that helps to generate more members of this family of reactive species or aids the development of new methodical concepts, such as optional site selectivity.

Keywords: acidity • fluorine • gas-phase chemistry • metalations • substituent effects

1. Introduction

If we had to explain to a pupil the great variety of chemical reactions known, we would probably choose a paradigmatic approach. We would try to reduce the infinite manifold of possibilities and project them on a few archetypal reaction patterns. Subsequently, we would have to breathe life into these reaction chimeras by illustrating them with real examples.

Three types of chemical processes are particularly suited to schematically cover a maximum of reaction events and thus would have to become the cornerstones of our attempt to systematize: redox processes, electrophile–nucleophile interactions, and proton transfers occurring between acid/base

couples. The latter category is arguably the most fundamental one; a concept as indispensable for inorganic as for organic chemistry.

This review endeavors to explore some phenomena associated with acidity by using fluorine as a probe. This element combines a pronounced electronic individuality with steric modesty, mimicking hydrogen, as far as Van der Waals radii and bond lengths are concerned, closely enough to delude enzymes and receptors.^[1–3] Thus, the lessons it teaches us are informative with respect to physicochemical theory, modern organic synthesis, and the engineering of biological activity.

2. Dissociation Equilibria in Aqueous Medium

Common organic solvents lack sufficient dielectric capacity to sustain ion dissociation. Therefore, no thermodynamically valid acid/base equilibria can be measured in such media. For practical purposes, it is nevertheless important to develop a

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feeling for proton mobilities in ethereal solution. A promising approach to this end is to compare the rates of irreversible deprotonation in organic media with acid dissociation constants, as determined in aqueous solution (pK_a) and in the gas phase (pK_g). If such a correlation can be established it could be applied to predict the site-specific rates with which yet unknown though synthetically useful intermediates may be generated by hydrogen/metal interconversion processes.

Sections 2 and 3 in this review deal solely with thermodynamic parameters, whereas Section 4 presents mainly though not exclusively kinetic data. Acid/base equilibrations by hydrogen/metal countercurrent transfer in organic, polar, or unpolar media (dimethyl sulfoxide, cyclohexylamine, or tetrahydrofuran) are treated in the Sections 4.1–4.5 in connection with hydrogen isotope exchange and metalation rates as well as in Section 2.5 in the context of aqueous dissociation constants of hydrocarbon acids.

2.1. Amino Acids

Fluorinated α -amino acids are man-made analogues of vital natural building blocks. Like their halogen-free congeners, they have two acidic sites: a carboxy and an ammonio functional group. As a consequence, two dissociation coefficients pK_a can be measured.^[4] Their interpretation, however, is not straightforward since there is an ammonium cation and a carboxylate anion, each of them entertaining equilibria with *two* electrochemically neutral species, an uncharged and a zwitterionic one. It is indeed not apparent, for example, why only the second and third halogen atom should cause strong acidification^[5] when fluorine is progressively introduced into the β -position of alanine ($\Delta pK_a^{\text{COOH}} = 2.3$, $\Delta pK_a^{\oplus\text{NH}_3} = 9.9$),^[4] while the first substituent has a surprisingly small, practically negligible effect^[5] (see Table 1). The replacement of the methyl group in alanine by trifluoromethyl enhances the OH acidity (at the carboxy site) by 1.1 and the NH acidity (at the ammonio site) by 4.5 units.^[5, 6] The differences are similar when one compares α -aminoisobutyric acid ($\Delta pK_a^{\text{COOH}} 2.4$, $\Delta pK_a^{\oplus\text{NH}_3} = 0.2$)^[4] with its β,β,β -trifluorinated analogue (Table 2).^[7]

Unsurprisingly, the acidifying effect levels off with increasing distance between the trifluoromethyl and the acidic

Table 1. Shift in the pK_a values (ΔpK_a) of β -fluoro-, β,β -difluoro-, and β,β,β -trifluoroalanine^[5] relative to the parent compound ($\Delta pK_a^{\text{COOH}} = 2.3$, $\Delta pK_a^{\oplus\text{NH}_3} = 9.9$ ^[4]).

X	X'	X''	$\Delta pK_a^{\text{COOH}}$	$\Delta pK_a^{\oplus\text{NH}_3}$
H	H	H	0.0	0.0
F	H	H	+ 0.1	– 0.1
F	F	H	– 0.8	– 1.5
F	F	F	– 1.1	– 4.5

Table 2. ΔpK_a of β,β,β -trifluoroalanine, α -amino- β,β,β -trifluoroisobutyric acid,^[5, 6] and α -aminoisobutyric acid^[7] relative to alanine.^[4]

X	R	$\Delta pK_a^{\text{COOH}}$	$\Delta pK_a^{\oplus\text{NH}_3}$
H	H	0.0	0.0
F	H	– 1.1 ^[5] (– 0.0 ^[6])	– 4.5 ^[5] (– 4.3 ^[6])
H	CH ₃	+ 0.1 ^[4]	+ 0.3 ^[4]
F	CH ₃	– 0.3 ^[7]	– 4.0 ^[7]

groups in the α -aminopropionic, -butyric, -valeric, and -capronic acid derivatives. Nevertheless it is still perceptible even in the latter case (Table 3).^[5]

Such effects can be more or less attenuated in the aromatic series. The introduction of fluorine into the 4-position makes anthranilic acid ($\Delta pK_a^{\text{COOH}} = 2.2$, $\Delta pK_a^{\oplus\text{NH}_3} = 4.9$)^[4] considerably more acidic, while the same substituent in the 5-position causes only minor changes (Table 4).^[8] Unfortunately, the two other isomers have not yet been investigated.

2.2. Carboxylic Acids

Fluorine substituents exert remarkably strong effects on the dissociation constants of simple carboxylic acids. Thus, the

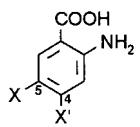


Manfred Schlosser was born in 1934 in Ludwigshafen (Germany). He studied chemistry and, to some extent, medicine, at the Universität Heidelberg, graduating in 1957. He carried out his thesis work under the supervision of Professor Georg Wittig and received his doctorate in 1960. After a research year in Brussels and his “Habilitation” in Heidelberg (1966) he accepted the position of a group leader (“Oberarzt”) at the German Cancer Research Center in Heidelberg. In 1971 he was appointed as the successor of Professor Jiri Sicher at the University of Lausanne. He has lectured as a visiting professor in Italy (Perugia, Firenze), Germany (Berlin), Hungary (Budapest), USA (San Jose), and Japan (Kyoto). His research work is characterized by an intimate interplay between novel mechanistic insight and synthetic applications. He coordinates a European network of research in the organofluorine area and is author or editor of three books on organometallic chemistry, a second edition of the most recent one is presently in preparation (Organometallics in Synthesis: A Manual, Wiley, Chichester, 1998).

Table 3. ΔpK_a of α -aminobutyric, -valeric, and -capronic acid and of their ω,ω,ω -trifluoro derivatives^[5] relative to alanine.^[4]

$$X_3C-(CH_2)_n-\underset{\text{NH}_2}{\underset{|}{CH}}-COOH$$

X	n	$\Delta pK_a^{\text{COOH}}$	$\Delta pK_a^{\text{NH}_2}$
H	0	0.0	0.0
F	0	−1.1 ^[5]	−4.5 ^[5]
H	1	0.0 ^[4]	−0.1 ^[4]
F	1	−0.6 ^[5]	−1.6 ^[5]
H	2	0.0 ^[4]	−0.1 ^[4]
F	2	−0.2 ^[5]	−0.9 ^[5]
H	3	0.0 ^[4]	−0.1 ^[4]
F	3	−0.2 ^[5]	−0.2 ^[5]

Table 4. ΔpK_a of 4- and 5-fluoroanthranilic acid^[8] relative to the halogen-free parent compound.^[4]


X	X'	$\Delta pK_a^{\text{COOH}}$	$\Delta pK_a^{\text{NH}_2}$
H	H	0.0	0.0
F	H	−0.2 ^[8]	−0.1 ^[8]
H	F	−0.8 ^[8]	−0.3 ^[8]

pK_a values steadily decrease by one to two units when one moves from acetic acid ($pK_a=4.8$)^[9] to mono-, di-, and trifluoroacetic acid^[10–13] (see Table 5). When the trifluoromethyl moiety is placed in progressively more remote

Table 5. ΔpK_a of mono-, di-, and trifluoroacetic acid relative to the parent compound.^[9–13]

$$\begin{array}{c} X'' \\ | \\ X-C-COOH \\ | \\ X' \end{array}$$

X	X'	X''	ΔpK_a
H	H	H	0.0
F	H	H	−2.2 ^[10]
F	F	H	−3.5 ^[11, 12]
F	F	F	−4.6 ^[13]

positions, the acidity difference to the halogen-free reference compound rapidly decreases without vanishing completely^[13, 14] (Table 6). The remaining, if small, acidifying effect of three fluorine atoms linked to the α -carbon atom of valeric

Table 6. ΔpK_a of a series of fatty acids and their ω,ω,ω -trifluoro derivatives^[13, 14] relative to acetic acid ($pK_a=4.8$).^[9]

$$X_3C-(CH_2)_n-COOH$$

X	n	ΔpK_a
H	0	0.0
F	0	−4.6 ^[13]
H	1	+0.1 ^[9]
F	1	−1.9 ^[13]
H	2	0.0 ^[9]
F	2	−0.6 ^[14]
H	3	0.0 ^[9]
F	3	−0.3 ^[13]

acid is startling. It can hardly be rationalized on the basis of an σ -inductive electron withdrawal, since the latter would have to propagate itself across seven consecutive bonds.

Multiple bonds are superior to saturated skeletons in the transmission of polar effects over a long range. (*E*)- γ,γ,γ -trifluoro-2-butenic acid is considerably more acidic than crotonic acid ($\Delta pK_a=1.3$), while the difference between γ,γ,γ -trifluorobutyric and butyric acid ($\Delta pK_a=0.6$)^[9] is much smaller (Table 7).^[13–15] On the other hand, when halogen is

Table 7. ΔpK_a of crotonic, 4,4,4-trifluorobutanoic, and (*E*)-4,4,4-trifluoro-2-butenic acid^[13–15] relative to butanoic acid ($pK_a=4.8$).
$$X_3C-Y-COOH$$

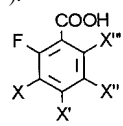
X	Y	ΔpK_a
H	−CH ₂ −CH ₂ −	0.0
F	−CH ₂ −CH ₂ −	−0.6 ^[14]
H	(<i>E</i>)−CH=CH−	−0.1 ^[9]
F	(<i>E</i>)−CH=CH−	−1.4 ^[13–15]

directly attached to the olefinic double bond, the unsaturated acids may be of equal or even inferior strength than saturated analogues (Table 8).^[16] Chloro-substituted acids are in general more acidic than their fluorinated counterparts. A comparison of trifluoro- and trichloroacrylic acid^[16] confirms this rule-of-thumb (Table 8).

Table 8. ΔpK_a of 3,3-difluoro-, 2-fluoro-, 2,3,3-trifluoro-, and 2,3,3-trichloro-2-propenoic acid relative to the halogen-free parent compound ($pK_a=4.3$)^[9].
$$X_2C=CX'-COOH$$

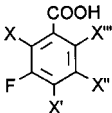
X	X'	ΔpK_a
H	H	0.0
F	H	−1.1
H	F	−1.7
F	F	−2.5
Cl	Cl	−3.1

Electronic transmission also operates effectively in aromatic systems. A fluorine atom or a trifluoromethyl group attached to the *meta* position (Table 10) and, in particular, *ortho* position (Table 9) of benzoic acid enhances the acidity of the latter (ΔpK_a 5.5)^[9] quite significantly as does a *para*-trifluoromethyl substituent (Table 12)^[17–21]. On the other hand, the effect of a *para*-fluoro substituent (Table 11) is a

Table 9. ΔpK_a of 2-fluoro- and four difluorobenzoic acids relative to the parent compound ($pK_a=4.3$)^[9].


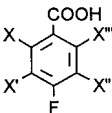
X	X'	X''	X'''	ΔpK_a
H	H	H	H	−0.7 ^[17,18]
F	H	H	H	−1.1 ^[18]
H	F	H	H	−0.8
H	H	F	H	−1.1 ^[18]
H	H	H	F	−2.0 ^[18]

Table 10. ΔpK_a of 3-fluoro- and four difluorobenzoic acids relative to the parent compound ($pK_a = 4.3^{[9]}$).



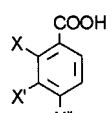
X	X'	X''	X'''	ΔpK_a
H	H	H	H	$-0.3^{[17]}$
F	H	H	H	$-1.1^{[18]}$
H	F	H	H	$-0.4^{[18]}$
H	H	F	H	$-0.7^{[18]}$
H	H	H	F	$-1.1^{[18]}$

 Table 11. ΔpK_a of 4-fluoro- and two difluorobenzoic acids^[17] relative to the parent compound ($pK_a = 4.3^{[9]}$).



X	X'	X''	X'''	ΔpK_a
H	H	H	H	$0.0^{[17]} (-0.1^{[18]})$
F	H	H	H	$-0.4^{[18]}$
H	F	H	H	$-0.8^{[18]}$

 Table 12. ΔpK_a of 2-, 3-, and 4-(trifluoromethyl)benzoic acid^[19–21] relative to the parent compound ($pK_a = 4.3^{[9]}$).



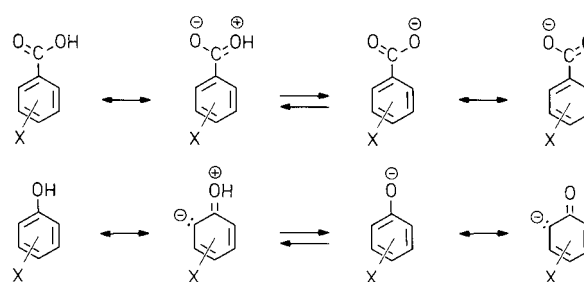
X	X'	X''	ΔpK_a
CF ₃	H	H	$-0.0^{[19]}$
H	CF ₃	H	$-0.4^{[19, 20]} (-0.6^{[21]})$
H	H	CF ₃	$-0.4^{[19, 20]} (-0.6^{[21]})$

subtle balance between inductive electron-withdrawing and mesomeric electron-donating resonance effects; the two opposed contributions tend to cancel each other.^[17, 18]

2.3. Alcohols and Phenols

When hydrogens bound to the carbon atom in methanol are replaced by trifluoromethyl groups, the acidity of the alcohol is enhanced each time by approximately four powers of ten. The pK_a values of 2,2,2-trifluoroethanol, 1,1,1,3,3,3-hexafluoro-propan-2-ol, and 1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-ol are 12.4, 9.3, and 5.2, respectively.^[22]

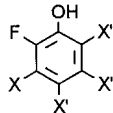
On the basis of a simple comparison of limiting structures (see Scheme 1), one would assume phenols to reflect substituent effects much more sensitively than benzoic acids do. One reason is that the distance between an aromatic substituent and the negatively charged oxygen in a phenolate is shorter by one bond length than the same distance in a benzoate and, as a corollary, electrostatic through-space



Scheme 1. Limiting structures of benzoic acids, phenols, and their anions.

interactions should be much stronger. Moreover, the aryl moiety occupies a nodal position at the carboxylate (“1,3-dioxallyl”) anion, whereas direct electronic resonance between the oxo center and an *ortho* or *para* substituent can occur. In reality, the difference is less marked than may have been expected. The acidifying effect of *ortho*- and *meta*-fluoro substituents is approximately 50 % stronger in the phenol than in the benzoic acid series (compare the data in Tables 13 and

 Table 13. ΔpK_a of 2-fluorophenol and derivatives^[23–25] relative to the parent compound ($pK_a = 10.0^{[9]}$).

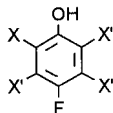


X	X'	X''	X'''	ΔpK_a
H	H	H	H	$-1.2^{[23, 24]}$
F	H	H	H	$-2.3^{[24]}$
H	F	H	H	$-1.6^{[24]}$
H	H	H	F	$-2.9^{[24]}$
F	F	F	F	$-4.5^{[24, 25]}$

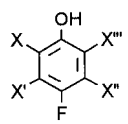
14 with that in Tables 9 and 10, respectively). The effect of a fluorine substituent in the *para* position^[23] is virtually negligible in both cases (Table 15 vs. Table 11). Apparently inductive electron withdrawal and mesomeric electron donation compensate each other in the *para*-fluorophenolate anion.

Again trifluoromethyl groups enhance the OH acidity more strongly than does a single fluorine atom (Table 16).^[27] Furthermore, the CF₃ effect is a far reaching one; the *para*-(trifluoromethyl)phenol is only slightly less acidic than the *ortho* isomer.^[27, 28] Trifluoromethyl groups attached to the

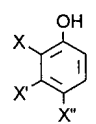
 Table 14. ΔpK_a of 3-fluorophenol and derivatives^[23–25] relative to phenol ($pK_a = 10.0^{[9]}$).



X	X'	X''	X'''	ΔpK_a
H	H	H	H	$-0.7^{[23]}$
F	H	H	H	$-2.3^{[24]}$
F	F	F	F	$-4.5^{[24, 25]}$

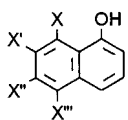
Table 15. ΔpK_a of 4-fluorophenol and derivatives^[23, 24, 26] relative to phenol ($pK_a = 10.0$ ^[9]).


X	X'	X''	X'''	ΔpK_a
H	H	H	H	-0.1 ^[23, 26]
F	H	H	H	-1.6 ^[24]
F	F	F	F	-4.5 ^[24, 26]

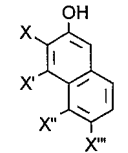
Table 16. ΔpK_a of the three (trifluoromethyl)phenols^[27, 28] relative to phenol ($pK_a = 10.0$ ^[9]).


X	X'	X''	ΔpK_a
H	H	H	0.0
CF ₃	H	H	-1.7 ^[27]
H	CF ₃	H	-1.0 ^[27, 28]
H	H	CF ₃	-1.3 ^[27, 28]

non-phenolic benzene ring of 1-naphthol (Table 17) and 2-naphthol (Table 18) still lower the pK_a values by at least half a unit, thus stressing the long-range potential of this substituent.^[27] 8-Trifluoromethyl-1-naphthol is the only somewhat mysterious exception (Table 17).^[27]

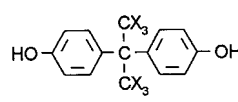
Table 17. ΔpK_a of (trifluoromethyl)-1-naphthols^[27] relative to 1-naphthol ($pK_a = 9.4$ ^[9]).


X	X'	X''	X'''	ΔpK_a
H	H	H	H	0.0
CF ₃	H	H	H	+0.7 ^[27]
H	CF ₃	H	H	-0.6 ^[27]
H	H	CF ₃	H	-0.5 ^[27]
H	H	H	CF ₃	-0.6 ^[27]

Table 18. ΔpK_a of (trifluoromethyl)-2-naphthols^[27] relative to 2-naphthol ($pK_a = 9.6$ ^[9]).


X	X'	X''	X'''	ΔpK_a
H	H	H	H	0.0
CF ₃	H	H	H	-1.2 ^[27]
H	CF ₃	H	H	-0.9 ^[27]
H	H	CF ₃	H	-0.5 ^[27]
H	H	H	CF ₃	-0.6 ^[27]

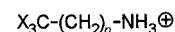
4,4'-(1,1,1,3,3,3-hexafluoropropan-2,2-diyl)diphenol is a widely used component for thermal fluoroelastomer curing. For reasons of solubility, dissociation constants had to be determined in dimethyl sulfoxide.^[29] As it turned out, a *para*- $\beta,\beta,\beta'\beta'$ -hexafluoroalkyl substituent exerts only a minor acidifying effect (Table 19).^[29]

Table 19. ΔpK_a of 4,4'-(propane-2,2-diyl)diphenol^[29] and its hexafluoro derivative^[29] relative to phenol ($pK_{DMSO} = 13.7$ ^[30]).


X	ΔpK_{DMSO}
H	-0.4 ^[29]
F	-1.3 ^[29]

2.4. Aliphatic and Aromatic Amines

A series of straight-chain (ω,ω,ω -trifluoroalkyl)ammonium salts is compared with the corresponding halogen-free parent compounds in Table 20.^[32] As one would have predicted, the acidifying effect decreases with distance. This effect is similar

Table 20. ΔpK_a of (ω,ω,ω -trifluoroalkyl)ammonium salts relative to the halogen-free ethyl, propyl, and butyl parent compounds (for all three: $pK_a = 10.7$ ^[4]).^[32, 33]


X	n	ΔpK_a
H	1	0.0 ^[4]
F	1	-4.8 ^[31, 32]
H	2	0.0 ^[4]
F	2	-1.8 ^[31]
H	3	0.0 ^[4]
F	3	-1.1 ^[31]

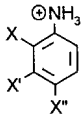
in magnitude to that found with ω,ω,ω -trifluorinated fatty acids having the same number of carbon atoms (see Table 6).

As assumed with phenolates (see Section 2.3), direct resonance interactions between the basic nitrogen center and *ortho* or *para* substituents should occur also within anilines. The quantitative agreement between the acidities of anilinium ions^[4] (Table 21) and the phenols (Tables 13–16) is satisfactory (anilinium ions: $\Delta pK_a = -1.2$ (*o*-F), -1.0 (*m*-F), 0.0 (*p*-F); phenols: $\Delta pK_a = -1.2$ (*o*-F), -0.7 (*m*-F), 0.1 (*p*-F)). The long-range effect of a *para*-positioned trifluoromethyl group (Table 21) is again remarkable.^[35–37]

2.5 Arylmethanes and Cyclopentadienes

In general, pure hydrocarbons are not acidic enough to dissociate in aqueous media. Therefore, acidity measurements dealing with such kinds of substrates are mostly performed in dimethyl sulfoxide or cyclohexylamine.

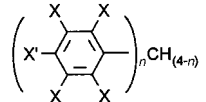
The data collected with substrates of the diaryl- and triarylmethane series are too few to permit a quantification

Table 21. ΔpK_a of fluoro- and (trifluoromethyl)anilinium ions relative to the parent ion ($pK_a = 4.6^{[41]}$).^[35–37]


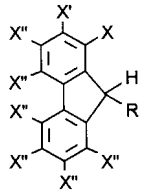
X	X'	X''	ΔpK_a
H	H	H	0.0
F	H	H	– 1.4 ^[4, 33–35]
H	F	H	– 1.0 ^[4, 33, 34]
H	H	F	0.0 ^[4, 33, 35]
CF ₃	H	H	– 1.8 ^{[36][a]}
H	CF ₃	H	– 1.1 ^[4, 37]
H	H	CF ₃	– 2.1 ^[4, 37]

[a] Measured: $pK_a = 2.85$ at 20 °C;^[36] estimated: $pK_a = 2.80$ at 25 °C, the reference temperature of all dissociation constants listed in this article.

of the effect of individual fluorine atoms upon pK values. However, replacement of a phenyl by a pentafluorophenyl ring favors the dissociation to the extent of approximately five pK units (Tables 22 and 23).^[38, 39]

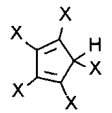
Table 22. ΔpK_{DMSO} and $\Delta pK_{C_6H_{11}NH_2}$ of fluorinated di- and triarylmethanes relative to diphenylmethane ($pK_{DMSO} = 32.2$; $pK_{C_6H_{11}NH_2} = 33.1$).^[38, 39]


X	X'	n	ΔpK_{DMSO}	$\Delta pK_{C_6H_{11}NH_2}$
H	H	2	0.0 ^[38]	0.0 ^[39]
F	F	2	– 10.2 ^[38]	– 11.8 ^[39]
H	H	3	– 1.6 ^[38]	– 1.6 ^[39]
F	H	3	– 18.8 ^[38]	–
F	F	3	–	– 17.3 ^[39]

Table 23. ΔpK_{DMSO} of fluorinated fluorenes relative to fluorene ($pK_{DMSO} = 22.6$).^[38]


X	X'	X''	R	ΔpK_{DMSO}
H	H	H	H	0.0
F	H	H	H	– 1.6 ^[38]
H	F	H	H	– 0.5 ^[38]
F	F	F	H	– 11.8 ^[38]
H	H	H	C ₆ H ₅	– 4.7 ^[38]
H	H	H	C ₆ F ₅	– 7.9 ^[38]

Most cyclopentadienes are chemically unstable and undergo rapid cyclodimerization. Such problems hamper reliable acidity measurements. According to the available approximate data, cyclopentadiene^[40] and pentafluorocyclopentadiene^[41] have quite similar pK_a values, whereas pentakis(trifluoromethyl)cyclopentadiene^[42] is a very strong acid (Table 24).

Table 24. ΔpK_{DMSO} of pentafluorocyclopentadiene^[41] and pentakis(trifluoromethyl)cyclopentadiene^[42] relative to cyclopentadiene^[40] ($pK_a = 16.0$; 15.6 per hydrogen atom).


X	ΔpK_a
H	0 ^[40]
F	ca. – 2 ^[41]
CF ₃	≤ – 18 ^[42]

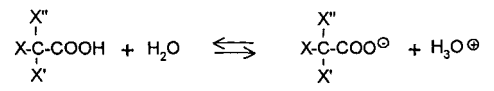
3 Dissociation Equilibria in the Gas Phase

So far, one could have gained the impression that fluorine operates mainly through anion stabilization by inductive electron withdrawal and that exceptions from this rule, if observed, can easily be accounted for. This picture is too simplistic, however. First of all, substituents affect the ground state energy levels of both, acid and base, regardless of whether they are directly conjugated to a double bond or attached to the nodal point of an allyl (or dioxaallyl) moiety.^[43, 44] The substituent may stabilize or destabilize both the neutral and the charged species, but it may also exert opposite effects on each of them. Whenever such an uncertainty exists it may invalidate an attempt at rationalization.

Another principle objection to an uncritical view that focuses exclusively on electronegativity is that such a one-parameter model entirely neglects the specific role of the solvent. It is evident, however, that the solvent must be of paramount importance whenever charged species are involved.

3.1. Carboxylic Acids

The acidity enhancing effect of fluorine or other hetero-substituents is most frequently ascribed to anion stabilization by a straightforward inductive effect. Actually, the thermodynamic parameters (Table 25) of the fatty acid dissociation are incompatible with such an assumption. They rather argue in

Table 25. The acidity of acetic acid and halogenated congeners in aqueous medium as well as free energies (ΔG_a°), enthalpies and (ΔH_a°) entropies (ΔS_a°) of dissociation.^[45]


X	X'	X''	pK_a	ΔG_a° ^[a]	ΔH_a° ^[a]	ΔS_a° ^[a]
H	H	H	4.8	6.4	– 0.1	– 22
I	H	H	3.2	4.3	– 1.4	– 19
Br	H	H	2.9	4.0	– 1.2	– 17
Cl	H	H	2.9	3.9	– 1.1	– 17
F	H	H	2.6	3.5	– 1.4	– 17
F	F	H	1.3	1.7	0.0	– 6
F	F	F	0.2	0.3	0.0	– 1

[a] [kcal mol^{–1}]

favor of a dipole-mediated assistance to solvent organization. Thus, halogen substituents have little effect on the enthalpy of dissociation ΔH_a^0 , which is small anyway (-1.5 to $0.0 \text{ kcal mol}^{-1}$), but can substantially lower the dominant entropy term $\Delta S_a^0 T$ (from 6.5 to $0.3 \text{ kcal mol}^{-1}$ when going from acetic to trifluoroacetic acid). Thus, polarization of the surrounding medium rather than of the acid/base pair itself seem to be at the origin of halogen effects on the acidity of carboxylic acids.^[45]

Gas phase studies provide an unambiguous test of the hypothesis of substituent-mediated solvent organization. In the absence of any solvent, the entropies of ionization vary little within the family of acetic acids and all fall in the range of $22\text{--}25 \text{ cal mol}^{-1} \text{ K}^{-1}$,^[46] a number which is consistent with the disorder-favoring splitting of one molecule into two particles, partially compensated by the loss of one degree of rotational freedom upon deprotonation. The enthalpy term is largely preponderant this time, reflecting the absence of cation and anion solvation (Table 26).

Table 26. Free energies (ΔG_g^0) and enthalpies (ΔH_g^0) of deprotonation of acetic acid derivatives in the gas phase.^[46]

$$\begin{array}{c} \text{X}'' \\ | \\ \text{X}-\text{C}-\text{COOH} \\ | \\ \text{X}' \end{array} \rightleftharpoons \begin{array}{c} \text{X}'' \\ | \\ \text{X}-\text{C}-\text{COO}^- \\ | \\ \text{X}' \end{array} + \text{H}^+$$

X	X'	X''	ΔG_g^0 [a]	ΔH_g^0 [a]
H	H	H	341.5	348.5
I	H	H	327.7	334.7
Br	H	H	328.2	335.2
Cl	H	H	329.0	336.0
F	H	H	331.6	338.6
F	F	H	323.8	330.8
F	F	F	317.4	324.4

[a] [kcal mol^{-1}].

3.2. Amines

The introduction of one fluorine atom into α -, β -, or γ -positions of primary or tertiary amines (Tables 27 and 28, respectively) diminishes the basicity drastically. The substituent effect appears to be roughly additive and, of course, decreases as a function of distance. Thus the proton affinities of these amines decrease by about 10, 4, 1.5, and $0.5 \text{ kcal mol}^{-1}$ per fluorine atom in the α -, β -, γ -, or δ -position.^[47]

Gas phase studies offer the advantage that one can cover an extraordinarily wide spectrum of acidities, ranging from

Table 27. Shift in the proton affinities ($\Delta\Delta G_g^0$) in the gas phase of fluorinated amines relative to ethylamine.^[47]

$\text{H}_2\text{NCH}_2\text{R}$	
R	$\Delta\Delta G_g^0$ [kcal mol^{-1}]
CH_3	0.0
CH_2F	-3.2
CHF_2	-8.1
CF_3	-13.7
CH_2CF_3	-5.0
$\text{CH}_2\text{CH}_2\text{CF}_3$	-1.7

Table 28. Shift in the proton affinities ($\Delta\Delta G_g^0$) in the gas phase of dimethyl(trifluoromethyl)amine and dimethyl(β,β,β -trifluoroethyl)amine relative to trimethylamine ($\Delta G_g^0 = 222.1 \text{ kcal mol}^{-1}$).^[47]

$(\text{H}_3\text{C})_2\text{N-R}$	
R	$\Delta\Delta G_g^0$ [kcal mol^{-1}]
CH_3	0.0
CF_3	-30.2
CH_2CF_3	-9.6

strong mineral acids to extremely weak hydrocarbons ("CH acids"). By constructing isoionic or isoelectronic relationships, the acidities of, for example, phenols can be correlated with those of anilines and similarly those of toluenes with anilinium ions (see Figure 1). When one plots the free

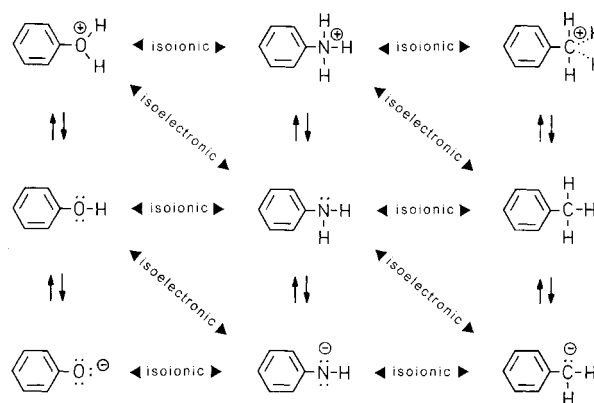


Figure 1. Isoionic and isoelectronic relationships between phenol, aniline, and toluene and their ions.

energies of the gaseous deprotonation of anilinium ions against that of toluenes, the result is quite impressive (Figure 2).^[47] Most points fall closely on a straight line. The moderate deviation of the *meta*- and *para*-nitro substituents can be well understood. The only "strayshot" is caused by the *meta*-cyano group, for as yet unknown reasons.

Noteworthy is the effect of *p*-fluoro substituents. Both *p*-fluoroanilinium and *p*-fluorotoluene are distinctly more acidic than the corresponding parent compounds. This may be again considered as a manifestation of the "volume effect" (see Section 3.5), the improved anion stabilization due to the polarization of a larger assembly of atoms. Interactions with counterions and solvent molecules widely replace this specifically intramolecular mechanism of anion stabilization through charge dispersion when the charged species is surrounded by an organic medium. New factors become crucial such as lone-pair/lone-pair repulsions between excess electron density and adjacent heteroatoms.^[48, 49] Previously, evidence was presented according to which a fluorine atom, when directly attached to a carbanionic center, exerts a destabilizing effect.^[50] More recently, two striking examples of benzyl anion destabilization by a *para*-positioned fluorine atom have been identified.^[51, 52] Lithium 2,2,6,6-tetramethylpiperidide (LITMP) in the presence of potassium *tert*-butoxide and *N,N,N',N',N''*-pentamethyldiethylenetriamine was found to abstract a proton from the benzylic position of

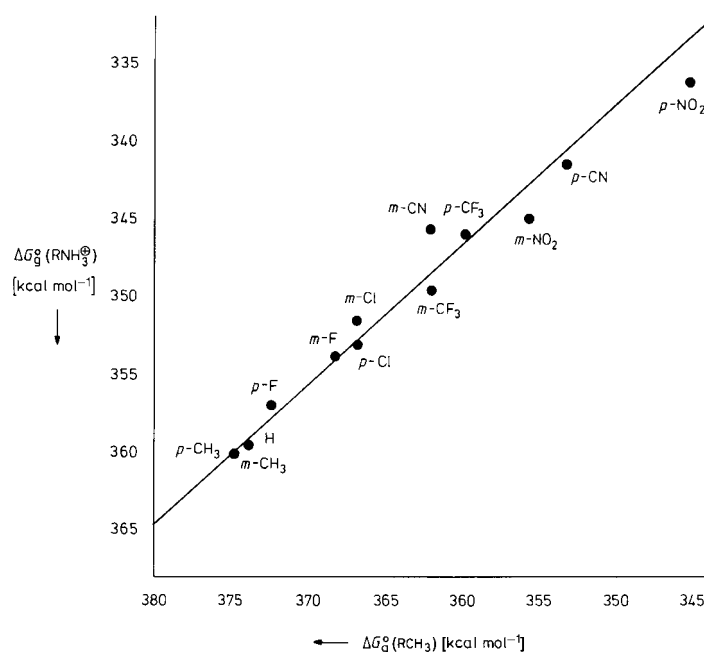


Figure 2. Free energies of deprotonation in the gas phase: correlation between anilinium ions ($\Delta G_g^0(\text{RNH}_3^+)$) and toluenes ($\Delta G_g^0(\text{RCH}_3)$).^[47]

p-fluorotoluene 10 times more slowly than from toluene, while the reactivity of the *meta* and *ortho* isomer was 10 times higher than that of the reference compound.^[51] The proton mobility of *all* chloro- and bromotoluenes proved to be 3 to 30 times that of toluene under the same conditions.^[51] The introduction of a fluorine atom into the *para* position of the benzyl group of the triphenylphosphonio- α -phenylmethanide, a benzylic phosphorus ylid, lowers the barrier to rotation around the $\text{C}^\alpha\text{--C}^i$ axis from 8.5 to 7.7 kcal mol^{−1}, while *o*- or *m*-fluoro substituents or chloro substituents at any position raise the torsional energy.^[52] The latter is a measure for the benzylic resonance delocalization.

3.3. Mono-, Di-, and Polyfluorohydrocarbons

The proton affinities of trifluoromethyl^[53] and pentafluoroethyl^[54] anions are in the gas phase some 40 kcal mol^{−1} smaller than that of the methyl anion. According to ab initio MO calculations, the perfluoro-*tert*-butyl anion is again about 40 kcal mol^{−1} more stable than the trifluoromethyl anion.^[55]

A compilation of the gas phase acidities of fluorobenzene, pentafluorobenzene, and all di-, tri-, and tetrafluorobenzene isomers was published recently.^[56] What makes these experimental data particularly meaningful is their completeness and consistency (Table 29). The measured free enthalpies of deprotonation can be reproduced with high fidelity (standard deviation < 1 kcal mol^{−1}) when “acidity increments” of 12, 6, and 4 kcal mol^{−1} are assigned to each extra fluorine atom located at an *ortho*, *meta*, and *para* position, respectively. Thus, the additivity of substituent effects as well as their distance dependence has been convincingly demonstrated.

Table 29. Absolute and relative^[a] free deprotonation enthalpies (ΔG_g^0 and $\Delta\Delta G_g^0$, respectively) as well as relative^[a] logarithmic dissociation constants (ΔpK_g) of benzene^[57, 58] and fluorinated benzenes^[56] in the gas phase.

Substitution	ΔG_g^0 ^[b]	$\Delta\Delta G_g^0$ ^[b]	ΔpK_g
–	391	+ 12	+ 8.8
F	379	0	0
1,2-F ₂	370	− 9	− 6.6
1,3-F ₂	366	− 13	− 9.6
1,4-F ₂	372	− 7	− 5.1
1,2,3-F ₃	367	− 12	− 8.8
1,2,4-F ₃	362	− 17	− 12
1,3,5-F ₃	361	− 18	− 13
1,2,3,4-F ₄	361	− 18	− 13
1,2,3,5-F ₄	355	− 24	− 18
1,2,4,5-F ₄	353	− 26	− 19
F ₅	349	− 30	− 22

[a] Relative to fluorobenzene. [b] [kcal mol^{−1}].

3.4. Mono-, Bis-, and Tris(trifluoromethyl)benzenes

Highly trifluoromethylated arenes are not only difficult to prepare but are also of relatively low volatility. Therefore, gas phase studies^[59] have not embraced all members of the poly(trifluoromethyl)benzene family. Nevertheless, the results are conclusive (Table 30). Accumulated substituent

Table 30. Absolute and relative^[a] free deprotonation enthalpies (ΔG_g^0 and $\Delta\Delta G_g^0$, respectively) as well as relative^[a] logarithmic dissociation constants (ΔpK_g) of benzene and trifluoromethyl-substituted benzenes in the gas phase.^[59]

Substitution	ΔG_g^0 ^[b]	$\Delta\Delta G_g^0$ ^[b]	ΔpK_g
–	391	+ 13	+ 9.6
CF ₃	378	0	0
1,2-(CF ₃) ₂	369	− 10	− 7.0
1,3-(CF ₃) ₂	365	− 14	− 9.6
1,4-(CF ₃) ₂	367	− 12	− 8.4
1,2,3-(CF ₃) ₃	357	− 221	− 16
1,2,4-(CF ₃) ₃	355	− 23	− 17
1,3,5-(CF ₃) ₃	354	− 24	− 18
1,2,4,5-(CF ₃) ₄	341	− 36	− 27

[a] Relative to (trifluoromethyl)benzene. [b] [kcal mol^{−1}].

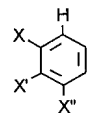
effects are again additive. (Trifluoromethyl)benzene has approximately the same gas phase acidity as fluorobenzene. However, in contrast to what has been found in the fluoroarene series (see Section 3.3), the acidifying effect of a trifluoromethyl unit shows only a weak distance dependence. While it favors the deprotonation at the *ortho* position by approximately 13 kcal mol^{−1}, it still causes an acidity exaltation of some 10 kcal mol^{−1} at both *meta* and *para* positions (Table 30). This divergence in substituent behavior clearly indicates that inductive electron withdrawal cannot be the only operative mechanism of anion stabilization. Presumably the polarization^[60] of the aromatic sextet by π donation^[61] (by fluorine) and hyperconjugation^[62] (by trifluoromethyl) plays an equally important role.

3.5. Chlorobenzene

The *o*-chlorophenyl anion has been generated in the gas phase by direct deprotonation, the *m*- and *p*-chlorophenyl

anions by fluoride-promoted desilylation of the corresponding (chlorophenyl)trimethylsilanes.^[63] The astonishingly similar basicities (Table 31) are most remarkable provided they stand the test of independent verification.

Table 31. Free deprotonation enthalpies $\Delta\Delta G_g^0$ of chlorobenzene^[63] relative to benzene ($\Delta G_g^0 = 391 \text{ kcal mol}^{-1}$ ^[57, 58]).



X	X'	X''	$\Delta\Delta G_g^0 [\text{kcal mol}^{-1}]$
H	H	H	0.0
Cl	H	H	− 11
H	Cl	H	− 9
H	H	Cl	− 9

Attention is also drawn to the quasi-identity of fluorobenzene and chlorobenzene gas phase acidities ($\Delta G_g^0 = 379$ and $380 \text{ kcal mol}^{-1}$, respectively). On the basis of deprotonation studies in solution one might have expected a considerably greater difference. At this stage a word of warning may be appropriate. To work in the gas phase avoids complications arising from interactions with solvent molecules and counterions. At the same time, a special artefact is introduced. Left without any possibility of external stabilization, the electron excess of the anion spreads out over the entire species in such a way that it creeps over its molecular surface and covers it like a film. The bulkier the particle, the more effective the charge dissipation (the “volume effect” already briefly mentioned in Section 3.1). This kind of polarization is, for example, the reason why in the gas phase *tert*-butyl alcohol is more acidic than methanol, and the latter more acidic than water,^[64] and may also explain why in the gas phase iodoacetic acid is considerably more acidic than fluoroacetic acid.^[46]

4. Deprotonation Rates and Equilibria in Organic Solvents

The aqueous standard state and the gas phase represent two extremes. Somewhere in between condensed media of moderate or low polarity are situated (Figure 3). Organic

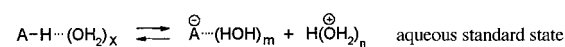
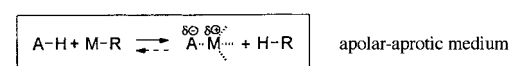
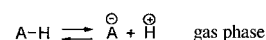


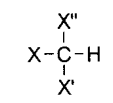
Figure 3. Three fundamental options to select a reaction medium: water, organic solvent, or gas phase.

and, in particular, organometallic reactions are typically carried out in such solvents. It is quite instructive to scrutinize the three systems for similarities and discrepancies.

4.1. Alkanes

Although far less acidic than chloroform ($\text{p}K_a = 24$ ^[65]), trifluoromethane (fluoroform, $\text{p}K \approx 30$ ^[66]) dissociates much more readily than the parent compound methane ($\text{p}K \geq 47$ ^[67]). Replacement of one fluorine atom by a trifluoromethyl stabilizes the anion by $3.0 \pm 0.8 \text{ kcal mol}^{-1}$ (Table 32). The relative acidities have been probed by base-catalyzed isotope exchange in methanol^[68] and have been subsequently linked to the ion pair acidity scale established with cesium cyclohexylamide in cyclohexylamine^[66] (Table 32).

Table 32. $\Delta\text{p}K_{\text{H}_3\text{COH}}$ of polyfluoroalkanes relative to methane ($\Delta\text{p}K_{\text{C}_6\text{H}_{11}\text{NH}_2} \approx 47.5$ ^[68]).

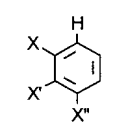


X	X'	X''	$\Delta\text{p}K_{\text{C}_6\text{H}_{11}\text{NH}_2}$
H	H	H	0.0
F	F	F	− 17.0
F_{13}C_6	F	F	− 17.8
F_3C	F	F	− 19.3
F_3C	F_3C	F	− 22.3
F_3C	F_3C	F_3C	− 26.5

4.2. Mono-, Di-, and Trifluoroarenes

When fluorobenzene is treated with alkyllithium reagents in ethereal solvents, a hydrogen/lithium exchange occurs exclusively at the *ortho* position.^[69, 70] However, as can be shown indirectly, also the *meta* and *para* positions are acidified. The effect of fluorine can be monitored at any ring site, when the deprotonation is brought about under the conditions of a base-catalyzed deuterium exchange, a process that energetically involves an “up-hill reaction” as the crucial step. The relative rates of deprotonation measured in liquid ammonia^[71, 72] (Table 33) and those found in methanol^[73] correlate with differences in activation energies. These reflect

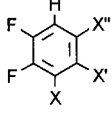
Table 33. Deprotonation of fluorobenzene under the conditions of a potassium amide catalyzed deuterium/hydrogen exchange in liquid ammonia: Rates $k_{\text{rel}}^{\text{H/D}}$ relative to benzene ($k_{\text{rel}}^{\text{H/D}} = 1.0$).^[71]



X	X'	X''	$k_{\text{rel}}^{\text{D-H}}$
H	H	H	1×10^0
F	H	H	$\geq 4 \times 10^6$
H	F	H	4×10^3
H	H	F	2×10^2

the differences in gas phase acidities to the extent of approximately 60%. The attenuation of basicities in the condensed phase can be attributed to carbanion stabilization by hydrogen-bonding with the solvent. In general, the reprotonation (“backward” or “off”) rates of such isotope exchange processes are supposed to be diffusion-controlled and hence identical for all members of a substrate family. Under these circumstances the deprotonation (“forward” or “on”) rates parallel equilibria positions. Direct or indicator-mediated equilibration of metalated intermediates has been achieved by employing lithium cyclohexylamide in cyclohexylamine and cesium cyclohexylamide in tetrahydrofuran or cyclohexylamine (Table 34).^[73] Under these conditions the differences in the gas phase basicities are retained to the extent of roughly 45 %, 55 %, and 60 %, respectively.^[73]

Table 34. The cesium pair acidities $\Delta pK_{C_6H_{11}NH_2}$ of polyfluorobenzenes relative to benzene ($pK_{C_6H_{11}NH_2} = 43.0$).^[73]



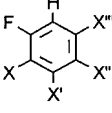
X	X'	X''	$\Delta pK_{C_6H_{11}NH_2}$
H	H	H	− 8.0
F	F	H	− 11.5
F	F	F	− 17.2

In contrast, the hydrogen/metal exchange (“metalation”) by treatment of a fluoroarene with a strong organolithium base (e.g. *sec*-butyllithium in tetrahydrofuran) is a “downhill process”. It has not yet been possible to directly compare the lithiation rate of fluorobenzene with that of benzene itself. Indirect evidence, however, places the rate ratio in the range of 10^4 to 10^5 .^[56] If this is true, the multiple substituent effects are no longer additive as can be deduced from the relative proton mobilities of the di- and trifluorobenzenes (Table 35).^[56]

4.3. Mono-, Bis-, and Tris(trifluoromethyl)benzenes

The base-catalyzed isotope exchange in deuterium-labeled (trifluoromethyl)benzenes (benzotrifluorides) confirms the

Table 35. Lithiation of di- and trifluorobenzenes with *sec*-butyllithium in THF: relative rates (k_{rel}) and rate factors (k_{rel}^f).^[56]

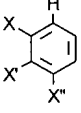


X	X'	X''	X'''	k_{rel}	k_{rel}^f [a]
H	H	H	H	2.0	1.0
F	H	H	H	40	20
H	H	H	F	800	800
H	H	F	H	40	10
F	H	H	F	2000	2000
H	F	H	F	3600	1200

[a] Corresponds to k_{rel} divided by the number of equivalently acidic sites.

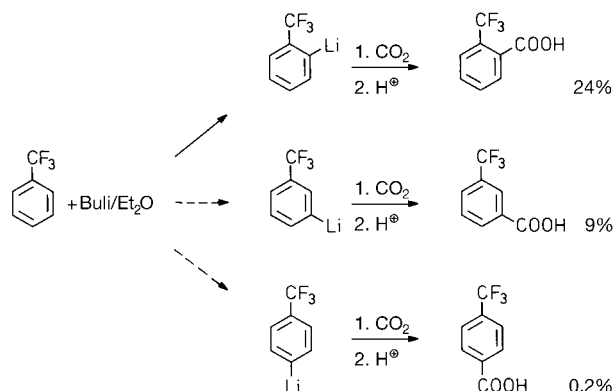
long-range action of the trifluoromethyl group. The proton mobility at the *meta* and *para* positions falls behind that at the *ortho* position by less than two powers of ten (Table 36).^[71, 72]

Table 36. Treatment of 2-, 3-, and 4-deutero(trifluoromethyl)benzene with potassium amide in liquid ammonia at -33°C : Rates of isotope exchange relative to monodeutero benzene ($k_{rel}^{H \rightarrow D} = 1.0$).^[71]



X	X'	X''	$k_{rel}^{D \rightarrow H}$
CF ₃	H	H	6×10^5
H	CF ₃	H	1×10^4
H	H	CF ₃	1×10^4

The simultaneous activation of all aromatic sites compromises the site-selective metalation of (trifluoromethyl)benzene. When butyllithium in refluxing diethyl ether is employed as the reagent, subsequent trapping of the organometallic intermediates with carbon dioxide affords, besides *o*-(trifluoromethyl)benzoic acid (24 %), substantial amounts of the *meta* isomer (9 %) and traces of the *para* isomer (0.2 %) (Scheme 2).^[74] Only the superbasic mixture of butyllithium and potassium *tert*-butoxide in tetrahydrofuran at -75°C is capable of accomplishing clean *ortho* metalation (67 %).^[70, 75]

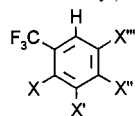


Scheme 2. Metalation of (trifluoromethyl)benzene.

Hydrogen/metal exchange studies are difficult to execute with poly(trifluoromethyl)benzene. In particular, single-electron transfer and nucleophilic addition processes compete with proton abstraction or outperform it.^[76] As a consequence, the data listed below (Table 37) are incomplete and subject to large error derivations.^[59] Moreover, the necessity to employ bulky amides as bases makes steric hindrance a crucial factor.

4.4. Chlorobenzenes and Bromobenzenes

A direct comparison between various halobenzenes may provide the clue to identify the origin of heteroatom effects on acidity. A key experiment was the simultaneous lithiation of

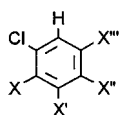
Table 37. Rates k_{rel} of the deprotonation of bis- and tris(trifluoromethyl)-benzene relative to mono(trifluoromethyl)benzene ($k_{\text{rel}} = 1.0$).^[a]^[59]

X	X'	X''	X'''	k_{rel}
H	H	H	H	1×10^0
CF ₃	H	H	H	$1 \times 10^{2[b]}$
H	H	CF ₃	H	6×10^2
H	CF ₃	H	H	$3 \times 10^{2[c]}$
H	CF ₃	H	CF ₃	6×10^2
H	CF ₃	CF ₃	H	$5 \times 10^{4[d]}$

[a] Reaction with lithium 2,2,6,6-tetramethylpiperidide (LITMP) in diethyl ether. [b] Deprotonation at the 2- and 3-positions in the ratio 3:1. [c] Deprotonation at the 2, 4-, and 5-positions in the ratio <1:50:500. [d] Deprotonation at the 3-, 5-, and 6-positions in the ratio <1:50:20.

fluoro- and chlorobenzene under the conditions of competition kinetics. Fluorobenzene proved to be eight times more reactive than chlorobenzene towards *sec*-butyllithium in tetrahydrofuran at -100°C ^[77]. The reactivity difference exceeded 20 when lithium 2,2,6,6-tetramethylpiperidide (LITMP) was employed in tetrahydrofuran at -75°C .

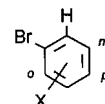
Equilibration studies that employ cesium cyclohexylamine as the base in tetrahydrofuran have been performed with a series of polychlorobenzenes (Table 38). Under the assumption of additivity of individual substituent contributions, one

Table 38. Deprotonation of polychlorobenzenes by cesium cyclohexylamide and equilibration of the resulting organometallic intermediates in THF: factorized (statistically corrected) dissociation constants $\Delta pK_{\text{Cs/THF}}^{\text{f}}$ relative to benzene ($\Delta pK_{\text{Cs/THF}}^{\text{f}} = 47.0$).^[73]

X	X'	X''	X'''	$\Delta pK_{\text{Cs/THF}}^{\text{f}}$
H	Cl	H	Cl	-10.7
Cl	H	Cl	H	-10.9
Cl	Cl	Cl	H	-11.8
Cl	Cl	H	Cl	-13.2
Cl	H	Cl	Cl	-15.1
Cl	Cl	Cl	Cl	-15.9

can define acidity by increments $\Delta pK_{\text{Cs/THF}}$ of -4.2 , -2.7 , and -2.1 for each chlorine atom in an *ortho*, *meta* or *para* position with respect to the deprotonation site ($\Delta\Delta G_{\text{Cs/THF}} = -4.8$, -3.1 and $-2.4 \text{ kcal mol}^{-1}$, respectively)^[73].

When treated with lithium piperidide in diethyl ether, bromoarenes set free 1,2-dehydroarenes (“arynes”) which are instantaneously trapped by the nucleophilic addition of the amide^[78]. The over-all reaction occurs in several steps, the first one being a deprotonation at the halogen adjacent position generating a 2-bromoaryllithium species. Since according to all available evidence this process is a reversible one, the relative rates of dehydrobromination (listed in Table 39)^[78] may be taken as a measure of 2-haloaryl anion stability.

Table 39. Rates of dehydrobromination of *ortho*-, *para*-, and *meta*-substituted bromoarenes k_{rel}^o , k_{rel}^p , and k_{rel}^m , respectively, relative to bromobenzene ($k_{\text{rel}} = 1.0$).^[78]

X	k_{rel}^o	k_{rel}^p	k_{rel}^m
Br	140	83	940
F	34	25	1700
CF ₃ ^[a]	4.6	3.4	58
OCH ₃	1.4	1.2	600
N(CH ₃) ₂	0.58	0.23	7.3
C ₆ H ₅	1.9	2.0	1.8
CH ₃	0.50	0.45	0.35
CH(CH ₃) ₂	0.37	0.53	0.19

[a] Chloroarenes instead of bromoarenes were used as the substrates.

4.5. Fluorohalobenzenes

Intramolecular competition experiments have revealed the relative “*ortho* directing” power of various halo substituents. In all examples investigated, fluorine was found to outperform the heavier halogens chlorine^[79] and bromine^[80] let alone the trifluoromethyl substituent.^[70] Both chlorine and bromine have a stronger acidifying effect than trifluoromethyl^[80] but differ little from each other.^[81]

Although it is certainly helpful to have identified such a *qualitative* hierarchy of reactivity, *quantitative* relationships would be far more conclusive. For example, 1,3-dichlorobenzene^[82] and 1,3,5-trichlorobenzene^[83] react with butyllithium or *sec*-butyllithium much more readily than chlorobenzene.^[84] However, is this reactivity gap big enough to enable selective transformations if both structural features are present in the same starting material?

Furthermore, in the case of di- and polysubstituted arenes one certainly wishes to distinguish whether the subsidiary halogens occupy *ortho*, *meta*, or *para* positions with respect to the metalation site. To address the latter question, sets of substrates having the proper regioisomeric pattern were selected and submitted to competition experiments. All *m*-fluorohalobenzenes are deprotonated at the doubly activated position flanked by the two substituents. In other words, both the fluoro and the other halo atom occupy an *ortho* position with respect to the center attacked by the base. Lithium alkylamides are mandatory to avoid halogen/metal interconversions with bromo- and iodoarenes. Under these conditions, proton abstraction occurred roughly 2.5 times more rapidly, when the second halogen was also fluorine rather than chlorine or bromine, and almost five times more rapidly when it was fluorine rather than iodine (Table 40).^[77] When treated with *sec*-butyllithium, 1-chloro-3-fluorobenzene reacted faster than 1,3-dichlorobenzene and fluorobenzene, but more slowly than 1,3-difluorobenzene.^[77]

The effects of subsidiary halogen substituents located in *meta* positions can be evaluated with 1-fluoro-2-halobenzenes and 1-fluoro-4-halobenzenes. Remarkably, this time the heavier halogens enhance the proton mobility more strongly than fluorine does.^[77] 1,3-Difluoro-5-halobenzenes are suit-

Table 40. Deprotonation rates of 1-fluoro-3-halobenzenes:^[a] Rates (k_{rel}), statistically corrected rate factors (k_{rel}^f), and the logarithm thereof ($\lg k_{\text{rel}}^f$) relative to fluorobenzene ($k_{\text{rel}}^f = 1.0$).

X	k_{rel}	k_{rel}^f	$\lg k_{\text{rel}}^f$
H	2.0	1.0	0.0
F	800	800	2.9
Cl	315	315	2.5
Br	355	355	2.6
I	175	175	2.2

[a] Reaction with lithium 2,2,6,6-tetramethylpiperide (LITMP) in THF at -75°C .

able models to probe the effect of a subsidiary halogen at the *para* position. The results are in line with the expectations: the more distant the substituent is, the smaller is its contribution to the overall acidity of the substrate.^[77]

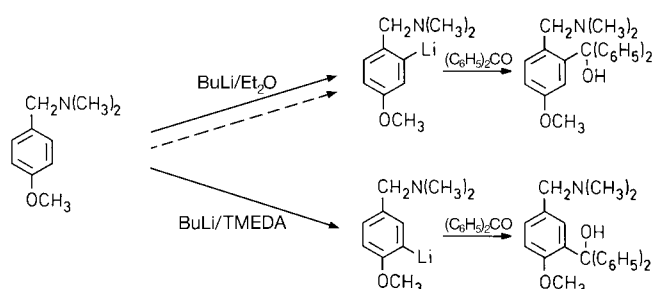
One issue still needs to be clarified. How can one claim to have generated haloaryllithium species irreversibly (“under kinetic control”) if a lithium amide acts as a base and hence inevitably an amine is present? Should, under such circumstances, not instantaneous reprotonation occur and, as a corollary, the organometallic intermediates be subject to rapid equilibration (i.e. form “under thermodynamic control”)? The latter menace does exist and it needs a trick to prevent it. Whenever relative rates were determined, the intermediates were trapped in situ^[85] by treating the haloarene *simultaneously* with LITMP and chlorotrimethylsilane. The variation of the electrophile concentration did not alter the product ratios. This means, the haloaryllithium species were more rapidly intercepted by silylation rather than by reprotonation.

On the other hand, the acid–base pairs will interconvert if one of the involved haloaryllithium species is separately generated before being incubated with the partner haloarene. The time required to approach the equilibrium from both extremes depends on several reaction parameters, in particular the concentration of the free amine. Generally a few hours suffice. The product ratios are more extreme when the lithiation reactions are accomplished under reversible rather than irreversible conditions. This appears to be plausible. Ground states (equilibrating species) should be more sensitive to noncoordinative substituent effects than transition states (rate-determining structures).^[78]

5. Optional Site Selectivities

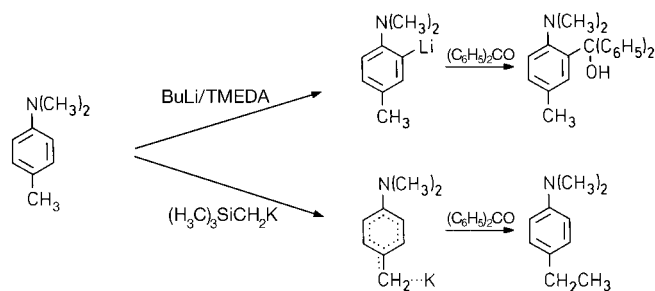
The term “optional site selectivity” has been coined to characterize a crossing of synthetic pathways. More precisely, it refers to the fortunate situation that the same substrate can be alternatively metalated at either of two or three different positions just by choosing the appropriate reagent and other variable reaction parameters. An early impressive example of this type was reported almost three decades ago. When treated with butyllithium in diethyl ether, (4-methoxybenzyl)dimethylamine undergoes a lithium/hydrogen exchange cleanly at a position adjacent to the nitrogen-bearing side

chain (Scheme 3).^[85] However, in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) the same reagent attacks preferentially, though not exclusively, the aromatic sites in the immediate vicinity of the methoxy group (regioisomeric ratio $\approx 1:8$)^[86, 87] (Scheme 3).



Scheme 3. Optional site selectivity in the metalation of (4-methoxybenzyl)dimethylamine.

Similarly, the proper choice of the reagent permits the selective proton abstraction either from the nitrogen-adjacent or the benzylic position of *N,N*-4-trimethylaniline (Scheme 4). Upon consecutive treatment with TMEDA-activated butyl-



Scheme 4. Selective proton abstraction from *N,N*,4-trimethylaniline.

lithium in hexane at 25°C and benzophenone, (2-dimethylamino-5-methylphenyl)diphenylmethanol (80 %)^[88] is formed, while generation of an organometallic intermediate with trimethylsilylmethylpotassium in tetrahydrofuran at -75°C and subsequent trapping with methyl iodide affords 4-ethyl-*N,N*-dimethylaniline (65 %).^[89]

Often the reaction can be controlled only in one sense. Pentylsodium in hexane was reported to convert *o*-methyl anisole (*o*-cresyl methyl ether) cleanly into 2-methoxybenzylsodium (acid obtained after carboxylation: crude product 69 %, pure product 21 %).^[90] The reaction with butyllithium in refluxing diethyl ether turns the *p* isomer into 2-methoxy-5-methylphenyllithium (crude product 32 %).^[90] TMEDA or potassium *tert*-butoxide activated butyllithium^[91–93] give product mixtures due to simultaneous proton abstraction from benzylic and aromatic positions.

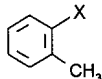
Lack of regioselectivity is also frequently encountered with alkylarenes. For example, butyllithium in the presence of potassium *tert*-butoxide (LIC-KOR) or trimethylsilylmethylpotassium, are required to deprotonate toluene^[92] and cumene (isopropylbenzene),^[94] respectively, exclusively at the benzylic position. Concomitant attack at benzylic and aromatic sites occurs under all other reaction conditions.^[95–98]

This compilation of regioselectively sensitive metalations was aimed at tracing the origins of optionally site controlled reactions. In the meantime, mechanistic rationale for the various dichotomies observed has been elaborated.^[99] Since then, new examples have emerged in rapid succession. For reasons of space limitations they cannot be exhaustively covered. The following Sections are limited to cases where substitution with fluorine plays a crucial role.

5.1. Halotoluenes

Competition experiments have been carried out to assess the proton mobility in the various fluoro-, chloro-, and bromotoluene isomers.^[51] The data collected (Tables 41–43) are very approximate since under the reaction conditions (lithium 2,2,6,6-tetramethylpiperidide in tetrahydrofuran in the presence of potassium *tert*-butoxide and *N,N,N',N'',N'''*-pentamethyldiethylenetriamine at -75°C or -100°C) the *o*-chloro- and *o*-bromoaryl lithium intermediates instantaneously lose lithium halide to set free 1,2-dehydroarenes (“arynes”)

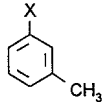
Table 41. Rates of the deprotonation of 2-halotoluenes^[a] relative to toluene.^{[b][51]}



X	$k_{\text{rel}}^{\Sigma} \text{ [c]}$	$k_{\text{rel}}^o \text{ [d]}$	$k_{\text{rel}}^a \text{ [e]}$
F	13	3	10
Cl	10	5	5
Br	75	50	25

[a] Reaction with lithium 2,2,6,6-tetramethylpiperidide, potassium *tert*-butoxide, and *N,N,N',N'',N'''*-pentamethyldiethylenetriamine in THF at -75°C ($\text{X}=\text{F}$) or -100°C ($\text{X}=\text{Cl}, \text{Br}$). [b] Toluene is exclusively deprotonated at the methyl group ($k_{\text{rel}}^{\Sigma}=k_{\text{rel}}^a \equiv 1.0$). [c] Rate of global deprotonation ($k_{\text{rel}}^{\Sigma}=k_{\text{rel}}^o+k_{\text{rel}}^a$) relative to toluene. [d] Relative rate of deprotonation at halogen-adjacent arene positions. [e] Relative rate at benzylic positions.

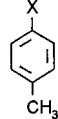
Table 42. Rates of the deprotonation of 3-halotoluenes^[a] relative to toluene.^{[b][51]}



X	$k_{\text{rel}}^{\Sigma} \text{ [c]}$	$k_{\text{rel}}^o \text{ [d]}$	$k_{\text{rel}}^a \text{ [e]}$
F	13	3	10
Cl	10	5	5
Br	30	25	5

[a] Reaction with lithium 2,2,6,6-tetramethylpiperidide, potassium *tert*-butoxide, and *N,N,N',N'',N'''*-pentamethyldiethylenetriamine in THF at -75°C ($\text{X}=\text{F}$) or -100°C ($\text{X}=\text{Cl}, \text{Br}$). [b] Toluene is exclusively deprotonated at the methyl group ($k_{\text{rel}}^{\Sigma}=k_{\text{rel}}^a \equiv 1.0$). [c] Rate of global deprotonation ($k_{\text{rel}}^{\Sigma}=k_{\text{rel}}^o+k_{\text{rel}}^a$) relative to toluene. [d] Relative rate of deprotonation at halogen-adjacent arene positions. [e] Relative rate at benzylic positions.

Table 43. Rates of the deprotonation of 4-halotoluenes^[a] relative to toluene.^{[b][51]}

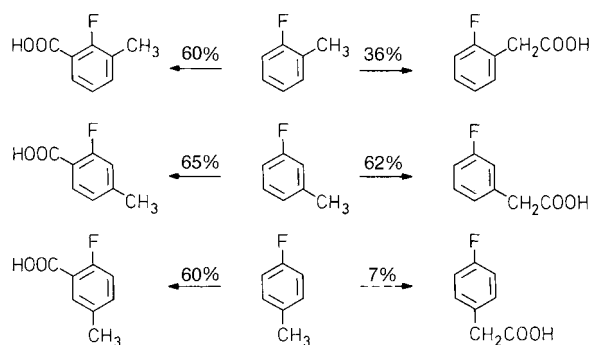


X	$k_{\text{rel}}^{\Sigma} \text{ [c]}$	$k_{\text{rel}}^o \text{ [d]}$	$k_{\text{rel}}^a \text{ [e]}$
F	10	10	0.1
Cl	13	10	3
Br	33	30	3

[a] Reaction with lithium 2,2,6,6-tetramethylpiperidide, potassium *tert*-butoxide, and *N,N,N',N'',N'''*-pentamethyldiethylenetriamine in THF at -75°C ($\text{X}=\text{F}$) or -100°C ($\text{X}=\text{Cl}, \text{Br}$). [b] Toluene is exclusively deprotonated at the methyl group ($k_{\text{rel}}^{\Sigma}=k_{\text{rel}}^a \equiv 1.0$). [c] Rate of global deprotonation ($k_{\text{rel}}^{\Sigma}=k_{\text{rel}}^o+k_{\text{rel}}^a$) relative to toluene. [d] Relative rate of deprotonation at halogen-adjacent arene positions. [e] Relative rate at benzylic positions.

as transient species. Nevertheless, trends are apparent. The introduction of a chlorine substituent in any ring position of toluene accelerates proton abstraction by one power of ten; aromatic and benzylic sites are attacked at roughly equal rates ($k_{\text{rel}}^o \approx k_{\text{rel}}^a$). The three bromotoluenes behave similarly, although the deprotonation of all aromatic positions and of the α -position in the *ortho* isomers appears to occur still more readily than with the chloro analogue. Most intriguing are the results found with the fluorotoluenes. While the kinetic acidity of the halogen-adjacent aromatic sites has uniformly increased by a factor of 3–10, only the *ortho* and *meta* isomers undergo metalation at the α -position more rapidly, in fact 10 times more rapidly, than toluene itself (Tables 41 and 42). In contrast, deprotonation of *p*-fluorotoluene at the α -position occurs 10 times more slowly than with the halogen-free parent compound (Table 43, $k_{\text{rel}}^a = 0.1$).^[51]

The deactivation of the benzylic site in *p*-fluorotoluene seems to be caused by n - π electron–electron repulsion^[48, 49] (Section 3.2). This has practical consequences. 4-Fluorophenylacetic acid can be obtained in not more than 7% yield when 4-fluorotoluene is consecutively treated with potassium *tert*-butoxide activated lithium diisopropylamide (LIDA-KOR) in tetrahydrofuran at -75°C and carbon dioxide, whereas the *ortho* and *meta* isomers form in yields of 37% and 62%, respectively (Scheme 5).^[100]

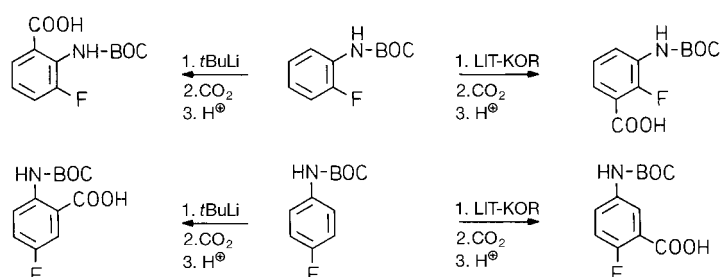


Scheme 5. Different yields in the deprotonation and carboxylation of the benzyl position of *o*-, *m*-, and *p*-fluorotoluene.

5.2. Fluorinated Anilines, Benzylamines, and Anisoles

Optional site selectivity can also be established with aromatic substrates bearing two different heterosubstituents. The mechanism-based rule of thumb is that the more polar reagent (e.g., LIC-KOR) favors the metalation in the immediate vicinity of the more electronegative function, whereas uncomplexed alkyl lithium complexes preferentially attack positions adjacent to a strong electron-donating and hence metal-coordinating moiety.^[99, 101] The success depends entirely on the appropriate matching of reagents and reaction conditions with the targeted neighboring groups.

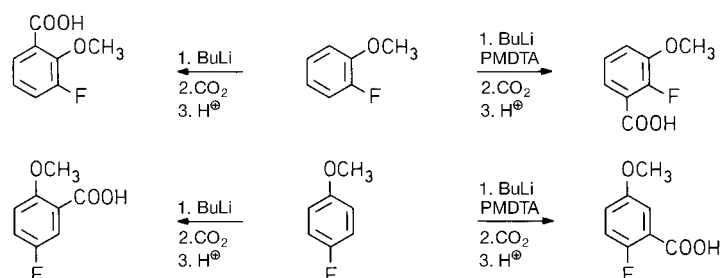
The *N*-*tert*-butoxycarbonyl(BOC)-2-fluoroaniline and -4-fluoroaniline react with two equivalents of *tert*-butyllithium in tetrahydrofuran at -50°C exclusively at the *N*-adjacent site (86 % and 80 %, respectively, of the corresponding anthranilic acids after carboxylation; Scheme 6).^[102] On the other hand,



Scheme 6. Optional site selectivity for *N*-*tert*-butoxycarbonyl(BOC) fluoroanilines.

the same substrates are metalated at the position next to the halogen when *tert*-butyllithium is employed in the presence of potassium *tert*-butoxide (42 % and 36 % of the corresponding 2-fluorobenzoic acids are obtained after consecutive treatment with LiT-KOR in tetrahydrofuran at -75°C and carbon dioxide; Scheme 6).^[102, 103]

2- and 4-Fluoroanisole offer other striking examples of optional site selectivity. The reactions with butyllithium in tetrahydrofuran at -75°C followed by carboxylation afford the 2-methoxybenzoic acids (50 % each), but only 2-fluorobenzoic acids (87 % and 85 %) when the metalation is carried out in the presence of *N,N,N',N'',N'''*-pentamethyldiethylenediamine (PMDTA) under otherwise unaltered conditions (Scheme 7). All products are regioisomerically uncontaminated.



Scheme 7. Site selectivity for 2- and 4-fluoroanisole.

5.3. *meta*-Substituted (Trifluoromethyl)benzenes

The trifluoromethyl entity is relatively large.^[105] When another group is located in the *meta* position, the site flanked by the two substituents, even if doubly activated, may be sterically too congested to be reached by a bulky reagent. This opens the door to optional site selectivity. Thus, 3-(trifluoromethyl)phenol (Table 44; R = H) reacts with butyllithium

Table 44. Optional site selectivities for *meta*-(trifluoromethyl)phenol derivatives.

OR	MR	Solvent	Yield [%]	
H	LIC-KOR-TMEDA	hexane	5	91
OCH ₂ OCH ₃	LIC-KOR	THF	0	100
OCH ₂ OCH ₃	LIS-TMEDA	THF	94	0

in the presence of potassium *tert*-butoxide and *N,N,N',N''*-tetramethylethylenediamine (TMEDA) in hexane at 0°C at positions 2 and 4 in the ratio of 93:7.^[77] After protection of the hydroxy group as a methoxymethyl ether (R = CH₂OCH₃), the metalation by a 0.1M solution of potassium *tert*-butoxide activated butyllithium in tetrahydrofuran at -75°C occurs exclusively at the 2-position but with *sec*-butyllithium (LIS) in the presence of TMEDA exclusively at the 4-position.^[77]

Although the space requirements of a single fluorine atom are moderate, the site between the substituents in 1-fluoro-3-trifluoromethylbenzene seems to be already too crowded to accommodate a reagent as bulky as the *sec*-butyllithium/PMDTA complex. Besides small amounts of the “double-*ortho*” derivative, mainly the trapping product of the intermediate generated by metalation of the F-adjacent, CF₃-remote site is obtained (Table 45, X = F).^[70] When LIC-KOR is used, only the former 1,2,3-trisubstituted isomer is iso-

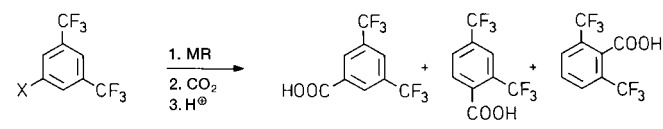
Table 45. Optional site selectivities for *meta*-halo(trifluoromethyl)benzenes.

X	MR	Yield [%]	
F	LIS-PMDTA	68	17
F	LIC-KOR	0	46
Cl	LIS	80	0
Cl	LIC	0	67

lated.^[106] With 1-chloro-3-trifluoromethylbenzene the optional site selectivity becomes once again perfect. Metalation with butyllithium and subsequent carboxylation gives the 2,6-disubstituted benzoic acid, whereas the same reaction performed with *sec*-butyllithium affords pure 2-chloro-4-(trifluoromethyl)benzoic acid.^[107]

1,3-Bis(trifluoromethyl)benzene leads to the greatest variety of organometallic intermediates. It is selectively deprotonated at the 2-position by the superbasic LIC-KOR mixture and at the 4-position by LIS-PMDTA, both times in tetrahydrofuran at -75°C (Table 46).^[70] When *tert*-butyllithium (LIT) in tetrahydropyran at -25°C is employed, the 4- and 5-position are simultaneously attacked and a 1:1 mixture of

Table 46. Optional site selectivities for *meta*-bis(trifluoromethyl)benzenes.



X	MR	Solvent	Yield [%]		
Br	LIC	Et ₂ O	94	—	—
H	LIT	THP ^[a]	43	39	—
H	LIS-PMDTA	THF	—	56	—
H	LIC-KOR	THF	—	—	78

[a] THP = tetrahydropyran.

the respective organolithium species is obtained.^[70] Pure 3,5-bis(trifluoromethyl)phenyllithium can be generated by halogen/metal interconversion between 1-bromo-3,5-bis(trifluoromethyl)benzene and butyllithium (LIC) in diethyl ether.^[108]

6. Conclusions and Outlook

Acidity is not only a physicochemical key property but it also controls many features of reactivity and bioactivity. Apart from a few exceptions, fluorine stabilizes anions and hence facilitates ionic dissociation. Thus, the smallest halogen may be used to fine-tune acidity. Organophosphorus compounds can serve to illustrate this. Alkylphosphonic acids are often tested as enzymatically stable mimics of monoalkyl phosphates. However, their dissociation constants ($\text{p}K_{\text{a}} \approx 2.6$, $\text{p}K'_{\text{a}} \approx 8.1$) are significantly lower than those of the phosphates ($\text{p}K_{\text{a}} \approx 1.9$, $\text{p}K'_{\text{a}} \approx 6.7$).^[109] The introduction of one or two fluorine atoms into the α -position of phosphonic acids brings the critical second dissociation constants $\text{p}K'_{\text{a}}$ (about 6.2 and 5.6) back in the desired range. The acidity readjustment overshoots upon introduction of a third halogen atom, trifluoromethylphosphonic acid having a $\text{p}K'_{\text{a}}$ of 3.9.^[110]

When moving from OH through NH to CH acids, the acidity progressively decreases. Strong bases have to be employed in inert solvents to achieve deprotonation of alkanes, arenes, and heterocycles. The degree to which fluorine enhances the kinetic and thermodynamic acidity of such substrates depends on many factors. Electrostatic forces alone cannot explain the observed variations in acidity; all available evidence points to a subtle balance of different effects including induction, resonance, polarization, hyperconjugation, and dipole interactions, both of the internal type (causing conformational changes) and external type (affecting the solvent shell). Thus, the detailed knowledge of heteroelement effects on anion stability provides a basis for understanding the origin and transmission of electronic interactions.

At the same time, such fundamental studies give valuable clues about how to generate new reactive species that can be exploited for synthetic purposes.

Progress in the rationalization of fluorine effects has not only been made in the area of anionic, but also cationic^[111–118] and radical^[119] species. In contrast, little is known about exactly how fluorine and other halogens improve the metabolic stability of aliphatic and aromatic hydrocarbons, in particular by retarding cytochrome P-450 promoted oxidations. Resistance to catabolic degradation is, of course, a prime target in pharmaceutical chemistry. The same holds for the lipophilicity of drugs on which also depends their membrane permeability and specific tissue accumulation. Related are phenomena such as the surface tension and wettability of highly fluorinated coatings and the elasticity of many fluoropolymers. Fluorine substituents play a crucial role also in other technologically important fields. For example, they increase the dielectrical anisotropy of liquid crystals and thus enable the design of improved thin film transistor liquid crystal displays.^[120] The details of how fluorine alters all such physical properties are still poorly understood if not mysterious. In other words, much remains to be done until one can claim to have succeeded in the “parametrization” of fluorine.

This review is an extended version of a lecture presented at the ACS meeting held from 19 to 23 January 1997 in St. Petersburg Beach. The author takes advantage of the opportunity to express his appreciation for the stimulating discussions he had on this occasion and throughout the years with numerous American colleagues, in particular with Prof. Milos Hudlicky, Blacksburg, Dr. Bruce E. Smart, Wilmington, and Prof. John T. Welch, Albany. The contributions from the Lausanne laboratories would not have been possible without the enthusiastic and competent work of the collaborators quoted in the list of references. However, a few names deserve to be explicitly mentioned here: Dr. Florence Mongin, Miss Nadia Brügger, and Dr. Olivier Desponds. Financial support was provided by the Swiss National Science Foundation, Bern, under the grant 20-41'887.94 and by the Federal Office of Science and Education in the framework of a COST D2 action (contract 874.12.02).

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Homoleptic Isocyanide Metalates

Lothar Weber

Isocyanides are derived from CO by replacing the oxygen atom with the isoelectronic—but less electronegative—NR unit. Therefore it is not surprising that isocyanides also form stable metal complexes that are similar to metal carbonyls in terms of composition and structure. Remarkably, however, up to the middle of this century a large number of neutral and anionic metal carbonyl complexes was without exception opposed only by homoleptic isocyanide complex cations.^[1–5] These compounds were either obtained by the exhaustive alkylation of cyanometalates or by treatment of metal salts with the free ligand.^[1]

The first homoleptic metal carbonyl, [NiCO₄], was already described in 1890,^[6] whereas information about the first analogous isocyanide systems, [Ni(CNPh)₄] and [Ni(CNC₆H₄OEt)₄], only dates back to the 1950s.^[7, 8] Even to date the number of neutral homoleptic metal carbonyls known clearly exceeds that of the corresponding isocyanide complexes (Table 1).^[3] On the other hand homoleptic

isolable and thermally surprisingly stable salts with cations such as [Au(CO)₂]⁺, [Hg(CO)₂]²⁺, [M(CO)₆]²⁺ (M = Fe, Ru, Os), and [Ir(CO)₆]³⁺, if one does not take into consideration complexes such as [M(CO)₆]⁺ (M = Mn, Tc, Re) that have been known for a longer time.^[9] There are also blank areas in the field of isocyanide complex chemistry, which have remained for more than a century: homoleptic isocyanide metalates [M_n(CNR)_m]^{x–}, to which a large number of—partly highly reduced—carbonyl analogues [M_n(CO)_m]^{x–} correspond.^[10, 11]

It was deduced from preparative results, IR data, electrochemical studies, and theoretical calculations that CO—as a weak σ-donor, but excellent π-acceptor ligand—is ideally suited to stabilize metal complexes in oxidation states ≤ 0. In contrast, alkyl and aryl isocyanides proved to be much stronger σ-donor, but poorer π-acceptor ligands than CO. It has, however, to be emphasized that the acceptor capability of CNR can be tuned within certain limits by the nature of R.^[5]

Table 1. Fully characterized cationic and neutral homoleptic metal–isocyanide complexes.^[3]

Group 5	6	7	8	9	10	11
[V(CNR) ₆] ⁺	[Cr(CNR) ₆] [Cr(CNR) ₆] ⁺ [Cr(CNR) ₆] ²⁺ [Cr(CNR) ₆] ³⁺ [Cr(CNR) ₇] ²⁺ [Mo(CNR) ₆] [Mo(CNR) ₇] ²⁺	[Mn(CNR) ₆] ⁺	[Fe(CNR) ₅] [Fe ₂ (CNR) ₉]	[Co ₂ (CNR) ₈] [Co(CNR) ₃] ⁺ [Co(CNR) ₃] ²⁺ [Co ₂ (CNR) ₁₀] ²⁺	[Ni(CNR) ₄] [Ni ₄ (CNR) ₇] [Ni(CNR) ₄] ²⁺	[Cu(CNR) ₄] ⁺
			[Ru(CNR) ₅] [Ru ₂ (CNR) ₉] [Ru ₂ (CNR) ₁₀] ²⁺	[Rh(CNR) ₄] ⁺ [Rh ₂ (CNR) ₈] ²⁺ [Rh ₂ (CNRNC) ₄] ^{2+ [a]}	[Pd ₃ (CNR) ₆] [Pd ₂ (CNR) ₆] ²⁺ [Pd ₃ (CNR) ₈] ²⁺ [Pd(CNR) ₄] ²⁺	[Ag(CNR) ₂] ⁺
	[W(CNR) ₆] [W(CNR) ₇] ²⁺	[Re(CNR) ₆] ⁺	[Os(CNR) ₅] [Os ₂ (CNR) ₁₀] ²⁺	[Ir(CNR) ₄] ⁺	[Pt ₃ (CNR) ₆] [Pt ₇ (CNR) ₁₂] [Pt(CNR) ₄] ²⁺ [PdPt(CNR) ₆] ²⁺ [Pt ₂ (CNR) ₆] ²⁺	[Au(CNR) ₂] ⁺

carbonyl metal cations have—compared to the numerous stable isocyanide complexes of metals in positive oxidation states—been one of the missing links in the field of carbonyl chemistry for nearly a hundred years. Recent research, however, has provided us with the missing information about

Not unexpectedly, these bonding concepts did not encourage efforts to prepare homoleptic carbonyl metal cations or isocyanide metalate anions. Therefore it is not all that surprising that the above-mentioned carbonyl metal cations were discovered by researchers working on fluorine chemistry and not those working on organometallic chemistry.^[9]

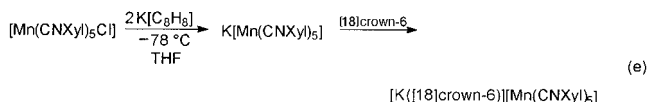
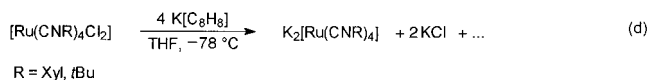
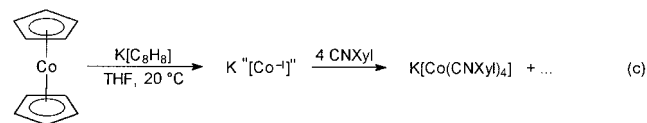
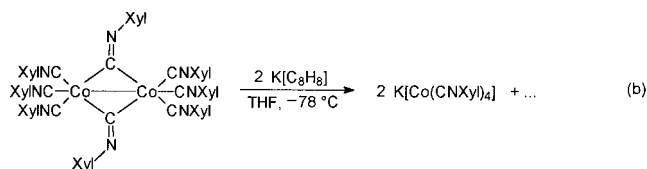
Essentially at the same time as these studies, Cooper et al. reported on the synthesis, structure, and reactivity of K[Co(CNXyl)₄] (Xyl = 2,6-Me₂C₆H₃), the first isocyanide

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metallate.^[12] Such exotic complexes are now well on the way to becoming familiar reagents in the synthetic arsenal of preparative chemists.

Preparation

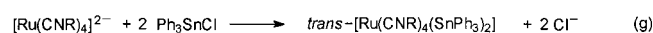
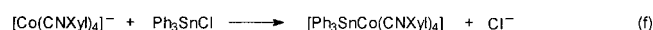
The synthesis of the orange-yellow complex $\text{K}[\text{Co}(\text{CNXyl})_4]$ was initially achieved by substituting all ethene ligands in $\text{K}[\text{Co}(\text{C}_2\text{H}_4)_4]$ with xyllyl isocyanide [Eq. (a)].^[12] Subsequently, this compound was prepared analogously to carbonyl metallates by reducing octakis(isocyanide)dicobalt [Eq. (b)] or cobaltocene with potassium naphthalenide [Eq. (c)].^[13] The potassium naphthalenide reduction of $[\text{Co}(\text{CNR})_5\text{BF}_4]$ as well as $[\text{Co}(\text{CNR})_4\text{I}_2]$ also afforded the desired compound



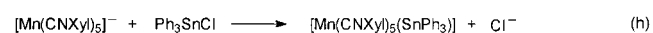
in similar good yields (70–80 %). Burgundy-red solutions in THF of the thermally unstable and not isolable salts $\text{K}_2[\text{Ru}(\text{CNR})_4]$ (R = Xyl, *t*Bu) were obtained analogously at -78°C [Eq. (d)].^[14] The existence of isocyanide ruthenates was supported by derivatization with Ph_3SnCl and other trapping reagents (see below). The same strategy was successfully applied for the synthesis of the manganate ion $[\text{Mn}(\text{CNXyl})_5]^-$. Black-red crystals of the compound $[\text{K}([18]\text{crown-6})][\text{Mn}(\text{CNXyl})_5]$ were isolated in 53 % yield from the blood-red THF solution, which was generated by the reduction of $[\text{Mn}(\text{CNXyl})_5\text{Cl}]$ and subsequent addition of [18]crown-6 [Eq. (e)].^[15]

Chemical Properties

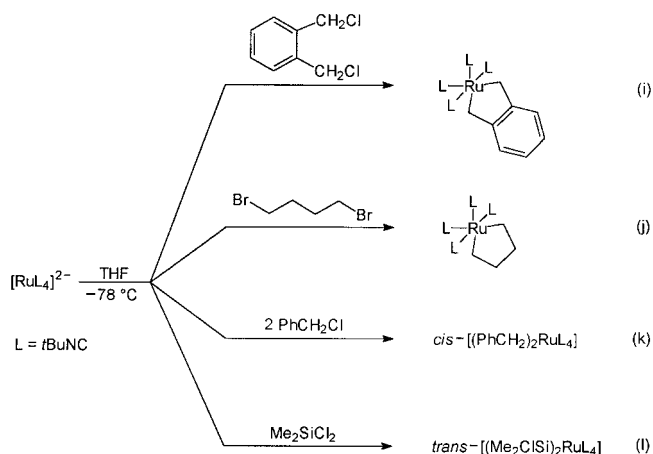
In analogy to carbonyl metallates,^[11] the presented extremely reactive anions are transformed into stable neutral complexes by reaction with equivalent amounts of Ph_3SnCl [Eqs. (f)–(h)]. The compound $\text{K}_2[\text{Ru}(\text{CN}t\text{Bu})_4]$ also oxida-



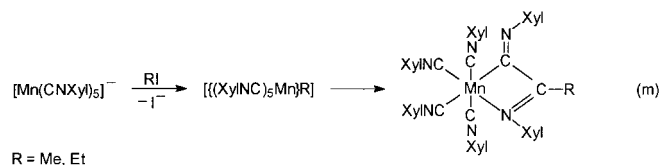
R = Xyl, *t*Bu



tively adds electrophiles with Si and C as central atoms [Eqs. (i)–(l)]. In contrast, the alkylation of pentakis(isocyanide)manganate with methyl iodide or ethyl iodide^[16] took a

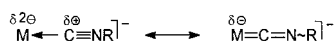


different course and can be compared to the methylation of $[\text{Fe}(\text{CN}t\text{Bu})_5]$.^[17] In both cases the alkylation at the metal center was followed by the insertion of two isocyanide ligands under the formation of 1,4-diazabutadien-2-yl-complexes [Eq. (m)]. If *t*BuNC was added before the methylation, the mixed complex $[\text{Mn}(\text{XylNC})_3(\text{tBuNC})\{\text{XylN}=\text{C}-\text{C}(\text{Me})=\text{NXyl}\}]$ was formed.^[16]



Bonding and Structures

The negative charge results in strong metal-CN- π -back donation by which the antibonding π^* -CN-orbitals are filled (Scheme 1). Thus, the wavenumbers of the $\tilde{\nu}$ (CN) stretching



Scheme 1. The strong metal-CN- π -back donation in homoleptic isocyanide metalates under participation of antibonding π^* -CN-orbitals.

vibrations of the terminal xylyl isocyanide ligands were shifted from $\tilde{\nu} = 2150, 2115 \text{ cm}^{-1}$ in the cation $[\text{Co}(\text{CNXyl})_5]^+$ to $\tilde{\nu} = 2010 \text{ cm}^{-1}$ in neutral $[\text{Co}_2(\text{CNXyl})_8]$ to $\tilde{\nu} = 1815 \text{ cm}^{-1}$ in the anion $[\text{Co}(\text{CNXyl})_4]^-$. In the free ligand $\tilde{\nu}(\text{CN})$ was determined at 2116 cm^{-1} (Table 2).

Table 2. CN vibrational stretching frequencies $\tilde{\nu}(\text{CN})$ [cm^{-1}] of homoleptic isocyanide complexes.

Isocyanide complex	$\tilde{\nu}(\text{CN})$ [cm^{-1}]	Solvent	Ref.
$[\text{Co}(\text{CNXyl})_4]^-$ [a]	1890 sh, 1815 br.	THF	[12, 13]
$[\text{Co}_2(\text{CNXyl})_8]$	2010, 1680	THF	[13]
$[\text{Co}(\text{CNXyl})_5]^+$	2150, 2115	THF	[13]
$[\text{Ru}(\text{CNXyl})_4]^{2-}$	1670 vs	THF	[14]
$[\text{Ru}(\text{CN}t\text{Bu})_3]^{[b]}$	2059 sh, 2032 s, 1832 s br.	<i>n</i> -C ₆ H ₁₄	[18]
$[\text{Fe}(\text{CN}t\text{Bu})_5]$	2110 sh, 2005 s, 1830 s	<i>n</i> -C ₆ H ₁₄	[18]
$[\text{Fe}(\text{CNXyl})_5]$	2036 sh, 1978 vs, 1870 sh	<i>n</i> -C ₆ H ₁₄	[18]
$[\text{Mn}(\text{CNXyl})_5]^-$	1920 s, 1710 m	THF	[15]

[a] $\tilde{\nu}(\text{CNXyl})$ (in THF) = 2116 cm^{-1} . [b] $\tilde{\nu}(\text{CN}t\text{Bu})$ (in CCl₄) = 2145 s , 2115 w , 2079 w .

The X-ray structure analyses of $[\text{K}(\text{dme})][\text{Co}(\text{CNXyl})_4]$ and $[\text{K}([18]\text{crown-6})\text{dme}](\text{Mn}(\text{CNXyl})_5)]$ (dme = 1,2-dimethoxyethane) feature besides discrete cations discrete distorted tetrahedral $[\text{Co}(\text{CNXyl})_4]^-$ and trigonal-bipyramidal $[\text{Mn}(\text{CNXyl})_5]^-$ ions, respectively. The isocyanide ligands of the cobaltate ion are nonlinear, their C-N-C angles range between $147.7(9)$ and $165.2(14)^\circ$. In contrast, the structure of the manganate ion resembles that of the homoleptic neutral complex $[\text{Fe}(\text{CN}t\text{Bu})_5]$.^[17, 18] The valence angles at the axial isocyanide ligands are markedly more obtuse (163°) than those at the equatorial isocyanide ligands (143 – 149°). This can be explained with a more effective π -back-bonding from the negatively charged metal center to the equatorial isocyanide ligands. Accordingly, we find nearly linear C-N-C units in cationic isocyanide complexes, in which π -back-bonding is of only marginal importance.^[4, 19–23]

Outlook

With the first results on the synthesis, structure, and reactivity of the homoleptic isocyanide metalates $[\text{Co}(\text{CNXyl})_4]^-$, $[\text{Ru}(\text{CN}R)_4]^{2-}$ ($R = \text{Xyl}$, $t\text{Bu}$), and

$[\text{Mn}(\text{CNXyl})_5]^-$ the door to the chemistry of this class of compounds has been opened significantly. It has been impressively demonstrated that the capability of isocyanides to stabilize metals in negative oxidation states has probably been underestimated. In view of the versatile chemistry of carbonyl metalates one eagerly awaits the further development of isocyanide metalate chemistry.

German version: *Angew. Chem.* **1998**, *110*, 1597–1599

Keywords: cobalt • isocyanide complexes • manganese • ruthenium

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X-Ray Structure of Bacteriorhodopsin at 2.5 Å Resolution

Ferdinand Hucho*

Scientific researchers often approach broad topics by working with models. Brain power and funding are applied in amounts that outsiders sometimes find absurd, but which are justified by leaps in fundamental understanding. In the end the “ultimate truth”, chapters in textbooks, can be written.

Biochemists work this way, too. They investigate various molecules to clarify fundamental principles of life, which then flow, almost unnoticed, into the vast pool of basic knowledge. Hemoglobin, for example, is one of these model molecules. It allowed us to understand how molecular activity (such as oxygen intake and output) is regulated, how a protein molecule is put together, and how hereditary diseases are brought about by point mutations. The *lac* operon became a model for gene regulation, the acetylcholine receptor a model for molecules processing signals, and glycogen phosphorylase a model for key regulatory enzymes in metabolism.

Now bacteriorhodopsin (BR), another model molecule, grabs our attention once again (Figure 1). After twenty years of attempts, researchers have finally been able to crystallize

this molecule and elucidate its X-ray structure.^[1] Is bacteriorhodopsin, a “light-driven proton pump” essential for the survival of a purple bacterium that lives in warm saline solution, merely an exotic molecule crucial only for that one somewhat uninteresting organism? The pioneer researchers in this field, Oesterhelt, Stoekenius,^[2] and others, would disagree. BR demonstrates a fundamental concept:^[3] How can light energy be directly (and in a much simpler process than that used by plants) transformed into chemical energy?^[4] How can membranes be used for energy conservation? How does “active transport” work? In other words, how are ions or molecules transported against a concentration gradient? (Biochemists call this active process “pumping”.)

BR is found in two-dimensional crystalline arrays in the membrane of the halophile archaeobacteria *Halobacterium salinarium*. It spans the lipid membrane that separates the inside of the bacterium (containing low salt concentration) from its oxygen-deficient, inhospitable surroundings. BR consists of a single polypeptide chain folded into seven transmembrane helices.

The chromophore retinal, which is bound as a Schiff base to a lysine residue (for the experts: Lys216), is embedded between the seven helices (Figure 2). In the resting state retinal exists in its all-*trans* conformation, and after absorbing a photon, it isomerizes to the 13-*cis* isomer. The movement triggered by this isomerization is carried over to the protein, so that the carboxylate group of aspartate residue 85 takes up the proton from the Schiff base and then passes it on via a network of water molecules to glutamate 204 and, finally, to the extracellular surface of the bacterium. Then the chromophore re-isomerizes to all-*trans*-retinal after taking up a proton from the inside of the cell and passing it on via aspartate 96 to the Schiff base. This reestablishes the inactive state and completes the cycle. The process can be observed spectroscopically and can be described by the intermediate states J, K, L, M, N, and O (see Figure 2).

This (and much more) was known before the elucidation of the recently published X-ray structure.^[1] Over the past 25 years data accumulated from high-resolution electron microscopy,^[5] time-resolved FTIR spectroscopy,^[6] neutron scattering,^[7] and classic biochemical methods (spectroscopy and molecular biology) has provided a detailed picture of the proton's path from the inside to the outside, which can be described almost Ångström by Ångström and millisecond by millisecond. Three basic questions pop up when one reads the recent *Science* article: 1) Was the old model of the light-driven proton pump wrong, and do we need to correct it based on the crystal structure at hand? 2) What is the principally new aspect of the recently published X-ray analysis that justifies the sensation of publishing in a “high-impact journal”? 3) Is this the end of BR research; do we know everything now, and can we write the definitive textbook chapter?

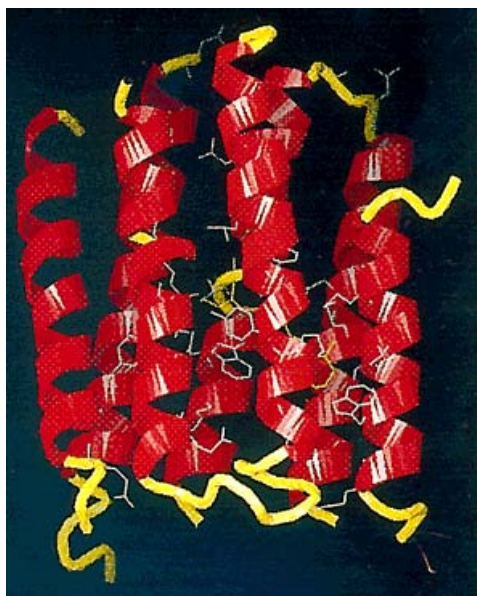


Figure 1. Ribbon model of the bacteriorhodopsin monomer. α Helices are red, loops are yellow, and the side chains crucial for proton transfer are white. The bundle made up of the seven transmembrane helices is perpendicular to the plane of the cell membrane. (The figure was kindly provided by Eva Pebay-Peyroula, IBS Grenoble, and Jurg Rosenbusch, Biozentrum Basel.)

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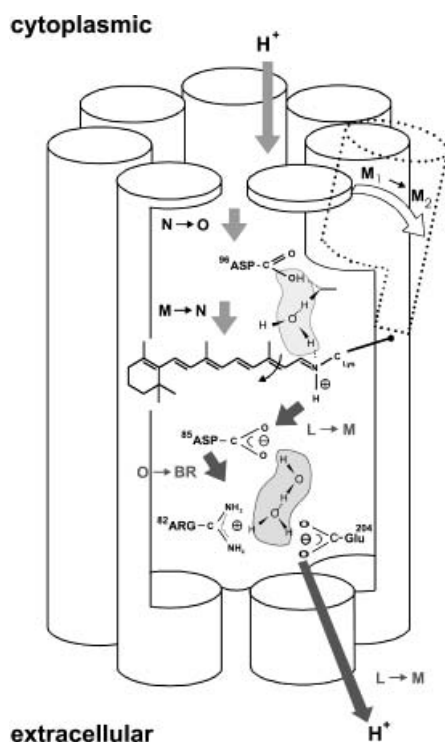


Figure 2. The proton pump model of bacteriorhodopsin. After the isomerization of retinal, the proton of the Schiff base is passed on to Asp85 in the $L \rightarrow M$ transition. Simultaneously, an additional proton is released to the outside from the hydrogen bonding network. The Schiff base is reprotonated by Asp96 in the $M \rightarrow N$ reaction. Internal water molecules between the Schiff base and Asp96 play an important role here. Furthermore, the movement of a helix in the $M_1 \rightarrow M_2$ step is important for the pump's directionality. In the $N \rightarrow O$ reaction Asp96 is reprotonated and retinal reverts to the all-trans form. Finally, Asp85 is deprotonated in the $O \rightarrow BR$ reaction, bringing the system back to the initial state. (The figure was kindly provided by Klaus Gerwert, Bochum.)

In answer to the first question: Nothing in the model was completely wrong. Luckily, we can state that the results obtained by “classical” methods were correct and that our interpretations and models still stand. Minor corrections are required on the loops that connect the seven transmembrane helices. There are, however, bigger problems in the proton canal: the distance between aspartate 85 and the Schiff base is too large for the proton to manage in one step.

In answer to the second question: If the mere confirmation of “classical” biochemical and biophysical methods is not sufficient, then we would like to point to the quantum leap achieved with these analyses. For the first time microcrystals with dimensions of 20–40 μm (and a mere 5 μm thick) were used. This was possible with a new beam focus in Grenoble's electron synchrotron.^[1] The second breakthrough: a mem-

brane protein was crystallized in a totally new way by using a special lipid phase obtained by mixing lipids with water.^[8] Researchers hope that this method will solve the fundamental problem of crystallizing integral membrane proteins.

In answer to the last question: Please be patient—we are near the end of the BR chapter, not because we know everything now, but because we finally have information and tools that allow us to really understand the proton pump process. As mentioned above, there are problems with the distances that the “pumped” proton has to overcome. Here we need X-ray structures with higher resolutions ($\leq 2 \text{ \AA}$) which will let us more accurately localize additional water molecules that can serve as proton carriers^[9] (hopefully they won't be too mobile for the X-ray!). Other missing pieces in the puzzle are X-ray structures of artificial mutants, which would be able to prove the significance of individual protein side chains, in particular, for the water structure. And then the final phase of BR research should follow. A satisfactory description of the pumping process includes not only the proton's exact path, but more importantly, the energetics of the process: How are the intermediate states formed? How are the barriers of activation energy separating the various states overcome? We still need the molecular dynamics, the calculation of the mobility, and the energetics of the structures involved. X-ray analysis provides a snapshot, but the movie is missing. The secret of biomolecules' special activity lies in their dynamics, and with BR we may, for the first time ever, see the connection between dynamics and activity.

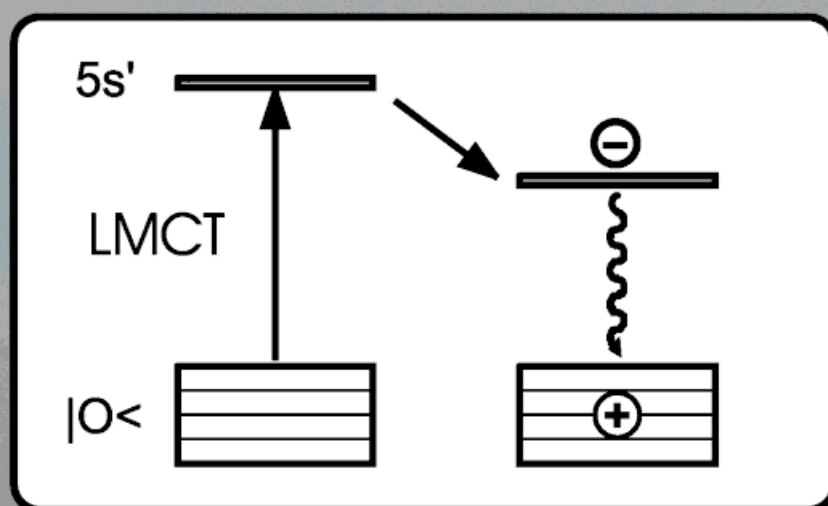
German version: *Angew. Chem.* **1998**, *110*, 1600–1601

Keywords: bacteriorhodopsin • membrane proteins • protein structures • proton transfer • structure elucidation

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The cause of the yellow color of activated silver-containing zeolite A

Colorless in the hydrated state, silver-containing zeolite A turns yellow to brick-red upon activation. This color change is reversible with respect to desorption/adsorption of water. The reason for this phenomenon, which has been known since 1962, was unclear until now. It is now shown that a charge-transfer transition from the oxygen atoms of the zeolite lattice to the empty 5s orbital of the silver ions is responsible for the yellow coloring.



The Yellow Color of Silver-Containing Zeolite A**

Roland Seifert, Andreas Kunzmann, and Gion Calzaferri*

Zeolites are crystalline aluminosilicates with a cavity structure. Their lattices are enormous polyanions which contain cations for charge compensation. In the nonactivated state, the cavities are filled with water. As a rule, these structures absorb light neither in the visible nor in the near ultraviolet range. Zeolite A has a three-dimensional network of cavities,^[1] and the composition of its Na⁺ form is Na₁₂[(SiO₂)₁₂(AlO₂)₁₂]. The Na⁺ cations can be partially or fully exchanged with Ag⁺ ions.

Ag⁺Na_{12-x}A, colorless in the hydrated state becomes a yellow to brick-red color upon activation. Rálek et al. observed this property for the first time after thermal activation under vacuum.^[2] Later it was discussed by various authors in connection with the formation of silver clusters.^[3] An autoreduction mechanism which involves formation of Ag⁰ and release of O₂ from the zeolite framework was assumed. We show here that upon activation under high vacuum Ag⁺Na_{12-x}A turns yellow already at room temperature and that all absorption bands appearing in the UV/Vis region only depend on the hydration of the Ag⁺ ions. We explain this coloring as electronic transitions from the lone pairs of the oxygen atoms of the zeolite lattice to the empty 5s orbital of the Ag⁺ ions (ligand-to-metal charge transfer, LMCT).

Figure 1 shows the colors which occur after activation of the zeolites under high vacuum in gas-tight glass ampoules.

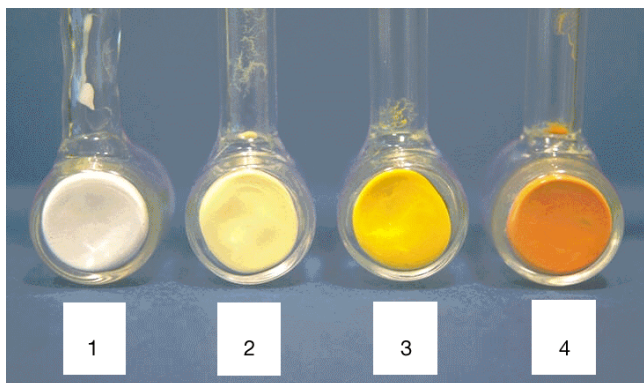


Figure 1. Upon activation, colorless zeolite A containing Ag⁺ ions turns yellow to brick-red, depending on the conditions. Samples of Na₁₂A (1), Ag_{0.13}Na_{11.87}A (2), and Ag₆Na₆A (3), activated under high vacuum at room temperature, are shown. Ampoule 4 contains Ag₆Na₆A, which was treated at 200 °C under high vacuum.

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Ampoules 1–3 contain Ag⁺Na_{12-x}A ($x=0, 1/8$, and 6, respectively) after activation at room temperature. In ampoule 4, zeolite activated at 200 °C with six Ag⁺ ions per pseudo unit cell is shown. The optical properties depend on the quality of the zeolite as well as the conditions during the activation.^[4] For this reason, we measured spectra of chemically pure and highly crystalline Na₁₂A which was partially and fully exchanged with Ag⁺ ions. It was activated under defined conditions which were as mild as possible.

Figure 2 shows UV/Vis spectra of Ag⁺Na_{12-x}A after activation under high vacuum (2×10^{-7} mbar) and at room temperature. The spectra of samples with a degree of

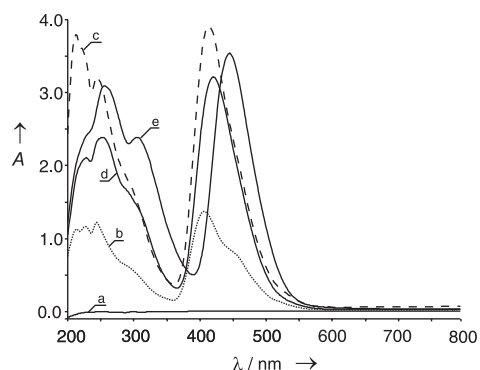


Figure 2. Dependency of the UV/Vis absorptions on the degree of exchange of the zeolite activated under high vacuum at room temperature: a) Na₁₂A, b) Ag_{0.5}Na_{11.5}A, c) Ag₁Na₁₁A, d) Ag_{1.5}Na_{10.5}A, e) Ag₆Na₆A.

exchange of up to one Ag⁺ ion per pseudo unit cell show a band at 420 nm with a shoulder at 450 nm. At a higher degree of exchange, the shoulder dominates, and with six or more Ag⁺ ions per pseudo unit cell upwards it is the only band in the visible range. Higher loading thus leads to a slight bathochromic shift of the long wavelength absorption band maximum. However, regardless of the degree of exchange, the coloring remains yellow.

Figure 3 shows the statistical distribution of Ag⁺ ions in the unit cells as a function of the mean degree of exchange. It was calculated on the simplifying assumption that no coordination site is occupied with preference. With this we can qualitatively understand the dependency of the spectra on the degree of

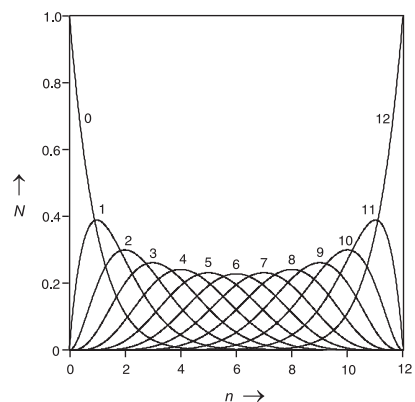


Figure 3. Calculated distribution of the Ag⁺ ion in an Ag⁺Na_{12-x}A model with 12 equivalent sites per cage. The graph shows which share (N) of the cages contains 0,1,2,...12 Ag⁺ ions at a chosen average degree (n) of exchange.

exchange. The absorption band at 420 nm is caused by the presence of an individual Ag^+ ion in a cage. An emerging bathochromic shift indicates the occurrence of interactions with further Ag^+ ions entering the cage. The distribution shows that the share of unit cells with one Ag^+ ion increases until an average content of one Ag^+ ion per unit is reached. With an average degree of exchange as low as 1.5 Ag^+ ions per unit cell, the share of cells with only one Ag^+ ion is already substantially smaller and roughly corresponds to the sum of the shares with more than one Ag^+ ion. The spectra thus demonstrate an increase and decrease in the intensity of the band at 420 nm and a bathochromic shift which starts at a degree of exchange as low as 1.5 Ag^+ ions per cage.

The counterpart of the activation process is the readsorption of water. The reversibility of the activation was examined. The results for $\text{Ag}_6^+\text{Na}_6^+\text{A}$ activated at room temperature are shown in Figure 4. All absorption bands

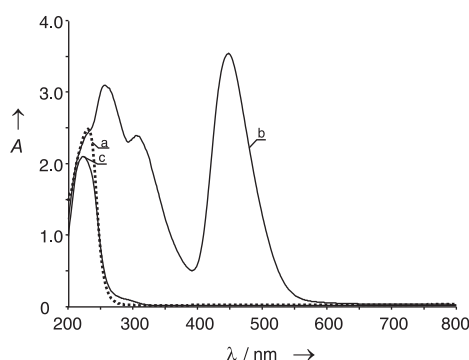


Figure 4. UV/Vis spectra of silver-containing zeolite A. The absorptions occurring because of the activation are reversible with respect to the readsorption of water. a) Freshly exchanged, nonactivated $\text{Ag}_6^+\text{Na}_6^+\text{A}$; b) $\text{Ag}_6^+\text{Na}_6^+\text{A}$ activated under high vacuum at room temperature; c) like b) but exposed to pure water vapor after activation. A = absorption.

occurring during the activation (spectrum b) disappear after the adsorption of pure water vapor (spectrum c). This reaction clearly contradicts an autoreduction in which Ag^0 is produced and O_2 is released. It clearly corresponds to a dehydration/hydration of the Ag^+ ions.

If zeolite activated at room temperature is heated with six Ag^+ ions per pseudo unit cell under high vacuum, new bands are formed at 360 and 510 nm, and the sample becomes brick-red. Figure 5 shows the spectra of $\text{Ag}_6^+\text{Na}_6^+\text{A}$ which was activated between room temperature and 250 °C. For these samples with additional thermal activation, the reversibility with respect to the desorption and adsorption of water is restricted to the visible range. Between 300 and 400 nm, bands with decreased intensity remain.

To better classify the occurrence of the reversible yellow coloring and to understand the electronic structure of the system, quantum-chemical EHMO-EDiT calculations (EHMO = extended Hückel molecular orbital, EDiT = electronic dipole induced transitions) were carried out at an α cage with alternating Al and Si atoms.^[5] In place of the neighboring cell, the free valencies were saturated with OH groups, creating a situation similar that in zeolite A. Charge neutrality was achieved by adding protons. The model thus

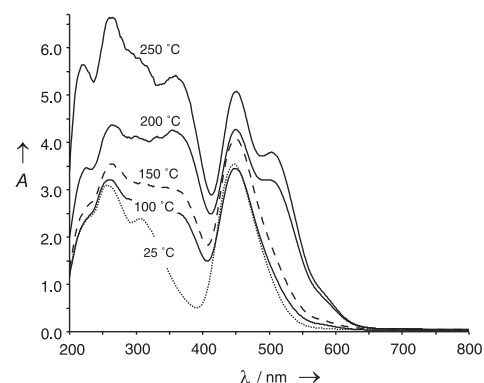


Figure 5. UV/Vis spectra of $\text{Ag}_6^+\text{Na}_6^+\text{A}$ zeolites activated under high vacuum at different temperatures. Between 150 and 200 °C, the zeolite begins to color brick-red. A = absorption.

consisted of 240 atoms. The examination of possible sites for Ag^+ ions in the model cage leads to the result shown in Figure 6, which corresponds to the data available from X-ray

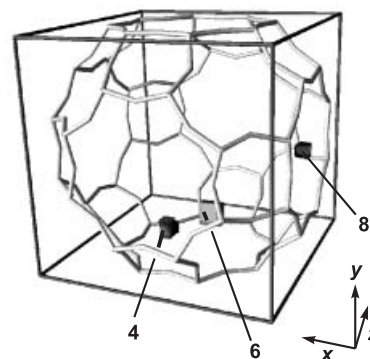


Figure 6. A model cage framed by a cube, which was used for the EHMO calculations. A calculated coordination site for Ag^+ ions over the four-, six-, and eight-rings is shown.

experiments. In the present case the energy levels and the oscillator strengths are significant for the electronic transitions in the HOMO/LUMO region. In Figure 7 we show these

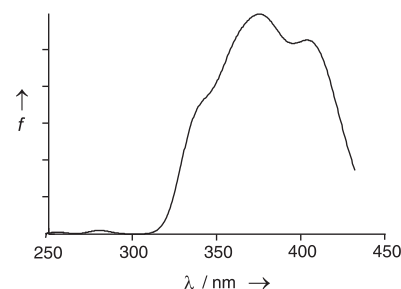


Figure 7. Result of an EHMO-EDiT calculation with a Ag^+ ion coordinated over the six-ring in the α cage. A simulated spectrum from the transitions with the highest oscillator strength f are shown.

for the important situation in which an Ag^+ ion is coordinated over the six-ring in a completely dry zeolite. The calculated spectrum can be compared with the long-wavelength part of spectrum b ($\lambda > 300\text{nm}$) in Figure 2. The other coordination

sites lead to similar results. The HOMO region corresponds to lone pairs of the oxygen atoms bonded to the zeolite lattice. The LUMO is located on the Ag^+ ion and corresponds to the empty 5s orbital. On the six-ring, two transitions from the lone pairs of two oxygen atoms to the Ag^+ 5s orbital [$\text{Ag}^+(5s) \leftarrow \text{O}(n)$] are found (340, 380 nm). The third band at 405 nm is a transition from the oxygen atoms corresponding to the connections to the neighboring α cage. If the Ag^+ ion is coordinated by water only, the $\text{Ag}^+(5s) \leftarrow \text{O}(n)$ transition is found below 250 nm. The first ionization energy of water is 12.6 eV, which means that the HOMO lies at -12.6 eV. For silicates, however, it is found at -10.7 eV, which explains the long-wavelength situation of the LMCT.^[6] The coordination of only one water molecule to a Ag^+ ion which is coordinated to zeolite oxygen atoms leads to a destabilization or a raising of the $\text{Ag}^+(5s)$ level, and therefore to a blue shift of the LMCT transitions.

We were able to show that activation at room temperature of silver-containing zeolite A with very low degrees of exchange already leads to a yellow coloring, and that the absorption of light and therefore the impression of yellow coloring are reversible with respect to the desorption/adsorption of water. The dependency of the absorption bands on the degree of exchange can be explained with a simple model of the cation distribution. Quantum-chemical calculations show that electronic transitions from the lattice oxygen atom to the silver ion are allowed, that these transitions are in the visible range, and that they experience a blue shift if coordinated with water. Hence, an observation first described 35 years ago has been quantified and explained in a noncontradictory way.

Experimental Section

Chemically pure zeolite was produced and characterized by a known procedure.^[7] For the examinations, 80 mg of zeolite were freshly exchanged each time with 0.1 M AgNO_3 (Merck, Titrisol). At degrees of exchange up to six Ag^+ ions, the zeolite was placed in 5 mL of H_2O , and a calculated amount of AgNO_3 was added and suspended for 15 min. Quantitative uptake of the Ag^+ ions can be assumed.^[8] The zeolite was washed with water twice. The zeolite stored at 92% humidity was assumed to have 27 H_2O molecules per formula unit.^[1] To obtain samples fully exchanged with Ag^+ ions, the zeolite was suspended twice in 20 mL of AgNO_3 solution for 15 min and washed three times with 15 mL of H_2O . The exchanged zeolite was put into 2 mL of H_2O and transferred to a quartz ampoule (cylinder with a height of 2 cm and a radius of 0.75 cm) which was connected to a HV-Flansch Adapter in a gas-tight way. The ampoule was connected to the pump in a horizontal position so that the zeolite could be deposited evenly at the bottom of the ampoule. The extra water was vaporized at 10 mbar (2–3 h). For activation, the turbo pump (Alcatel) was connected until the final pressure of the apparatus was achieved (48–72 h, $1-2 \times 10^{-7}$ mbar). After activation at room temperature, temperature-treated samples were gradually brought to the desired temperature ($\pm 5^\circ\text{C}$) with an adjustable heat pistol. The heating rate was chosen such that the pressure within the apparatus did not exceed 5×10^{-6} mbar, to avoid irreversible brown color changes. The ampoule with the sample sufficiently adhered to the bottom was separated from the pump with a burner under gas-tight conditions and transferred to the spectrometer. UV/Vis spectra were measured as diffuse reflection spectra at room temperature with a Perkin Elmer Lambda 14 spectrometer with an integration sphere (Labshere RSA-PE-20). Before they were graphically represented, the automatically collected data were converted using the Kubelka–Munk formula.

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A Lysoganglioside/Poly-L-glutamic Acid Conjugate as a Picomolar Inhibitor of Influenza Hemagglutinin**

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Cell surfaces are often covered with oligosaccharides that play important roles in many cellular recognition events, including infection, cancer metastasis, and other intercellular adhesion processes.^[1] Hemagglutinins (HAs) of influenza virus are typical examples of such receptor molecules. These trimeric proteins are capable of binding to sialylated oligosaccharides on the epithelial cell surface.^[2] The minimum

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structure involved in this recognition is either α -Neu5Ac-(2 $\rightarrow$ 3)- β -Gal or α -Neu5Ac-(2 $\rightarrow$ 6)- β -Gal as the nonreducing terminal saccharide, depending on the strain of the virus.^[3] The HAs are also known to help trigger fusion between the viral membrane and a lysosomal-lipid bilayer through changes in their conformations.^[4] Thus, inhibition of either or both of these processes could prevent viral infection. We report here the synthesis of polyvalent inhibitors that contain a hydrophobic moiety designed to disturb the fusion mechanism initiated by the protein-carbohydrate recognition process.

One problem associated with carbohydrate-receptor interactions is their relatively low binding affinity. A possible approach to increase the affinity is to use multivalent ligands with specific monomeric carbohydrate ligands.^[5] For this reason, functionalized polymers,^[5d, 6, 7] peptides,^[8] dendrimers,^[9] or liposomes that contain sugars^[10] have recently attracted interest, and some have been shown to exhibit higher affinities to receptors.^[5] Various types of polymers that incorporate sialic acid residues have also been synthesized in an attempt to inhibit the influenza virus.^[5d, 7] Because this virus has both HA and neuraminidase (NA) on its surface, polymers with sialic acid residues bound through noncleavable linkages have emerged as stable and potent inhibitors of HA. Alternatively, introduction of a second functionality to provide additional affinity for the target or nearby molecules might increase the affinity. Hydrophobic groups, for example, could be used to enhance binding affinity by their interaction with hydrophobic amino acid side chains and/or the membrane; the latter interaction might in turn interfere with the conformational change of the membrane-fusion domain of HA even after the first inhibition process has had its effect. An infection by influenza virus could thus be inhibited at two different stages: first during initial binding, and later in the course of HA-mediated membrane fusion.

To test the hypothesis that hydrophobic groups in a polymer might contribute to enhanced binding and disruption of the virus, we chose the molecule lysoganglioside GM₃ (lyso-GM₃), α -Neu5Ac-(2 $\rightarrow$ 3)- β -Gal-(1 $\rightarrow$ 4)- β -Glc-(1 $\rightarrow$)-sphingosine,^[11] which differs from the ganglioside GM₃ by the absence of the stearic acid residue. This was then conjugated with the polymer poly-L-glutamic acid (PGA). The reason for our choice of lyso-GM₃ is that GM₃ is the simplest ganglioside recognized by HA^[2]. The amino functionality of the sphingosine is suitable for connection to the polymer. The amphiphilic nature of sphingosine, which is directly attached to the oligosaccharide moiety, could help present the epitope unit to the surface of the synthetic polymer by the formation of either intra- (folded) or intermolecular aggregates (Figure 1). PGA (degree of polymerization = 540) was selected because of its low toxicity, low immunogenicity, and biodegradability.^[12] Furthermore, its length is sufficient to meet the criteria for the "chain lock" strategy to be effective, as described above. Another advantage of this strategy is that, because we chose the natural form of the oligosaccharide as ligand, galactosyl residues exposed on the virus surface after cleavage of sialic acids by NA may lead to galactose-mediated endocytosis. We describe here the synthesis of a lyso-GM₃/poly-L-glutamic acid conjugate and its inhibitory effect on HAs that bind the α -sialyl-(2 $\rightarrow$ 3)-galactosyl residue.

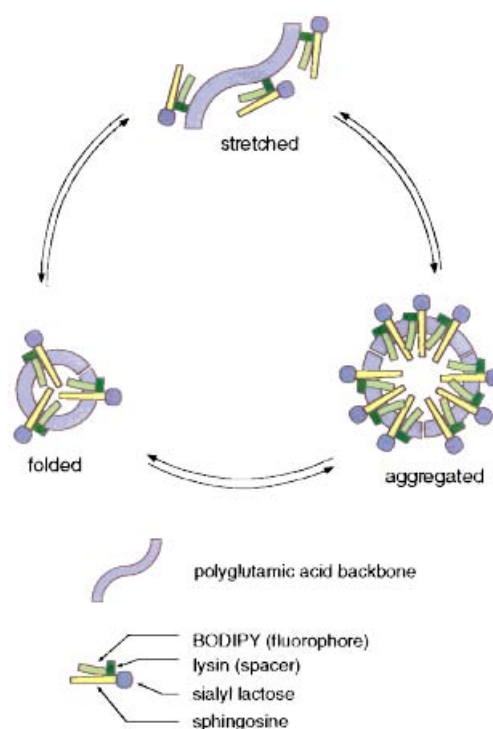
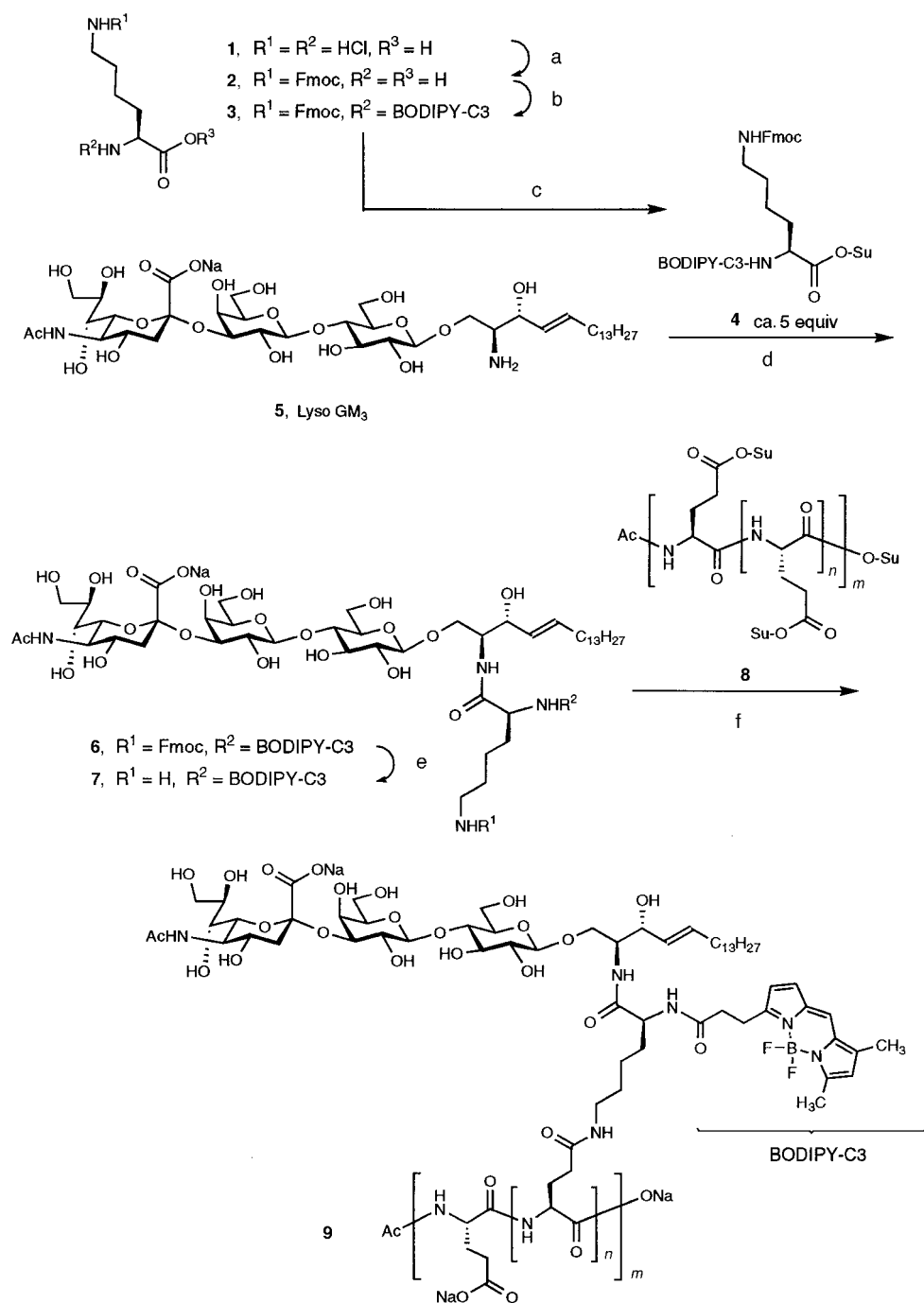


Figure 1. Schematic representation of lyso-GM₃-PGA, which exists in a stretched form in methanol and in either folded or aggregated forms in aqueous media.

The synthesis (Scheme 1) begins with derivatization of L-lysine, which was used as a spacer between lyso-GM₃ and the polymer backbone and as the trifunctional linker for incorporation of a fluorescent dye. The latter was expected to facilitate subsequent quantification and visualization of the disruption process if the polymer-virus complexes were indeed taken up by macrophages. The copper chelate of L-lysine was used to protect the ϵ -amino functionality with a 9-fluorenylmethyloxycarbonyl (Fmoc) group under basic conditions (58.2%). The fluorescent tag, a 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-propionyl (BODIPYFLC3) group,^[13] was then attached to the α -amino functionality (87%). Compound **3** was next transformed into active ester **4**, which without further purification was coupled with lyso-GM₃ (**5**) to provide condensate **6**^[14] (quantitative yield based on thin-layer chromatography with fluorescence detection). The Fmoc group was removed under standard conditions, although it was found that prolongation of the reaction resulted in a poor yield because of decomposition of the fluorescent tag. The coupling reaction between **7** and poly-L-glutamic acid (PGA) activated as its succinimidyl ester (**8**) proceeded smoothly to give, after treatment with sodium bicarbonate and purification by gel-permeation chromatography (GPC) over a Superose-12-pg column (Pharmacia Biotech), a polymer that contained lyso-GM₃ (**9**).^[15] The lyso-GM₃ (or sialic acid) content was calculated on the basis of absorption at 508 nm (BODIPY; in MeOH) and was determined to have an average value of 44.6 nmol per mg of polymer (0.72 mol %).

Synthetic polymer **9** was unique in the sense that the green luminescence observed in MeOH disappeared in water,



Scheme 1. a) 1. $\text{CuCO}_3\text{Cu}(\text{OH})_2 \cdot \text{H}_2\text{O}$, H_2O ; 2. Fmoc-O-Su , 10% Na_2CO_3 , 1,2-dimethoxyethane, 58.2%; b) BODIPYFLC3-O-Su , 10% Na_2CO_3 , MeOH, 87%; c) HO-Su , 1,3-diisopropylcarbodiimide, CH_2Cl_2 ; d) Et_3N , MeOH/DMF, quantitative; e) piperidine, DMF, 34%; f) DMF/MeOH. Su = succinimidyl; $m = 270$, $n:m \approx 1.5:100$.

whereupon the solution acquired a faint orange color, even though BODIPYFLC3 itself displays a green luminescence in both of these media as well as in NaOAc solution ($c \approx 10 \text{ nmol mL}^{-1}$; Figure 2). Quenching of the fluorescence and the observed shift in the absorption maximum were attributed to folding or aggregation in water caused by the hydrophobicity of sphingosine and the BODIPY fluorophore. The lyso-GM₃ content of the polymer may cause the fluorophore in the synthetic polymer to be highly localized and thus able to interact in the ground state, evidenced by an 83.3% decrease

in fluorescence ($\lambda_{\text{em}} = 512$, $\lambda_{\text{ex}} = 480 \text{ nm}$) and a slight shift in the absorption maximum ($\lambda_{\text{max}} = 504.6$ and 507.8 nm in MeOH and H_2O , respectively; Figure 3). Neither a shift in emission wavelength nor additional peaks were found to arise from excimer interactions. The BODIPY fluorophore is known to be insensitive to the pH value and largely independent of its environment; however, it can form aggregates, which results in self-quenching in aqueous media. The observed self-quenching is not a result of a high concentration of fluorophore incorporated into the polymer, because quenching did not occur for the free fluorophore under the same conditions. The lyso-GM₃ content was also consistent with the quantities of materials used in the condensation of lyso-GM₃-Lys(BODIPY)-NH₂ (7) with activated PGA (8). We therefore conclude that the synthetic polymer 9 exists in a stretched form in methanol and as a folded or aggregated form in aqueous media.

We investigated the inhibitory activity of the polymer toward influenza A/PR/8/34 (H1N1) with an enzyme-linked immunosorbent assay (ELISA).^[16] The IC_{50} value for 9 was $1.9 \times 10^{-12} \text{ M}$ based on the lyso-GM₃ content (or $7.5 \times 10^{-12} \text{ M}$ based on the sialic acid content; estimated from the UV absorption of the fluorophore). For comparison, the IC_{50} values for GM₃, lyso-GM₃ (5), and sialyllac-

tose (the trisaccharide portion of GM₃) were also determined (1×10^{-9} , 3×10^{-9} , and $1.5 \times 10^{-7} \text{ M}$, respectively). Sialyl-PGA was much less active than 9. PGA showed no inhibition up to a concentration of $1 \times 10^{-9} \text{ M}$; compound 9 was also assayed at this concentration (Table 1).

We have thus developed a new strategy for the inhibition of influenza virus, and the process itself can now be studied with the aid of an incorporated fluorophore. Experimental evidence was obtained to support the "chain lock" mechanism (Figure 4). Enhancement in the fluorescence emission of

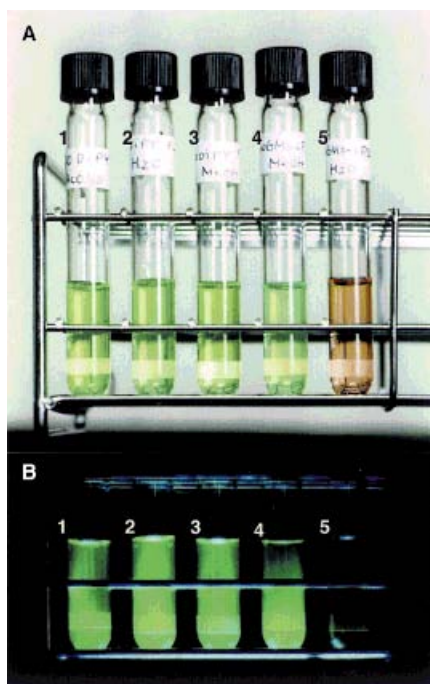


Figure 2. Solutions of lyso-GM₃-PGA (**9**) and BODIPY fluorophore in different media: BODIPYFL C3 in 1) NaOAc, 2) water, and 3) MeOH, as well as solutions of lyso-GM₃-PGA in 4) MeOH and 5) water, all at 26 °C. The upper photograph (A) was taken with ambient light; for the lower photograph (B) the solutions were irradiated with UV light (365 nm).

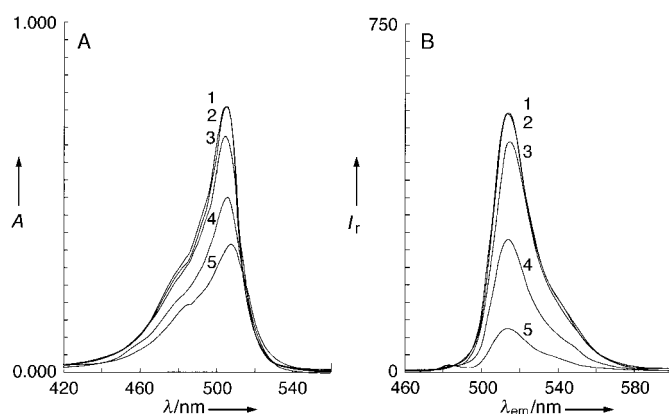


Figure 3. A) UV/Vis (0.1 mg mL⁻¹) and B) fluorescence emission spectra (80 μg mL⁻¹, λ_{ex} = 480 nm) of solutions of lyso-GM₃-PGA (**9**) in 1) MeOH, 2) 75 % MeOH, 3) 50 % MeOH, 4) 25 % MeOH, and 5) water. A = absorbance, I_r = relative fluorescence intensity.

Table 1. Inhibitory activity of synthetic polymer **9** and related compounds with respect to the influenza virus A/PR/8/34 (H1N1).

Compound	IC ₅₀ [M] ^[a]	Compound	IC ₅₀ [M] ^[a]
9	1.9 × 10 ⁻¹²	lyso-GM ₃ 5	3 × 10 ⁻⁹
9	7.5 × 10 ⁻¹² ^[b]	sialyllactose	1.5 × 10 ⁻⁷
GM ₃	1.0 × 10 ⁻⁹	PGA	— ^[c]

[a] Relative to the sialyllactose content. [b] Relative to the sialic acid content. [c] No inhibition.

BODIPY (λ_{em} 510, λ_{ex} 480 nm) was observed immediately after the addition of polymer **9** to a virus solution, which suggests an unfolding of the polymer after an initial self-

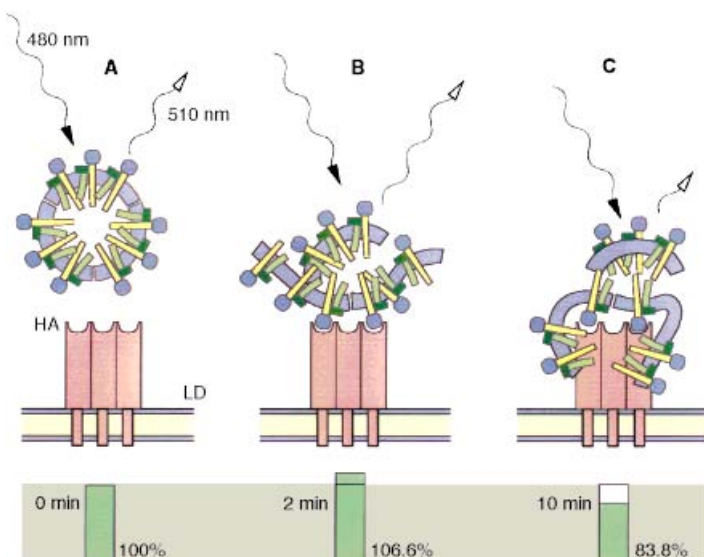


Figure 4. Schematic representation of the “chain lock” inhibition strategy. A) The aggregated polymeric inhibitor with a specific ligand, in this case sialyllactose, approaches the receptor, here hemagglutinin (HA). B) The aggregated polymer interacts with the receptor, whereby the fluorescence intensity increases. Emission from the exposed BODIPY fluorophore is greater than the energy loss caused by energy transfer to a Trp residue at the binding site. C) Hydrophobic interaction occurs to cause formation of a stable complex. The hydrophobic groups in HA, including the aromatic residues, lead to a further decrease in the fluorescence emission of BODIPY as a result of energy transfer. The bar graphs (bottom) indicate the relative fluorescence intensity (λ_{em} = 510, λ_{ex} = 480 nm) of the assay medium. The emission intensity of the mixture at t = 0 min was set to be 100 %. See Figure 1 for an explanation of the symbols. LD = lipid double layer of the virus.

quenching in a folded state. The emission intensity then decreased upon further incubation at 10 °C, perhaps explained by energy transfer to the aromatic amino acid residues of HA. When the tryptophane residue was irradiated (λ_{ex} = 287 nm), emission from BODIPY (λ_{em} 510 nm) was also observed, indicative of energy transfer between BODIPY and the Trp residues.^[17] The tight binding may be a consequence of initial multivalent interactions between **9** and the virus, followed by a hydrophobic interaction between the ligand and the receptor. Alternatively, the hydrophobic interaction may occur first. Both GM₃ and lyso-GM₃ might form liposomes and micelles and exhibit a multivalent effect, but not as effectively as **9**.

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- [14] $R_f = 0.27$ ($\text{CHCl}_3/\text{CH}_3\text{OH}/15\text{ mm CaCl}_2$ (60/35/8, v/v/v), ^1H NMR (600 MHz, CD_3OD): $\delta = 7.34$ (s, 1H, BODIPY), 6.93 (d, 1H, BODIPY), 6.26 (d, 1H, BODIPY), 6.13 (s, 1H, BODIPY), 3.13 (m, 2H, BODIPY- CH_2), 2.62 (t, 2H, BODIPY- CH_2), 2.42 (s, 3H, BODIPY- CH_3), 2.19 (s, 3H, BODIPY- CH_3), 4.2–4.3 (1H, $\text{C}_a\text{-H}$), 3.03 (m, 2H, $\text{C}_\beta\text{-H}$), 1.5–1.65 (m, 4H, $\text{C}_\beta\text{-H}$, $\text{C}_\gamma\text{-H}$), 1.69 (m, 2H, $\text{C}_\delta\text{-H}$), 4.21 (d, 1H, $J = 8.1$ Hz, Glc-H1), 4.32 (d, 1H, $J = 8.1$ Hz, Gal-H1), 3.93–3.95 (1H, Gal-H3), 3.80 (br. s, 1H, Gal-H4), 2.81 (dd, 1H, Neu5Ac-H3 $_{eq}$), 1.54 (1H, Neu5Ac-H3 $_{ax}$), 1.91 (3H, Neu5Ac-NHCOCH $_3$), 5.32–5.38 (m, 1H, sphingosine, olefinic H4), 5.56–5.59 (m, 1H, sphingosine, olefinic H5), 1.19 (16H, sphingosine- CH_2), 0.80 (sphingosine- CH_3); ESI-MS positive ions: calcd for $[\text{M}2\text{Na} - \text{H}]^+$: 1362, found: 1362; calcd for $[\text{M} + \text{Na}]^+$: 1340, found: 1340; negative ions: calcd for $[\text{M} - \text{H}]^-$: 1316, found 1316.
- [15] The average molecular weight ($\bar{M}_n$) was estimated to be 87 kDa based on the lyso-GM $_3$ content (0.72%; $m = 536.1$, $n = 3.9$) and the degree of polymerization ($\text{DP} = 540$) of PGA. $\bar{M}_n$ of **9** estimated by GPC to be 336 kDa (Waters Ultrahydrogel Liner column (7.8 $\times$ 300 mm), elution with 0.1 M NaNO_3 , flow rate 1 mL min $^{-1}$, UV detection at 500 nm and 40°C). Millenium 2010 with GPC software was used to analyze the data. Polyethylene oxides were employed as standards and detected by refractive index. The GPC result is apparently erroneous with respect to the number of introduced lyso-GM $_3$ groups ($\bar{M}_n(\text{GPC})/\bar{M}_n(\text{UV}) = 3.86$), perhaps as a result of aggregation.
- [16] The inhibitory activity of polymer **9** toward influenza virus A/PR/8/34 (H1N1) was determined with an ELISA. Thus, an ethanol solution with 1 nmol of GM $_3$ was added to each well of 96-microwell plates. The solvent was evaporated at 37°C, and the remaining binding sites on the wells were blocked for 12 h at 4°C with 200 μL of phosphate-buffered saline (PBS; 0.15 M NaCl, 8.1 mM Na_2HPO_4 , 1.5 mM NaH_2PO_4) that contained 2% bovine serum albumin (BSA). The wells were then washed five times with PBS. A series of dilutions, each by a factor of two, was prepared from a solution of the polymer (200 pmol) in 0.2% BSA-PBS. These dilute solutions were preincubated at 4°C for 2 h with 50 μL of the influenza virus suspension (32 hemagglutinin units (HAU) and then introduced into the wells. The plates were incubated at 4°C for 12 h, washed five times with PBS, and then incubated for 2 h at 4°C with a 1000-fold diluted 0.2% BSA-PBS solution of 50 μL of anti-influenza virus antibodies and treated at 4°C for 2 h with horse radish peroxidase (HRP)-conjugated protein A diluted 1000-fold with solution A. The virions bound to GM $_3$ and immobilized in the wells were detected with *o*-phenylenediamine (OPD) solution that contained 4 mg of OPD and 0.01% H_2O_2 in 100 mM of phosphate buffer (adjusted to pH 5.0 with citric acid). The reactions were terminated by addition of 4 N H_2SO_4 , and viral binding activities in the form of color development were determined at 492 nm (reference wavelength 630 nm). Serial dilutions (dilution factor two) of sialyl lactose (2 μmol), PGA (800 pmol), and lyso-GM $_3$ (20 nmol) were tested as controls in the manner described.
- [17] The HA trimer of H1 serotype influenza virus contains a total of 15 Trp residues.

Assembly of DNA/Fullerene Hybrid Materials**

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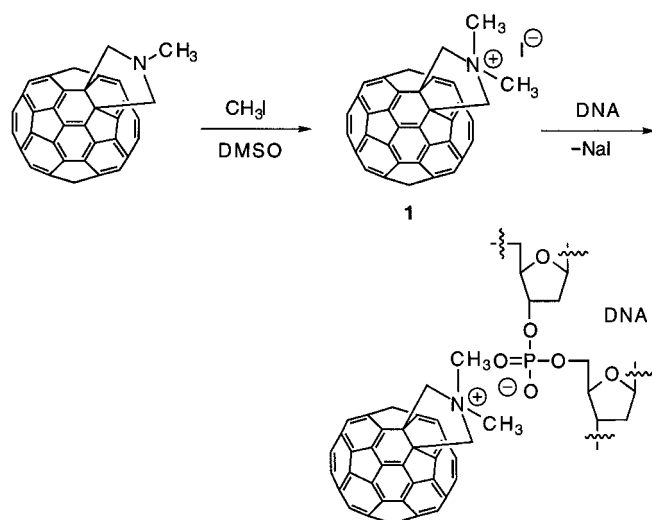
There are biochemical approaches to molecular structures of precisely defined dimensions ranging from 1 nm to 10 μm in length. Conversely, the synthesis of precisely defined unnatural molecular architectures beyond 25 nm in length is often unattainable due to solubility, material through-put, and characterization constraints.^[1] Therefore, as nanotechnological needs advance, syntheses could rely upon self-assembling strategies using natural scaffolds as templates for the construction of synthetic nanostructures.^[2] DNA is particularly

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well-suited for use as a molecular-based scaffold due to its structural regularity, its ability to reversibly assemble through hydrogen bonding, and the relative ease in obtaining materials of precise length well beyond the 25 nm regime. Most studies involving DNA self-assembly have focused on the duplex interactions between complementary DNA strands, the insertion of synthetic units through covalent tethering to specific nucleotides, or intercalation strategies. There are fewer studies involving the assembly of materials through electrostatic interactions on the phosphate groups along a DNA backbone.^[3] We sought to exploit these successive negatively charged groups to rapidly assemble cationic molecules along the exterior of a DNA template. Furthermore, the analysis of large nanostructured materials is often tedious. A notable exception is seen with carbon nanotubes where transmission electron microscopy (TEM) provides high-contrast images without the need for heavy-metal coating or staining (which can severely inhibit resolution).^[4] Thus, fullerene derivatives^[5] were chosen as the DNA complexing agents, and we report here a new and facile route to nanostructures constructed from DNA/fullerene hybrids that can be rapidly imaged using TEM.

*C*₆₀-*N,N*-Dimethylpyrrolidinium iodide (**1**) was synthesized to serve as the complexing agent (Scheme 1).^[6] Molecular



Scheme 1. DNA is complexed by cation exchange of compound **1** with DNA.

modeling indicated that the complexation of **1'** (the iodide-free fullerene) along successive phosphate groups of a DNA backbone is sterically permitted (Figure 1) and that the thickness of the double-stranded DNA/**1'** complex would be 5–6 nm. DNA/**1'** complexes were then prepared by mixing the DNA solution with a solution of **1** in dimethyl sulfoxide. Indeed, the hybrid DNA/fullerene-based nanoarchitectures were easily imaged by TEM without heavy metal. Figure 2 shows the excellent contrast that was obtained between the complexed DNA and the carbon-film background.

Initially, the vast amount of aggregation (and possible supercoiling) hindered us from measuring the length and diameter of individual plasmids. We suspected that the enhanced aggregation arose in part from favorable van der Waals interactions between the hydrophobic portions of the

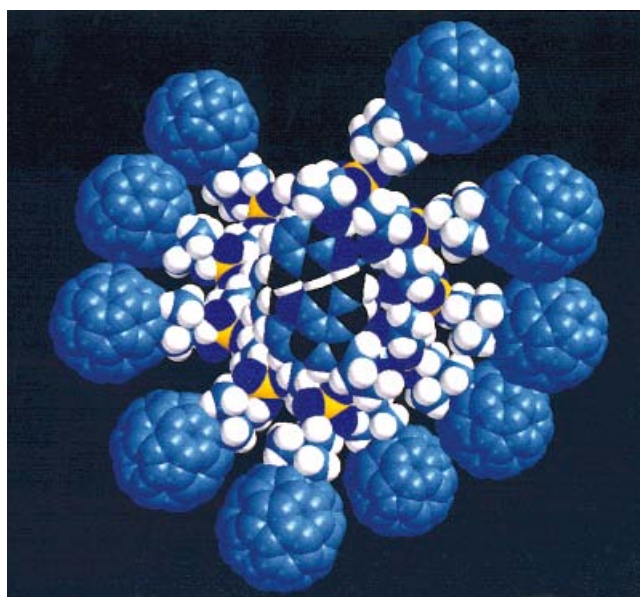


Figure 1. End-on view of the space-filling model of the CG duplex hexamer of DNA complexed with **1'**. Molecular modeling was performed with a Silicon Graphics Power Indigo2 work station employing MacroModel 4.5 for both structure drawing and energy minimization. Energy minimization of **1** was conducted with the MM2* force field, and energy minimization of oligonucleotides was conducted with the AMBER* force field. A third energy minimization calculation was then performed on the complex using the MM2* force field. All energy calculations were minimized over a large number of iterations to convergence at the local minima nearest in energy to the initial energies of the starting compounds.

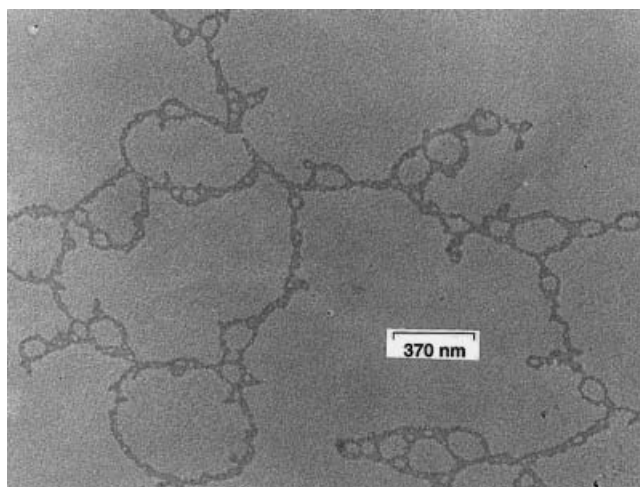


Figure 2. A solution of plasmid DNA (ϕ X174RFII, a popular electron microscopy standard, prerelaxed plasmid, 5386 bp, $10 \mu\text{g mL}^{-1}$, 10 mM Tris-HCl, pH 8.5) was mixed with a solution of *C*₆₀-*N,N*-dimethylpyrrolidinium iodide (5 mM in dimethyl sulfoxide, 150 equivalents of **1** per base) by gently shaking the mixture. After 4 h, 10 μL of the DNA/**1'** complex solution was placed on a microscope slide positioned in a petri dish that contained distilled water. The solution traveled down the slide and spread as it contacted the water surface. A carbon-film coated TEM grid was then streaked across the top of the water, and the DNA/**1'** complexes were absorbed. The grid was wicked dry with a piece of filter paper, and placed under vacuum at 30°C for 1 h. The grid was placed in a Hitachi H-8000 electron microscope and imaged at 100 k eV accelerating voltage.

fullerenes once the complexes were spread on water. We then screened a series of surfactants for their ability to lessen the fullerene attractive interactions in the DNA/**1'** complexes.

Surfactants were chosen that would not undergo cation exchange with the DNA/**1** complexes, for example, anionic, neutral, or zwitterionic surfactants. The surfactants were added to the water surface before the DNA/**1** complex solution (10 μ L). A neutral surfactant, Tween 20^[7] (a trihydroxyl-terminated oligoether), did not change the previously observed structure of the DNA/**1** complexes imaged by TEM; they remained highly aggregated. Coco Betaine ((Me₃SiO)₂MeSiO(CH₂CH₂O)_nH) kept the DNA/**1** complexes segregated, but they remained condensed (compacted) and highly supercoiled. The best results were obtained with Zonyl (CF₃(CF₂)₈CO₂Na), Admox 12 (CH₃(CH₂)₁₁N(CH₃)₂O), and Admox 14 (CH₃(CH₂)₁₃N(CH₃)₂O). Each of these surfactants availed segregated complexes. Instead of being completely aggregated (as in Figure 2), the complexes were in a condensed form in which the plasmids retained a contorted circular shape (Figure 3). Interestingly, the measured strand

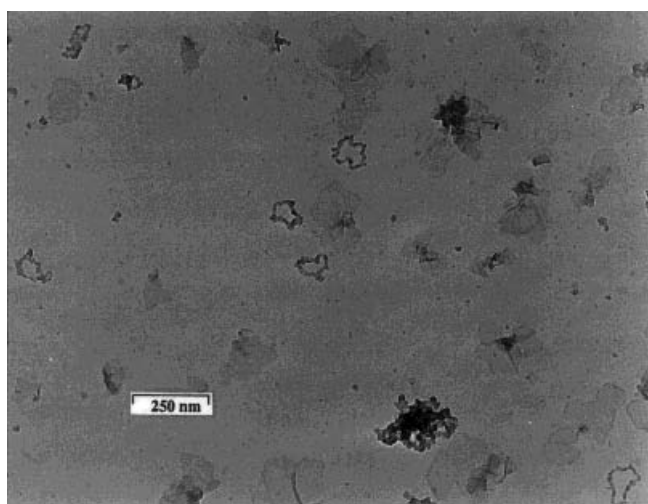


Figure 3. Image of condensed plasmid DNA (same as used for Figure 2) spread in the presence of Admox 14 (10 μ M). The other structures could be salts such as surfactant aggregates with **1** or Tris-HCl.

thicknesses of the plasmids in Figure 3 ranged between 15 and 30 nm. While the diameters of the DNA/**1** rings in Figure 3 ranged between 100 and 150 nm, the diameters of the prerelaxed plasmid DNA should be 580 nm if no condensation occurs;^[8] the measured diameter was therefore 1/4–1/6 the expected diameter. Although bacterial DNA does not

have histones, this condensed state is noteworthy since it is reminiscent of DNA packing by histones in chromatin where the typical diameters of the solenoid are 30 nm.^[9] The same effect was seen when we subjected linear DNA/**1** complexes to the surfactant series; again a condensed linear complex formed (Figure 4). The measured length of the

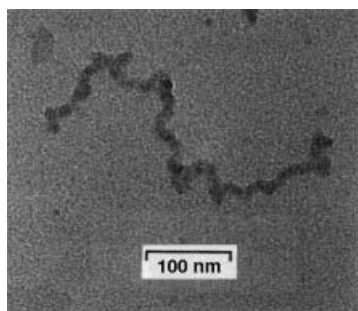


Figure 4. Image of condensed linear DNA (5686 bp, 1.93 μ m B-form length) spread in the presence of Admox 14 (10 μ M).

linear DNA/**1** complex is approximately 0.88 μ m, while its expected length is 1.93 μ m. The condensation is likely due to an intramolecular attraction of the fullerenes. We suspect the surfactant permits well-segregated DNA/**1** structures on water, thereby making the nonaggregated species abundant.

For the control experiments, we were unable to image DNA mixed with surfactants in the absence of **1**. Therefore, the surfactants do not complex with the DNA, or they do not provide enough electron density for imaging by TEM. Additionally, the use of **1** (or **1**/surfactant) without DNA does not afford these controlled nanostructures.

Although complexation of all the phosphates groups is sterically permitted (vide supra), the actual degree of substitution could not be assessed. Exhaustive substitution is unlikely, but the dramatic condensation insures sufficient fullerene density to permit contiguous imaging of the structure.

Use of a ferrocene-derived ammonium salt^[10] instead of **1** resulted in image contrast inferior to that obtained from the DNA/**1** complexes. Therefore, in spite of the metal atoms in the ferrocene salts, fullerenes remained superior as contrast agents.

DNA can be used as a framework for the assembly of fullerene materials through electrostatic interactions with the phosphate groups along the DNA backbone. Since exhaustive substitution on the phosphate moieties could not be verified, the DNA/fullerene complexes described here are not assured of a precise structure. However, this method provides a rapid one-step route to hybrid nanoarchitectures in size regimes inaccessible by traditional synthetic methods; therefore, this and analogous DNA-templating routes may prove to be of enormous utility. While we anticipate that complexation of other cationic species will also yield well-ordered nanostructures, fullerenes provide the necessary imaging contrast for TEM analysis. Further work to intramolecularly cross-link the fullerenes along the DNA backbones would provide a route to more rigid polyfullerenes.

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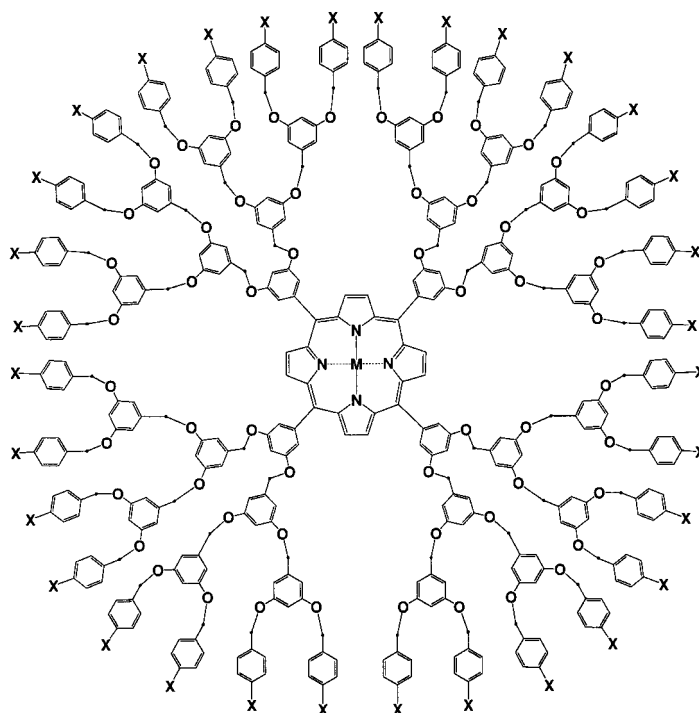
Electrostatic Assembly of Dendrimer Electrolytes: Negatively and Positively Charged Dendrimer Porphyrins**

Nobuyuki Tomioka, Daisuke Takasu, Toshie Takahashi, and Takuzo Aida*

Dendrimers are nanosized hyperbranched macromolecules with well-defined three-dimensional shapes^[1] and are potential building blocks for the construction of organized functional materials with nanometric precision. Therefore, it is important to develop a synthetic method that enables controlled spatial arrangement of functional dendrimers. Recently some conelike dendrimers (dendrons) were reported to self-assemble with the aid of van der Waals, hydrogen-bonding, and metal-ligating interactions into superstructures with spherical, disklike, and other configurations.^[2, 3] Here we present results of the first study on electrostatic assembly of dendrimer electrolytes.^[4] For this purpose we utilized negatively and positively charged dendrimers that contain within their frameworks a fluorescence probe in the form of a porphyrin (either as a free base or as a zinc complex).

We previously reported the convergent synthesis^[5] of a negatively charged, water-soluble dendrimer zinc porphyrin (32[–]DPZn) with 32 carboxylate ion functionalities on its exterior surface.^[6] This photofunctional macromolecule consists of a four-layered aryl ether dendrimer framework, and is expected to adopt a spherical conformation with an estimated

diameter of 4–5 nm.^[7] We have now synthesized from 32[HO₂C]DPZn^[6] a positively charged dendrimeric zinc porphyrin, 32[+]DPZn, with 32 ammonium ion functionalities on its periphery.



32[MeO ₂ C]DPH ₂ :	X = CO ₂ Me, M = H ₂
32[MeO ₂ C]DPZn:	X = CO ₂ Me, M = Zn
32[HO ₂ C]DPH ₂ :	X = CO ₂ H, M = H ₂
32[HO ₂ C]DPZn:	X = CO ₂ H, M = Zn
32[–]DPH ₂ :	X = CO ₂ [–] K ⁺ , M = H ₂
32[–]DPZn:	X = CO ₂ [–] K ⁺ , M = Zn
32[Me ₂ N]DPZn:	X = CONH(CH ₂) ₂ NMe ₂ , M = Zn
32[+]DPZn:	X = CONH(CH ₂) ₂ N ⁺ Me ₃ Cl [–] , M = Zn

To investigate the possibility of electrostatic assembly between the negatively and positively charged dendrimer electrolytes 32[–]DPH₂ (free-base porphyrin) and 32[+]DPZn, the transmittance at 500 nm^[8] was monitored when solutions of the two in phosphate buffer (pH 6.9, 1.5 μM) were mixed at 20 °C. As shown in Figure 1, the transmittance of the solution was highly dependent upon the molar ratio of the two dendrimer electrolytes, and it dropped sharply when the two concentrations were nearly equal. Fluorescence microscopy of a 100 μM phosphate buffer solution of either 32[–]DPZn (Figure 2a) or 32[+]DPZn excited at 400–440 nm (Soret bands) revealed strong, homogeneous emission from the entire solution. On the other hand, when the two solutions were mixed in an equimolar ratio ([32[–]DPZn]:[32[+]DPZn] = 1:1) the microscope image became dark, and large fluorescent aggregates (10–20 μm) were observed (Figure 2b). If this mixture was allowed to stand for a day at room temperature, the aggregates continued to grow and then precipitated out of the solution. If either 32[–]DPZn or 32[+]DPZn was present in excess, no aggregate formation was detected. Thus, 32[–]DPZn and

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[+] Mass spectra

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

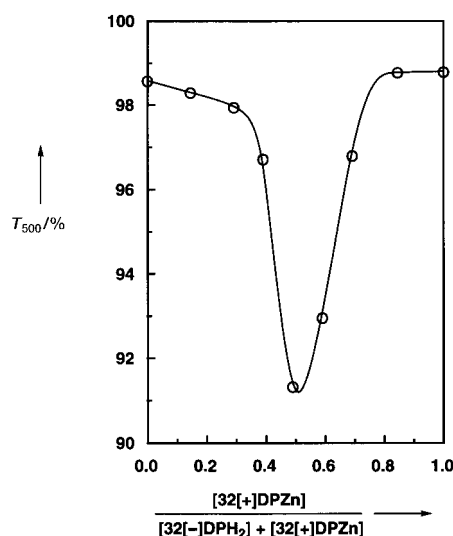


Figure 1. Change in transmittance at 500 nm when phosphate buffer solutions (pH 6.9, 1.5 μM) of 32[-]DPH₂ and 32[+]DPZn are mixed at 20 °C.^[8]

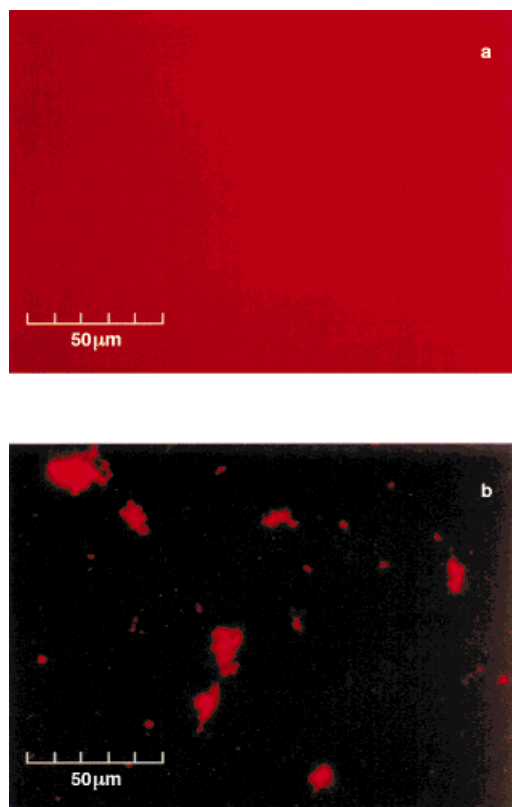


Figure 2. Fluorescence microscopic images of aqueous solutions (100 μm) of a) 32[-]DPZn and b) an equimolar mixture of 32[-]DPZn and 32[+]DPZn upon excitation at 400–440 nm (Soret band) at room temperature.

32[+]DPZn are able to assemble electrostatically in aqueous media to form a polyelectrolyte complex whose size is highly dependent upon the molar ratio of the negatively and positively charged dendrimers. This contrasts sharply with the general trend for electrostatic assembly of linear polyelectrolytes in aqueous media, where precipitates form over a wide range of molar ratios for the polyanion and polycation.

Mixtures of the two dendrimer electrolytes in alcoholic media do not form precipitates, irrespective of the composition. We therefore conducted spectroscopic investigations on interactions of these materials. First, a fluorescence-polarization profile was investigated for 32[-]DPH₂ upon addition of 32[+]DPZn.^[9] In general, excitation by polarized light of a chromophore with limited rotatability produces polarized fluorescence. The degree of polarization P is expressed as $(I_{\parallel} - I_{\perp}) / (I_{\parallel} + I_{\perp})$, where $I_{\parallel}$ and $I_{\perp}$ are fluorescence intensities of the parallel and perpendicular components. Thus, P should increase with the size of the fluorescent molecule or aggregate. Excitation with polarized light at 520 ± 1 nm (Q band) of a solution of 32[-]DPH₂ (1.25 μM) in methanolic KOH (0.1 M) at 20 °C caused the free-base porphyrin to emit polarized fluorescence at 654 and 718 nm, with $P(718 \text{ nm}) = 0.04$. Addition of 32[+]DPZn^[10] to this solution resulted in an increase in P , with a clear inflection point in the titration curve at a molar ratio [32[+]DPZn]:[32[-]DPH₂] = 4:1 (Figure 3 a, ●).^[11] On the other hand, when negatively charged 32[-]DPZn^[10] was mixed with 32[-]DPH₂ under otherwise identical conditions, P increased only slightly (○),^[12] where no saturation tendency was evident.

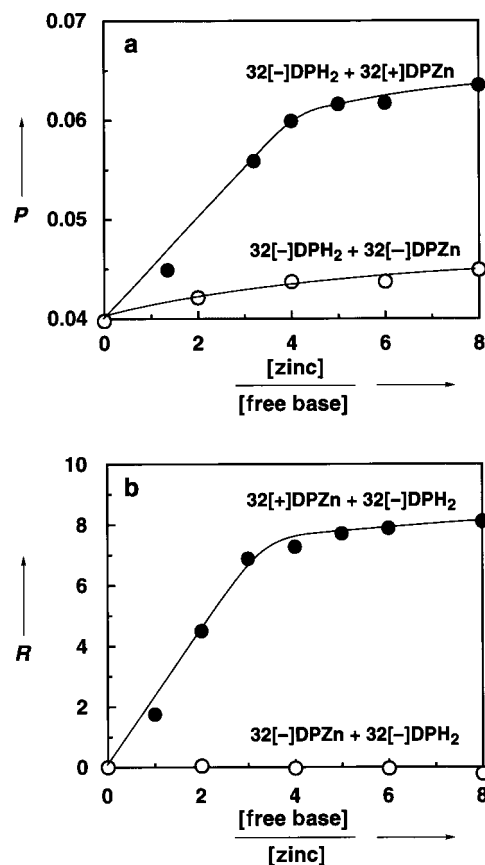


Figure 3. Fluorescence profiles of the systems 32[-]DPH₂/32[+]DPZn and 32[-]DPH₂/32[-]DPZn in deoxygenated methanolic KOH at 20 °C: a) fluorescence polarization $P = (I_{\parallel} - I_{\perp}) / (I_{\parallel} + I_{\perp})$ of 32[-]DPH₂ in the presence of 32[+]DPZn (●) or 32[-]DPZn (○) upon excitation at 520 ± 1 nm ($I_{\parallel}$ and $I_{\perp}$ represent fluorescence intensities of the parallel and perpendicular components, respectively) and b) degree of energy transfer $R = I_{\text{free base}} / I_{\text{zinc}}$ from 32[+]DPZn (●) observed at 718 and 613 nm) or 32[-]DPZn (○, observed at 718 and 608 nm) to 32[-]DPH₂ upon excitation at 439 ± 1 nm.^[14]

In the course of this study we also investigated the assembly of the dendrimer electrolytes with energy-transfer measurements as the probe. Zinc and free-base porphyrins, when they are in sufficiently close proximity, interact photochemically by energy transfer from the zinc compound to the free-base compound.^[13] We therefore studied the energy transfer communication between 32[+]DPZn as a donor (1.25 μM) and 32[-]DPH₂ as an acceptor in 0.1M methanolic KOH. When 32[+]DPZn alone was excited at 439 ± 1 nm (Soret band), the zinc porphyrin within the molecule fluoresced at 613 and 664 nm. In the presence of an equimolar amount of 32[-]DPH₂ the fluorescence bands from 32[+]DPZn decreased in intensity and new fluorescence bands appeared at 654 and 718 nm^[14] associated with 32[-]DPH₂ and suggestive of a singlet energy transfer from 32[+]DPZn to 32[-]DPH₂. A plot of the degree of energy transfer R (relative fluorescence intensity $I_{\text{free base}}/I_{\text{zinc}}$)^[14] again displays a clear saturation point at a molar ratio [32[-]DPH₂]:[32[+]DPZn] of approximately 4:1 (Figure 3b, ●). This indicates that there is a critical concentration of 32[-]DPH₂ for the efficient transfer of energy from 32[+]DPZn to 32[-]DPH₂. In sharp contrast, no energy transfer from 32[-]DPZn to 32[-]DPH₂ took place under the same conditions with the electrostatically repulsive combination 32[-]DPZn/32[-]DPH₂ (○). When one takes into account the saturation phenomenon in the fluorescence polarization (Figure 3a), the energy-transfer profile in Figure 3b (●) indicates that 32[+]DPZn can bind at most four molecules of 32[-]DPH₂ within a range that permits energy transfer (Scheme 1). For reference purposes, the energy-transfer profile of 32[+]DPZn was investigated with 5,10,15,20-tetrakis(4-carboxyphenyl)porphine (TCPPH₂), an anionic acceptor that bears only four negative charges. The fluorescence of 32[+]DPZn was in this case much less efficiently quenched by the addition of TCPPH₂ ($I_{\text{free base}}/I_{\text{zinc}} = 1.6$ at [TCPPH₂]:[32[+]DPZn] = 4:1).

Energy transfer rate constants are known to reflect the distance between donor and acceptor.^[13] We measured the fluorescence lifetime τ_0 of 32[+]DPZn in methanolic KOH (2.5 μM) at 20 °C to be 1.7 ns, which is close to that observed for 32[-]DPZn (1.4 ns)^[6] under the same conditions. In the presence of 32[-]DPH₂ (1.25 μM) as acceptor, a new, short-lived component ($\tau = 0.3$ ns, 70 %) appeared in the fluorescence-decay profile of 32[+]DPZn. The energy transfer rate constant k_{ENT} ($k_{\text{ENT}} = \tau^{-1} - \tau_0^{-1}$) was $3.0 \times 10^9 \text{ s}^{-1}$. Based on reported k_{ENT} values for fixed-distance energy-transfer sets,^[13] the observed k_{ENT} value is reasonable for a model in which the donor 32[+]DPZn and the acceptor 32[-]DPH₂ interact with each other directly.

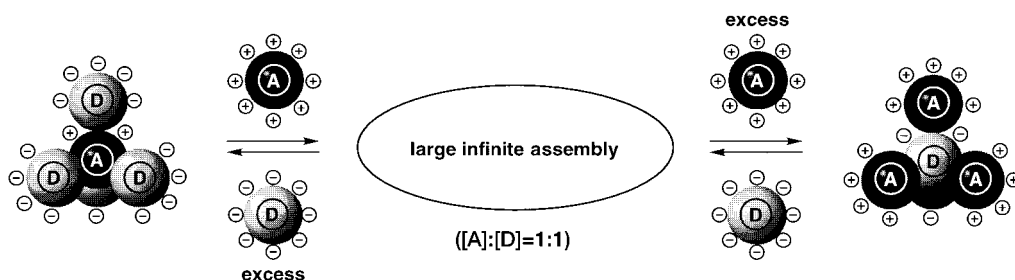
We have thus demonstrated that oppositely charged dendrimer electrolytes in protic media interact electrostatically to form an organized assembly (Scheme 1) in which the topology of functionalities within the molecule is established in advance. The present study therefore provides a new strategy for the controlled spatial arrangement, with nanometric precision, of two functionalities that communicate; this is a strategy that could contribute significantly toward progress in nanoscopic chemistry and nanomaterials science. Although dendrimer electrolytes bear a morphologic resemblance to ionic micelles, they are not subject to loss of their own structural identities when assembled electrostatically because they consist of single molecules characterized by covalent linkages.

Experimental Section

32[-]DPH₂: Methyl ester 32[MeO₂C]DPH₂^[15] was hydrolyzed with KOH in THF/water for 30 h. The reaction mixture was poured into acetic acid, and the resulting precipitate was collected by centrifugation, washed with dilute aqueous HCl, and freeze-dried to give 32[HO₂C]DPH₂. ¹H NMR (270 MHz, [D₆]DMSO, 80 °C): δ = 8.84 (s, 8H, pyrrole- β), 7.80, 7.32 (both d, ³ J = 8.10 Hz, 128H, Ar-*o*-H, Ar-*m*-H), 7.48 (s, 8H, Ar-*o*-H), 7.14 (s, 4H, Ar-*p*-H), 6.76 (d, ⁴ J = 2.7 Hz, 16H, Ar-*o*-H), 6.61 (d, ⁴ J = 2.7 Hz, 32H, Ar-*o*-H), 6.58 (s, 8H, Ar-*p*-H), 6.51 (d, ⁴ J = 2.7 Hz, 16H, Ar-*p*-H), 5.18 (s, 16H, OCH₂), 4.95 (s, 64H, OCH₂), 4.93 (s, 32H, OCH₂). 32[HO₂C]DPH₂ was dissolved in phosphate buffer (pH 6.8) or 0.1M KOH in methanol to generate 32[-]DPH₂. UV/Vis (KOH/MeOH): λ_{max} (lge) = 427 (5.29), 517.8, 553, 592, 648.4 nm; fluorescence (KOH/MeOH): λ = 654, 718 nm.

32[-]DPZn: 32[HO₂C]DPZn was prepared from 32[MeO₂C]DPZn by alkaline hydrolysis of the exterior methyl ester groups and isolated as described for 32[-]DPH₂. MALDI-TOF-MS (3-indolacrylic acid matrix): m/z = 8030 (calcd 8028); ¹H NMR (270 MHz, [D₆]DMSO, 80 °C): δ = 8.81 (s, 8H, pyrrole- β), 7.81, 7.33 (both d, ³ J = 8.34 Hz, 128H, Ar-*o*-H, Ar-*m*-H), 7.43 (s, 8H, Ar-*o*-H), 7.09 (s, 4H, Ar-*p*-H), 6.74 (s, 16H, Ar-*o*-H), 6.60 (s, 32H, Ar-*o*-H), 6.55 (s, 8H, Ar-*p*-H), 6.50 (s, 16H, Ar-*p*-H), 5.17 (s, 16H, OCH₂), 4.96 (s, 64H, OCH₂), 4.91 (s, 32H, OCH₂). ¹³C NMR (68 MHz, [D₆]DMSO, 20 °C): δ = 166.85 (CO₂H), 159.32, 159.10, 141.59, 139.24, 129.91, 129.22, 127.06, 106.30, 101.04 (aromatic C), 69.07, 68.58 (CH₂O). 32[HO₂C]DPZn was dissolved in 0.1M KOH/methanol to produce 32[-]DPZn.^[6] UV/Vis (KOH/MeOH): λ_{max} (lge) = 429.5 (5.44), 559.8, 600.4 nm; fluorescence (KOH/MeOH): λ = 608, 660 nm.

32[+]DPZn: A solution of 32[HO₂C]DPZn (20.4 mg, 2.54×10^{-3} mmol), 1-methyl-2-chloropyridinium iodide (427 mg, 1.67 mmol),^[16] and *N,N*-dimethylethylenediamine (0.7 mL, 6.3 mmol) in *N,N*-dimethylacetamide (10 mL, distilled) was heated at 50 °C for 6 d. The reaction mixture was then subjected to dialysis against water for 4 d and freeze-dried to give 32[Me₂N]DPZn (23.2 mg, 88.9 %). MALDI-TOF-MS (3-indolacrylic acid matrix): m/z = 10261 (calcd 10268); ¹H NMR (270 MHz, [D₆]DMSO, 80 °C): δ = 8.87 (s, 8H, pyrrole- β), 8.14 (s, 32H, amide-NH), 7.74, 7.32 (both d, ³ J = 8.23 Hz, 128H, Ar-*o*-H, Ar-*m*-H), 7.45 (s, 8H, Ar-*o*-H), 7.13 (s, 4H, Ar-*p*-H), 6.76 (s, 16H, Ar-*o*-H), 6.61 (s, 32H, Ar-*o*-H), 6.58 (s, 8H, Ar-*p*-H), 6.52 (s, 16H, Ar-*p*-H), 5.17 (s, 16H, OCH₂), 4.97 (s, 64H, OCH₂), 4.93 (s, 32H, OCH₂), 3.28 (br, 128H, NCH₂ and NHCH₂ overlapped with H₂O), 2.22 (s, 192H, NCH₃); ¹³C NMR (68 MHz, [D₆]DMSO, 20 °C): δ = 165.65 (CONH), 159.28, 159.06, 139.72, 139.11, 133.48, 127.15, 126.89, 106.37, 100.98 (aromatic C), 69.14, 68.60 (CH₂O), 57.46 (CH₂N), 44.35 (CH₃N), 36.52 (NHCH₂). Quantitative conversion of the acid into the amide function was confirmed by the absence of a signal at δ = 166.85. A mixture of 32[Me₂N]DPZn (15.2 mg, 1.48×10^{-3} mmol) and methyl iodide (0.60 mL, 9.6 mmol) in DMSO



Scheme 1. Schematic representation of the electrostatic interaction between negatively and positively charged dendrimer electrolytes. D represents a donor and A an acceptor in energy transfer.

(10 mL, distilled) was refluxed for 3 d. After removal of volatile fractions from the reaction mixture the residue was subjected to dialysis against pure water for 3 d and freeze-dried to give the iodide salt of 32[+]-DPZn (17.3 mg, 79.0%). This salt was then dialyzed for 2 d against saturated NaCl solution and an additional 2 d against pure water, after which it was freeze-dried. ¹H NMR (270 MHz, [D₆]DMSO, 80 °C): δ = 8.97 (s, 8H, pyrrole-β), 8.73 (s, 32H, amide-NH), 7.84, 7.43 (d, ³J = 7.42 Hz, 128H, Ar-o-H, Ar-m-H), 7.51 (s, 8H, Ar-o-H), 7.23 (br s, 4H, Ar-p-H), 6.87 (s, 16H, Ar-o-H), 6.72 (s, 32H, Ar-o-H), 6.66 (s, 8H, Ar-p-H), 6.57 (s, 16H, Ar-p-H), 5.27 (s, 16H, OCH₂), 5.07 (s, 64H, OCH₂), 5.01 (s, 32H, OCH₂), 3.68 (br q, 64H, CH₂), 3.54 (br t, 64H, CH₂), 3.14 (s, 288H, NCH₃); ¹³C NMR (68 MHz, [D₆]DMSO, 20 °C): δ = 166.02 (CONH), 159.30, 159.10, 140.25, 139.18, 132.82, 127.20, 106.68, 100.95 (aromatic C), 68.68 (CH₂O), 63.68 (CH₂N), 52.57 (CH₃N), 33.75 (NHCH₃); UV/Vis (KOH/MeOH): λ_{max} (lgε) = 436.5 (5.49), 563, 608 nm; fluorescence (KOH/MeOH): λ = 613, 664 nm.

Electronic absorption spectra were recorded with a Jasco Model V-560 UV/Vis spectrometer. Fluorescence-polarization and energy-transfer experiments were performed at 20 °C with a Jasco Model FP-777 fluorescence spectrometer. In the energy-transfer experiments with 32[-]DPH₂ as acceptor, undesirable contamination of the fluorescence bands as a result of direct excitation of the acceptor was evaluated by a control experiment without donor under otherwise identical conditions. The spectrum that resulted was subtracted from the overall fluorescence spectrum for the donor/acceptor systems. The spectral profile of 32[-]DPH₂ in the control experiment was shown to obey the Lambert–Beer law.

Fluorescence lifetimes were measured in deoxygenated 0.1M methanolic KOH at 20 °C with a Hamamatsu Model C4780 picosecond fluorescence lifetime measuring system equipped with a Model C4334 streak scope and a N₂ laser pumped coumarin 440 dye laser as excitation source. The N₂ laser was an LN120C2 device (15 Hz, peak width (FWHM) 350 ps, 10 mJ per pulse), and the excitation wavelength was 430 nm. Fluorescence bands were isolated from scattered laser light by a 600 nm glass cutoff filter. Emission was collected in the wavelength range 600–680 nm and analyzed with the program Photolumi version 2.4.4 after deconvolution of the instrument-response function (time resolution 50 ps).

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A Synthetic Cation-Transporting Calix[4]arene Derivative Active in Phospholipid Bilayers**

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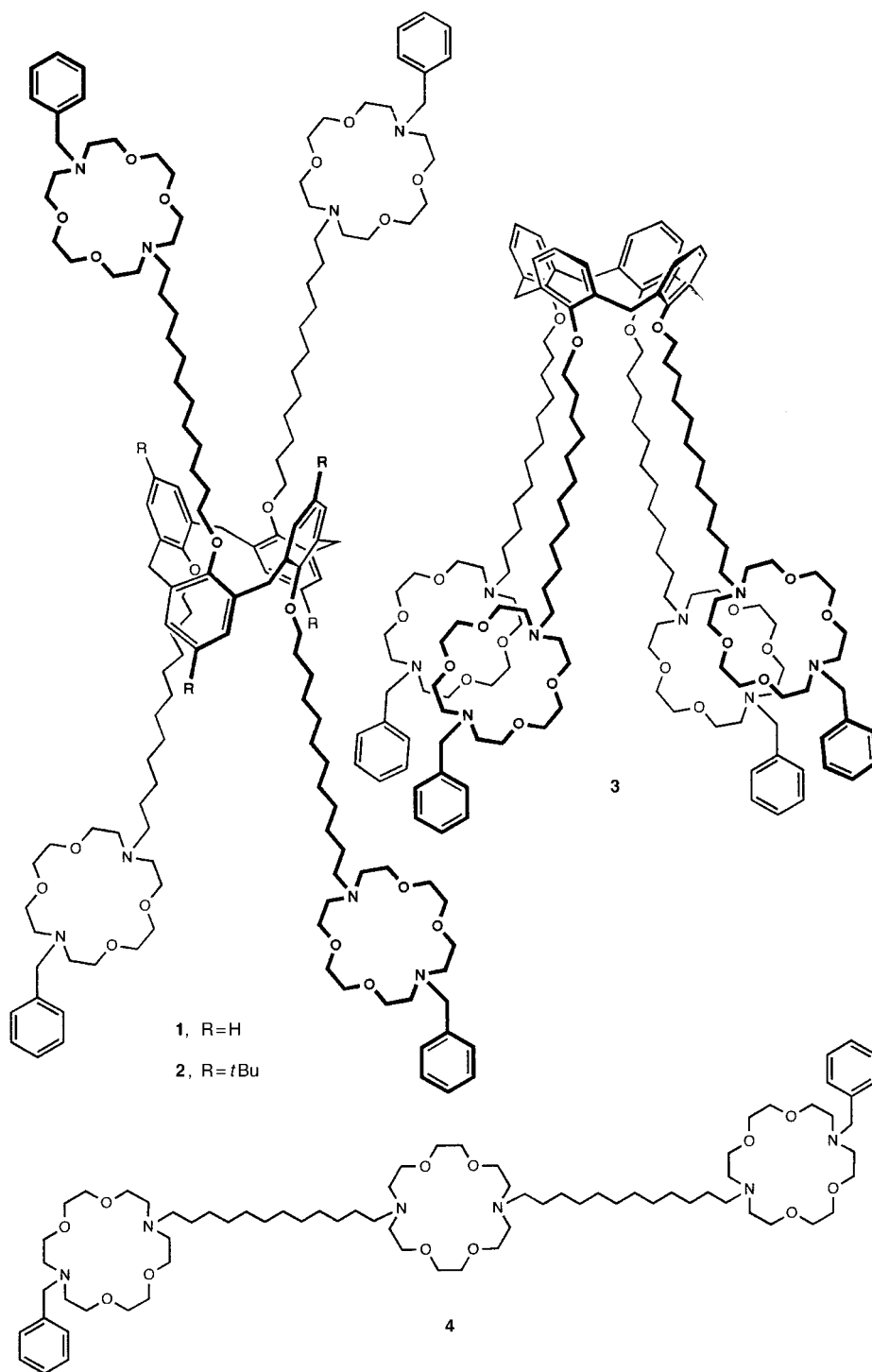
The transport of cations through bilayer barrier membranes is a ubiquitous biological process, and one of the most critical for sustaining life. Cation transport in vivo is usually mediated by proteins having one or more transmembrane helices that organize into pores. Increasing evidence suggests that channel function may also be achieved by compounds such as the remarkable C peptide.^[1] Although a vast amount is known about the biophysics of membrane transport, much of this information is descriptive and does not reveal mechanistic details;^[2,3] how transport occurs is simply not understood at the molecular level. Thus, several model ion transporters have been devised, including short-chain or “minimalist” peptides^[4] and a variety of synthetic organic compounds such as tubelike structures, “half-channel” elements, single-strand compounds,^[5,6] and the tris(macrocylic) channel model **4** that we devised.^[7] Compound **4** has proved to be an effective conductor of Na⁺ ions.^[7] The two distal diaza[18]crown-6 macrocycles serve as headgroups in the amphiphilic sense, and as entry and exit points for cations traversing the bilayer.^[8] Passage of the transient cation through the medial macrocycle, however, is not necessary.^[7]

We describe herein two new channel compounds **1** and **2** having a calix[4]arene central unit in a 1,3-*alternate* conformation. Passage of cations through the center of such a rigid

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framework has recently been demonstrated.^[9] If successful, the movement of the cation through the calix would constitute a useful strategy for the design of synthetic channels.^[10] In compound **2** the calix[4]arene is substituted by bulky *tert*-butyl groups. For comparison, the cone derivative of **1** (i.e., **3**) was also prepared and studied. In all cases, dodecyl chains terminated in 10-benzyl-1,10-diaza[18]crown-6 units were attached to each of the calixarene phenol groups to allow direct comparison with the already studied tris(macrocycle) channel compound **4**.

Compounds **1–3** was synthesized by attachment of four THP-protected (THP = 2-tetrahydropyranyl) 12-bromododecanol chains to the lower rim of the corresponding calix[4]arene ($\text{Cs}_2\text{CO}_3/\text{DMF}$ for the 1,3-*alternate* conformation, NaH for the cone conformation).^[11] The chains were deprotected and brominated ($\text{CBr}_4/\text{PPh}_3$), and the resulting tetrabromo derivatives were allowed to react with 10-benzyl-1,10-diaza[18]crown-6 to afford channels **1** and **2** as waxy solids in 42% yield. Cone compound **3** was obtained similarly in 26% yield.^[12]

Since the ring does not invert at room temperature, two arms must radiate from either side of the central platform. The diazacrown units are presumed to be head-groups that stabilize the sidearms in an extended arrangement at the membrane boundaries, but whether the crowns are perpendicular or parallel to the lipid axis is unknown.^[13] Thus, the overall length of the channel lies between 34 and 60 Å and is enough to span the lipid portion of a typical bilayer membrane (normally about 30 Å thick).

The ability of calix[4]arene compounds **1–3** to conduct cations was assessed by using the planar bilayer conductance (PBC) technique.^[14] In this method, a pinhole in a Teflon disk is covered by a phospholipid mixture^[15] to create a planar bilayer membrane (black lipid). Addition of **1** or **2** (1 µL of a 1 µM solution, i.e., 1 pmol of substance) in the bilayer dramatically increased either the Na^+ or K^+ permeability of the previously nonpermeable membrane. Data on sodium transport obtained for **1** and **2** at +100 mV are shown in Figure 1. Doubling the amount of **1** or **2** added increased the intensities and frequencies of the

observed transitions. Both compounds exhibited “burst” events of nearly 300 pS. These intense ion fluxes normally persisted less than a second, but the presumed overlap of several conductance events resulted in occasional episodes of longer than 3 s.

Compound **3**, the “control” structure having the cone conformation, did not conduct cations when added to the bilayer in concentrations as high as 100 pmol (2 µL of a 50 µM solution) under otherwise identical conditions. Inspection of CPK models showed that **3** is too short to span the

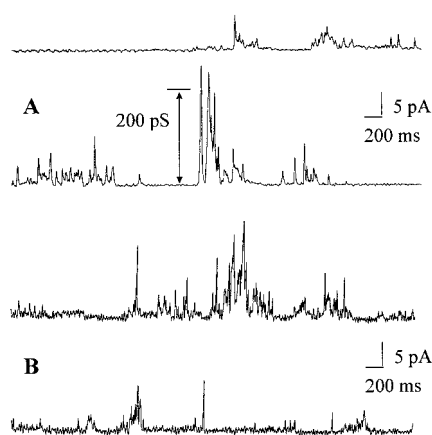


Figure 1. Planar bilayer conductance data for **1** (A) and **2** (B; 1 pmol of each in THF); [NaCl] = 0.5 M, +100 mV applied potential.

phospholipid bilayer. On the other hand, when amounts of **1**–**3** approaching 1 nmol were added, the membranes apparently lost their well-defined structure and exhibited erratic permeability behavior.

The bursts shown in Figure 1 are reminiscent of the behavior seen in bilayers in the absence of any channel former when very high voltages (≥ 200 mV) are applied across the membrane (electroporation experiments).^[16] To discount this possibility, additional data were collected in separate runs conducted at ± 40 , ± 60 , ± 80 , and ± 100 mV (data for **1** at ± 40 mV are shown in Figure 2). The observed pattern of current amplitudes was proportional to that recorded at 100 mV, showing that the channels behave generally as expected for a symmetrical ion transporter.

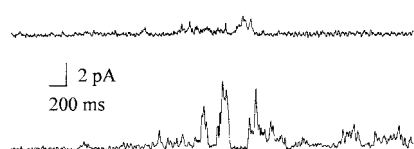


Figure 2. Planar bilayer conductance data for **1** (1 pmol in THF); [NaCl] = 0.5 M, +40 mV applied potential.

Compound **4**, the tris(macrocyclic), typically shows single open–close transitions in the PBC experiment.^[7] The amplitudes of these transitions are normally integral and range between 10 and 20 pS, a value typical for gramicidin and many natural sodium-transporting proteins. The behavior of novel channels **1** and **2** is dramatically different in two senses. Not only are the amplitudes much higher (spiking to levels of hundreds of pS), but bursts rather than flat-topped integral transitions are observed. Similar behavior has recently been observed for an oligo-THF channel model system.^[6]

The unusual behavior of **1** and **2** can be rationalized by considering their overall structures. In the tris(macrocyclic) channel model **4**, a single crown ether group is thought to reside at each membrane surface to form a cation-conducting nanotube. In contrast, in **1** and **2** the two crown ether groups on each side may rapidly exchange positions; this leads, on average, to a much larger opening in the membrane. If the

sidearms sweep out a conical surface in each direction from the bilayer midplane, conductance should be quite high, and the great flexibility of the system would lead to the observed spikes.

Does either Na^+ or K^+ pass through the hole of calix[4]-arenes **1** and **2**? In the solid state, the mean distance between two aryl groups in a calix[4]arene in the 1,3-*alternate* conformation is about 5.9 Å (between the centers of the aryl ring).^[17] This value is compatible with those from theoretical calculations on ideally sandwiched benzene- M^+ -benzene arrangements, where $\text{M}^+ = \text{Na}^+$ (4.96 Å) or K^+ (5.84 Å).^[18] Shinkai and co-workers^[9] have shown that cations can pass through a 1,3-*alternate* calix[4]arene. However, in the case of tetra-*tert*-butyl derivative **2**, CPK models show that the core is completely blocked at both sides of the 1,3-*alternate* conformation when the aryl rings are parallel to each other. Thus, to permit cations to penetrate the calix with any significant frequency the conformation must distort markedly in a sequential way: Two rings open slightly while the others close accordingly. The reverse process should then occur at the other end of the hole to allow the cations to exit. The essential similarity of the PBC traces for Na^+ and K^+ with both **1** and **2** suggests that cations cross the bilayer by similar mechanisms, and makes it highly unlikely that either Na^+ or K^+ cations pass through the calix. In other words, since passage through the calix is hampered in **2**, ions must pass outside the rings *also* in **1**. This does not prove that cations never penetrate the calix, but if the phenomenon were favored evidence for it would be expected from experiments such as this one.

In conclusion, a novel class of cation-conducting channels, with high conductance levels for both Na^+ and K^+ cations, has been developed. In these compounds, however, the core calix[4]arene in 1,3-*alternate* conformation behaves as a preorganized platform that organizes the tails at either side rather than acting as a tube for ions. Channels have been designed around other platforms—such as self-assembling cyclic peptides^[6f] or cyclodextrins^[6c]—and could utilize the wider, more flexible, calix[6]arenes. These higher oligomers of calixarenes are currently under investigation.

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X-Ray Structural Analysis of a Novel Lithium Hydride/Lithium *tert*-Butoxide Superaggregate: Li₃₃H₁₇(OtBu)₁₆**

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The high lattice energy of lithium hydride drastically reduces its reactivity and is responsible for its insolubility in organic solvents.^[1,2] Consequently, any form of lithium hydride, whether complexed by ligands or uncomplexed, is an amorphous solid. Crystal structures of lithium hydride or of mixed aggregates containing lithium hydride have not been reported. We have recently provided evidence that the photochemical and thermal decomposition^[3] of *tert*-butyllithium/lithium *tert*-butoxide mixtures^[4] (molar ratio 3:7) in cyclopentane leads to highly reactive, hydrocarbon-soluble LiH^[5] in the form of mixed LiH/LiOtBu aggregates.^[6] Precipitation of amorphous lithium hydride from such mixtures is apparently prevented by the excess of lithium *tert*-butoxide, which assists in solubilizing the LiH by incorporating it in mixed aggregates.^[7,8] Previous NMR spectroscopic studies revealed that the photochemical decomposition product is the decamer Li₁₀H(OtBu)₉, while the thermal decomposition product is dodecameric Li₁₂H(OtBu)₁₁.^[6] It is noteworthy that these mixed aggregates form only at high alcoholate:alkyllithium ratios (ROLi:RLi $\geq$ 7:3), that is, when a large excess of *tert*-butoxide ligands is present. At lower ROLi:RLi ratios, amorphous lithium hydride precipitates from solution.

X-ray structural analyses of crystals grown from photolyzed *t*BuOLi/*t*BuLi mixtures (ca. 7:3) showed the presence of the hydride-rich superaggregate Li₃₃H₁₇(OtBu)₁₆ (**1**, Figure 1).^[9] The synthesis is reproducible and, under the conditions chosen, exclusively yields crystals of **1**. To our knowledge, this is the largest lithium-containing aggregate so far known. The structural framework consists of fused cubic subunits (Figure 2), whose arrangement to form an infinite lattice is disrupted by the incorporation of the sterically demanding *tert*-butoxide groups. The inner core of the aggregate is hydride-rich, while in the outer shell *tert*-butoxide ligands are

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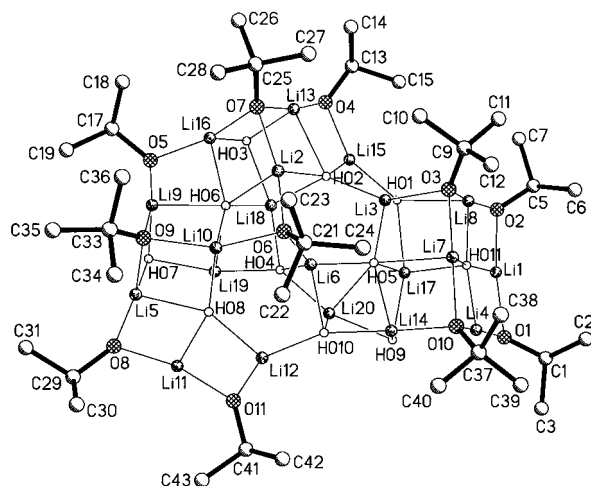


Figure 1. Asymmetric unit of **1**: Li–H distances 181(4)–224(4) pm; Li–O distances 185.1(11)–203.5(8) pm.

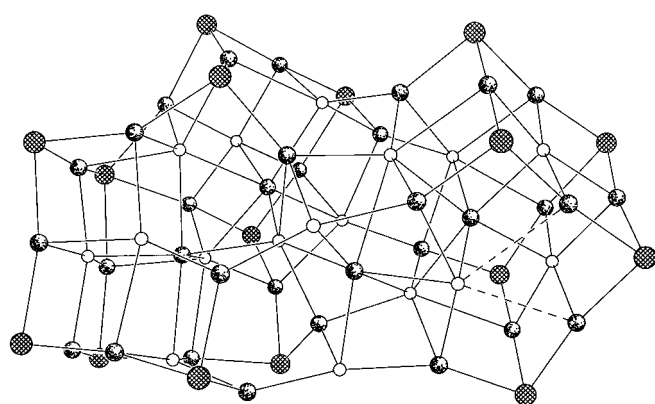


Figure 2. The Li–H–O framework of **1** (*tert*-butyl groups are omitted for clarity). Empty, shaded, and hatched circles represent hydrogen, lithium, and oxygen atoms, respectively. The two dashed lines represent long-range electrostatic Li...H interactions.

abundant. The *tert*-butoxide ligands at the periphery provide a nonpolar cover, which makes the aggregate highly hydrocarbon-soluble. Similar lipophilically wrapped polyion aggregates were recently discussed by Bock et al.^[10] The arrangement of **1** within the lattice provides channels in which solvent molecules (cyclopentane) are incorporated (Figure 3).

Figure 2 shows the Li–H–O framework of **1** without the *tert*-butyl groups. It has C_s symmetry and is generated from the asymmetric unit by a mirror plane (the plane of the page in Figure 1). Among the numerous atoms in special positions are Li1, Li11, Li15, and Li17–Li20. The lithium cations exhibit a variety of coordination modes (Figure 2) that range from three- and four-coordinate to six-coordinate. The four three-coordinate lithium cations (Li4, Li12, and their symmetry equivalents) are located at the periphery of the aggregate where the fused cubic cells are disrupted; these cations are surrounded by one hydride ion and two *tert*-butoxide ligands or by two hydride ions and one *tert*-butoxide ligand. The abundant four-coordinate lithium cations at the periphery of the cluster (Li1–Li16 and their symmetry equivalents, except Li4 and Li12 and their symmetry equivalents) are surrounded by two hydride ions and two *tert*-butoxide ligands or by three

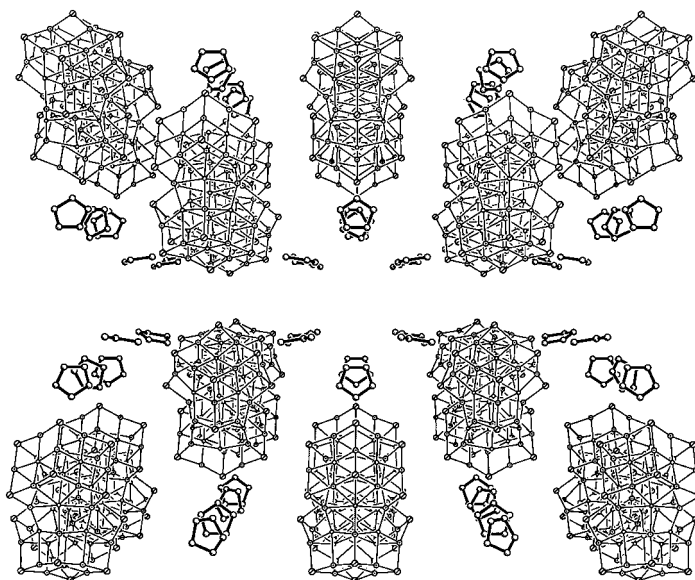


Figure 3. View of the packing of **1** in the lattice illustrating the incorporation of uncoordinated cyclopentane solvent molecules in channels between isolated aggregates (*tert*-butyl groups are omitted for clarity).

hydride ions and one *tert*-butoxide group. The six-coordinate lithium cations (Li17–Li20) are located in the core of the aggregate and are exclusively encapsulated by hydride ions in a distorted octahedral arrangement. With the exception of H09 and H010, which are four-coordinate, all other hydride ions are surrounded by five or six lithium cations.

A wide range of Li–H distances (181(4)–224(4) pm) is found in **1**. The shortest Li–H distance (Li3–H05 181(4) pm) in **1** is slightly longer than that in $[(\text{Me}_3\text{Si})_2\text{NAI}(\text{H}_3\text{Li} \cdot 2\text{Et}_2\text{O})_2]$ (177.7 pm)^[11] and significantly shorter than those in the LiH lattice (204.0 pm),^[12] LiAlH_4 (188–216 pm),^[13] and $[\text{LiAlH}(\text{NEt}_2)_3 \cdot n\text{THF}]$ (195.1 pm).^[14] Shorter Li–H distances are known for $(t\text{Bu}_3\text{AlHLi})_2$ (168 pm)^[15] and for molecular LiH^[16] in the gas phase (159.6 pm). The Li–O distances range between 185.1(11) and 203.5(8) pm, values typical of lithium alkoxides and lithium enolates in which three cations are μ^3 -bridged by an oxygen anion.^[17]

Aggregates such as **1** result when lithium hydride is trapped in its nascent state by self-assembly with lithium *tert*-butoxide. The energetically favorable, largely ionic $\text{Li}^{\delta+} \cdots \text{H}^{\delta-}$ and $\text{Li}^{\delta+} \cdots \text{O}^{\delta-}$ interactions contribute to the stability of the cluster. Further growth of the superaggregate is presumably prevented by van der Waals interaction of the *tert*-butyl groups in the lipophilic hydrocarbon shell.

Complexes such as **1** can be regarded as models of superbasic mixtures or “unimetal superbases” (“complex bases”).^[5d, 18] Solutions of LiH/LiOtBu react smoothly with 3,3-dimethyl-2-butanone (pinacolone) to give the corresponding enolate and hydrogen gas, whereas commercially available lithium hydride is completely unreactive.^[5a, b] The ease of preparation of this system offers considerable advantages over other superactive lithium hydrides.^[5a–c] Mixtures of *tert*-butyllithium with protic amines or silazanes may yield the corresponding LiH/amide or LiH/silazide aggregates upon photolysis. The strategy used to synthesize **1** could provide a general, facile route to a variety of superactive, hydrocarbon-

soluble lithium hydride reagents. This is currently under investigation.

Experimental Section

1: All manipulations were performed by standard Schlenk and needle/septum techniques under an argon atmosphere. All solvents were dried over Na/K alloy and freshly distilled before use.

At -40°C , *tert*-butyllithium (26 mL, 1.5 M in pentane, 39 mmol) was added dropwise to a solution of *tert*-butanol (2.5 mL, 26.5 mmol; dried over MgSO_4) in cyclopentane (10 mL). The reaction mixture was allowed to warm to room temperature and then irradiated for 7 h with a medium-pressure Hanovia Hg-vapor lamp (purchased from ACE). Ice water was used as an external coolant. The resulting pale yellow solution was concentrated in vacuo and layered with *n*-pentane. Crystals suitable for X-ray analysis were obtained after several weeks at -90°C . The crystals are extremely temperature-sensitive and rapidly disintegrate when handled outside the mother liquor.

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A Novel Copper Chelate Catalyzed Ring Closure Reaction of 1,2-Bisketenes with Alcohols To Give 5-Alkoxy-2,3-dihydrofuran-2-ones**

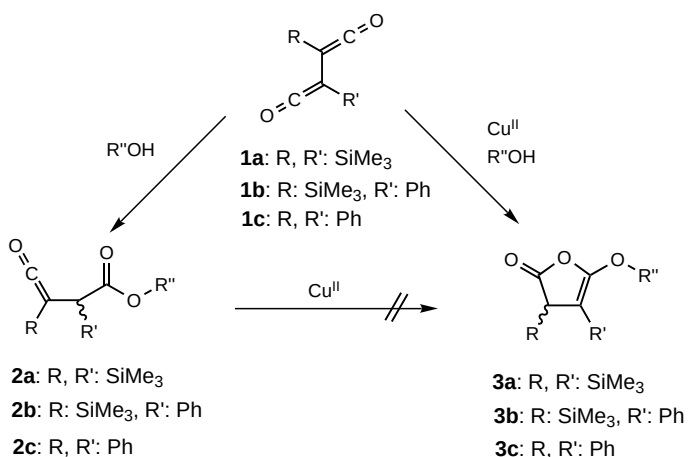
Michael M. Dejmek and Rüdiger Selke*

In memoriam Horst Pracejus

In the course of investigations with 1,2-bisketenes **1a–c**, which are readily accessible by a method developed by Tidwell et al.,^[1] and their reaction with alcohols or phenols, respectively, we have discovered a new chelate catalyzed ring closure reaction that results in the formation of 5-alkoxy- or 5-aryloxy-2,3-dihydrofuran-2-ones **3a–c**. Up to now, only two compounds are known in which a comparable structure has been established with some certainty.^[2] An efficient synthesis of this class of very reactive, β,γ -unsaturated dihydrofuran-2-ones with ketene acetal substructure is of particular interest, because numerous similarly structured, mostly α,β -unsaturated dihydrofuran-2-ones show biomimetic activity^[3] for instance as antibiotics,^[3a] cancerostatics,^[3b,c] herbicides,^[3a,d,e] or anthelmintics.^[3a] Furthermore, they are also of considerable importance as part of digitalis glycosides.^[3f] As the only known 5-aryloxy-substituted $\Delta^{\beta,\gamma}$ -butenolide also displays antibiotic activity,^[2b] interesting biological activities can also be expected from the new compounds.

One special feature of the newly discovered ring closure reaction is that until now it only succeeds catalytically and with very high selectivity. Metal complexes of ketenes as possible intermediates in catalytic reactions, such as the fixation of carbon dioxide or the CO activation, have been investigated intensively.^[4] Except for a few chelate-mediated conversions of ketenes, which have mostly been stoichiometric,^[5] the reaction of bisketenes mediated by complexes has not been described. Until now only interesting ring closure reactions of bisallenenes, ketene allenenes, and vinyl allenenes, which frequently involve carbon monoxide, had been reported.^[6] A bisketene complex $[\eta^5\text{-CpCo}(\eta^4\text{-bisketene})]$ has also been isolated.^[7] Here we present the first metal complex catalyzed conversion of 1,2-bisketenes (Scheme 1).

As in an early study by Samtleben and Pracejus^[8] copper(II) acetylacetonate had been employed successfully as catalyst for the alcoholysis of monoketenes, we started our investigations with this square-planar complex. However, there was no reaction between bisketene **1a** and ethanol in the presence of this catalyst. In contrast, the copper(II) complex of hydroxy-methylene camphor **7**,^[9] which in solution adopts a distorted tetrahedral conformation, catalyzed the conversion of the bisketene **1a** with ethanol. However, rather than the expected alcoholysis product **2a** ($R'' = \text{Et}$), cyclization occurred to give



Scheme 1. Reaction of bisketenes **1** with alcohols.

the 2,3-dihydrofuran-2-one **3a** ($R'' = \text{Et}$) (Scheme 1). We were able to prove that this reaction does not proceed via the ketenyl ester but directly from the 1,2-bisketene to the dihydrofuran-2-one.

We achieved the highest selectivity (99% at a conversion of 98%) with the complex of the Schiff base **8** (Table 1).^[10] The common feature of the most successful catalysts for this

Table 1. Influence of the catalyst on the reaction of **1a** with ethanol to give **3a**.^[a]

Ligand LH (or LH ₂)	Catalyst	Conversion [%]	Selectivity [%] 3a ^[13]
6	[Cu ^{II} L ₂]	< 1	–
7	[Cu ^{II} L ₂]	95	92
8	[Cu ^{II} L ₂]	98	99
9	[Cu ^{II} L ₂]	< 1	–
10	[Cu ^{II} L] [Ni ^{II} L] [Co ^{II} L] [Pd ^{II} L]	86 < 1 < 1 < 1	83 – – –
11	[Cu ^{II} L]	82	78
12 L = C ₈ H ₁₂	[Cu ^I (cod) ₂][BF ₄]	85	83
13 L = Ph ₂ PCH ₂ CH ₂ PPh ₂	[Cu ^I (dppe) ₂ Cl] ₂	36	72

[a] Reaction conditions: 3 mL of a toluene solution—0.1 M of bisketene and 0.11 M of ethanol—was stirred with 3.3 mol % catalyst (prepared as a solid) for 12 h at 25 °C.

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reaction is a distorted tetrahedral structure in solution. The ring-closing reaction also took place with the tetrahedral copper(I) complexes of (*Z,Z*)-cycloocta-1,5-diene (cod) **12** or 1,2-bis(diphenylphosphanyl)ethane (dppe) **13**, whereas no conversion was observed in the presence of the square-planar bisligand complex of 1,8-hydroxyquinoline **9** or with complexes with salene or porphyrin type ligands.

Table 2. Influence of the solvent on the reaction of **1a** with ethanol; catalyst [CuL₂], LH = **8**.^[a]

Solvent	Conversion [%]	Selectivity [%]
<i>n</i> -hexane	99	99
toluene	98	99
CH ₂ Cl ₂	85	89
THF	23	45
DMF	<1	–

[a] Reaction conditions see Table 1.

Since pseudo-square-planar monoligand chelates of tridentate Schiff bases derived from salicylic aldehyde and 1,2-amino alcohols **10**^[11] or α -amino acids **11**^[12] can be used as catalysts, we concluded that the metal center either has two free coordination sites in *cis* position or that these—as in the case of the tetrahedral complexes—can be readily created. Thus we assume the crucial step in the reaction to be the nucleophilic attack of the hydroxylic component at a copperasketene complex that has a structure analogous to that described for a cobalt 1,2-basketene chelate.^[7] However, attempts to react this cobalt basketene complex with alcohol to give the dihydrofuran-2-one failed; the only metal to catalyze the cyclization was copper; chelates of 14 other metals were tested (Ti, Cr, Mn, Fe, Co, Ni, Zn, Mo, Rh, Pd, Ag, Cd, Pt, Pb) but all of them turned out to be inactive.

Apolar solvents are especially suitable as reaction medium (see Table 2); with increasing coordination ability of the solvent, turnover and selectivity decrease.^[13]

The structure of the component bearing the hydroxy group has no significant influence on the reaction. Thus, the ring closure was achieved with all 50 alcohols used; the conversion with tertiary alcohols is less than with primary and secondary alcohols; however, the selectivities remain higher than 95 % and decrease only slightly with phenols (Table 3). The latter is presumably attributed to the higher acidity of the phenols which in turn could result in a competing acid-catalyzed reaction, leading exclusively to the ketenyl esters **2a–c**.

Use of the distinctly more reactive unsymmetrically substituted basketene **1b** had only a minor influence on the yield

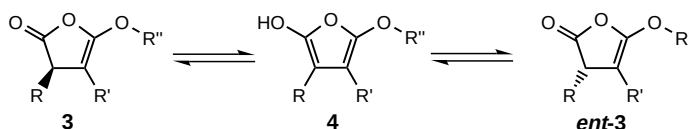
(see Table 4); the regioisomer **3b** was the only detectable product of the reaction. The further increased reactivity of the basketene **1c** for the noncatalyzed reaction to the ketenyl ester

Table 4. Reaction of the basketenes **1** with ethanol; catalyst [CuL₂], LH = **8**.^[a]

Basketene	R	R'	Conversion [%]	Selectivity [%]
1a	SiMe ₃	SiMe ₃	99	99
1b	Ph	SiMe ₃	99	91
1c	Ph	Ph	92	65

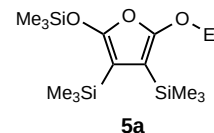
[a] Reaction conditions see Table 1; compound **1a** was generated thermally as a solid, **1b, c** by irradiation at 350 nm *in situ*.^[1b]

2c led to a decrease in selectivity so that only 65 % of the desired 2,3-dihydrofuranone **3c** could be obtained. It was not possible to conduct the reaction enantioselectively by using chiral catalysts. The reason for this could be a racemization, in which the 2,3-dihydrofuran-2-ones **3a–c** interconvert through the furanes **4** (Scheme 2). We were able to trap furane **4a** as isolable trimethylsilyl ether **5a**.



Scheme 2. Racemization of the 2,3-dihydrofuranones **3**.

These new findings that copper complexes open up specifically a formerly unknown reaction pathway for the reaction of 1,2-basketenes with alcohols should stimulate future research in the long-neglected field of metal complex catalyzed reactions with ketenes.



Experimental Section

3a: A solution of **1a** (5.0 g, 22 mmol),^[1] ethanol (1.1 g, 23 mmol), and catalyst **8** (0.3 g, 3 mol %)^[10] in toluene (70 mL) was stirred for 12 h at room temperature. The solvent was removed and the residue was fractionally distilled under vacuum to give **3a** as a colorless fraction with a boiling point of 62 °C (1 mbar). Yield: 5.8 g (95 %). ¹H NMR (400 MHz, C₆D₆, 25 °C): δ = 4.06 (q, ³J(H,H) = 7.1 Hz, 1H; CH₂), 3.96 (q, ³J(H,H) = 7.1 Hz, 1H; CH₂), 2.94 (s, 1H), 1.25 (t, ³J(H,H) = 7.13 Hz, 3H; CH₃), 0.11 (s, 9H; SiMe₃), 0.09 (s, 9H; SiMe₃); ¹³C NMR (400 MHz, C₆D₆, 25 °C): δ = 176.9 (C2), 159.0 (C5), 84.3 (C4), 66.9 (CH₂), 43.7 (C3), 14.7 (CH₃), –0.3 (C4-Si(CH₃)₃), –2.7 (C3-Si(CH₃)₃). IR (toluene, CaF₂, 0.1 mm, 25 °C): ν = 1796 cm^{–1} (C=O), 1638 cm^{–1} (C=C).

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Table 3. Influence of the alcohol on the reaction with **1a** in toluene; catalyst [CuL₂], LH = **8**.^[a]

R''	Conversion [%]	Selectivity [%]	B.p./p [°C]/[mbar]	decomp [°C]
Et	98	99	62/1.0	–
<i>i</i> Pr	97	98	67/0.5	–
adamantyl	78	96	–	87
Ph	98	91	–	94
<i>p</i> -nitrophenyl	93	89	–	91
<i>p</i> -methoxyphenyl	95	83	–	–

[a] Reaction conditions see Table 1.

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- [13] The turnovers are related to the disappearance of the bisketenes **1a–c** and the selectivities to the formation of the dihydrofuranones **3a–c**. The values were obtained by IR spectroscopy after 12 h; the standard deviation is about $\pm 1\%$. The ketenyl esters **2a–c** were the only observable by-products.

Rhodium and Iridium Pyrazolato Blues**

Cristina Tejel, Miguel A. Ciriano,* José A. López, Fernando J. Lahoz, and Luis A. Oro*

Since the first report in 1908, great progress^[1] has been made concerning the knowledge of the fascinating “platinum blues”. These cationic complexes generally exhibit a chain of four platinum atoms of mixed valencies, and metal-metal interactions. They also show antitumor activity.^[2] The tetranuclear chain is held together by an unsupported metal-metal bond between two dinuclear complexes. These invar-

ably display a face-to-face structure bridged by two ligands of the type N-C-O (such as 2-pyridonate and related ligands; N represents an endocyclic nitrogen) in a head-to-head arrangement. This configuration contains two different platinum centers; one of which is O,O-coordinated and the other N,N-coordinated. Noticeably, the unsupported metal-metal bond is always formed between the O,O-coordinated platinum atoms, which are the less hindered centers. Interdimer bond formation between the N,N-coordinated platinum atoms has never been observed. Furthermore, as already pointed out by Matsumoto et al.,^[2] the synthetic methods for some antitumor active blue compounds are not reproducible.

In contrast, related cationic compounds of the neighboring metals are rare for gold^[3] and unknown for iridium. On the other hand, a range of oligomeric mixed-valence rhodium complexes has been reported,^[4a] based on electronic spectroscopy solution studies, but full characterization has been carried out in only a few cases.^[5] Closely related to this work is an intensely colored $[\text{Rh}_4]^{6+}$ species proposed by Gray et al.,^[4b] and shown to be a mixed-valence compound by Mann et al.^[5b] In all cases, the coordination planes in the metal chain are almost parallel, which is the most sterically favorable situation for the formation of oligomers. Once again, the parent species are dinuclear complexes with face-to-face arrangement or, alternatively, mononuclear compounds. Here we describe a straightforward and reproducible reaction from open-book dinuclear pyrazolato complexes, to form novel tetranuclear iridium and rhodium blue compounds.

Beautiful blue, EPR-silent solutions are obtained by mixing equimolecular amounts of the recently reported^[6] yellow complexes $[\{\text{Rh}(\mu\text{-pz})(\text{CNtBu})_2\}_2]$ (**1**) and $[\{\text{Rh}(\mu\text{-pz})(\text{CNtBu})_2(\text{NCMe})\}_2](\text{PF}_6)_2$ (**2**), from which crystals of the new tetranuclear “rhodium blue” complex $[\{\text{Rh}(\mu\text{-pz})(\text{CNtBu})_2\}_4](\text{PF}_6)_2$ (**3**) were isolated (Figure 1; pz = pyrazolato). Alternatively, complex **3** can be obtained by oxidation of **1** with $[\text{FeCp}_2]\text{PF}_6$ (in a 1:1 molar ratio) in acetonitrile, and recrystallization of the crude solid from acetone/diethyl ether.

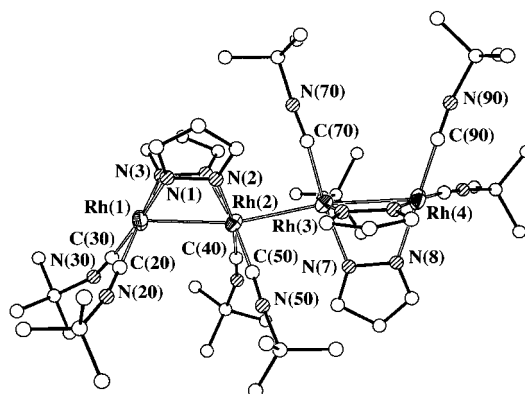


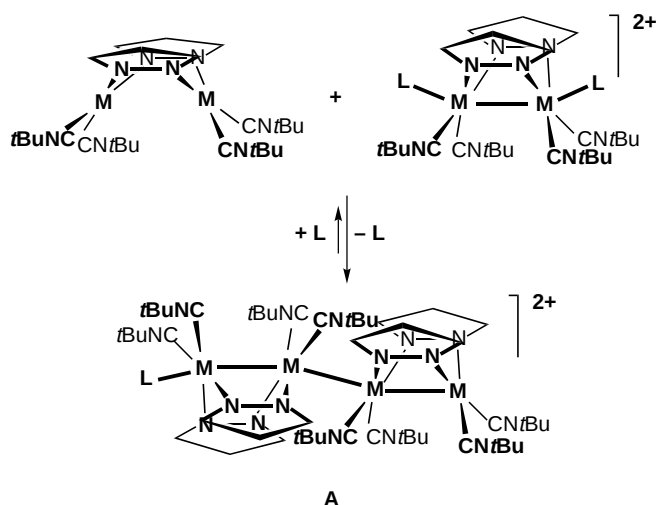
Figure 1. Molecular representation of the cation in the tetranuclear complex $[\{\text{Rh}(\mu\text{-pz})(\text{CNtBu})_2\}_4](\text{PF}_6)_2$ (**3**). Only one group of atoms has been drawn for the disordered ligands. Selected bond lengths [Å] and angles [°]: Rh(1)–Rh(2) 2.721(4), Rh(2)–Rh(3) 2.713(4), Rh(3)–Rh(4) 2.723(4), Rh–N 1.99(3)–2.13(3), Rh–C 1.84(3)–1.97(4); Rh(1)–Rh(2)–Rh(3) 165.51(14), Rh(2)–Rh(3)–Rh(4) 167.17(15), Rh–C–N 172(3)–179(3), C–N–C 159(4)–176(4).

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The crystal structure of **3**, determined by single-crystal X-ray diffraction, reveals tetranuclear cations together with PF_6^- anions and solvent molecules.^[7] Each tetranuclear complex is composed of two pyrazolato-bridged dinuclear $[(\text{CNtBu})_2\text{Rh}(\mu\text{-pz})_2\text{Rh}(\text{CNtBu})_2]$ moieties linked through a nonsupported metal–metal bond (2.713(4) Å). The two dinuclear moieties show the usual boat conformation for the $\text{Rh}(\mu\text{-pz})_2\text{Rh}$ group,^[6] with dihedral angles of 49.4(9) and 48.2(8)° between the two rhodium coordination planes and Rh–Rh bond lengths of 2.721 and 2.723(4) Å. Interestingly, the two dinuclear moieties are arranged in a staggered conformation with respect to each other (N(4)–Rh(2)–Rh(3)–N(5) torsion angle 137(1)°), which allows the two metals to form the unsupported Rh(2)–Rh(3) bond. The three metal–metal bonds in the crystal structure are almost linear, with intermetallic bond angles of 165.5(2) and 167.2(2)°, analogous to those reported for the tetrameric platinum blue compounds $[(\text{NH}_3)_2\text{Pt}(\text{C}_5\text{H}_5\text{N}_2\text{O}_2)_2\text{Pt}(\text{NH}_3)_2]^{2+}$ (164.81 and 165.02(5)°) and $[(\text{en})\text{Pt}(\text{C}_5\text{H}_4\text{NO})_2\text{Pt}(\text{en})]^{2+}$ (164.33(3)°)^[8] (en = ethylenediamine). Moreover, the related mixed-valence cation $[\text{Rh}^{\text{II}}\text{Rh}^{\text{I}}(\text{s-pqdi})_4(\text{pqdi})_2]^+$ (s-pqdi = 9,10-phenanthrosemiquinonediimine, pqdi = 9,10-phenanthroquinonediimine) exhibits^[5c] an unbridged trinuclear linear metal chain with very similar intermetallic separations (av 2.754(2) Å), although in this case, the electronic interactions between the chelating ancillary ligands lead to an eclipsed conformation of the square-planar environment of the metal atoms.

Interestingly, NMR studies show that when the rhodium(i) and rhodium(ii) complexes **1** and **2** are mixed, a fast equilibrium on the NMR time scale is formed with the cationic tetranuclear species **A**, which contains an additional acetonitrile ligand coordinated at an axial position (Scheme 1). Thus, a concentrated and cold blue solution of the mixture in $[\text{D}_6]\text{acetone}$ shows four signals in the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum for the C3 and C5 atoms and two signals for the C4 atom of the pyrazolate ligands, corresponding to **A**. However, a NOESY NMR spectrum indicates exchange of all the isocyanide and pyrazolate ligands, and they become equivalent in a diluted blue solution. Consequently, three



Scheme 1. Postulated chemical equilibrium for the formation of the tetranuclear adducts **A**. L = acetonitrile, M = Rh, Ir.

averaged signals, two for the pyrazolate and one for the isocyanide ligands, are observed at room temperature in the ^1H NMR spectrum. The dramatic influence of the concentration on the rate of exchange supports the assumption of an intermolecular process, and the exchange agrees with the proposed chemical equilibrium (Scheme 1). In contrast to the reported cleavage of $[\{\text{Rh}(\text{MeCN})_4\}(\text{BF}_4)_{1.5}]_\infty$ into defined valence species when dissolved,^[5a] it is remarkable that our tetrairidium chain persists in the blue solutions. The formation of the unusual adduct **A** probably arises from the lability of the nitrile ligands in **2** along with the nucleophilic character of the rhodium centers in **1**. Moreover, the tetrametallic chain results from a redox-condensation reaction, so that the four metal atoms each possess a formal oxidation state of 1.5. Delocalization of the metal–metal bond through the four metal atom chain would account for the intense color. Coordination of a ligand (acetonitrile or the donor solvent) at the free axial position should break the unsupported Rh–Rh bond to regenerate the starting dinuclear complexes. Internal electron transfer in the tetrametallic chain, however, facilitated by the metal–metal bond delocalization, results in the interconversion of $[\{\text{Rh}(\mu\text{-pz})(\text{CNtBu})_2\}_2]$ and $[\{\text{Rh}(\mu\text{-pz})(\text{CNtBu})_2(\text{NCMe})\}_2](\text{PF}_6)_2$ upon cleavage, as observed for the fluxional process.

Addition of iodide to the blue solutions leads to a yellow, equimolecular mixture of **1** and $[\{\text{Rh}(\mu\text{-pz})(\text{I})(\text{CNtBu})_2\}_2]$, in which the tetrametallic chain is not regenerated. Therefore, at least one labile ligand *trans* to the metal–metal bond in the Rh^{II} complex is required to bring about the above-mentioned condensation.

In a similar way, beautiful purple, EPR-silent solutions can be obtained by mixing the iridium complexes $[\{\text{Ir}(\mu\text{-pz})(\text{CNtBu})_2\}_2]$ (**4**) and $[\{\text{Ir}(\mu\text{-pz})(\text{CNtBu})_2(\text{NCMe})\}_2](\text{PF}_6)_2$ (**5**). The spectroscopic properties of the blue rhodium complex and purple iridium complex in solution are similar. Thus, the ^1H NMR spectrum of the latter shows three averaged resonances for the pyrazolate and isocyanide ligands even at low temperature, indicative of a faster rate of exchange than for the rhodium-containing solution. In addition, the purple solutions are extremely air- and light-sensitive. In close analogy to the rhodium species, these purple solutions of the iridium complex can also be obtained by oxidation of **4** with $[\text{FeCp}_2]\text{PF}_6$ (in a 1:1 molar ratio) in acetonitrile. Oxidation of **4** with iodine (in a 1:0.5 molar ratio) yields a neutral red complex $[\{\text{Ir}(\mu\text{-pz})(\text{CNtBu})_2\}_2]$ (**6**) which contains a tetrairidium chain, similar to that found for $[\{\text{Rh}(\mu\text{-pz})(\text{CNtBu})_2\}_4]^{2+}$. In fact, the molecular structure of **6** (Figure 2)^[9] is analogous to that observed for the cationic rhodium complex **3**, but contains two additional iodine atoms bonded to the terminal metal centers. Most of the geometric descriptors are similar for both structures: staggered conformation of the dinuclear $[(\text{CNtBu})_2\text{Ir}(\mu\text{-pz})_2\text{Ir}(\text{CNtBu})_2]$ moieties (131.0(3)°), parallel arrangement of the internal metal coordination planes (6.8(3)°), and an almost linear metal chain (166.56(2)°). However, the presence of the terminal iodine ligands significantly affects the metal–metal separation. Thus, while the pyrazolate-bridged Ir(1)–Ir(2) bond distance of 2.7268(7) Å is identical to the mean value in **3** (2.722(4) Å), the internal unsupported Ir–Ir separation is

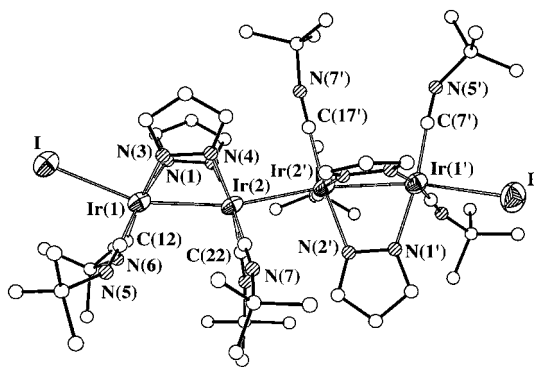


Figure 2. Molecular representation for the tetranuclear iridium complex $[[(\text{CNtBu})_2\text{Ir}(\mu\text{-pz})_2\text{Ir}(\text{CNtBu})_2]_2]$ (**6**). Only one moiety has been drawn for the disordered CNtBu ligands. Selected bond lengths [Å] and angles [°]: Ir(1)–Ir(2) 2.7268(8), Ir(2)–Ir(2') 2.8037(10), Ir(1)–I 2.8907(10), Ir(1)–N(1) 2.081(8), Ir(1)–N(3) 2.058(8), Ir(2)–N(2) 2.109(7), Ir(2)–N(4) 2.099(7), Ir–C 1.870(9)–1.896(8); Ir(1)–Ir(2)–Ir(2') 166.57(2), I–Ir(1)–Ir(2) 159.04(3), Ir–C–N 172.1(12)–178.8(9), C–N–C 147.3(11)–170.2(12). Primed atoms are related by the symmetry transformation $2 - x, y, 1/2 - z$.

elongated to 2.8038(8) Å. This situation has also been reported for the closely related complex $[[(\text{CO})_2\text{Ir}(\mu\text{-btzt})_2\text{Ir}(\text{CO})_2]_2]$ (btzt = benzothiazol-2-thiolate),^[10] which has a face-to-face arrangement of the coordination planes in a head-to-head configuration, with intermetallic separations of 2.731(2) Å (ligand-bridged) and 2.828(2) Å (unsupported bond).

An extended Hückel molecular orbital (EHMO) calculation^[11] fully supports the proposed stabilization of the unsupported metal–metal bond, and therefore the formation of the tetranuclear blue complexes. Figure 3 shows a qualitative MO diagram of the metal–metal bonding system

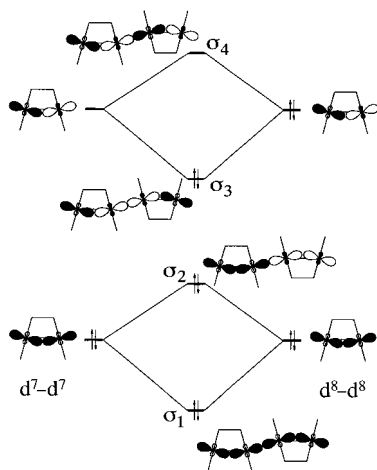


Figure 3. Qualitative fragment MO diagram for the metal–metal bonding system.

calculated from the interaction of two dinuclear d^7 – d^7 and d^8 – d^8 fragments, under the assumption of the geometry in **3**. Mixed-valence condensation gives rise to a fractional oxidation state for all metal centers. Partial filling of the frontier orbitals σ_3 and σ_4 appears to be essential for the stabilization of these tetranuclear complexes, as shown for the platinum

blue compounds, in which these MO orbitals are fully (σ_3) and partially (σ_4) occupied.^[12]

In summary, tetrametallic chains of rhodium and iridium with unsupported metal–metal bonds and fractional oxidation states, analogous to the platinum blue compounds, have been obtained. These chains are stable enough to persist in solution, and form even though the starting dinuclear complexes do not present the most favorable steric requirements for an unsupported metal–metal bond. To generate the tetranuclear chain, a noticeable deformation of the environments of the inner metal atoms must occur. This observation illustrates the greater influence of electronic over steric effects on the formation of this type of rhodium and iridium blue compounds.

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Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

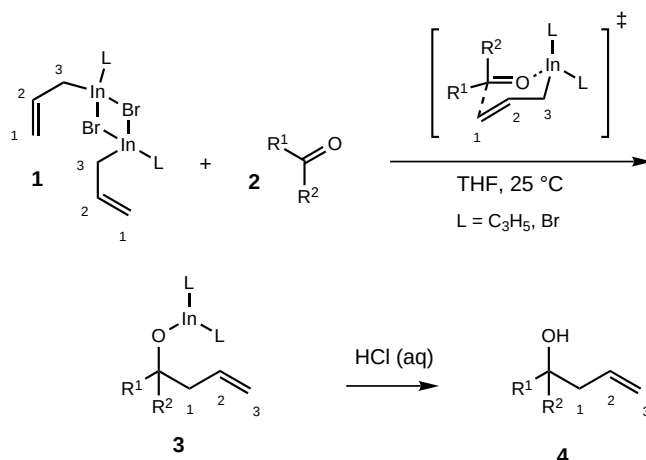
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Homoallyl-Substituted Vinylcyclopropanes from α,β -Unsaturated Ketones and Allylindium Derivatives**

Henning A. Höpfe, Guy C. Lloyd-Jones,* Martin Murray, Torren M. Peakman, and Kenneth E. Walsh

Organoindium species are of particular appeal as reagents for organic synthesis because they are often stable under aqueous and even mildly acidic conditions and are compatible with many organic functional groups.^[1] Allylindium sesquihalides (allyl)₃In₂X₃ and dihalides (allyl)₂In₂X₄ **1**, prepared by the reaction of allyl halides with indium metal^[2] or indium

halides,^[3] react smoothly with aldehydes and ketones^[4] **2** via transition states of the Zimmermann–Traxler type to afford indium alkoxide intermediates **3** (Scheme 1). Hydrolysis yields homoallylic alcohols **4**.^[5] Here we report on the



Scheme 1. Reaction of allylindium sesquibromide **1** with ketones **2** to give **3** and **4** via a Zimmerman–Traxler transition state.

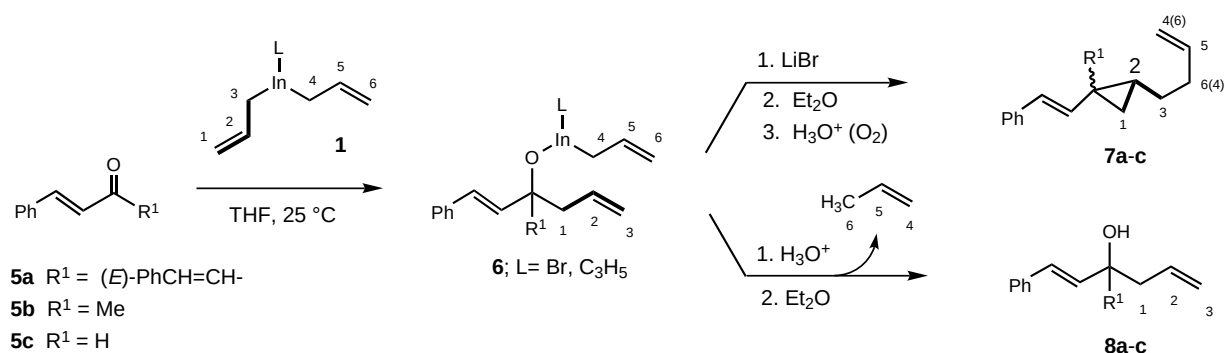
reaction of **1** with α,β -unsaturated ketones or aldehydes **5** to produce homoallylic indium alkoxide intermediates **6**, which can be induced to undergo a deoxygenative rearrangement that results in vinylcyclopropane derivatives of type **7** (Scheme 2).

In initial experiments, dibenzylideneacetone **5a** was allowed to react under nitrogen with freshly prepared (C₃H₅)₃In₂Br₃ (**1**) in anhydrous THF at 25 °C (**5a**:In = 1:1). After the mixture was diluted with Et₂O, worked up with 1M HCl, and subjected to column chromatography, we obtained analytically pure **7a** in yields of 40–60%.^[6] Thus, a reaction took place that did not lead to **8a**, but instead resulted in cleavage of the C–O bond. Presumably this involved coupling between the allylindium moiety (C(4)–C(6)) in **6a** and the C(3) terminus of the initially transferred allyl group (C(1)–C(3)) to afford the homoallyl-substituted vinylcyclopropane derivative **7a**. The overall reaction therefore involves deoxygenative sequential transfer of six carbon atoms (two allyl moieties) from the indium sesquihalide species **1** to the α,β -unsaturated ketone **5a**. A three-membered ring is formed by linkage of the carbonyl carbon atom with C(1) and C(2) of the first allyl unit. After many experiments it became clear that removal of the THF^[7] (which presumably stabilizes the intermediate) and exposure of the crude product to air in an acidic medium^[8] (which may induce homolysis of the C–In bond, possibly by insertion of O₂) is essential for efficient and reproducible diversion of **6** to **7** rather than to **8**.

We suspected that rearrangement of **6** to **7** might involve the reaction of CH₂=CHCH₂In(L)_x with aerobic oxygen to afford an intermediate of the type CH₂=CHCH₂(O)_nIn(L)_x ($n = 1, 2$). The following experiments were performed to circumvent the requirement of exposure to air. One equivalent of (C₃H₅)₂In₂I₄, in which each indium atom bears only one allyl group, was allowed to react with **5a** (THF, 25 °C,

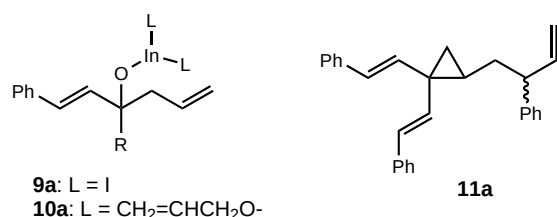
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Scheme 2. Acid-catalyzed rearrangement of intermediate **6** to homoallyl-substituted vinylcyclopropane **7** and hydrolysis to **8**.

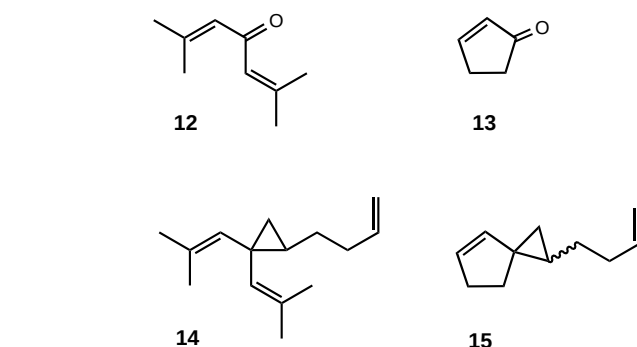
30 min) to generate **9a**, and then two equivalents of CH₂=CHCH₂ONa were added to exchange iodide with allyl



alkoxide and yield **10a** + NaI (or the corresponding indium “ate” complex).^[2b, 5d] After removal of the THF the residue was stirred in toluene (18 h), and **7a** was isolated in 83 % yield after workup. However, analogous reactions with (*E*)-PhCH=CHCH₂ONa afforded only **7a**, and not **11a**; this demonstrates that allylic moieties of the alkoxides are not incorporated. Hence, addition of allylic alkoxide did not bypass the oxidation stage, but addition of alkoxide did increase the yield of **7a** substantially—possibly by formation of an indium “ate” complex. Consistent with this interpretation, reaction of the more conveniently prepared (C₃H₅)₃In₂Br₃ (**1**) with **5a** in THF followed by (exothermic) addition of LiBr (or NaOH) and subsequent aerobic workup (addition of Et₂O and then aqueous HCl) afforded **7a** in 82–83 % yield. The formation of an “ate” complex could improve the yield in two distinct ways. First, allylindium “ate” complexes show enhanced reactivity^[5c] and selectivity^[5d] toward electrophiles relative to their neutral precursors. Second, because rearrangement may compete with hydrolytic cleavage of the In–OC or In–C(4) bonds, the negatively charged “ate” complex may be less susceptible to hydrolysis.

Based on the same procedure—addition of α,β -unsaturated carbonyl compound **5b**, **5c**, **12**, or **13** to allylindium sesquibromide **1** in THF at 25 °C (12 h) followed by formation of the “ate” complex (LiBr, THF, 24 h), dilution with Et₂O, admission of air, and then addition of 1M HCl—we prepared vinylcyclopropanes **7b** and **7c**, divinylcyclopropane **14**, and spiro-vinylcyclopropane **15** in yields of 79, 52, 92, and 38 %, respectively.

Curiously, α,β -unsaturated ketones and aldehydes have been reported to undergo indium-mediated Barbier-type allylations to afford allylic–homoallylic alcohols **8** in high yield (83–95 %) with no mention of cyclopropane formation (see Scheme 2).^[3a, 4b] Indeed, we were able to reproduce



reported allylations of **5b** and **5c** to **8b** and **8c** by treatment of allyl iodide with In or InI in THF or DMF and addition at 25 °C of **5b** or **5c** followed by workup after one hour by addition of 1M HCl. However, we were also able to detect a small amount of cyclopropane **7b** (4 %) in the crude product from reaction of **5b** ($\rightarrow$ **8b**) by thin-layer chromatography and NMR spectroscopy. Homogeneous acidic conditions (THF/H₃O⁺) cause hydrolysis of CO–In and allylic C–In bonds,^[4a] in this case converting **6b** and **6c** into **8b** and **8c**. Subsequent addition of Et₂O generates a biphasic mixture, which facilitates separation of the organic products.

Somewhat surprisingly, simply inverting the order of addition of aqueous acid and Et₂O (that is, dilution with Et₂O first and then addition of H₃O⁺) diverts the reaction pathway of intermediate **6** away from **8** to form **7** instead. The effect of Et₂O addition may be twofold: It reduces the THF concentration and, more important, it results in generation of a biphasic mixture upon addition of the aqueous acid. Intermediate **6**—which bears C(4), C(5), and C(6) prior to transfer—is more soluble in the ethereal phase, and may therefore be protected somewhat from acidic hydrolysis. Acid is essential, however, because under neutral conditions (i.e., addition of water instead of aqueous HCl) no generation of **7** is observed until dilute HCl is introduced.

The intimate details of the mechanism by which **6** is converted into **7** are not obvious. At present we have no evidence as to whether the overall homoallylic to methylene-cyclopropane skeletal rearrangement, formation of an allylic C–C bond, and cleavage of the C–OIn bond occurs by covalent, ionic, or radical intermediates. However, the rearrangement does appear to be facilitated by allylic placement of the C–OIn bond, because benzophenone does not lead to a cyclopropane product.

The potential applications of indium-mediated deoxygenative reactions are of considerable scope. Further investigations^[9] are underway and will be fully reported in due course.

Experimental Section

7a: Under N₂, allyl bromide (0.530 mL, 6.09 mmol) was added to indium powder (particle size: 100 mesh; Aldrich, 459 mg, 4.00 mmol) in THF (2 mL), which resulted in an exothermic reaction. After 70 min **5a** (235 mg, 1.00 mmol) was added as a solid. After 4 h LiBr (347 mg, 4 mmol) was added (exothermic reaction), and after a further 12 h air was admitted to the reaction vessel. Et₂O (10 mL) and 1M HCl (30 mL) were then introduced, and the biphasic mixture was shaken vigorously at intervals of 10 min over a period of 1 h. The organic phase was separated, dried (Na₂SO₄), and concentrated. Chromatographic purification (silica gel, hexane/EtOAc 19/1) afforded **7a**^[6] (249 mg, 83%) as a colorless oil. Elemental analysis calcd for C₂₃H₂₄: C 91.95%, H 8.05%; found: C 91.59%, H 8.30%. **7b**, **7c**, **14**, and **15** were prepared similarly. Tenfold scale-up with **5a** afforded **7a** in similar yield.

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[6] ¹H–¹H COSY, PECSY, DEPT, ¹³C–¹H COSY (long- and short-range), and 2D-¹³C INADEQUATE spectra, NOE studies, selective ¹H decoupling, and ¹J_{CC} coupling confirmed the structure of **7a**. Complete analytical data for **7b**, **7c**, **14**, and **15** will be reported elsewhere; the diastereomer ratios of **7b**, **7c**, and **15** were 1:1, 2:1, and 4:1. Analyses of the reaction mixtures by thin-layer chromatography indicated no traces of starting materials **5a–c**, **12**, or **13**. Lower yields for **7c** and **15** presumably reflect loss of material through polymerization or formation of highly polar materials.

[7] Compound **5a** reacts with (C₃H₅)₂In₂I₄ to give **9a** (and with **1** to give **6a**), as shown by ¹H NMR spectroscopy in [D₈]THF. Removal of THF from **9a** under reduced pressure (0.1 Torr), addition and subsequent removal of PhCH₃, and dissolution of the residue in [D₈]THF resulted in a fluxional ¹H NMR spectrum that revealed no trace of **9a**.

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1,4-Addition of a Terminal Phosphinidene Complex to [5]Metacyclophane**

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In general, carbenes^[1] and related electron-deficient species such as the metal complexes of phosphinidenes (phosphane-diylenes) [RPW(CO)₅]^[2] react with 1,3-dienes by [2+1] cycloaddition (1,2-addition) to furnish only vinylcyclopropanes or vinylphosphiranes, respectively. However, as vinylphosphiranes tend to rearrange to the corresponding phospholenes, products are frequently isolated that seemingly result from a formal [4+1] cycloaddition (1,4-addition).^[3, 4] To our knowledge, there is so far only one exception: A direct 1,4-addition does occur, in competition to 1,2-addition, in the reaction of dihalocarbenes with 1,3-dienes which are frozen in a cisoid conformation.^[5]

We here report on the 1,4-addition of a phosphinidene complex and highlight three exceptional aspects. 1) It is the first genuine 1,4-addition of a phosphinidene complex, 2) it is the first addition of a phosphinidene complex to a benzene ring, and 3) it is, as far as we know, the first [4+1] cycloaddition to an aromatic ring.

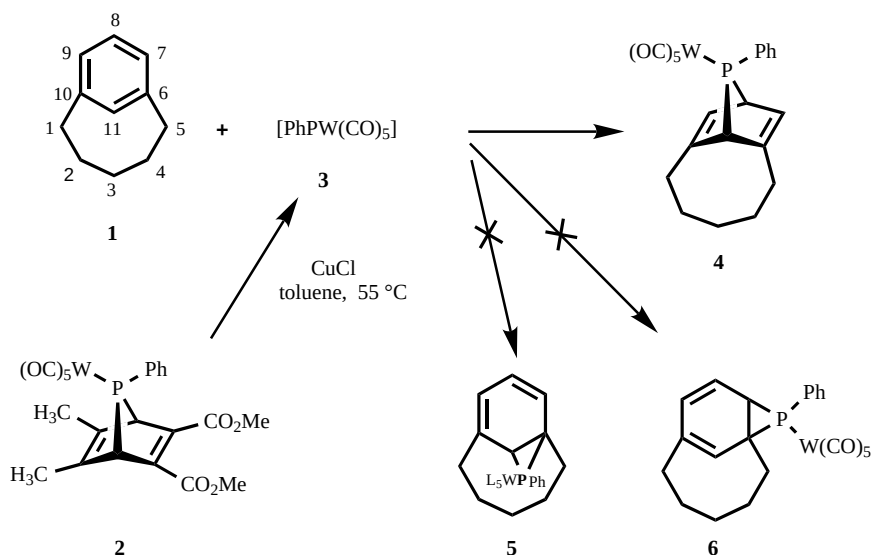
Because of its high strain energy and its bent benzene ring, [5]metacyclophane **1** reacts under unusually mild conditions with dienophiles at C8 and C11 by a [4+2] cycloaddition (Diels–Alder reaction).^[6] We therefore considered **1** to be a promising candidate for 1,4-additions with phosphinidene complexes. Indeed, reaction of **1** with the precursor **2** of the phosphinidene complex **3** (with 10% CuCl as catalyst in toluene at 55 °C)^[7] gives the 1,4-adduct **4** as the only product in the form of light yellow crystals in 52% yield after column chromatography and crystallization from pentane (Scheme 1).

The NMR data of **4** are in good agreement with those of other 7-phosphanorbornadienes (e.g. **2**). The phosphorus center is slightly more shielded ($\delta(^{31}\text{P}) = 191.1$) than in reference compounds ($\delta(^{31}\text{P}) = 208–240$ ^[7a, 8]); the two olefinic carbon atoms *anti* to the W(CO)₅ substituents display a strong coupling to the phosphorus atom ($^2J(\text{P,C}) = 21.2$ and

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Scheme 1.

17.3 Hz), whereas the corresponding coupling of the *syn*-carbon atoms is small ($^2J(\text{P},\text{C}) = 6.2$ and 4.2 Hz).^[7c, 8, 9]

The structure derived from the spectra was corroborated by a single-crystal X-ray structure determination (Figure 1).^[10] Again, the structural parameters of **4** show good agreement with those of other 7-phosphanorbornadienes;^[7a, 8] the only

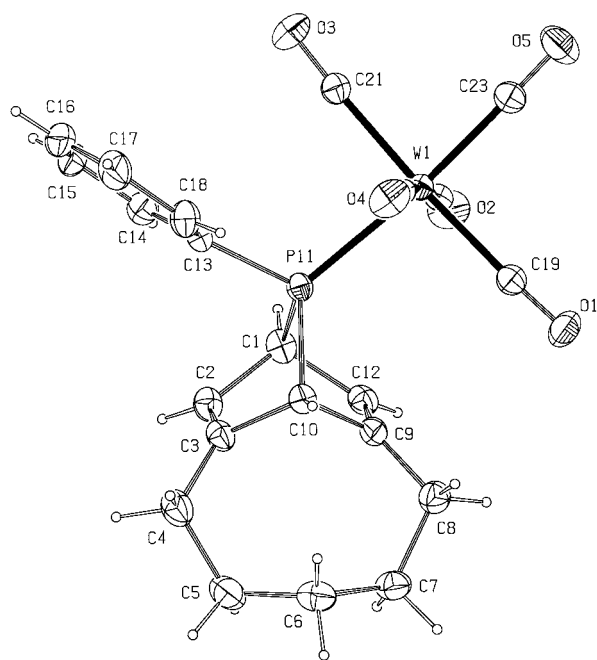


Figure 1. Structure of **4** in the crystal. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: W1–P11 2.487(1), P11–C13 1.817(4), P11–C1 1.864(4), P11–C10 1.874(4), C1–C2 1.526(6), C1–C12 1.540(5), C2–C3 1.331(6), C3–C10 1.529(5), C9–C12 1.334(6), C9–C10 1.527(5); C13–P11–C1 107.92(18), C13–P11–C10 109.15(17), C1–P11–C10 79.74(17), C13–P11–W1 111.27(12), C1–P11–W1 121.42(14), C10–P11–W1 123.30(12), C2–C1–C12 106.5(3), C2–C1–P11 100.8(3), C12–C1–P11 95.6(2), C3–C2–C1 111.2(3), C2–C3–C10 109.6(3), C12–C9–C10 109.7(3), C9–C10–C3 105.1(3), C9–C10–P11 97.1(3), C3–C10–P11 102.0(2), C9–C12–C1 110.8(3), C3–C4–C5 112.6(4), C4–C5–C6 117.3(5), C5–C6–C7 117.1(4), C6–C7–C8 118.5(5), C7–C8–C9 111.9(4); C1–C2–C3–C4 $-165.1(4)$, C8–C9–C12–C1 $169.0(0)$.

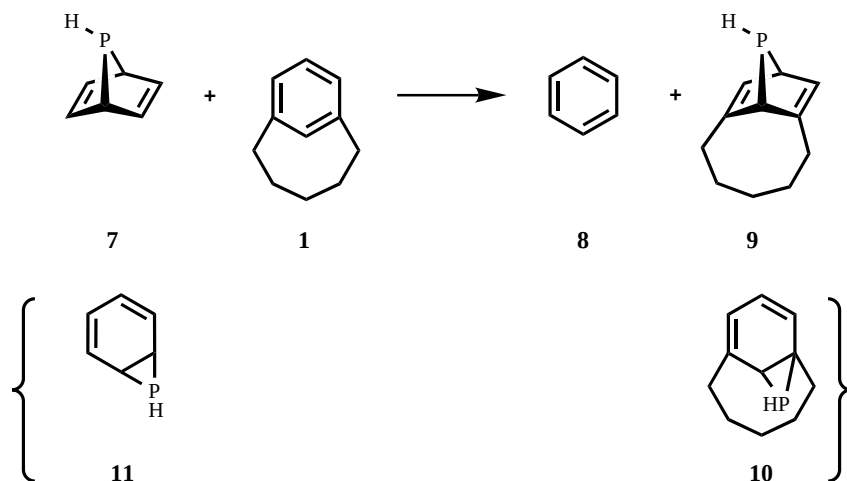
exceptions are the double bonds of the norbornadiene skeleton, which in **4** are clearly twisted (C1–C2–C3–C4 $-165.1(4)^\circ$, C8–C9–C12–C1 $169.0(4)^\circ$). A certain degree of strain is also apparent from the C–C angles of the pentamethylene bridge; these angles are enlarged for the three central methylene groups (117.1 – 118.5°), but less so than in the 8,11-dichloro derivative of **1** (122°).^[11] The somewhat reduced strain in **4** is also indicated by the bond angles at the benzylic methylene groups (111.9 – 112.6°), which are larger than those of the reference cyclophane mentioned (104.7°).^[11]

One must consider the possibility that this reaction, like the addition of other phosphinidene complexes, might proceed via a 1,2-adduct such as **5** or **6**, which in a second step rearranges to **4**. To investigate this alternative, the reaction progress was monitored by ^{31}P NMR spectroscopy. However, no indications for an intermediate product were obtained. ^{31}P NMR experiments also showed that **4**, being a 7-phosphanorbornadiene complex, is remarkably stable: In sharp contrast to **2**, **4** remained unchanged even on prolonged heating at 70°C in toluene in the presence of CuCl .

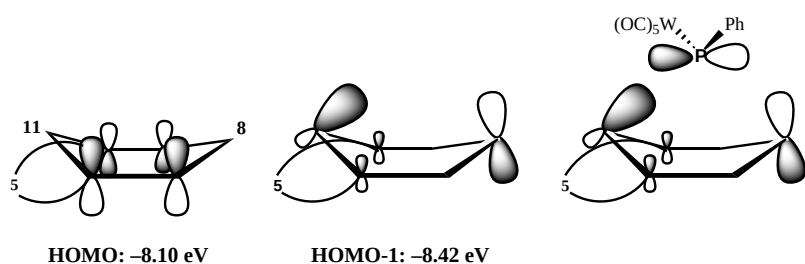
Theoretical calculations were performed (ADF^[12]) in order to better understand the reasons for this increased stability of **4**. The homodesmotic reaction $\mathbf{7} + \mathbf{1} \rightarrow \mathbf{8} + \mathbf{9}$ (Scheme 2) has a reaction enthalpy of -140 kJ mol^{-1} . This value is similar to the strain energy of **1** (174 kJ mol^{-1}), and shows that the strain in **9** (and likewise that in **4**) is considerably diminished, probably due to the removal of the “anti-Bredt” situation (cf. the formal double bond between C6 and C11 in **1**). Furthermore, the reverse reaction is strongly endothermic, which explains the stability of **4**. In contrast, the analogous cheletropic cleavage of **2** yields (besides the intermediate **3**) a planar, strain-free benzene derivative with ease.^[2a]

The calculations also support the mechanism of the reaction of **3** with **1** as being a direct 1,4-addition. According to frontier orbital theory, this reaction is largely governed by the interaction between the HOMO or HOMO -1 of **1** and the LUMO of **3** (Figure 2).

Both the HOMO (-8.10 eV) and the HOMO -1 (-8.42 eV) of **1** are clearly higher in energy than the corresponding orbitals of *m*-xylene (RHF/6-31G*:^[13] -8.59 and -8.89 eV, respectively), which will reduce the activation barrier of the cycloaddition. As the HOMO of **1** has a node in the mirror plane of the molecule, its interaction with the LUMO of **3** can only proceed by 1,2-addition at C6/C7 under formation of **6** (Scheme 1). However, this reaction pathway is unlikely because it hardly reduces the “Bredt strain”, let alone that quite complicated rearrangements are required to get from **6** to **4**. The 1,2-addition at C6/C11, which would furnish the less strained **5** (removal of the “anti-Bredt double bond” between C6 and C11!), can only occur through the HOMO -1 , but is unfavorable because of the small coefficient at C6.



Scheme 2.

Figure 2. Frontier orbitals of **1** and **3**.

Therefore, it is more likely that the addition of **3** to **1** is governed by the interaction between the LUMO of **3** and the HOMO – 1 of **1**, resulting in a symmetry-allowed 1,4-addition at C8 and C11 (Figure 2). Favorable factors in this reaction pathway are the high coefficients of the HOMO – 1 at C8 and C11; the boat shape of the aromatic ring of **1** and the pyramidalization at C8 and especially at C11, which minimize the geometric changes required for the cycloaddition; the increased electron density at the concave side of the aromatic boat of **1**, which increases the overlap with **3**; and the gain in reaction enthalpy, which in the model (Scheme 2) is 9.2 kJ mol⁻¹ higher for the formation of **9** than for **10**. In contrast, on addition of the phosphinidene HP: to (planar) benzene, the 1,2-adduct **11** is more stable than the 1,4-adduct **7** (Scheme 2; ADF: 65.8 kJ mol⁻¹; MP2(fc)/6-31G*: 53.1 kJ mol⁻¹[9]).

In conclusion, both the experimental data and the theoretical analysis support a direct, one-step 1,4-addition of phosphinidene complex **3** to the aromatic ring of **1**.

Experimental Section

4: A solution of **1** (41 mg, 0.28 mmol), **2** (177 mg, 0.27 mmol), and CuCl (≈ 10 mol %) in dry toluene (1.5 mL) was heated under nitrogen to 55 °C for 2 h. After evaporation of the volatile components in vacuo, the residue was dissolved in pentane/benzene (9/1), subjected to chromatography on silica, and crystallized from pentane to afford **4** as light yellow crystals (81 mg, 0.14 mmol, 52 %); m.p. 83 °C. ³¹P NMR (250 MHz, CDCl₃): δ = 191.1 (¹J(P,W) = 224.4 Hz); [¹H]¹³C NMR (100 MHz, CDCl₃): δ = 24.81 (s; C6), 33.08 (s; C4), 33.4 (s; C5), 33.4 (s; C8), 33.55 (s; C7), 52.17 (d, ¹J(C,P) = 20.2 Hz; C10), 60.64 (d, ¹J(C,P) = 26.2 Hz; C1), 128.17 (d, ³J(C,P) = 7.3 Hz;

m-Ar, C15, C17), 128.39 (d, ²J(C,P) = 8.8 Hz; *o*-Ar, C14, C18), 128.77 (d, ⁴J(C,P) = 0.9 Hz; *p*-Ar, C16), 129.33 (d, ²J(C,P) = 4.2 Hz; C2), 129.96 (d, ²J(C,P) = 17.3 Hz; C12), 142.75 (d, ¹J(C,P) = 17.2 Hz; *i*-Ar, C13), 154.20 (d, ²J(C,P) = 6.2 Hz; C3), 154.89 (d, ²J(C,P) = 21.2 Hz; C9), 196.81 (d, ²J(C,P) = 6.7 Hz; *cis*-CO, C19–C22), 199.74 (d, ²J(C,P) = 23.7 Hz; *trans*-CO, C23); ¹H NMR (400 MHz, CDCl₃): δ = 0.963 (m, ²J(H,H) = -14.0, ³J(H,H) = 10.8, ³J(H,H) = 9.2, ³J(H,H) = 4.2, ³J(H,H) = 1.2 Hz; H6), 1.068 (m, ²J(H,H) = -14.5, ³J(H,H) = 11.8, ³J(H,H) = 9.2, ³J(H,H) = 4.2, ³J(H,H) = 1.2 Hz; H10), 1.438 (m, ²J(H,H) = -15.7, ³J(H,H) = 9.2, ³J(H,H) = 9.2, ³J(H,H) = 1.1, ³J(H,H) = 1.1 Hz; H7), 1.912 (m, ²J(H,H) = -15.7, ³J(H,H) = 9.8, ³J(H,H) = 9.8, ³J(H,H) = 1.2, ³J(H,H) = 1.2 Hz; H8), 2.041 (m, ²J(H,H) = -14.0, ³J(H,H) = 9.8, ³J(H,H) = 4.2, ³J(H,H) = 4.2, ³J(H,H) = 1.1 Hz; H3), 2.160 (m, ²J(H,H) = -14.5, ³J(H,H) = 9.8, ³J(H,H) = 4.6, ³J(H,H) = 4.2, ³J(H,H) = 1.1, ⁴J(H,H) ≈ 1.0 Hz; H9), 2.372 (m, ²J(H,H) = -13.1, ³J(H,H) = 4.2, ³J(H,H) = 4.2, ⁴J(H,H) < 1 Hz; H4), 2.453 (m, ²J(H,H) = -13.2, ³J(H,H) = 11.8, ³J(H,H) = 4.6, ⁴J(H,H) ≈ 1.6 Hz; H12), 2.762 (m, ²J(H,H) = -13.2, ³J(H,H) = 4.2, ³J(H,H) = 4.2, ⁴J(H,H) < 1 Hz; H11), 3.482 (m, ⁴J(H,H) = 2.6, ⁴J(H,H) = 1.4, ⁴J(H,H) = 1.4, ²J(H,P) = 2.8 Hz; H13), 3.878 (m, ³J(H,H) = 4.2, ³J(H,H) = 3.8, ⁴J(H,H) = 2.6, ²J(H,P) ≈ 0.3 Hz; H1), 5.951 (m, ³J(H,H) = 3.8, ⁴J(H,H) = 1.4, ⁴J(H,H) < 1, ⁴J(H,H) ≈ 1.2, ³J(H,P) = 7.6 Hz; H2), 6.466 (m, ³J(H,H) = 4.2, ⁴J(H,H) = 1.4, ⁴J(H,H) < 1, ⁴J(H,H) ≈ 1.6, ³J(H,P) = 8.0 Hz; H14), 7.159 (m, ³J(H,H) = 7.6, ⁴J(H,H) = 1.6, ⁴J(H,H) = 1.2, ⁵J(H,H) = 0.6, ³J(H,P) = 8.9 Hz; *o*-Ar), 7.286 (m, ³J(H,H) = 7.5, ⁴J(H,H) = 1.2, ⁵J(H,P) = 1.3 Hz; *p*-Ar), 7.358 (m, ³J(H,H) = 7.6, ³J(H,H) = 7.5, ⁴J(H,H) = 1.4, ⁵J(H,H) = 0.6, ⁴J(H,P) = 1.9 Hz; *m*-Ar); HR-MS: calcd for C₂₂H₁₉O₃P¹⁸²W [M⁺]: *m/z* 578.0480; found: 578.0479 ± 0.0004; elemental analysis calcd for C₂₂H₁₉O₃PW: C 45.70, H 3.31, P 5.36; found C 45.28, H 3.27, P 5.32.

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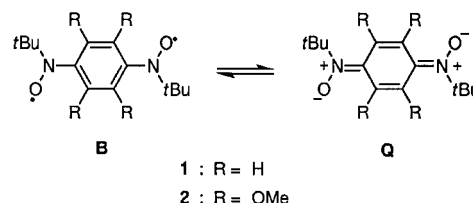
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Stabilization of *p*-Phenylenebis(*N*-*tert*-butylaminoxyl) Relative to *p*-Benzoquinone-diimine *N,N'*-Dioxide**

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For typically triplet *m*-quinodimethane derivatives,^[1, 2] recent theoretical and experimental work revealed that they can have singlet ground states when sterically and/or electronically perturbed.^[3–7] We designed the diradical *p*-phenylenebis(*N*-*tert*-butylaminoxyl) **B**, which is expected to be stabilized as the closed-shell *p*-benzoquinonediimine *N,N'*-dioxide **Q** (Scheme 1). The synthesis, X-ray crystal structure analysis, and EPR characterization of unsubstituted **1** and its tetramethoxy derivative **2** are reported here.



Scheme 1. Equilibrium between the benzenoid (**B**) and quinonoid forms (**Q**) of **1** and **2**.

The *p* isomers were prepared, analogous to the procedure used to synthesize the triplet *m* isomers,^[3] by the oxidation of the corresponding hydroxyamines with Ag₂O. The resulting orange and red powders were crystallized from diethyl ether to give orange prismatic and red bricklike crystals of **1** and **2**, respectively. The X-ray crystal structure analysis (see Experimental Section) of **1** revealed the presence of two pairs of independent molecules A and B in the unit cell. The molecular structures are very similar and have a C₂ symmetry axis at the center of the ring which is nearly coplanar with the planes of the aminoxyl groups (Figure 1, top; Table 1). In the unique molecule of **2** a C₂ axis passes through the midpoints of the C2–C3 and C2*–C3* bonds. The planes of the aminoxyl groups are almost perpendicular to the central ring (Figure 1, bottom). Although the two aminoxyl groups in most of the reported *m* isomers have *syn* configuration in the crystal,^[2c, 3] the observed *anti* form in **2** can be rationalized

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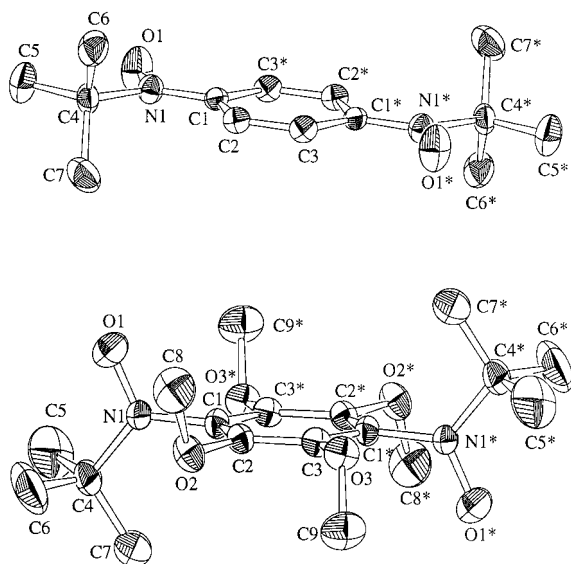


Figure 1. ORTEP drawings (ellipsoids for 50% probability) of one of the two molecules in **1** (top) and **2** (bottom).

Table 1. Bond lengths, bond angles, and dihedral angle in **1** and **2**.

	1		2
	A	B	
bond lengths [Å]			
C2–C3	1.362	1.358	1.397
C1–C2	1.423	1.417	1.392
C1–N1	1.354	1.362	1.428
N1–O1	1.291	1.287	1.269
bond angles [°]			
C4–N1–O1	115.4	116.1	118.1
dihedral angle [°]			
O1–N1–C1–C2	1.2	3.4	84.5

by aligning the bulky *tert*-butyl groups and the methyl groups of the methoxy substituents alternately up and down out of the plane of the ring to avoid steric congestion. The structural difference between **1** and **2** is best demonstrated by the bond lengths of the six-membered rings (Table 1). Whereas the ring C–C bond lengths are rather uniform in **2**, the C2–C3 bond length in **1** is clearly shorter than C1–C2 and close to 1.344 Å for the C–C double bond in *p*-benzoquinone. Consequently, **1** and **2** are concluded to have quinonoid (**Q**) and benzenoid forms (**B**), respectively, in the crystalline state.^[8]

Isomer **1** is EPR-silent in solution and in the crystal from room temperature down to cryogenic temperatures, and shows two sharp singlets at $\delta = 7.40$ and 1.68 in the ¹H NMR spectrum. In contrast, an EPR spectrum of **2** in toluene shows a broad signal ($\Delta H_{pp} = 30$ G) with five peaks overlapping as shoulders ($g = 2.006$ and $a_N/2 = 6.8$ G). In the solid state, a single EPR line is observed with $\Delta H_{pp} = 18$ G. In frozen toluene, **2** shows a set of signals characteristic of a triplet state with $|D/hc| = 0.013$ cm^{−1} together with one signal due to a $\Delta m_s = \pm 2$ transition at $g = 4$. By applying a point-dipole approximation to the $|D/hc|$ value, the average distance between the radical centers was estimated to be 5.78 Å; this is in adequate agreement with the value of 6.36 Å observed between the radical centers ($r_{N1N1^*-O1O1^*}$) by X-ray analysis. The dependence of the intensity I of the triplet signal at $g = 4$

on the temperature T between 10 and 100 K was determined by a plot of I versus $1/T$. Below 20 K there is a deviation downward from the linear relationship, indicating that the triplet and singlet states are nearly degenerate. Furthermore, the singlet state is the ground state, and the excited triplet state is higher in energy by 20 cal mol^{−1} or less. The molar paramagnetic susceptibility χ_{mol} of a crystalline sample of **2** was measured with a SQUID magnetometer/susceptometer in the temperature range of 2–300 K. The $\chi_{mol}T$ values above 60 K were constant at 0.73 emu K mol^{−1} and decreased below 60 K with decreasing temperature to become nearly zero at 2 K. The observed temperature profile reveals that a singlet ground state is present. The values above 60 K are in good agreement with theoretical value of 0.75 emu K mol^{−1} calculated for a diradical having degenerate singlet–triplet states or isolated spins. A Bleaney–Bowers equation for an singlet–triplet model^[9] fit the experimental data reasonably well to give a singlet ground state; the lowest excited triplet lies 14.7 ± 0.12 cal mol^{−1} higher in energy.^[10]

The UV/Vis spectra of **1** and **2** in CH₂Cl₂ measured at room temperature were completely different from each other. Strong and broad absorptions were observed at $\lambda_{max} = 404$ nm ($\epsilon = 8.8 \times 10^4$) for **1** ($\lambda_{max} = 403$ nm ($\epsilon = 6.6 \times 10^4$) for the *N*-*sec*-butyl derivative^[11a]) due to the quinonoid form and at $\lambda_{max} = 483$ nm ($\epsilon = 550$) for **2** due to the *N*-arylaminoxyl radical.

All this information leads to the conclusion that **1** has only the **Q** form^[11] in solution as well as in the crystalline state. The energy gained by aromatization does not appear to be enough to stabilize the **B** form. In the *p* isomer, which has no barrier to rotation about the C1–N1 bond, the planar structures **1-Q** and **1-B** should be considered as resonance hybrids rather than isomers in the equilibrium shown in Scheme 1; this equilibrium is predominantly directed to the **1-Q** form. Isomer **2**, which has a large torsion angle, has only the **B** form in solution as well as in the solid state. Therefore, the stability of the **B** form in solution depends on the magnitude of the torsion of the aminoxyl radicals; the **B** form can only be stabilized when there is a barrier to achieving the coplanar structure.^[12] The analogous 2,5-dimethoxy-*p*-phenylenebis-(aminoxyl) diradical, which is expected to have a much lower barrier to rotation than **1**, has the **Q** form in the solid state, but is able to equilibrate between the **B** and **Q** forms in solution and is EPR-active.^[12, 13]

In summary, stabilization of the diradical **B** form relative to the **Q** form has been achieved by steric effects in the case of the *p* isomer. Subtle changes in the total number of electrons^[14] as well as electronic and steric effects of the substituents are concluded to tune the **B**–**Q** equilibrium and similar tautomerisms.

Experimental Section

1.^[11] *p*-Dibromobenzene (1.0 g, 4.23 mmol) in Et₂O was lithiated with a 1.64 M solution of *tert*-butyllithium (10 mL, 16.4 mmol) at -78°C and then treated with 2-methyl-2-nitrosopropane (0.92 g, 10.6 mmol). The reaction mixture was stirred for 1 h at -78°C and then left overnight at room temperature. The crude hydroxyamine, containing a small amount of the corresponding oxidized product, was obtained as a pale yellow solid (1.05 g, ca. 60% yield). This solid (0.53 g, 2.1 mmol) was oxidized without further

purification with freshly prepared Ag₂O (1.42 g) in CH₂Cl₂ to afford an orange precipitate (0.21 g, 0.84 mmol, 40%). Recrystallization from Et₂O gave **1** as orange prisms. M.p. 200–202 °C, ¹H NMR (270 MHz, CDCl₃): δ = 7.40 (s, 4H), 1.68 (s, 18H); FAB-MS (*m*-nitrobenzyl alcohol matrix): *m/z* 252 [*M*⁺+2]; elemental analysis calcd for C₁₄H₂₂N₂O₂: C 67.17, H 8.86, N 11.19; found: C 67.22, H 8.85, N 11.17. Crystal data: C₁₄H₂₂N₂O₂, *M*_r = 250.34, monoclinic, space group *P*2₁/*c* (no. 14) *a* = 10.572(1), *b* = 11.829(2), *c* = 11.658(2) Å, β = 96.720(8)°, *V* = 1447.9(3) Å³, *T* = 296 K, *Z* = 4, ρ_{calcd} = 1.148 g cm⁻³, μ(Cu_{Kα}) = 6.16 cm⁻¹; of 2417 total reflections, 2281 were independent; *R* = 0.081 and *R*_w = 0.100 for 1754 reflections with *I* > 3σ(*I*).^[15]

2: 1,2,4,5-Tetramethoxybenzene (1.0 g, 5.3 mmol) in Et₂O (60 mL) was lithiated with a 1.6 M solution of *n*-butyllithium (19.3 mL, 32.0 mmol) in the presence of TMEDA (7.7 g, 66 mmol) at –78 °C and then treated with 2-methyl-2-nitrosopropane (5.5 g, 63.2 mmol). The reaction mixture was stirred for 1 h at –78 °C and then left overnight at room temperature. The crude hydroxylamine, containing a small amount of the corresponding diradical, was obtained as a brown solid (0.44 g, ca. 23% yield) and oxidized as for **1**. Recrystallization from Et₂O gave **2** as red bricklike crystals. M.p. 252 °C; FAB-MS (*m*-nitrobenzyl alcohol matrix): *m/z* 372 [*M*⁺+2]; elemental analysis calcd for C₁₈H₃₀N₂O₆: C 58.36, H 8.16, N 7.56; found: C 58.61, H 8.13, N 7.50. Crystal data: C₁₈H₃₀N₂O₆, *M*_r = 370.44, triclinic, space group *P*1 (no. 2) *a* = 19.087(2), *b* = 19.288(2), *c* = 6.261(2) Å, α = 92.89(2), β = 106.48(2), γ = 86.48(2)°, *V* = 504.4(2) Å³, *T* = 296 K, *Z* = 1, ρ_{calcd} = 1.217 g cm⁻³, μ(Cu_{Kα}) = 7.55 cm⁻¹; of 1604 total reflections, 1493 were independent; *R* = 0.071 and *R*_w = 0.084 for 1240 reflections with *I* > 3σ(*I*). The structure was solved by direct methods, and the refinement converged with the full-matrix least-squares method of the TEXSAN program (version 1.6, Molecular Structure Corporation).^[15]

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Adaptation of the Barton Reaction to Carborane Chemistry: The Synthesis and Reactivity of 2-Hydroxyimino-1-hydroxymethylnona-*B*-methyl-1,12-dicarba-*closo*-dodecaborane(12)**

Axel Herzog, Carolyn B. Knobler, and M. Frederick Hawthorne*

In memory of Sir Derek H. R. Barton

Recently, we reported the synthesis of deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane(12) (**1**) by electrophilic methylation of 1,12-dicarba-*closo*-dodecaborane(12) with methyl trifluoromethanesulfonate (methyltriflate). Permethylated 1,12-dicarba-*closo*-dodecaborane(12) (**2**) was obtained by a similar method from 1,12-dimethyl-1,12-dicarba-*closo*-dodecaborane(12).^[1] Since this initial report, preparations of other permethylated polyhedral boranes have appeared.^[2, 3] These results, and those to follow, establish “camouflaged” carboranes (and similarly constituted polyhedral boranes) as a new branch of polyhedral borane chemistry with compounds that show novel structure–reactivity relationships and new applications in chemistry. Species **1** and **2** provide a unique hydrocarbon surface due to their methyl substituents. This lipophilic surface offers excellent solubility and improved stability and, most importantly, it allows chemical transformations at the boron cluster surface which are independent

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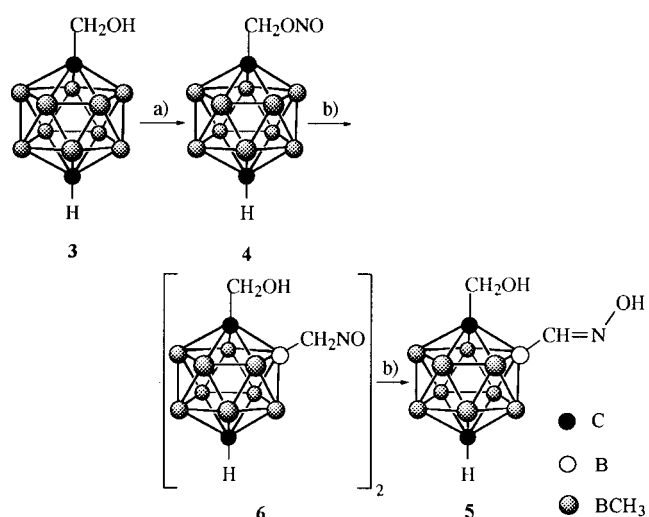
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of the delocalized polyhedral cage bonding. The utility of **1** as a synthetic intermediate has already been demonstrated by its facile photochlorination to produce decakis(dichloromethyl)-1,12-dicarba-*closo*-dodecarborane.^[4] Since reactions of this type are characteristic of aliphatic hydrocarbons, both **1** and **2** should be viewed as such.

Here we focus on the exclusive functionalization of **1** at one of its ten available methyl groups, which leads to an isomerically pure product.^[5] Normal radical-mediated reactions of hydrocarbons are generally nonselective, and under stoichiometric control alone mono- or disubstituted products derived from **1** or **2** cannot be obtained. However, an intramolecular regiospecific radical reaction capable of activating the C–H bonds of pendant methyl groups was viewed as an attractive approach. Such a reaction is the well-known Barton reaction,^[6] the photochemical decomposition of a nitrite to produce both NO and an alkoxy radical, both in close proximity to a C–H bond. The latter is most often present in a methyl group with a rigid and favorable orientation with respect to the nitrite functionality. Mechanistic studies of the Barton reaction have demonstrated that a cyclic six-membered transition state, containing the alkoxy radical and the targeted C–H bond, results in a formal 1,5-hydrogen shift^[7] followed by collapse of the NO-alkyl radical pair to form the corresponding nitroso derivative. Isomerization of the latter leads to the observed oxime.

This reaction can be applied to the case at hand if a suitable nitrite functionality is attached to a carbon vertex of **1** since the NO and CH₂O[•] photointermediates would then be surrounded by a forest of methyl groups. Consequently, the nitrite **4**, derived from deca-*B*-methyl-1-hydroxymethyl-1,12-dicarba-*closo*-dodecarborane(12) (**3**) was prepared. The synthesis of **3** was achieved by lithiation of **1** with methyl lithium and subsequent addition of paraformaldehyde. The nitrite **4** was obtained by reaction of **3** with nitrosyl chloride in pyridine.^[8] In comparison to organic nitrites,^[9] **4** is more sensitive to moisture, especially in the presence of acids and bases. The purity of **4** may be determined from the ¹H NMR spectrum since the signal due to the methylene protons shifts from $\delta = 3.28$ in **3** to $\delta = 4.39$ in **4** in [D₆]benzene.

The time required for the photolysis of **4** can be monitored by ¹H NMR spectroscopy, by observing the disappearance of the characteristic nitrite methylene resonance at $\delta = 4.39$. The reaction time for the photolysis of **4** is dependent upon its concentration in benzene and ranges from 24 h (2.6×10^{-2} mol L⁻¹) to 60 h (8.3×10^{-3} mol L⁻¹). Furthermore, the composition of the resulting product mixture varied. In the first case, the predicted product, the hydroximinoalcohol **5**, was isolated by preparative thin-layer chromatography in 42% yield, while the alcohol **3** was recovered in 25% yield. With a less concentrated solution, the yields of **5** and **3** were 25 and 20%, respectively, and the nitroso dimer reaction intermediate **6** could be isolated in 30% yield (Scheme 1). The ¹H NMR spectrum of **6** in [D₈]toluene at 97 °C indicates, in contrast to previous reports,^[10] neither thermal rearrangement to **5** nor dissociation into its monomeric components. Hence, the rearrangement from **6** to **5** is apparently initiated by UV light, and the reaction rate is dependent upon the pathlength through benzene.



Scheme 1. Barton reaction adapted for carborane chemistry. a) NOCl, C₆H₅N/C₆H₆; b) UV light, C₆H₆, 24–60 h.

Recrystallization of **5** from benzene afforded single crystals suitable for an X-ray crystallographic analysis.^[11a] The unit cell contains two crystallographically unrelated molecules of **5**, herein labeled as A and B (Figure 1). Two molecules of A form a dimer with twofold rotation symmetry by hydrogen

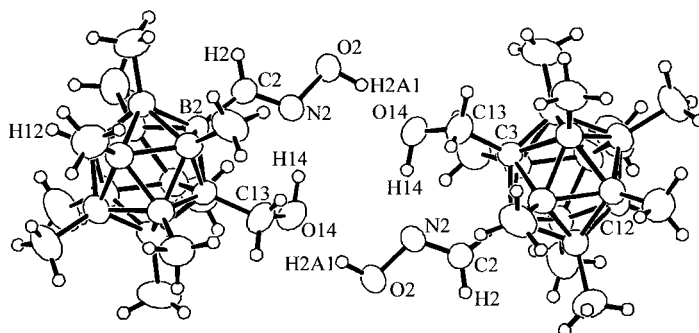


Figure 1. ORTEP representation of the crystal structure of **5**. Of the two crystallographically nonrelated molecules A (*C*₂ symmetry) and B (*C*_i symmetry), molecule A is shown. Selected bond lengths [Å] and angles [°]: O2–H2A1 0.78(6), H^{•••}O 1.92(6), O2^{•••}O14 2.678(4), C2–N2 1.266(5), B2–C2 1.572(6), C1–C13 1.528(6); O–H^{•••}O 162(6), C1–C13–O14 114.7(4), B2–C2–N2 122.1(4), C2–N2–O2 113.6(3).

bonding between the oxime hydrogen and the alcohol oxygen atoms (O–H 0.93(4), H^{•••}O 1.76(4), O^{•••}O 2.672(3) Å, O–H^{•••}O 165(3)°). Two molecules of B also form a dimer by means of the same type of hydrogen bonding (O–H 0.89(4), H^{•••}O 1.87(4), O^{•••}O 2.723(5) Å, O–H^{•••}O 158(4)°). Each molecule also contains an intramolecular hydrogen bond between the alcohol hydrogen atom and the nitrogen atom of the oxime (O–H 0.99(4) and 0.90(5) Å, H^{•••}N 1.75(4) and 1.81(5) Å, O^{•••}N 2.715(3) and 2.698(5) Å, O–H^{•••}N 164(4) and 171(5)°). The structural properties of the ten-membered HNO ring system forces the oxime into an exclusively *trans* solid-state configuration. The ¹H NMR data obtained for **5** show no indication of the presence of the *cis* isomer in solution. The length of the C–N double bond in **5** (mean 1.255 Å) is not significantly shorter

than those of typical oximes, including bulky substituted ketoximes.^[12] The carborane cage, therefore, has no apparent electron-withdrawing effect on the oxime functionality.

X-ray analysis of a single crystal of **6**^[11b] revealed that it is a centrosymmetric dimer linked by an N–N bond of 1.272(6) Å. This distance is in total agreement with the N–N bond of

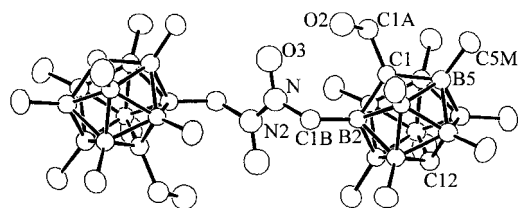
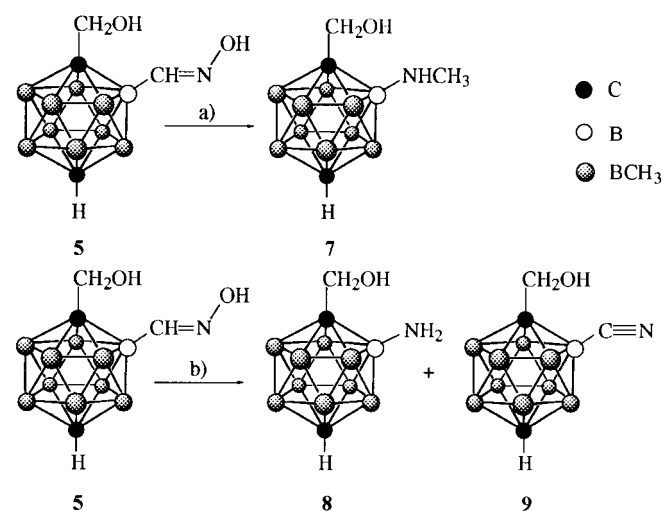


Figure 2. ORTEP representation of the crystal structure of **6**. Hydrogen atoms of the methyl groups are omitted for clarity. Selected bond lengths [Å] and angles [°]: N–N2 1.272(6), N–O3 1.293(6), O2...H 1.2, O3...H 1.6, O2O3 2.746(5); O3–N–N2 119.2(4)°.

organic nitroso dimers.^[13] An O–H...O hydrogen bond links the CH₂OH ligand to the oxygen atom of CH₂NO of the same carborane cage (O–H 1.2, O...H 1.6, O...O 2.746(5) Å). The six atoms of the ligand that link the two carborane moieties together (C1B, N2B, O3B) are coplanar within 0.008 Å.

A preliminary study investigated the possible reduction of **5** to the corresponding aminomethyl derivative. However, the methyl amino compound **7** was isolated in 75% yield when **5** was treated with LiAlH₄. The formation of the B–NHCH₃ moiety can be explained as a Beckmann rearrangement under reductive conditions. To the best of our knowledge, this is the first observation of a Beckmann rearrangement of a boron-substituted oxime.^[14] The yield of **7** is 45% if **5** is refluxed with diisobutylaluminum hydride (DIBALH, 10 equiv) in toluene for 12 h, but no reduction of the alcohol function was observed.^[15] The reduction of **5** with H₂/Pd on C^[16] in absolute ethanol in the presence of dry hydrogen chloride is exothermic and leads unexpectedly to the amine **8**. Nitrile **9** can be isolated as a by-product, as a result of a dehydration reaction (Scheme 2).



Scheme 2. Reduction of **5**. a) LiAlH₄, THF, reflux; b) H₂/Pd on C, EtOH/HCl, 60 °C.

The photochemical conversion of **4** into **5** is the first example of the application of the Barton reaction to organo-metallic syntheses and opens new dimensions in carborane chemistry. The deprotonation of the CH vertices of **1** provides valuable information on the stability and reactivity of deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane(12). We are currently exploring the use of **5** as a synthetic intermediate while further developing hydrocarbon functionalization chemistry as well as the application of the Barton reaction to other methylated carborane derivatives.

Experimental Section

Standard Schlenk-line techniques were used for the preparation of **3** and **4** and for the photolysis of **4**. The THF solvent was purified before use by distillation from sodium/benzophenone. The benzene solvent was distilled from potassium, and pyridine was distilled from calcium hydride. Additionally, benzene was degassed by two freeze-pump-thaw cycles. All reactions were carried out under argon. Compound **1**^[1] and nitrosyl chloride^[9] were prepared according to methods described in the literature. Paraformaldehyde (Fisher) was stored in a desiccator over concentrated sulfuric acid; methylolithium, LiAlH₄, DIBALH, H₂, and 5% Pd on carbon were purchased from Aldrich and used without further purification. The photolysis reaction was carried out with a 450W Hanovia high-pressure quartz mercury-vapor lamp (Ace Glass Inc.).

3: A 1.4M solution of MeLi (2.6 mL, 3.7 mmol) in Et₂O was added dropwise to a solution of **1** (1.00 g, 3.51 mmol) in THF at room temperature, and the mixture was stirred for 5 h. Solid paraformaldehyde (0.11 g, 3.7 mmol) was added, and the mixture was allowed to react for 30 min at room temperature and then for an additional 15 min at 50 °C. After hydrolysis of the mixture with dilute aqueous hydrochloric acid, the organic layer was separated from the water phase, the latter was extracted twice with Et₂O, and the combined organic phases were dried over MgSO₄. The solvent was removed under reduced pressure and the remaining off-white solid was purified by chromatography on silica gel (Et₂O/pentane 1/3) to yield **3** (*R*_f = 0.55) as a colorless solid (0.94 g, 85%); m.p. > 350 °C. ¹H NMR (400.13 MHz, CDCl₃): δ = 3.50 (s, 2H, CH₂OH), 2.05 (s, 1H, CH), 1.20 (brs, 1H, OH), 0.06, 0.03 (2 × s, 15H, BCH₃); [¹H]¹³C NMR (100.62 MHz, CDCl₃): δ = 78.43, 75.21 (2 × s, carboranyl C), 61.35 (CH₂OH), –4.04 (br, BCH₃); [¹H-coupled]¹¹B NMR (160.46 MHz, Et₂O): δ = –7.3, –8.6 (2 × s, 5B, BCH₃); IR (KBr): $\tilde{\nu}$ = 3444, 2963, 2908, 1434, 1322, 1261, 1099, 1044, 1018, 800 cm^{–1}; HR-MS (EI): *m/z* calcd 314.3613, found 314.3615 [*M*⁺].

4: Nitrosylchloride (0.66 g, 10.0 mmol) was condensed into a frozen solution of **3** (0.90 g, 2.86 mmol) in benzene (20 mL) and pyridine (20 mL) at –78 °C. The mixture was allowed to warm to room temperature and stirred for an additional 30 min. All volatile components were removed in vacuo, and **4** was isolated (0.93 g, 95%) by extraction with pentane (three times) followed by removal of the solvent. An analytically pure sample was obtained by repeated recrystallization from pentane; m.p. > 350 °C. ¹H NMR (400.13 MHz, C₆D₆): δ = 4.39 (s, 2H, CH₂ONO), 1.39 (s, 1H, CH), 0.06, 0.03 (2 × s, 15H, BCH₃); [¹H]¹³C NMR (100.62 MHz, C₆D₆): δ = 75.91 (br, CH), 66.21 (br, CH and CCH₂ONO),^[17] –3.91 (br, BCH₃); [¹H-coupled]¹¹B NMR (160.46 MHz, pentane): δ = –7.7, –8.6 (2 × s, 5B, BCH₃); IR (KBr): $\tilde{\nu}$ = 2956, 2909, 2833, 1673, 1434, 1322, 1261, 1190, 1150, 1117, 1046, 1014, 923, 800 cm^{–1}; HR-MS (EI): *m/z* calcd 343.3514, found 343.3506 [*M*⁺].

5: A solution of the nitrite **4** (0.90 g, 2.62 mmol) in benzene (100 mL) was placed in a 150-mL pyrex Schlenk tube and irradiated with a high-pressure quartz mercury-vapor lamp for 20 h. During irradiation, the reaction mixture was air-cooled with a ventilation device. The solvent was removed in vacuo, and the remaining off-white solid was purified by chromatography on silica gel (Et₂O/pentane 1/4) to yield **5** (0.38 g, 42%, *R*_f = 0.45) as a colorless solid; m.p. > 350 °C. ¹H NMR (400.13 MHz, C₆D₆): δ = 9.95 (brs, 1H, N=OH), 7.79 (s, 1H, CH=N), 6.06 (brs, 1H, OH), 3.52 (s, 2H, CH₂OH), 1.37 (s, 1H, CH), 0.29 (s, 6H, BCH₃), 0.01 (s, 6H, BCH₃), –0.03 (s, 15H, BCH₃); ¹H NMR (400.13 MHz, CDCl₃): δ = 10.10 (brs, 1H, N=OH), 7.58 (s, 1H, CH=N), 3.52 (s, 2H, CH₂OH), 2.13 (s, 1H, CH), 0.17

(s, 6H, BCH₃), 0.15 (s, 6H, BCH₃), 0.08 (s, 9H, BCH₃), 0.01 (br s, 6H, BCH₃); ¹H¹³C NMR (100.62 MHz, CDCl₃): δ = 152.50 (br, BCH=NOH), 79.70, 75.63 (2 × s, carboranyl C), -3.71 (br, BCH₃); ¹H-coupled¹³B NMR (160.46 MHz, Et₂O): δ = -6.2 (s, 4B, BCH₃), -7.0 (s, 3B, BCH₃), -8.1 (s, 5B, BCH₃), -11.2 (s, 1B, BCH=NOH); HR-MS (EI): *m/z* calcd 344.3593, found 344.3593 [*M*⁺+H].

6: Nitrite **4** (1.00 g, 2.91 mmol) dissolved in benzene (350 mL) was allowed to react in a 500-mL pyrex Schlenk tube for 48 h, and worked up as described for **5**. Chromatography on silica gel (Et₂O/pentane 1/4) provided **6** (0.38 g, 30 %, *R*_f = 0.35) as a colorless solid and **5** (25 %); m.p. > 350 °C. ¹H NMR (400.13 MHz, CDCl₃): δ = 5.05 (br s, 2H, OH), 4.39 (s, 4H, CH₂NO), 3.60 (s, 4H, CH₂OH), 2.12 (s, 2H, CH), 0.23 (s, 12H, BCH₃), 0.13 (s, 12H, BCH₃), 0.06 (s, 18H, BCH₃), 0.062 (s, 12H, BCH₃); ¹H¹³C NMR (100.62 MHz, CDCl₃): δ = 80.00, 76.10 (2 × s, carboranyl C), 61.18 (s, CH₂OH), 49.40 (br, CH₂NO), -3.70, -5.70 (br, BCH₃); ¹H-coupled¹³B NMR (160.41 MHz, Et₂O): δ = -6.9 (s, 5B, BCH₃), -8.3 (s, 4B, BCH₃), -12.2 (s, 1B, BCH₂NO); HR-MS (EI): *m/z* calcd 344.3593, found 344.3603 [*M*⁺+H].

7: Variation a: A solution of **3** (0.20 g, 0.58 mmol) in THF (30 mL) was added to a suspension of LiAlH₄ (0.13 g, 3.48 mmol) at 0 °C. The mixture was allowed to warm to room temperature, and then refluxed for 2 h and finally poured onto ice. Dilute NaOH solution was added, and the product mixture was extracted with Et₂O. Variation b: A 1 M solution of DIBAL in toluene (5.8 mL, 5.8 mmol) was added to a solution of **3** (0.20 g, 0.58 mmol) in toluene (20 mL). The reaction mixture was refluxed for 8 h and worked up as described for variation a. In both cases, the solvent was removed in vacuo and the remaining off-white solid was purified by chromatography on silica gel (Et₂O/pentane/NEt₃ 1/3/0.1) to provide **7** as a colorless solid (variation a: 0.14 g, 75 %, *R*_f = 0.4; variation b: 86 mg, 45 %); m.p. > 350 °C; ¹H NMR (400.13 MHz, CDCl₃): δ = 4.30–3.70 (brs, 1H, NHCH₃), 3.67 (s, 2H, CH₂OH), 2.62 (s, 3H, NHCH₃), 2.06 (s, 1H, CH), 0.24, 0.22 (2 × s, 12H, BCH₃), 0.02 (s, 6H, BCH₃), 0.00 (s, 3H, BCH₃), -0.07 (s, 6H, BCH₃); ¹H¹³C NMR (100.62 MHz, CDCl₃): δ = 74.2 (brs, both carboranyl C), 62.5 (s, CH₂OH), 31.2 (s, NHCH₃), -3.71 (brs, BCH₃); ¹H-coupled¹³B NMR (160.46 MHz, Et₂O): δ = -2.9 (s, 1B, BNHCH₃), -8.2 (s, 4B, BCH₃), -9.7 (s, 2B, BCH₃), -10.2 (s, 2B, BCH₃), -11.2 (s, 1B, BCH₃); HR-MS (EI): *m/z* calcd 329.3722, found 329.3721 [*M*⁺].

8 and 9: A solution of oxime **5** (0.25 g, 0.72 mmol) in absolute ethanol (30 mL) was hydrogenated at room temperature with palladium (0.1 g, 5 % Pd on carbon) for 3 h. During the reaction, dry hydrogen chloride was slowly passed through the solution. After 5 min an exothermic reaction occurred. The reaction mixture was stirred for a further 2.5 h, and filtered through celite. The ethanol was removed in vacuo, and the remaining off-white solid was purified by chromatography on silica gel (Et₂O/pentane/NEt₃ 1/4/0.1) to yield **8** (0.10 g, 45 %, *R*_f = 0.45) and **9** (71 mg, 30 %, *R*_f = 0.65) as colorless solids.

8: M.p. > 350 °C; ¹H NMR (400.13 MHz, CDCl₃): δ = 3.68 (s, 2H, CH₂OH), 2.10 (s, 1H, CH), 0.19 (s, 6H, BCH₃), 0.11 (s, 6H, BCH₃), 0.05 (s, 9H, BCH₃) - 0.05 (s, 6H, BCH₃); ¹H¹³C NMR (100.62 MHz, CDCl₃): δ = 77.5, 75.2 (2 × s, carboranyl C), 62.6 (s, CH₂OH), -4.9 (br, BCH₃); ¹H-coupled¹³B NMR (160.46 MHz, Et₂O): δ = -3.7 (s, 1B, BNH₂), -9.0 (s, 4B, BCH₃), -10.1 (s, 2B, BCH₃), -10.9 (s, 2B, BCH₃), -11.8 (s, 1B, BCH₃); HR-MS (EI): *m/z* calcd 315.3565, found 315.3559 [*M*⁺].

9: M.p. > 350 °C; ¹H NMR (400.13 MHz, CDCl₃): δ = 3.61 (s, 2H, CH₂OH), 2.21 (s, 1H, CH), 0.31 (s, 6H, BCH₃), 0.27 (s, 6H, BCH₃), 0.10 (s, 6H, BCH₃), 0.08 (s, 3H, BCH₃), 0.06 (s, 6H, BCH₃); ¹³C¹H NMR (100.62 MHz, CDCl₃): δ = 122.5 (brs, BCN), 80.5, 75.2 (2 × s, carboranyl C), 60.4 (s, CH₂OH), -4.5 (br, BCH₃); ¹B¹H coupled NMR (160.46 MHz, Et₂O): δ = -6.4 (s, 1B, BCH₃), -7.4 (s, 4B, BCH₃), -8.2 (s, 2B, BCH₃), -8.9 (s, 2B, BCH₃), -18.1 (s, 1B, BCN); HR-MS (EI) (*m/z*): calcd 325.3409, found 325.3415 [*M*⁺].

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calculations, but parameters were not refined. Methyl and methylene hydrogen atoms were placed in calculated positions. Hydrogen atoms were assigned isotropic displacement values based approximately on the value for the attached atom. The largest peak maximum and minimum on a final difference electron density map were 0.21 and $-0.25 \text{ e } \text{\AA}^{-3}$. Scattering factors for hydrogen atoms for both **5** and **6** were obtained from Stewart et al.^[19] and those for other atoms were taken from ref. [19]. Programs used in this work include locally modified versions of the following programs: CARESS (Broach, Coppens, Becker, and Blessing), peak-profile analysis, Lorentzian and polarization corrections; ORFLS (Busing, Martin, and Levy), structure-factor calculation and full-matrix least-squares refinement; SHELXL (Sheldrick), crystal structure refinement; SHELX86 (Sheldrick), crystal structure solution; ORTEP (Johnson). 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-101178. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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A Photoluminescent Copper(I) Complex with an Exceptionally High $\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}$ Redox Potential: $[\text{Cu}(\text{bfp})_2]^+$ (bfp = 2,9-bis-(trifluoromethyl)-1,10-phenanthroline)**

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The continued exploration of copper(I) bis(1,10-phenanthroline) complexes primarily results from their interesting photophysical properties.^[1] In these systems it has been established that emission originates from low-lying metal-to-

ligand charge transfer (MLCT) excited states.^[2] Since these states are best described as copper in the +2 oxidation state, it is believed that these pseudotetrahedral copper(I) complexes reorganize towards square-planar geometry in the excited state.^[3] Substituents at the 2 and 9 positions reduce the degree of excited-state distortion,^[3, 4] leading to room-temperature emission for most copper(I) complexes of 2,9-disubstituted-1,10-phenanthrolines.^[5] Photochemical studies of $[\text{Cu}(\text{N}-\text{N})_2]^+$ complexes (N–N = 1,10-phenanthroline ligand) with 2,9-dialkyl and 2,9-diaryl substituents have demonstrated that the steric bulk of the substituents has a profound effect on the ground-state electrochemistry and the emission properties of the complexes in solution.^[3, 4, 5b,g, 6] Bulkier substituents increase the $\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}$ redox potential by stabilization of the copper(I) species, and increase both the lifetimes and energies of the MLCT excited states.

Metal complexes of electron-deficient ligands are often studied as catalysts due to their high chemical stability and, in certain cases, enhanced reactivity.^[7] Since copper(I) complexes have been widely studied in photocatalytic processes,^[1b,c, 8] the effects of electron-withdrawing groups on the photochemistry of these complexes are of interest. Here we report the first investigation of the copper(I) complex cation $[\text{Cu}(\text{bfp})_2]^+$ (bfp = 2,9-bis(trifluoromethyl)-1,10-phenanthroline). In comparison to previously studied luminescent $[\text{Cu}(\text{N}-\text{N})_2]^+$ complexes, the trifluoromethyl groups dramatically perturb the electronic structure of the complex, and consequently enhance the ability of the copper(I) complex to act as a photooxidant.

The air-stable complex $[\text{Cu}(\text{bfp})_2](\text{PF}_6)$ was characterized by ^1H NMR spectroscopy, mass spectrometry, and X-ray crystallography.^[9] An ORTEP view of the cation is shown in Figure 1. The structure of $[\text{Cu}(\text{bfp})_2]^+$ resembles the known structures of the $[\text{Cu}(\text{dmp})_2]^+$ complex (dmp = 2,9-dimethyl-1,10-phenanthroline).^[10] However, there are notable differences. In the solid state, the $[\text{Cu}(\text{dmp})_2]^+$ cation tends to show variable degrees of distortion from D_{2d} symmetry, which has

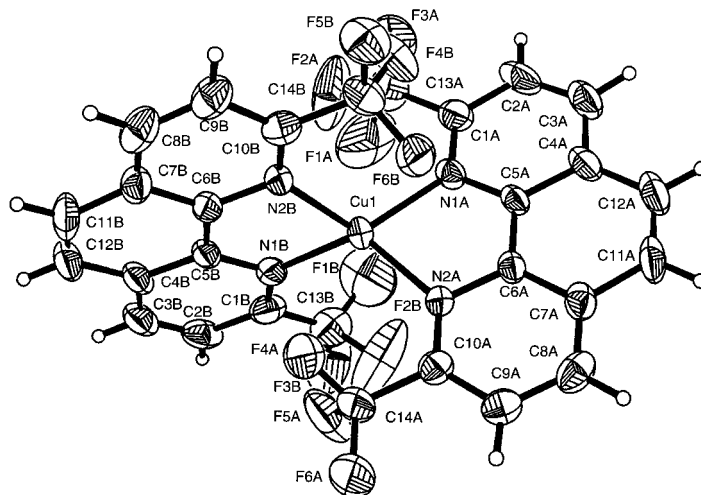


Figure 1. ORTEP diagram of the complex cation $[\text{Cu}(\text{bfp})_2]^+$. Selected bond distances [$\text{\AA}$] and angles [$^\circ$]: Cu1–N1A 2.037(6), Cu1–N2A 2.052(6), Cu1–N1B 2.025(6), Cu1–N2B 2.063(7); N1A–Cu1–N2A 83.3(3), N1B–Cu1–N1A 134.6(3), N1A–Cu1–N2B 118.4(3), N1B–Cu1–N2A 124.2(3), N2A–Cu1–N2B 117.0(3), N1B–Cu1–N2B 83.2(3).

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been attributed to crystal packing forces.^[11] The primary distortion usually seen is a flattening of the two ligands relative to one another (towards a square-planar geometry), with a dihedral angle of 72–83° between the ligand planes. However, in the structure of $[\text{Cu}(\text{bfp})_2]^+$ the interligand dihedral angle is 87°, closer to 90°, to minimize the interactions between the CF_3 groups on opposing ligands. In addition, the structure of the complex $[\text{Cu}(\text{bfp})_2]^+$ is significantly distorted from D_{2d} symmetry with a coordination geometry best described as distorted trigonal pyramidal (Figure 1).^[12] Unlike what is typically seen with complexes of $[\text{Cu}(\text{dmp})_2]^+$, there are no intermolecular ligand stacking interactions in $[\text{Cu}(\text{bfp})_2](\text{PF}_6)$.

The absorption and corrected emission spectra of $[\text{Cu}(\text{bfp})_2](\text{PF}_6)$ in dichloromethane at room temperature are shown in Figure 2. The absorption bands centered at 462 nm ($\epsilon_{462} = 10900 \text{ M}^{-1} \text{ cm}^{-1}$) are assigned to MLCT transitions, analogous to those of $[\text{Cu}(\text{dmp})_2]^+$.^[12] The excitation spectrum measured at 650 nm (not shown) parallels the absorption spectrum in the range of 400–500 nm. From the room-temperature emission spectrum, the free energy of the excited state is estimated to be 2.1 eV^[13] (Figure 2).

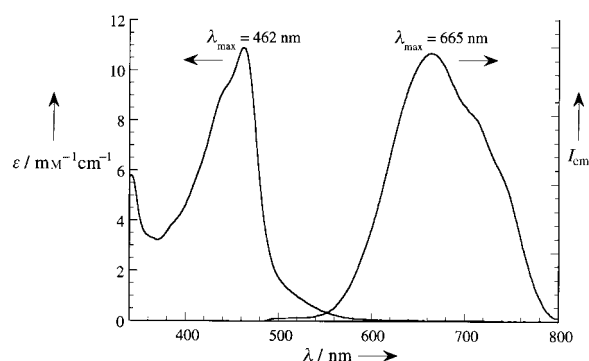


Figure 2. Absorption spectrum and corrected emission spectrum ($\lambda_{\text{ex}} = 450 \text{ nm}$) of $[\text{Cu}(\text{bfp})_2](\text{PF}_6)$ in CH_2Cl_2 at room temperature.

Excited-state lifetimes and quantum yields were determined at room temperature in deoxygenated dichloromethane. Data for the two well-studied complexes $[\text{Cu}(\text{dmp})_2]^+$ and $[\text{Cu}(\text{dpp})_2]^+$ (dpp = 2,9-diphenyl-1,10-phenanthroline) provide useful comparisons.^[5a,b] The lifetime of the excited state of $[\text{Cu}(\text{bfp})_2](\text{PF}_6)$ was 165 ns, which is approximately twice that of $[\text{Cu}(\text{dmp})_2](\text{PF}_6)$ ($\tau = 83 \text{ ns}$), yet shorter than that of $[\text{Cu}(\text{dpp})_2](\text{PF}_6)$ ($\tau = 243 \text{ ns}$).^[14] Significantly, the quantum yield for $[\text{Cu}(\text{bfp})_2]^+$ is approximately four times that for $[\text{Cu}(\text{dpp})_2]^+$, and approximately fourteen times that for $[\text{Cu}(\text{dmp})_2]^+$.^[15] The quantum yield for $[\text{Cu}(\text{bfp})_2]^+$ in dichloromethane is clearly one of the highest ever measured for a $[\text{Cu}(\text{N}-\text{N})_2]^+$ system, although the uncertainties associated with the determination of quantum yield preclude absolute ranking.^[5g] Among the three complexes, the trend observed for the quantum yields ($\text{dmp} < \text{dpp} < \text{bfp}$) is also the trend observed for the energies of the associated excited states.^[13] Examination of the nonradiative ($k_{\text{nr}} = (1 - \phi)/\tau$) and radiative ($k_{\text{r}} = \phi/\tau$) decay rate constants reveals that the trend in quantum yields is primarily due to changes in the

radiative decay rates. These results indicate that k_{r} values in these systems increase as excited-state energies increase, which is consistent with theory.^[16]

Cyclic voltammetry^[17] of $[\text{Cu}(\text{bfp})_2](\text{PF}_6)$ displays two reversible waves (both single-electron processes) that are assigned to a ligand-based redox couple^[18] ($E_{1/2} = -1220 \text{ mV}$ vs. saturated calomel electrode (SCE); $\Delta E_{\text{p}} = 70 \text{ mV}$; $i_{\text{pa}}/i_{\text{pc}} = 0.92$) and the $\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}$ couple^[2h, 5g, 18] ($E_{1/2} = +1550 \text{ mV}$ vs. SCE; $\Delta E_{\text{p}} = 62 \text{ mV}$; $i_{\text{pa}}/i_{\text{pc}} = 0.93$). To the best of our knowledge, this is the highest potential ever measured for a reversible $\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}$ couple in a mononuclear copper complex (Figure 3).^[19] The highly efficient electron-withdrawing nature of the CF_3 groups combined with their steric bulk result in a remarkable stabilization of the copper(II) oxidation state for $[\text{Cu}(\text{bfp})_2]^+$; the redox existence range (RER) of the copper(II) species is 2.77 V. The largest RER value previously reported for a $[\text{Cu}(\text{N}-\text{N})_2]^+$ system is 2.69 V.^[5g]

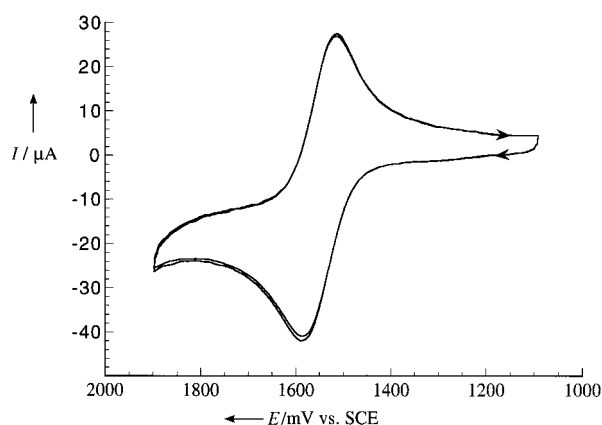


Figure 3. Cyclic voltammogram (two cycles) of $[\text{Cu}(\text{bfp})_2](\text{PF}_6)$ in CH_2Cl_2 . Conditions: 5 mM $[\text{Cu}(\text{bfp})_2](\text{PF}_6)$, 0.1 M $(\text{Bu}_4\text{N})(\text{PF}_6)$, glassy carbon working electrode, scan rate 0.3 V s^{-1} , internal reference $E_{1/2}(\text{ferrocene/ferrocenium}) = +450 \text{ mV}$.

Estimates of the energetics of $[\text{Cu}(\text{bfp})_2]^+$ in the excited state, $^*[\text{Cu}(\text{bfp})_2]^+$, reveal the potential use of the complex in photocatalytic and electron-transfer quenching processes. The excited-state potentials are $E(\text{Cu}^{*\text{II}}/\text{Cu}^{\text{II}}) = +920 \text{ mV}$ and $E(\text{Cu}^{\text{II}}/\text{Cu}^{*\text{I}}) = -590 \text{ mV}$ (vs. SCE).^[20] These data signify that $^*[\text{Cu}(\text{bfp})_2]^+$ is a very potent photooxidant, and also an effective photoreductant. For $^*[\text{Cu}(\text{bfp})_2]^+$ to act as a photooxidant however, a significant barrier to reductive quenching may limit the electron-transfer kinetics. This barrier results from the high inner-sphere reorganization energy associated with the repopulation of a $\text{d}\sigma^*$ orbital.^[6, 21] On the other hand, oxidative quenching of $^*[\text{Cu}(\text{bfp})_2]^+$, which involves removal of an electron from a ligand orbital with primarily π^* character, is expected to occur with much faster kinetics.^[2h, 21, 22] In addition, oxidative quenching with viologens can be anticipated to occur with very high cage-escape yields.^[2h] Thus, a photocatalytic cycle that generates the highly oxidizing $[\text{Cu}(\text{bfp})_2]^{2+}$ complex in the ground state can be envisioned. Investigations of $[\text{Cu}(\text{bfp})_2]^+$ in photocatalytic processes are in progress.

Experimental Section

[Cu(dmp)₂](PF₆) and [Cu(dpp)₂](PF₆) were prepared according to reference [2h].

[Cu(bfp)₂](PF₆): Ligand bfp^[24] (2 equiv) is added to [Cu(CH₃CN)₄](PF₆)^[23] (1 equiv) in deoxygenated CH₂Cl₂, and the solution is taken to dryness. Recrystallization (CH₂Cl₂/Et₂O) affords bright orange crystals in 76 % yield. ¹H NMR (CDCl₃): δ = 8.35 (d, H_{4,7}), 8.42 (s, H_{5,6}), 9.00 (d, H_{3,8}); FAB-MS: *m/z* (%): 695 (100) [*M*⁺].

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Solid-Phase Synthesis of Oligosaccharides: Construction of a Dodecasaccharide**

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The synthesis of combinatorial libraries^[1] of organic compounds for biological screening remains one of the severest bottlenecks in drug discovery and development. We have recently disclosed a reiterative approach^[2] to solid-phase synthesis of oligosaccharides^[3] that used thioglycosides as the carbohydrate donors and a photolabile linker,^[4] and culminated in the total synthesis of HPE, a heptasaccharide phytoalexin elicitor. Despite its efficiency, this methodology^[2] suffers from a) the presence of both α - and β -anomers at every cleavage stage and b) the need to reactivate the cleavage product prior to its possible reincorporation into the growing oligosaccharide chain on the solid phase. Herein we wish to report new solid-phase synthetic technology which provides solutions to both problems by incorporating an appropriate spacer between the photolabile linker and the anomeric position of the first glycoside, and which appears ideal for block-type oligosaccharide synthesis (Figure 1). The new technology allowed the construction of the stereochemically homogeneous dodecasaccharide **1** (see Scheme 2) which, to our knowledge, represents the largest oligosaccharide to be constructed on solid phase thus far. By virtue of its generality, this method could prove highly enabling for the construction of large and diverse libraries of oligosaccharides (see Figure 1).

The key elements of this new synthetic technology are demonstrated in Scheme 1. Thus, 5-hydroxy-2-nitrobenzaldehyde was loaded onto Merrifield resin in the presence of Cs_2CO_3 and $n\text{Bu}_4\text{NI}$, and the product was reduced with NaBH_4 to afford resin **6** (98 % yield over 2 steps).^[5] The β -phenolic ester **7** was obtained from thioglycoside **A**^[6] by reaction with 4-benzyloxybenzoic acid in the presence of NIS^[7] (84%; for abbreviations, see legends in schemes), followed by hydrogenation of the benzyl protecting group (72 %). Attachment of **7** to the solid support **6** by a Mitsunobu^[8] reaction furnished conjugate **8** (100 %),^[5, 9] and removal of the silyl group with $\text{HF}\cdot\text{py}$ afforded conjugate **9** (100 %). Structure **8** offers, by design, a) exclusively β -

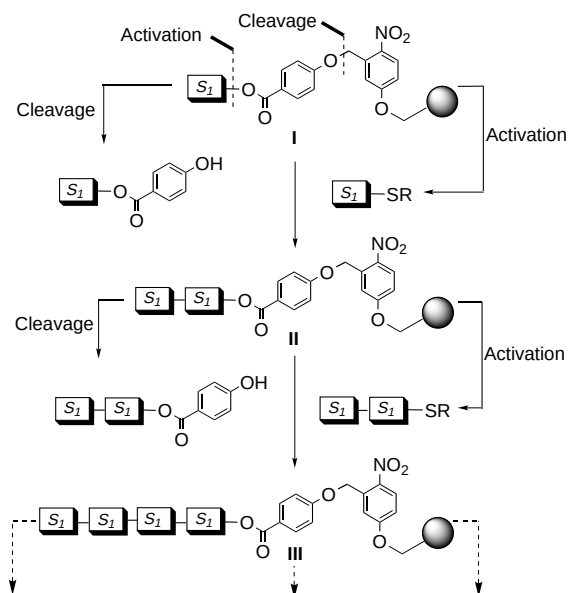
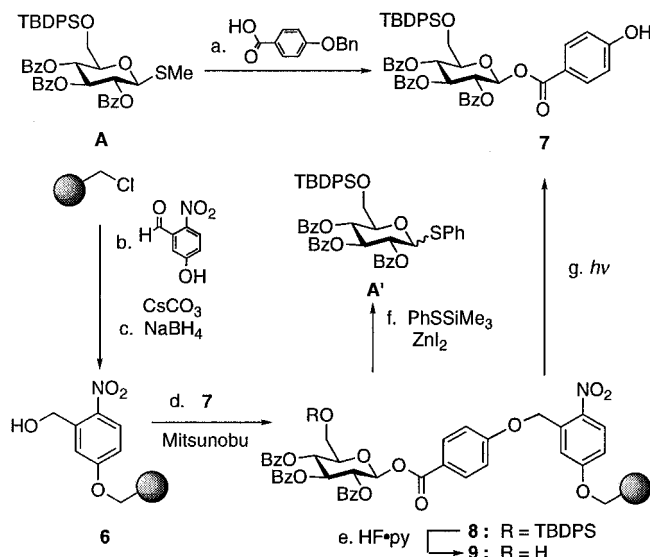


Figure 1. General block-type solid-phase strategy for the construction of complex oligosaccharides with a photolabile linker and thioglycoside donors.



Scheme 1. Synthesis of photolabile linker, loading and cleavage. Reagents and conditions: a) i. 4-benzyloxybenzoic acid (1.3 equiv), NIS (1.2 equiv), TfOH (cat.), CH_2Cl_2 , 25 °C, 2 h, 84%; ii. HCO_2NH_4 (10.0 equiv), 10% Pd/C, MeOH/THF (1/1, v/v), 25 °C, 2.5 h, 72%; b) 5-hydroxy-2-nitrobenzaldehyde (4.0 equiv), Cs_2CO_3 (4.0 equiv), $n\text{Bu}_4\text{NI}$ (0.1 equiv), DMF, 80 °C, 12 h; c) NaBH_4 (5.0 equiv), THF/EtOH (95/5, v/v), 0 °C, 4 h, 98%; d) **7** (3.0 equiv), $n\text{Bu}_3\text{P}$ (3.0 equiv), DIAD (3.0 equiv), $i\text{Pr}_2\text{NEt}$ (3.0 equiv), THF, 25 °C, 6 h, 100%; e) $\text{HF}\cdot\text{py}$, THF, 25 °C, 15 h; f) PhSiMe_3 (6.0 equiv), ZnI_2 (2.5 equiv), $n\text{Bu}_4\text{NI}$ (1.0 equiv), $\text{ClCH}_2\text{CH}_2\text{Cl}$, 40–45 °C, 3 h, 92%; g) $h\nu$, THF, 25 °C, 6 h, 95 %. Bn = benzyl; Bz = benzoyl; DIAD = diisopropyl azodicarboxylate; py = pyridine; NIS = *N*-iodosuccinimide; TfOH = trifluoromethanesulfonic acid.

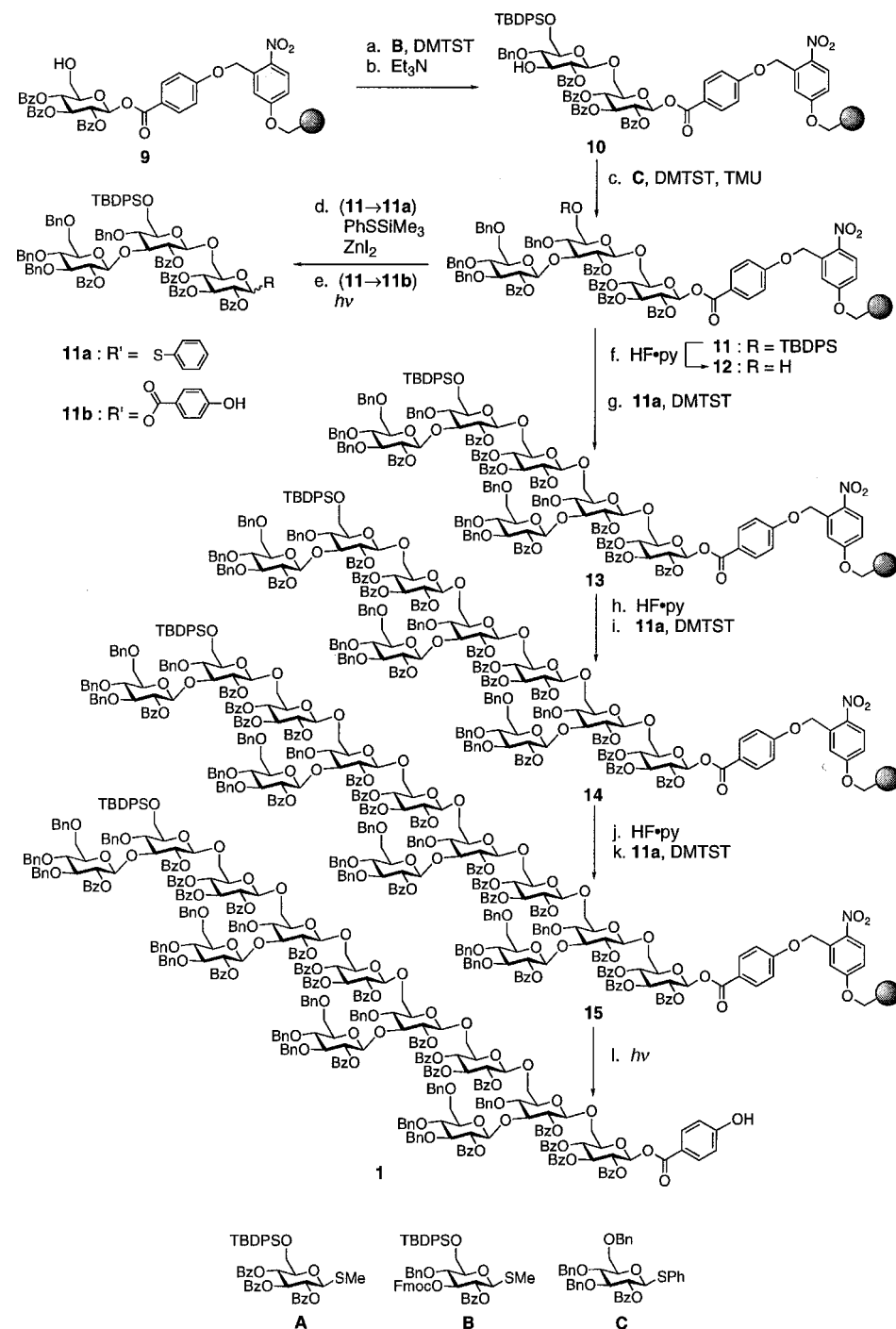
stereochemistry at the anomeric center, which is maintained throughout the synthetic scheme; b) the possibility of cleavage to a stereochemically homogeneous product **7** (ideal for analysis purposes and further elaboration); and c) the opportunity to cleave from the resin with simultaneous first-stage activation^[10] to a thioglycoside. The latter reactions were

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demonstrated by formation of compounds **7** (*hv*, THF, 25 °C, 95 %) and **A'**^[11] (PhSSiMe₃, ZnI₂, *n*Bu₄NI, 92 %),^[12] respectively (Scheme 1).

With the principle established, we proceeded to demonstrate its potential by targeting the dodecasaccharide **1** (Scheme 2) related to the phytoalexin elicitor family.^[13]



Scheme 2. Solid-phase synthesis of dodecasaccharide **1** with the key donors **A–C**. Reagents and conditions: a) **B** (3.0 equiv), DMTST (12.0 equiv), 4 Å MS, CH₂Cl₂, 25 °C, 12 h; b) Et₃N/THF (1/4, v/v), 25 °C, 1 h, 90 % over 2 steps; c) **C** (3.0 equiv), DMTST (12.0 equiv), TMU (12.0 equiv), 4 Å MS, CH₂Cl₂, 25 °C, 12 h, 78 %; d) PhSSiMe₃ (6.0 equiv), ZnI₂ (2.5 equiv), *n*Bu₄NI (1.0 equiv), ClCH₂CH₂Cl, 40–45 °C, 2 h, 76 %; e) *hv*, THF, 25 °C, 15 h, 63 % over 5 steps from **8**; f) HF·py, THF, 25 °C, 15 h; g) **11a** (3.0 equiv), DMTST (12.0 equiv), 4 Å MS, CH₂Cl₂, 25 °C, 12 h, 61 % over 2 steps; h) HF·py, THF, 25 °C, 15 h; i) **11a** (3.0 equiv), DMTST (12.0 equiv), 4 Å MS, CH₂Cl₂, 25 °C, 12 h, 56 % over 2 steps; j) HF·py, THF, 25 °C, 15 h; k) **11a** (3.0 equiv), DMTST (12.0 equiv), 4 Å MS, CH₂Cl₂, 25 °C, 12 h, 54 % over 2 steps; l) *hv*, THF, 25 °C, 20 h, 10 % overall yield from **8**. Bn = benzyl; Bz = benzoyl; DMTST = (dimethylthio)methylsulfonium triflate; py = pyridine; TBDPS = *t*-butyldiphenylsilyl; TMU = tetramethyl urea; MS = molecular sieves.

Scheme 2 summarizes the chemistry leading to the successful synthesis of this complex oligosaccharide. Thus, coupling of **9** to donor **B** with the activator DMTST^[14] and Fmoc removal (Et₃N) afforded the new conjugate **10** (90 % from **9**).^[15] Attachment of the third building block, thioglycoside **C**, onto the resin required both DMTST and tetramethyl urea, and furnished **11** (78 %), from which the silyl group was removed by exposure to HF·py in THF to afford **12**. Cleavage of the trisaccharide from polymer **11** under photolytic conditions (*hv*, THF, 25 °C) generated exclusively the β-anomer of **11b** in 63 % overall yield from **8** (Scheme 1). The protected trisaccharide was cleaved from the polymer **11** with concomitant activation by exposure to PhSSiMe₃/ZnI₂/*n*Bu₄NI at 40–45 °C, furnishing phenylthioglycoside donor **11a** (76 % yield). Building block **11a** was then loaded onto the polymer **12** by glycosidation with the DMTST method, affording the hexasaccharide-polymer conjugate **13** after desilylation (61 % from **11**). Reiteration of the process with trisaccharide **11a** led to dodecasaccharide conjugate **15** via intermediate **14**. Finally, cleavage from the resin was induced by photolysis (*hv*, THF, 25 °C), furnishing the targeted oligosaccharide **1** as a single stereochemical isomer (ca 10 % overall yield^[17] of isolated product from **8**, Scheme 1).

The advantages of this new technology include convergence for block-type constructions, high yielding glycosidation steps, maintenance of stereochemical integrity during loading and unloading, and flexibility. Strategies can now be devised and executed for the construction of multimembered

Table 1. Selected physical properties of compounds **1**, **11a**, and **11b**.

11a (β-anomer): $R_f = 0.49$ (silica gel, ethyl acetate/<i>n</i>-pentane 1/2); $[\alpha]_D^{25} = +29.8$ ($c = 1.00$, CHCl_3); IR (thin film): $\tilde{\nu} = 2926, 2857, 1732, 1602, 1453, 1364, 1264, 1094, 1070, 1027, 847, 748, 709 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.96\text{--}7.00$ (m, 60H, Ar-H), 5.66 (t, $J = 9.0 \text{ Hz}$, 1H), 5.28–5.21 (m, 2H), 5.15–5.09 (m, 3H), 4.86 (d, $J = 8.0 \text{ Hz}$, 1H), 4.73 (d, $J = 10.5 \text{ Hz}$, 1H), 4.65 (d, $J = 10.0 \text{ Hz}$, 1H), 4.59–4.39 (m, 7H), 4.25 (t, $J = 8.5 \text{ Hz}$, 1H), 3.83–3.76 (m, 5H), 3.72–3.66 (m, 3H), 3.59–3.55 (m, 2H), 3.52–3.50 (m, 1H), 3.38–3.36 (m, 1H), 0.98 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (125.7 MHz, CDCl_3): $\delta = 165.8, 165.4, 165.1, 164.5, 136.9, 138.6, 138.0, 137.7, 137.5, 135.8, 135.5, 133.7, 133.4, 133.1, 132.9, 132.8, 132.6, 132.1, 129.9, 129.8, 129.8, 129.7, 129.6, 129.6, 129.4, 129.0, 128.8, 128.7, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.6, 127.6, 127.5, 127.4, 127.3, 100.9, 100.1, 85.5, 83.0, 79.5, 78.5, 78.3, 75.9, 75.7, 75.6, 75.1, 75.0, 74.9, 74.1, 74.0, 73.9, 73.5, 70.8, 69.2, 68.7, 67.9, 62.5, 26.8, 19.8$; ES⁺ MS: calcd for $\text{C}_{103}\text{H}_{98}\text{O}_{20}\text{SSiNa}$ [$M + \text{Na}^+$] 1739, found 1739. 11b (β-anomer): $R_f = 0.23$ (silica gel, ethyl acetate/<i>n</i>-pentane 1/2); $[\alpha]_D^{25} = +10.1$ ($c = 1.00$, CHCl_3); IR (thin film): $\tilde{\nu} = 3387, 3068, 2931, 1735, 1606, 1452, 1265, 1092, 1070, 1026, 744, 706 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 8.04\text{--}7.00$ (m, 57H, Ar-H), 6.61 (d, 2H, $J = 9.0 \text{ Hz}$, Ar-H), 6.43 (bs, 1H), 6.00 (d, $J = 7.5 \text{ Hz}$, 1H, H_{A-1}), 5.82 (t, $J = 9.0 \text{ Hz}$, 1H), 5.65 (t, $J = 9.0 \text{ Hz}$, 1H), 5.36 (t, $J = 9.5 \text{ Hz}$, 1H), 5.25 (t, $J = 9.5 \text{ Hz}$, 1H), 5.14–5.07 (m, 2H), 4.88 (d, $J = 8.0 \text{ Hz}$, 1H), 4.74 (d, $J = 11.0 \text{ Hz}$, 1H), 4.58–4.38 (m, 7H), 4.24 (t, $J = 8.0 \text{ Hz}$, 1H), 4.00–3.94 (m, 2H), 3.85–3.78 (m, 3H), 3.69–3.50 (m, 6H), 3.30 (d, $J = 10.0 \text{ Hz}$, 1H), 0.95 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100.0 MHz, CDCl_3): $\delta = 165.6, 165.5, 165.1, 164.9, 164.7, 164.6, 164.0, 163.7, 160.8, 138.6, 138.1, 137.7, 137.5, 135.7, 135.5, 133.5, 133.3, 133.2, 133.1, 133.0, 133.0, 132.6, 132.3, 129.9, 129.8, 129.7, 129.6, 129.5, 128.8, 128.7, 128.7, 128.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.6, 127.6, 127.5, 127.3, 121.1, 120.6, 115.5, 115.2, 100.5, 100.2, 92.5, 83.0, 79.5, 78.1, 75.8, 75.7, 75.4, 75.2, 75.0, 74.9, 74.2, 73.9, 73.6, 72.7, 71.7, 71.0, 70.5, 69.3, 69.2, 66.6, 62.7, 26.7, 19.1$; ES⁺ MS: calcd for $\text{C}_{104}\text{H}_{98}\text{O}_{23}\text{SiNa}$ [$M + \text{Na}^+$] 1766, found 1765; ES[−] MS: calcd for $\text{C}_{104}\text{H}_{97}\text{O}_{23}\text{Si}$ [$M - \text{H}^-$] 1741, found 1741. 1: $R_f = 0.42$ (silica gel, ethyl acetate/<i>n</i>-pentane 1/1); $[\alpha]_D^{25} = -7.50$ ($c = 0.20$, CHCl_3); IR (thin film): $\tilde{\nu} = 3404, 3064, 2922, 2855, 1731, 1602, 1453, 1366, 1264, 1096, 1067, 1028, 746, 708 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.97\text{--}6.96$ (m, 192H, Ar-H), 6.62 (d, $J = 8.5 \text{ Hz}$, 2H, Ar-H), 6.11 (d, $J = 7.5 \text{ Hz}$, 1H, H_{A-1}), 5.85–5.76 (m, 4H), 5.69 (dd, $J = 8.5, 7.0 \text{ Hz}$, 1H), 5.47 (t, $J = 9.5 \text{ Hz}$, 1H), 5.34–5.28 (m, 4H), 5.25–5.03 (m, 12H), 4.90–4.67 (m, 12H), 4.57–4.23 (m, 25H), 4.17–3.92 (m, 12H), 3.86–3.36 (m, 32H), 3.30–2.83 (m, 12H), 0.87 (s, 9H, $\text{C}(\text{CH}_3)_3$); MALDI MS: calcd for $\text{C}_{347}\text{H}_{320}\text{O}_{82}\text{SiNa}$ [$M + \text{Na}^+$] 5869, found 5869.

combinatorial libraries of oligosaccharides for chemical biology and other studies. Table 1

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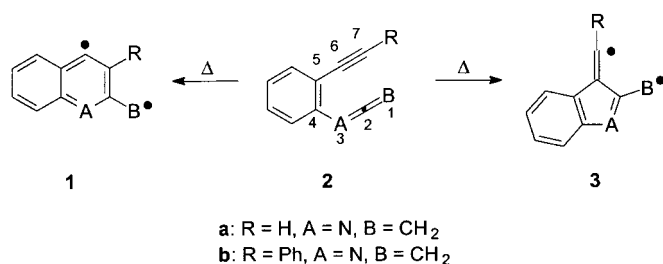
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Two Novel Thermal Biradical Cyclizations of Enyne-Ketenimines: Theory, Experiment, and Synthetic Potential**

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We recently reported a novel thermal C^2-C^6 cyclization of enyne-allenes **2** (A, B = carbon) to biradical **3**^[1] that completely displaces the well-known Myers–Saito (C^2-C^7) cycloaromatization^[2] to biradical **1** if an aryl substituent (R = phenyl) is attached at the alkyne terminus (Scheme 1). Because biradical intermediate **3** (A, B = carbon) can react in an intramolecular way to give formal $[4+2]$ ^[3] or $[2+2]$ ^[4] cycloadducts and ene products,^[5] it is a versatile intermediate for the construction of various ring systems.^[6]



Scheme 1. Biradical intermediates **1** and **3** for thermal C^2-C^7 and C^2-C^6 cyclizations, respectively.

The synthetic value of such biradical cyclizations should increase further if CH_n groups in the enyne-allene were replaced by heteroatoms. Indeed, a while ago enyne-ketenes (A = carbon, B = oxygen) were shown to undergo C^2-C^7 and C^2-C^6 cyclizations.^[7] We now report theoretical and experimental evidence that points to the occurrence of analogous biradical cyclizations in enyne-ketenimines (A = nitrogen, B = carbon), which makes these compounds interesting precursors for benzocarbazoles and quinolines.

To study the influence of substituents at the alkyne terminus on the reaction behavior of enyne-ketenimines we carried out quantum-chemical calculations. In contrast to our recent calculations on the thermal cyclization of enyne-allenes (A = CH, B = CH₂)^[8, 9] it was necessary in the present study to

include the annulated benzene ring, because otherwise the biradical intermediates are found to have a different electronic structure.^[10] A correct description of the biradical intermediates requires a multireference approach.^[11] However, because the biradical nature of the wave function develops only beyond the transition state (TS)—that is, in the density function theory (DFT) calculations [S^2] = 0 for all the transition states^[8]—the influence of substituents on the activation energy $\Delta E^\ddagger$ in both processes can be determined from DFT calculations. Consequently, activation energies were studied with a density functional approach in combination with a 6-31G* AO basis set, whereas a multireference configuration interaction (MR-CI) approach was used to compute the reaction energies (ΔE^r).^[12, 13]

Just as in the case of the enyne-allene (*Z*)-1,2,4-heptatrien-6-yne, the theoretical results (Table 1) suggest a change in the

Table 1. Summary of the calculated data. The energies of the reactants are in Hartree, and those for the other structures relative to the reactants are in kcal mol⁻¹. The energies of transition states are indicated in boldface.

Substituent	a: R = H	b: R = Ph
reactant 2 ^[a,b]	– 439.907358	– 670.050551
reactant 2 ^[a,c]	– 438.526790	–
C^2-C^7 cyclization		
$R_{C^2-C^7}$ = 2.1 Å ^[b]	23.4	30.0
$R_{C^2-C^7}$ = 2.0 Å ^[b]	25.3	33.1
$R_{C^2-C^7}$ = 1.93 Å ^[b]	25.8	34.1
$R_{C^2-C^7}$ = 1.8 Å ^[b]	23.9	31.1
$R_{C^2-C^7}$ = 1.43 Å (1) ^[c,d]	– 9.4	– 11 ^[e]
C^2-C^6 cyclization		
$R_{C^2-C^6}$ = 2.0 Å ^[b]	25.9	23.6
$R_{C^2-C^6}$ = 1.9 Å ^[b]	29.2	25.3
$R_{C^2-C^6}$ = 1.8 Å ^[b]	31.5	25.5
$R_{C^2-C^6}$ = 1.76 Å ^[b]	32.2	25.3
$R_{C^2-C^6}$ = 1.7 Å ^[b]	24.9	24.5
$R_{C^2-C^6}$ = 1.50 Å (3) ^[c,d]	15.2	4 ^[e]

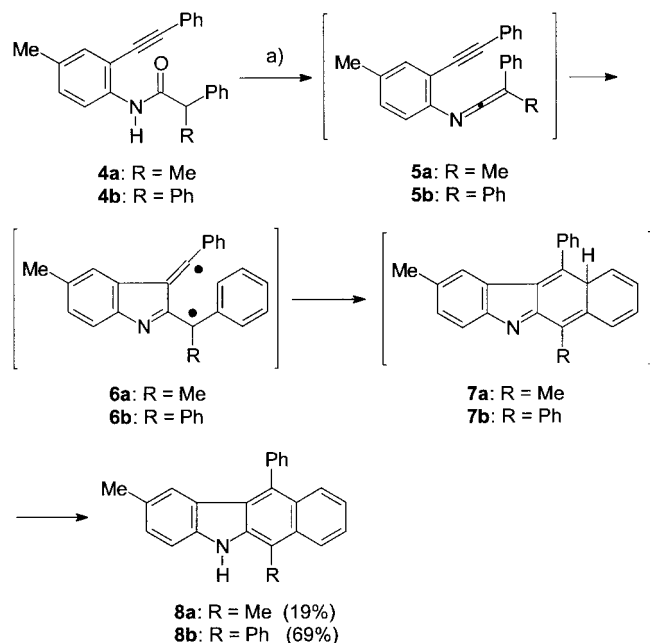
[a] $R_{C^2-C^7}$ = 3.55 Å, $R_{C^2-C^6}$ = 3.04 Å. [b] DFT(B3LYP) in combination with a 6-31G* basis set. [c] MR-CI + Q in combination with a double zeta polarization (DZP) basis set. [d] Biradical intermediate. [e] Reference [13].

regioselectivity of enyne-ketenimine cyclizations as a function of the group R at the alkyne terminus. While the C^2-C^7 cyclization **2a,b** → **1a,b** is exothermic for both systems, the alternative C^2-C^6 biradical cyclization is endothermic for **2a,b** → **3a,b**.^[13] Nevertheless, both cyclizations are kinetically controlled, because intra- or intermolecular follow-up reactions ($k > 10^6$ s⁻¹)^[14] of **1** and **3** are much more rapid than a ring-opening of biradical **1** or **3** to the enyne-ketenimine **2** (activation barrier > 17 kcal mol⁻¹).

For R = H our calculations predict an activation barrier $\Delta E^\ddagger$ of 26 kcal mol⁻¹ for the C^2-C^7 cyclization **2a** → **1a**, whereas it is much higher for a C^2-C^6 cyclization to **3a** ($\Delta E^\ddagger$ = 32 kcal mol⁻¹). Notably, the activation barrier increases to 34 kcal mol⁻¹ for the C^2-C^7 cyclization of **2b** to **1b** when H is replaced by Ph; however, it is decisively decreased for the C^2-C^6 cyclization of **2b** to **3b** ($\Delta E^\ddagger$ = 26 kcal mol⁻¹). The calculations confirm that the change from a C^2-C^7 cyclization to a C^2-C^6 ring closure is even more pronounced than with the corresponding enyne-allenes.^[9]

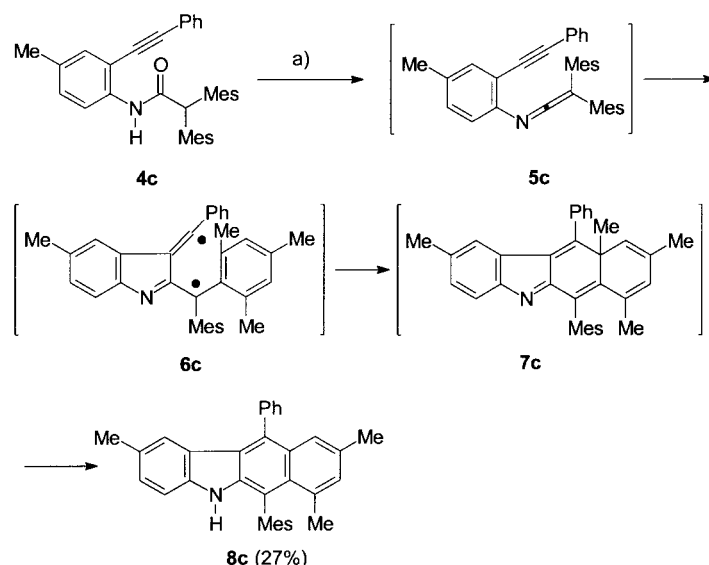
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To probe the above predictions, several enyne-ketenimines were prepared from the corresponding amides by standard procedures for simple ketenimines.^[15] As reported earlier,^[16] however, the desired enyne-ketenimines could not be isolated because under the reaction conditions they underwent thermal rearrangement in the sense of the anticipated thermal biradical cyclizations. Accordingly, when we tried to convert alkynylphenyl amides **4a,b** into enyne-ketenimines **5a,b**, benzocarbazoles **8a,b** were isolated directly (Scheme 2).^[17]



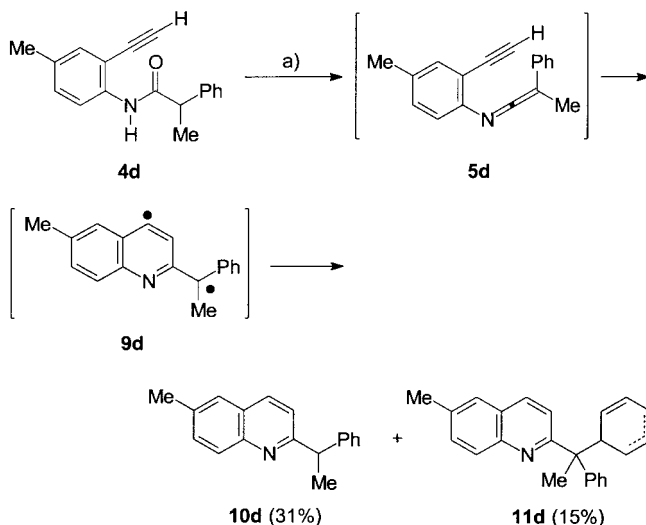
Scheme 2. Synthesis of benzocarbazoles **8a,b**. a) **8a**: Ph_3P , Br_2 , NEt_3 , CH_2Cl_2 , reflux, 15 h; **8b**: Ph_3P , Br_2 , NEt_3 , chlorobenzene, 80°C , 21 h.

Although formation of **8a,b** from **4a,b** was expected based on our calculations, isolation of these products cannot be taken as a rigorous proof of a biradical cyclization via **6**, because it could also be the result of a concerted Diels–Alder reaction **5**→**7**. Indeed, a similar cyclization was reported by Ghosez and Differding,^[16] although they did not recognize it to be a biradical cyclization, which prevented full exploitation of the reaction's synthetic potential. To demonstrate experimentally that biradical **6** is an intermediate, both phenyl groups in enyne-ketenimine **5b** were replaced by mesityl substituents. It is well established that concerted Diels–Alder reactions are prevented by *ortho*-alkyl substituents because of steric hindrance;^[14a, 18] therefore, the only option available to **5c** is a stepwise formal Diels–Alder cycloaddition. Transformation of **4c** into enyne-ketenimine **5c** produced benzocarbazole **8c** as the only low-weight product, which constitutes rather strong evidence for biradical intermediate **6c** (Scheme 3). This biradical subsequently closes to the formal Diels–Alder cycloadduct **7c**, from which a methyl group is then lost. The latter reaction can be explained by the assumption that after protonation at the nitrogen atom in **7c** the methyl group is eliminated in an $\text{S}_{\text{N}}2$ -type reaction, a transformation driven by the gain in aromatization energy.



Scheme 3. Synthesis of benzocarbazole **8c**. a) Florisil, P_2O_5 , 1,4-cyclohexadiene, pyridine, reflux, 30 h (61 % of **4c** recovered).

We also investigated the thermal cyclization of enyne-ketenimine **5d** with a hydrogen atom at the alkyne terminus to test experimentally the theoretical prediction of a preferred C^2 – C^7 cyclization of **2a** (Scheme 4). After converting amide



Scheme 4. Cyclization of **5d** to quinolines **10d** and **11d**. a) Florisil, P_2O_5 , 1,4-cyclohexadiene, pyridine, reflux, 3 d.

4d into enyne-ketenimine **5d** we obtained the quinolines **10d** (31 %) and **11d** (15 %); the latter is a product of addition of biradical intermediate **9d** to 1,4-cyclohexadiene.^[19] Both compounds clearly indicate a C^2 – C^7 biradical cyclization for enyne-ketenimines, whereas no C^2 – C^6 cyclization product has yet been detected.

We have thus provided both theoretical and experimental evidence for two novel thermal biradical cyclizations of enyne-ketenimines. The C^2 – C^6 cyclization pathway also opens the way to a straightforward synthesis of benzocarbazoles via azafulvenemethyl biradicals. The present results have encouraged us to engage in further investigations of

heteroenyne-allenes in which other CH_n groups are replaced by hetero units (e.g., $\text{B} = \text{NH}$ in **2**).

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X-Ray Absorption Spectroscopy of Dimethylcuprates: Evidence for Solvent-Dependent Aggregation**

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Organocopper reagents are widely used in organic synthesis. Although their properties depend on experimental conditions, with solvent often a key factor,^[1] only limited information is available on the solvent dependence of organocopper structures.^[2, 3] Vapor pressure depression and X-ray scattering measurements have suggested that lithium dimethylcuprate derived from cuprous halide is dimeric (Me_2CuLi)₂ in Et_2O .^[4a] This structure is supported by theoretical calculations.^[4b, 5] In contrast, recent cryoscopic measurements suggest that monomeric lithium dimethylcuprate is the major species in THF.^[3] Dimethylcuprates derived from cuprous halide give different ^1H and ^7Li NMR signals in THF and Et_2O ,^[2b] consistent with a solvent-dependent difference in structure. However, to date there have been no direct data

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comparing the copper structures as a function of solvent. Here we describe the use of X-ray absorption spectroscopy (XAS) to determine the structure of dimethylcuprates in Et₂O, THF, and dimethyl sulfide (DMS).

The XANES spectra (XANES = X-ray absorption near edge structure) for all of the dimethylcuprates are characterized by an intense 1s → 4p transition at 8982–8983 eV, consistent with two-coordinate Cu^I (Figure 1).^[6] However, in contrast with dimethylcuprates prepared from CuCN,^[7] there is a noticeable solvent dependence for the spectra of a mixture of CuI and two equivalents of MeLi.

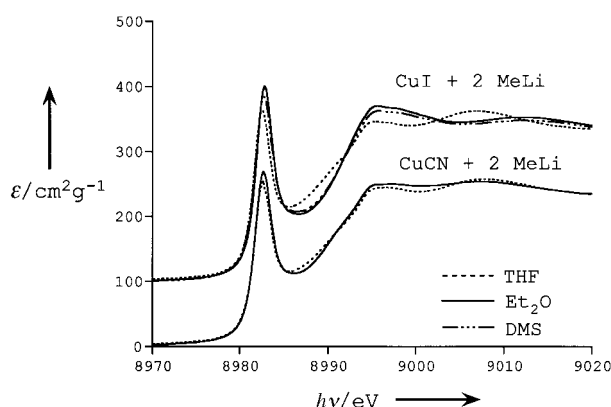


Figure 1. Normalized XANES spectra for CuI+2MeLi and CuCN+2MeLi.

Although all of the EXAFS data (EXAFS = extended X-ray absorption fine structure; Figure 2, Table 1) are domi-

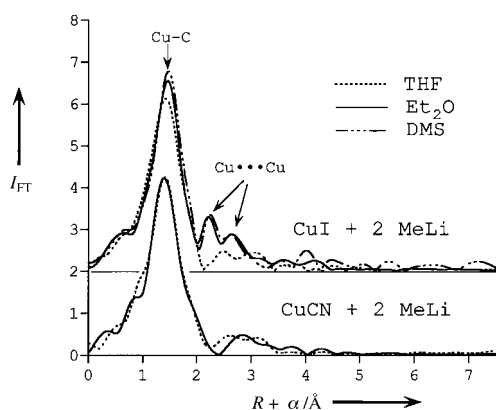


Figure 2. Fourier-transformed EXAFS spectra for CuI+2MeLi and CuCN+2MeLi. *I* = intensity.

nated by a first-shell peak at $R + \alpha \approx 1.5 \text{ \AA}$ (R = absorber–scatterer distance, α = phase shift, typically $\approx -0.4 \text{ \AA}$, $R_{\text{Cu-C}} = 1.95 \text{ \AA}$), typical of digonal Cu.^[6, 8] The outer-shell scattering is solvent-dependent. Samples prepared in Et₂O or DMS show peaks at $R + \alpha \approx 2.3$ and $2.7 \text{ \AA}$, respectively, which can be modeled as Cu–Cu interactions at 2.82 and $3.12 \text{ \AA}$. The observation of a strong Cu–Cu feature demonstrates that a substantial fraction of the Cu atoms are present in dimers or higher aggregates in Et₂O and DMS. There may also be outer-shell peaks for the sample in THF; however, they are much weaker and shifted to longer distances.

The Cu–Cu distances in crystallographically characterized [Me₂Cu]_n aggregates are $2.67\text{--}3.38 \text{ \AA}$.^[8, 9] The Cu–Cu distance of $2.82 \text{ \AA}$ determined by EXAFS is very similar to that in a [Ph₂Cu]Li₂ dimer crystallized from Et₂O ($2.87 \text{ \AA}$).^[10] The other distance of $3.12 \text{ \AA}$ determined by EXAFS may reflect a different dinuclear structure or indicate formation of a cluster with higher nuclearity. Neither of the Cu–Cu distances found by EXAFS is close to the value of $4.4 \pm 0.7 \text{ \AA}$ reported from X-ray solution scattering measurements.^[4a]

The presence of only weak outer-shell features for the sample in THF suggests that most of the cuprates are present either as the monomeric CuMe₂[−] ion or as weakly associated [CuMe₂][−]Li⁺ ion pairs (**2**), which is consistent with cryoscopic results.^[3] The EXAFS spectrum for a mixture of CuI and two equivalents of MeLi in THF/Et₂O (50/50) is identical to that in a 86/14 mixture, demonstrating that 50 % THF is sufficient to break apart the dimeric structure seen in Et₂O.

The solvent-dependent structural changes may be due to the differences in solvent polarity and dielectric constant (ϵ). The higher value of ϵ for THF leads to the stabilization of [CuMe₂][−] and Li⁺ ions, while neutral [CuMe₂Li]₂ dimers are favored in Et₂O. As a soft base, DMS might be expected to coordinate to the soft Cu^I ion, thus favoring formation of mononuclear cuprates. However, DMS and Et₂O give nearly identical spectra, with no evidence for Cu–S ligation in DMS. Evidently, two methyl ligands are sufficiently strong donors to prevent any significant coordination by solvent, resulting in retention of the dimeric structure in DMS.

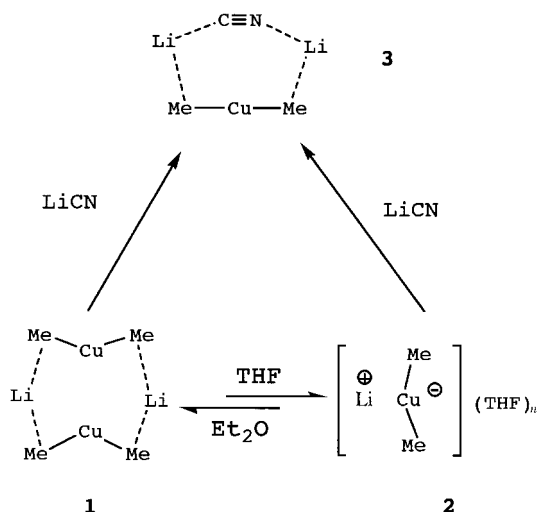
We reported previously that dimethylcuprates formed from CuCN and CuI have identical structures in THF.^[6a] In contrast, the Cu source does affect the dimethylcuprate structure in Et₂O. With CuCN, only weak outer-shell peaks are seen, suggesting a monomeric structure. There are small changes in ν_{CN} (from 2115 cm^{-1} in THF to $2104/2115 \text{ cm}^{-1}$ in Et₂O), but no change in the total IR intensity, indicating only

Table 1. Results of the EXAFS curve fitting.^[a]

Sample		Cu–C			Cu...Cu			Cu...Cu		
		C.N.	<i>R</i> [Å]	$\sigma^2 \times 10^3$	C.N.	<i>R</i> [Å]	$\sigma^2 \times 10^3$	C.N.	<i>R</i> [Å]	$\sigma^2 \times 10^3$
CuI+2MeLi	Et ₂ O	2.0	1.95	6.4	1.0	2.82	14.6	[b]	3.12	[b]
	THF	2.0	1.94	4.5						
	DMS	2.0	1.95	4.6	1.0	2.83	13.9	[b]	3.12	[b]
CuCN+2MeLi	Et ₂ O	2.0	1.96	6.1						
	THF	2.0	1.95	6.1						

[a] Results are for best fits using half-integer coordination numbers over $k = 1.5\text{--}12.5 \text{ \AA}^{-1}$ (k = photoelectron wave vector, $[2m_e(E - E_0)/\hbar^2]^{1/2}$, m_e = electron mass, E = X-ray energy, E_0 = threshold energy). Estimated uncertainties are $\pm 0.02 \text{ \AA}$ for R and ± 0.25 for C.N. (C.N. = coordination number). [b] C.N. and σ are highly correlated.

minor changes in the cyanide environment.^[11, 12] The lack of a strong solvent dependence for the IR spectra of cyanocuprates is most likely due to the interaction of CN^- , Li^+ , and $[\text{CuMe}_2]^-$ to give **3** (Scheme 1) regardless of solvent. The structure of **3** is supported by IR measurements and theoretical calculations.^[11] The present data suggest that, in the absence of cyanide, dimethylcuprate is largely dimeric **1** in Et_2O and monomeric **2** in THF.



Scheme 1. Structural conversion of dimethylcuprates in THF and Et_2O as well as in the presence of cyanide.

In summary, XAS measurements have revealed solvent-dependent effects for the structures of dimethylcuprates derived from CuI . Dimeric $(\text{CuMe}_2\text{Li})_2$ species are predominant in Et_2O and DMS, while a monomeric $[\text{CuMe}_2]^-$, or at most a weakly associated aggregate, appears to be the main species in THF. The structures of cyanocuprates are less susceptible to solvent, probably due to the association of the cyanide (or the $[\text{Li}_2\text{CN}]^+$ unit) with the $[\text{CuMe}_2]^-$ unit. This may account for the higher yield for cuprate reactions with CuCN as a precursor.

Experimental Section

Organocuprate samples (0.1M) were prepared under dry N_2 using Schlenk techniques.^[11] CuCN (99%), CuBr (99.999%), and CuI (99.999%) were purchased from Aldrich. Halide-free MeLi (1.4M in Et_2O , Aldrich) was titrated with 2-butanol using 1,10-phenanthroline as an indicator. THF was freshly distilled from Na/benzophenone ; Et_2O and DMS were freshly distilled from CaH_2 . The solutions in DMS and THF contain 14% Et_2O from MeLi addition. Sample preparation and data collection and analysis were previously described.^[6b] Solutions in THF and Et_2O were measured in the transmission mode, while solutions in DMS were measured in the fluorescence mode. Data for all samples were evaluated in an identical way.

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Ansa Macrolides as Molecular Workbenches: Stereocontrolled *syn* Additions to *E* olefins

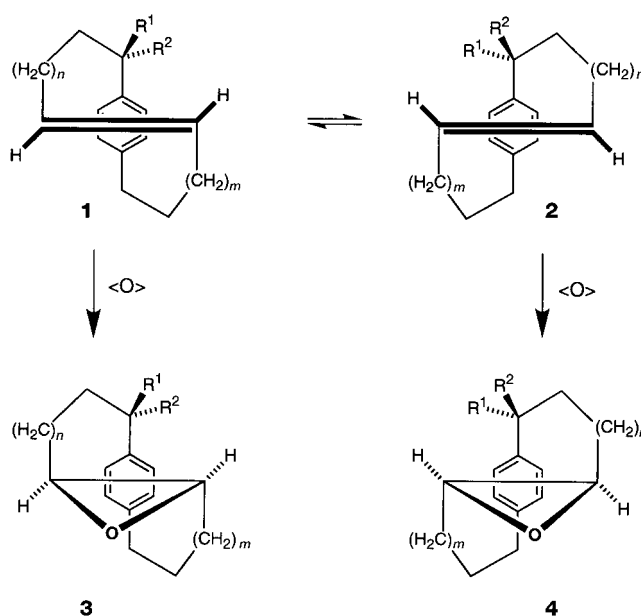
Johann Mulzer,* Karin Schein, Jan W. Bats, Jürgen Buschmann, and Peter Luger

Stereocontrolled dihydroxylations and epoxidations of acyclic 1,2-disubstituted *E* olefins are in favorable cases carried out catalytically,^[1] otherwise with substrate-induced diastereodifferentiation; this method, however, requires allylic or homoallylic hydroxy or amide groups.^[2] In general an effective face discrimination is difficult because of the high conformational mobility of the substrate. We herein report a new approach to solving this problem. In this, the acyclic *E*

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olefin is covalently attached to a benzene ring in the 1,4 positions through appropriate functional groups. This olefin is then sterically shielded from one side. A crucial problem is the conformational equilibrium which is to be expected^[3] between the two helical forms **1** and **2** (Scheme 1): Even if the double bond is attacked only from "the front side", two diastereomers are obtained, for example **3** and **4**, after epoxidation. A stereochemically defined outcome of the reaction is only possible if one of the two conformers **1** and **2** predominates under the influence of the arene. The latter then works as a "molecular workbench", fixing the substrate in a rigid conformation.

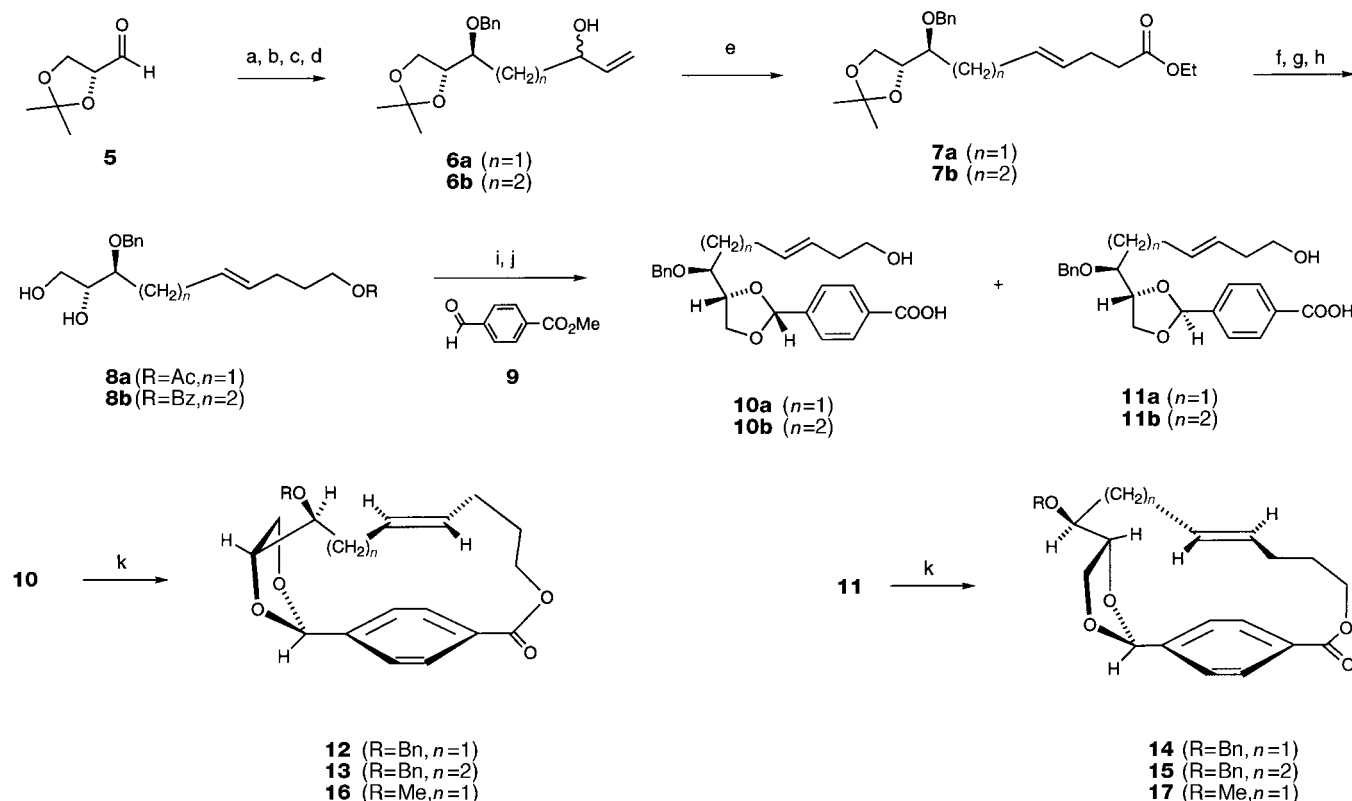
To put this concept into effect,^[4] we chose the easily accessible olefinic diols **8** as substrates, as they can be bonded to the arene **9** with the aid of the diol unit and (after deacylation) of the terminal hydroxy group, to form a cyclic ketal and an ester, respectively. With these functional groups a preferred conformational orientation is expected on closure to form the ansa macrolide ring, as five-membered ring ketals usually adopt an envelope conformation and the ester group should line up coplanar to the arene. The compounds **8** were synthesized stereoisomerically pure according to Scheme 2 from (*R*)-isopropylidene glyceraldehyde (**5**). The Claisen–Johnson rearrangement of **6** to **7** ensures the *E* configuration (>95%) of the alkene unit. The diastereomeric acetals obtained as a 1:1 mixture in the reaction of **8** with **9** were separated chromatographically and then transformed into the



Scheme 1. Aenes as "molecular workbenches".

seco acids **10a,b** and **11a,b** on a gram scale. These were then macrolactonized in a 10^{-4} M solution according to Yamaguchi's method^[5] in approximately 60% yield.

The macrolides **12**, **14**, and **15**, as well as the methoxy derivatives **16** and **17** prepared in an analogous fashion, are



Scheme 2. Synthesis of the ansa-macrolide alkenes **12–17**. a) Allyl- (for **6a**) or 3-butenylmagnesium bromide (for **6b**), THF, -30°C ; removal of the main isomer; b) NaH, BnCl, imidazole, DMF; c) O_3/PPh_3 , CH_2Cl_2 ; d) vinylmagnesium bromide, THF, 0°C ; **6a** 25%, **6b** 31%; e) $\text{CH}_3\text{C}(\text{OEt})_3$, cat. EtCO_2H , toluene, reflux; **7a** 79%, **7b** 79%; f) LiAlH_4 , THF, 0°C ; g) $n=1$: Ac_2O , $\text{CH}_2\text{Cl}_2/\text{NEt}_3$ (1/1); $n=2$: BzCl, pyridine; h) 50% HOAc; **8a** 83%, **8b** 86%; i) **9**, cat. TsOH, molecular sieve 4 Å, separation by HPLC; j) LiOH, $\text{H}_2\text{O}/\text{MeOH}/\text{THF}$; **10a** 40%, **10b** 38%, **11a** 38%, **11b** 33%; k) 2,4,6-trichlorobenzoyl chloride, NEt_3 , THF, 2 h, then DMAP, toluene, reflux, 20 h; **12** 62%, **13** 64%, **14** 60%, **15** 58%. Bn = benzyl, Bz = benzoyl, TsOH = *p*-toluenesulfonic acid, DMAP = 4-dimethylaminopyridine.

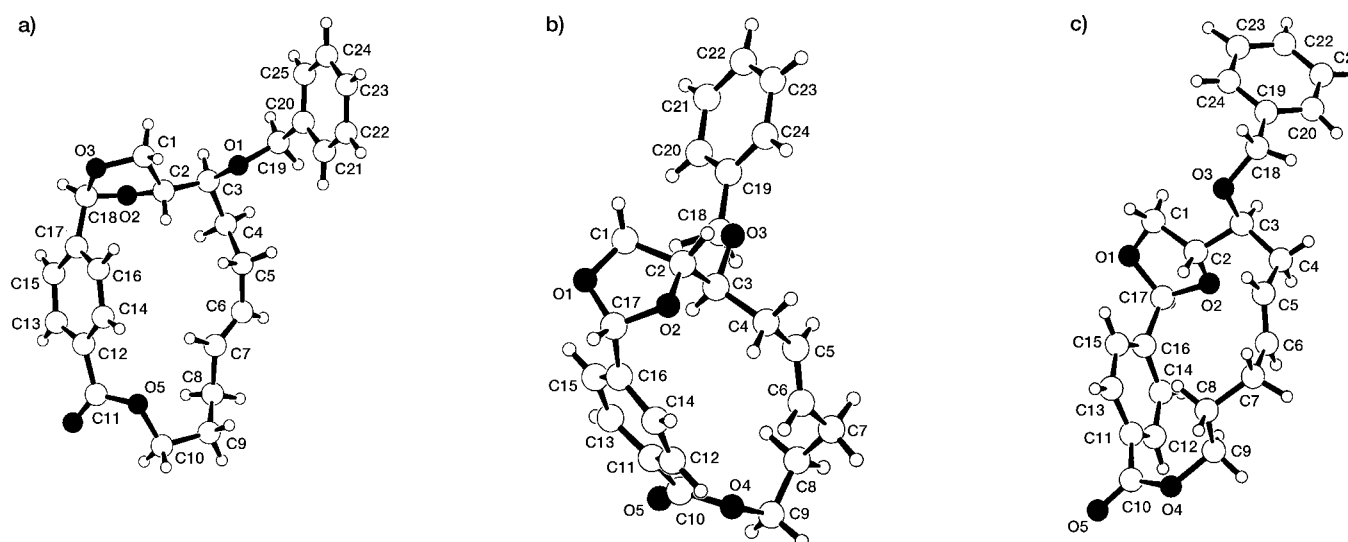
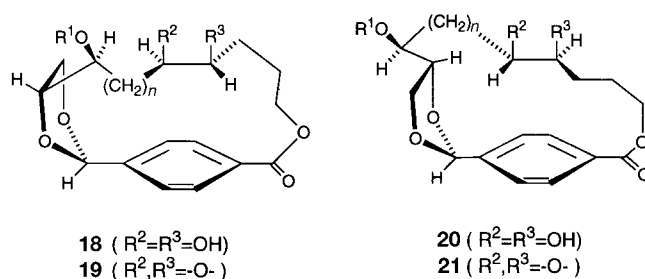


Figure 1. Structures of the ansa-macrolide olefins **15** (a), **12** (b), and **14** (c) in the crystal.^[6]

crystalline and were characterized by single-crystal X-ray diffraction (examples of the structures are given in Figure 1).^[6] A common feature of all compounds is the antiperiplanar arrangement of the C–O(R) bond and the vicinal C–O bond of the ketal, which is probably due to electrostatic repulsion and acts as a conformational anchor. The benzene rings are deformed in all five macrolides, with bow and stern of the boat lifted above the ring plane by about 0.07 Å each, regardless of the remaining structure. The “pore size” of the macrocycle and therefore its conformational mobility decreases when going from $n = 2$ to $n = 1$ and from the *cis*- to the *trans*-ketal; accordingly, the effective shielding of the “inner face” increases. Remarkably, the helicity of the double bond moiety in **12** and **14** as well as in **16** and **17** is determined by the configuration of the acetal center: **14** and **17** have the same helicity as **1**, whereas **12** and **16** show the same helicity as **2**, and no definite assignment is possible for **15**.

For a conformational analysis of the compounds in solution, ¹H NMR measurements were conducted between –75 and 100 °C. They show that in the “large” lactones **13** and **15**, the arene rotates around the *para* axis. The coalescence temperatures of the signals for the *ortho* and *meta* protons are about 80 (**15**) and –10 °C (**13**). This effect does not occur in **12** and **14**. Nevertheless, the ansa chain should display rapid helical inversion in the sense of **1** ⇌ **2** in all cases. Evidence for this inversion is obtained from preliminary studies on the molecular dynamics of **12**, **14**, **16**, and **17**, which, however, also show that the “helicamers” observed in the crystal dominate overall.

The stereoselectivities for epoxidations and dihydroxylation (Table 1) are fully in accordance with the expectations deduced from the structures: They are high for the “tight” macrolides **12**, **14**, **16**, and **17** and low for the “wide” macrolides **13** and **15**. The reagent preferentially attacks from the “outside”, as expected. This can be gathered from the structures^[6] of the diol derivatives **18a** and **20a** and of the epoxide **19c** in the crystal. Moreover, superimposition of the structures **16** and its epoxide **19c** shows that the conformation changes only slightly after the addition and that the arene can



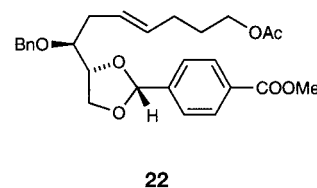
18, 19, 20, 21	R ¹	<i>n</i>
a	Bn	1
b	Bn	2
c	Me	1

Table 1. Diastereoselectivities for the *syn* addition to the ansa-alkenes **12**–**17**.

Alkene	Diastereoselectivity	
	Epoxidation ^[a]	Dihydroxylation ^[b]
13	1.6:1 (19b)	1.5:1 (18b)
15	2.0:1 (21b)	2.1:1 (20b)
16	7.1:1 (19c)	> 20:1 (18c)
12	9.5:1 (19a)	> 20:1 (18a)
17	> 20:1 (21c)	> 12:1 (20c)
14	> 20:1 (21a)	> 20:1 (20a)

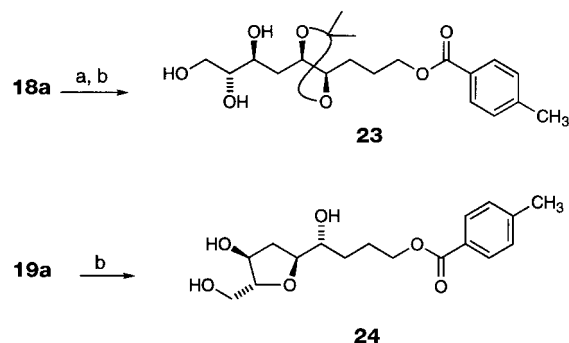
[a] *m*CPBA, CH₂Cl₂, 0.5 M NaH₂PO₄/Na₂HPO₄, 0 °C → RT, 3 h. [b] OsO₄, NMO, acetone, H₂O, 0 °C → RT, 12 h. Yields: 76–92 %. *m*CPBA = *m*-chloroperbenzoic acid, NMO = *N*-methylmorpholine-*N*-oxide.

indeed function as a workbench. The tolerance of the ansa macrolide ring toward a poor fit is surprisingly low. Thus, one CH₂ unit is already sufficient (compounds **12/13** and **14/15**) to obtain a conformationally nondetermined structure instead of a determined structure. The fact that the dihydroxylation and the epoxidation of **22**, the acyclic analogue of **12**, show almost



no selectivity clearly indicates that the stereogenic centers of the substrate are unsuitable for acyclic stereocontrol.

Can one dispose of the workbench after the job is done? As exemplified for the dihydroxylation product **18a**, the benzyl acetal can not be hydrolyzed under mild acid catalysis, but is easily cleaved hydrogenolytically (Scheme 3). Thus one



Scheme 3. Cleavage of the "workbench". a) 2,2-dimethoxypropane, PPTS, CH₂Cl₂, 94%; b) H₂/Pd/C, EtOAc; **23** 97%, **24** 97%. PPTS = pyridinium-*p*-toluene sulfonate.

obtains the partially protected hexol derivative **23**; the arene remains bonded to one of the primary hydroxy groups as the 4-methyl benzoate protecting group. Epoxides such as **19a** are transformed into tetrahydrofuran derivatives (e.g. **24**) by an S_N2 attack of the hydroxy group liberated after debenzilation. The arene **9** that is incorporated into the macrolide can therefore be understood as a polyfunctional protecting group that amplifies the influence of the substrate's stereogenic centers. As such it thus represents a new type of "stereoactive protective group".^[7]

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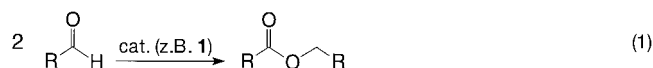
Crystallographic Data Centre as supplementary publication no. CCDC-100826. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code + (44) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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Homoleptic Lanthanide Amides as Homogeneous Catalysts for the Tishchenko Reaction**

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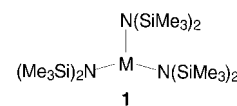
The Tishchenko reaction (or Claisen–Tishchenko reaction), that is, the dimerization of aldehydes to form the corresponding carboxylic ester [Eq. (1)], has been known for about a century.^[1] Its industrial importance is mirrored in the



great number of patents. Thus the Tishchenko ester of 3-cyclohexenecarbaldehyde is the precursor for the formation of epoxy resin, which is durable against environmental influences.^[2] Traditionally aluminum alkoxides^[2a, 3] have been used as homogeneous catalysts for the catalytic variations of the Tishchenko reaction. More recently other catalysts such as boric acid^[4] and a few transition metal complexes^[5] are used. However, these alternative catalysts are either only reactive under extreme reaction conditions (e.g. boric acid), difficult to prepare (e.g. [(C₅Me₅)₂LaCH(SiMe₃)₂]),^[5a] slow (e.g. [(C₅H₅)₂ZrH₂]),^[5b] expensive (e.g. [H₂Ru(PPh₃)₂]),^[5c] or give small yields (e.g. K₂[Fe(CO)₄]).^[5d]

Herein we report that the homoleptic bis(trimethylsilyl) amides of Group 3 metals and lanthanides, M[N(SiMe₃)₂]₃^[6] **1** (M = Sc, Y, Ln (lanthanide)), are highly active catalysts for the Tishchenko reaction. Compound **1** belongs to a class of materials that has been known for the last 25 years. Recently, in particular, it has proven to be a valuable starting material in lanthanide chemistry through the easy cleavage of the silylamide group.^[7] Compound **1** can either be prepared from a simple one-step synthesis or it can be bought (M = Y). Therefore it is even more surprising to find that up till now there is no known use of **1** as a catalyst.

To compare the reaction rates of **1** with other catalysts the standard reaction of benzaldehyde to benzyl benzoate was



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chosen, whereby the reaction rate and the yield were determined by NMR spectroscopy in C_6D_6 with approximately 1 mol % catalyst at 21 °C (Table 1). The turnover frequencies (TOFs) were determined from a turnover of 50 % (see below). A comparison of $La[N(SiMe_3)_2]_3$ (**1a**),

Table 1. Catalytic Tishchenko reaction of benzaldehyde to benzyl benzoate.

Catalyst	TOF	Yield [%]	T [°C]	Ref.
1a	87	98	21	—[a]
1b	80	98	21	—[a]
1c	63	70	21	—[a]
$[(C_5Me_5)_2LaCH(SiMe_3)_2]$		88	RT	[5a]
SmI_2	—	no reaction	21	—[a]
$La(OiPr)_3$	—	no reaction	60	[5a]
$Al(OiPr)_3$	8	51	21	—[a]
$[(C_5H_5)_2ZrH_2]$		7	17	[5b]
$[(C_5H_5)_2HfH_2]$		9	17	[5b]
$[H_2Ru(PPh_3)_2]$		23	20	[5c]
$K_2[Fe(CO)_4]$		71	60	[5d]
$B(OH)_3$		34	250	[4]

[a] Reaction conditions (this work): 1 mol % catalyst in C_6D_6 .

$Sm[N(SiMe_3)_2]_3$ (**1b**), and $Y[N(SiMe_3)_2]_3$ (**1c**) shows that by almost quantitative turnover **1a** has a higher activity than the corresponding Sm catalyst **1b**, whereas the Y catalyst **1c** produces smaller yields and is less active. The dependence of the TOF on the ionic radius of the central metal atom has already been observed.^[5a] A comparison with other easily accessible lanthanide compounds such as SmI_2 ^[8] or $La(OiPr)_3$,^[5a] which are used as Tishchenko catalysts, showed that these are inactive for the case of benzaldehyde. From the reaction with the standard aluminum catalyst ($Al(OiPr)_3$),^[3] under the reaction conditions described above, no quantitative yield was observed. The reaction rate observed with the use of $Al(OiPr)_3$, which agrees with earlier measured values,^[3a, 9] is roughly an order of magnitude smaller than that when **1a** is used. Although we do not know of a more active catalyst for the Tishchenko reaction, two compounds are described in the literature ($[(C_5Me_5)_2LaCH(SiMe_3)_2]$ ^[5a] and $Al(OCH_2Ph)_3$ ^[9]) that could compete with **1a**. $[(C_5Me_5)_2LaCH(SiMe_3)_2]$ probably would form the same catalytically active species as in **1a** (see below), but is, however, evidently more difficult to prepare. $Al(OCH_2Ph)_3$ reaches almost the same TOF as **1a**, but is exclusively optimized for the dimerization of benzaldehyde.^[9, 10]

The large range of applications of **1a** is given in Table 2. The reactions were carried out at 21 °C in C_6D_6 with approximately 1 mol % of catalyst in order to determine the TOF. Afterwards all the reactions were repeated on a preparative scale (5 g of reactant) without solvent or in hydrocarbons in order to determine the isolated yields, and to characterize the products by ^1H and ^{13}C NMR spectroscopy as well as elemental analysis. The work up of the reaction turned out to be very simple: In the case of the solvent free reaction the product can usually be easily transferred by vacuum. In the case of the reaction with *o*-phthalaldehyde the ester precipitates cleanly out of the solution. The extremely high TOFs for

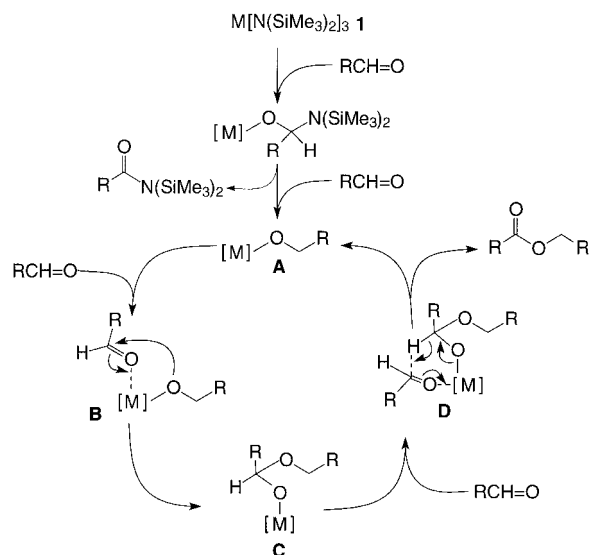
Table 2. Catalytic Tishchenko reaction with **1a** as the catalyst.

Reactant	Product	TOF	Yield [%] ^[a]	Yield [%] ^[b]
R = phenyl		87	98	87
R = 3-cyclohexenyl		> 1500	quant.	75
R = cyclohexyl		> 1500	quant.	80
R = 2-furanyl		2	40	36
R = 1-propyl		—	quant. ^[c]	45 ^[c,d]
		> 1500	90 ^[e]	85 ^[d]

[a] Analytical approach (NMR experiment): 21 °C, 1 mol % catalyst in C_6D_6 . [b] Yield of isolated product for the preparative approach: 21 °C, 5 g of reactant, 1 mol % catalyst, no solvent. [c] Reaction from $-78^\circ C \rightarrow RT$; trimers were formed as by-products. [d] Solvent: 50 mL of pentane/hexane (1/1). [e] Unknown by-product.

cyclohexanecarbaldehyde and 3-cyclohexanecarbaldehyde should be particularly noted. The reactions usually happen so quickly that only the product can be detected on NMR-scale reactions. The catalyst in the reaction solution is also still active after several days. Thus, a reaction that has subsided for some time can be restarted again by the addition of new reactant. Furthermore the suitability of **1a** for the dimerization of furfural should be emphasized, because up till now when this reaction is carried out with aluminum or tetracarbonylferrate catalysts either no or very low yields are observed. Although **1a** catalyzes the dimerization of aldehydes, with or without an α -H atom, quickly and in high yields, the reaction of butanal at 21 °C only higher coupling products are formed.^[3b, 11] If one starts the reaction at $-78^\circ C$ then butyl butyrate and 2-ethyl-1,3-hexanediol monobutyrate as dimeric and trimeric products are yielded in almost the same ratio.^[11a]

To present a provisional reaction mechanism, the dimerization of benzaldehyde was studied in more detail. ^1H NMR spectroscopy and GC/MS studies show that at the beginning of the reaction bis(trimethylsilyl)amine and benzylic acid bis(trimethylsilyl)amide are cleaved from **1** to give a lanthanide alkoxide **A** that is, most probably, the catalytically active species (Scheme 1). Investigations of the paramagnetic compound **1b** on catalytic and stoichiometric scales show that all three amide groups are cleaved without a significant induction time, and signals appear in the ^1H NMR spectra that may be attributed to $SmOCH_2$ groups. It can be assumed that the catalytically active species is either the same or very similar to the compound that is formed in the Tishchenko reaction with $[(C_5Me_5)_2LaCH(SiMe_3)_2]$.^[5a] This hypothesis is supported by the following observations: 1) with **1a** similar yields are achieved as for $[(C_5Me_5)_2LaCH(SiMe_3)_2]$, which is, incidentally, significantly more difficult to prepare. 2) During the reaction both catalysts can completely interchange the whole of their original ligand shells. ^1H NMR spectroscopic investigations show, however, that from the reaction of **1b** with stoichiometric amounts of benzylalcohol or benzylaldehyde different compounds are formed. Kinetic investigations show



Scheme 1. Suggested mechanism for the $M[N(SiMe_3)_2]_3$ -catalyzed Tishchenko reaction.

that $1/[\text{reactant}]$ is related linearly to the reaction time; that is, a second-order reaction with respect to the reactant occurs. Such reaction kinetics have already been established for the aluminum-catalyzed reaction for the dimerization of benzaldehyde.^[9] Presumably, a molecule of the reactant coordinates to **A** ($\rightarrow$ **B**), which in turn undergoes an alkoxide transfer ($\rightarrow$ **C**; Scheme 1). A second molecule of the reactant attaches itself to **C** followed by a hydride transfer that is probably the rate-determining step ($\rightarrow$ **D**).^[9]

In summary it should be emphasized that the bis(trimethylsilyl)amide compounds of the lanthanides represent a new class of Tishchenko catalysts as a result of the high Lewis acidity and the easy interchangeability of the ligand sphere. These compounds are distinguished by a number of practical advantages such as the ease of accessibility (one compound can be bought), inexpensive metals, extremely high activities (to our knowledge there are no catalysts that are more active), and a high durability of the catalysts. These advantages lead us to hope that **1**, which is already today a standard reagent in organolanthanide chemistry, will find further application as a Tishchenko catalyst.

Experimental Section

NMR-scale reaction: Compound **1** (0.015 mmol) was weighed under protective gas into an NMR tube. C_6D_6 (≈ 0.7 mL) was condensed into the NMR tube, and the mixture was frozen at -196°C . The reactant (1.5 mmol) was injected onto the solid mixture, and the whole sample was frozen at -196°C . To determine the reaction kinetics the sample was melted and mixed just before the insertion into the core of the NMR machine (t_0). The ratio between the reactant (product) and the catalyst was exactly calculated by comparison of the integration of all CHO (CH_2O) signals with the $N(SiMe_3)_2$ signals. The latter were used as an internal standard for the kinetic measurements.

Preparative-scale reaction: a) without solvent: Under protective gas the catalyst (1 mol %) was stirred in a tempered reaction flask. The reactant (5 g) was added directly to the catalyst. Usually an exothermic reaction was observed. After one day the product was isolated by distillation. b) In solution: The catalyst (1 mol %) and the reactant (5 g) were each dissolved in pentane/hexane (1/1, 25 mL). The reactant solution was added together

with the catalyst solution in a tempered flask. After one day the product was isolated by distillation.

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NaSn₅: An Intermetallic Compound with Covalent α -Tin and Metallic β -Tin Structure Motifs

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Under standard conditions tin exists in the β modification, in which each tin atom is surrounded by six other Sn atoms in a distorted octahedral arrangement (Figure 1a, Scheme 1, Table 1). Below 13.2°C transformation of β -tin into cubic α -tin (diamond structure), which is thermodynamically more stable by 2.09 kJ mol^{-1} , occurs.^[1] In this modification, which has a lower density, all tin atoms are four-coordinate, and the structure can be described by invoking localized two-center, two-electron ($2c-2e$) bonds (Scheme 1). All structurally

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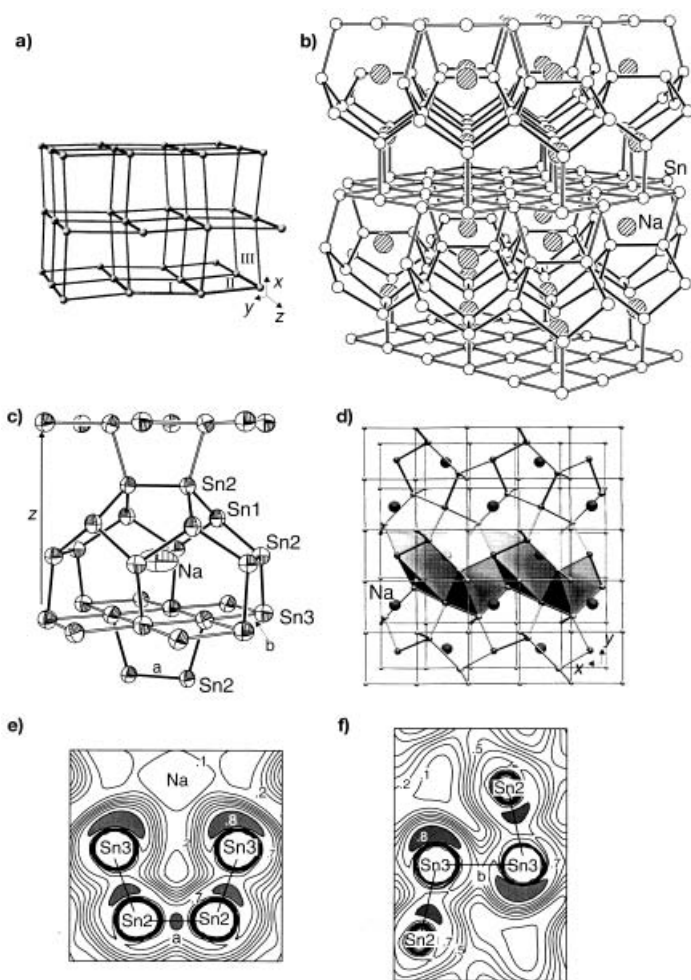
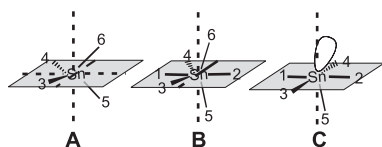


Figure 1. a) Section of the β -Sn structure. The atoms lie in layers parallel to the xz and xy planes. The shaded parallelograms are coplanar (I and II) or orthogonal (II and III; see **B** in Scheme 1). b)–d) Sections of the structure of NaSn_5 . b) A larger section showing the stacking of the five-membered ring units. c) The twelve Sn atoms of this section (Sn1 and Sn2 atoms) are not part of the quadratic network and form a polyquinane-like structural unit. When the eight bridging atoms of the quadratic network below are included, this unit is topologically equivalent to a pentagonal dodecahedron (see Scheme 2). The anisotropic displacement parameters are drawn at the 90 % probability level. d) Both shaded tub units are shown with their openings facing downwards. The convex indentations in a translationally symmetric arrangement of concave tub units are themselves tub units. Their openings face upwards and, along with the former units, completely fill the space between the quadratic networks. Distances and angles are given in Scheme 1 and the text. e) and f) The electron localization function (ELF) of cross-sections in the NaSn_5 structure parallel to the z direction and through the bonds labeled a and b in c). The ELF is normalized to values between 0 and 1. The contour lines are in steps of $\text{ELF} = 0.1$. In e) one can clearly recognize a preferential orientation of the electron lone pairs of the Sn3 atoms (see text for details).



Scheme 1. Distances and angles in α -Sn (**A**), β -Sn (**B**), and in the coordination sphere of Sn3 in NaSn_5 (**C**). **A**: $2.810 \text{ \AA}$ ($4 \times$); 109.5° ($6 \times$); **B**: Sn–Sn(3) to Sn–Sn(6) 3.016 , Sn–Sn(1) and Sn–Sn(2) $3.175 \text{ \AA}$; **C**: Sn3–Sn(1) to Sn3–Sn(4) 3.143 , Sn3–Sn(5) $2.886 \text{ \AA}$; the angles between the Sn atoms in **B** and **C** are listed in Table 1.

characterized tin-rich binary alkali metal stannides are, like α -tin, covalent compounds. According to the Zintl–Klemm–Busmann (ZKB) concept, the valence electrons of the electropositive alkali metal atoms are assigned to the tin atoms, and the number of three- and four-coordinate tin atoms and homoatomic bonds is determined by the $8 - N$ rule. The three-coordinate atoms carry a negative charge or a lone pair. The anionic substructures in ASn (i.e., A_4Sn_4 , $\text{A} = \text{Na} - \text{Rb}$; NaPb type),^[2] $\text{A}_8\text{Sn}_{44}\square_2$ ($\text{A} = \text{K}, \text{Cs}$, clathrate I structure type with two vacancies),^[3] and the recently reported

Table 1. Sn–Sn–Sn bond angles [$^\circ$] in structures **B** and **C**.

	3–4	5–6	1–3	1–4	2–3	2–4	1–5(6)	2–5(6)	3–5(6)	4–5(6)
B	149.5	149.5	74.8	74.8	105.2	105.2	105.2	74.8	94.0	94.0
C	178.0	–	89.0	90.0	90.0	91.0	102.2	79.5	102.2	79.5

$\text{Na}_5\text{Sn}_{13}$,^[4] can be described by formulating localized $2c-2e$ bonds and electron lone pairs. In addition to the three-membered tin rings of the tetrahedral cluster in ASn ,^[5] five-membered tin rings are the predominant structural motif. In $\text{Na}_5\text{Sn}_{13}$ these are assembled by edge sharing and external bonds to form a complex three-dimensional network; in the clathrate I structure type they appear as building blocks of pentagonal dodecahedra. The four-coordinate atoms in these structures have a distorted tetrahedral environment. The bonding motifs of the metallic tin modification are not reflected in any of the known intermetallic tin compounds.^[7]

Here we report on NaSn_5 , the most tin-rich phase of the Na–Sn system. This is the first example of a tin network in which fragments of pentagonal dodecahedra with tetravalent atoms are bound between planar networks of tin atoms. The tin atoms of the planar network have a distorted square-pyramidal coordination to five other tin atoms. These build, together with a free electron pair localized on the central tin atom, a distorted ψ -octahedral coordination polyhedron. A similar polyhedron occurs in the β -tin structure.

Single crystals^[8] of NaSn_5 were obtained by combination of the elements.^[9] The compound crystallizes in a new structure type with three independent Sn positions and one Na position (Pearson symbol tP12, Figure 1 b–d). The Sn3 atoms build a planar, mildly distorted quadratic network (Sn3–Sn3 $3.1429(5) \text{ \AA}$), and the Sn1 and Sn2 atoms form a fragment of a pentagonal dodecahedron (Figure 1 c). The twelve atoms of the latter unit are constructed from four five-membered rings with five shared edges. The result is a tublike half-shell with C_{2v} point symmetry that can be derived from the analogous polyquinane hydrocarbon.^[10] The tub can also be described as a ten-membered chain bridged by a handle. The bridging handle of Sn2 atoms and the six symmetry-equivalent atoms of the ten-membered chain (Sn2) are bound to the atoms of the quadratic network (Sn2–Sn3 $2.886(1) \text{ \AA}$). The polyhedral fragment spans eight Sn3 atoms (Figure 1 c). The relative arrangement of a fragment between two planar networks is detailed in Figure 1 d. The two-dimensional connectivity of the fragments leads to a layer of four-coordinate atoms that alternate along the z direction with the quadratic network (Figure 1 b). A layered arrangement of

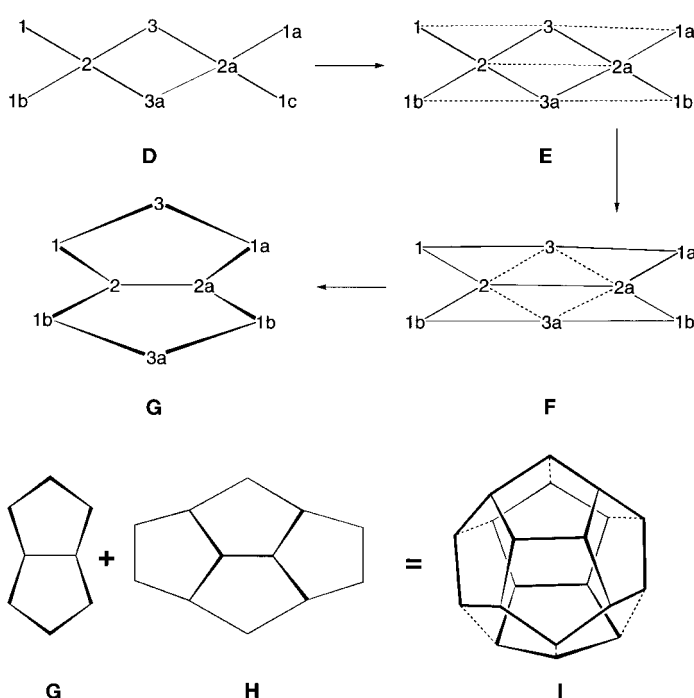
linked five-membered ring units is also present in the Zintl phases $\text{Li}_7\text{Ge}_{12}$ and Li_3NaSi_6 .^[11]

The Sn1 and Sn2 atoms are four-coordinate. The environment of Sn1 deviates only slightly from a tetrahedral arrangement: Sn1–Sn2 2.8626(6) Å; bond angles at Sn1 range from 108.32(1) to 111.80(3)°; Sn2–Sn3 2.886(1) Å; bond angles at Sn2 range from 101.94(2) to 117.25(2)°. The center of each tub is occupied by a Na atom, which exhibits short interatomic distances to two Sn2 atoms (3.054 (1) Å);^[12] the next-nearest neighbors are Sn2 atoms at distances of 3.409(6) and 3.415(6) Å ($2\times$), Sn1 atoms at a distance of 3.625(4) Å ($4\times$), and two further Sn2 atoms (the Sn2 atoms of the bridging handle, Figure 1 c) at a distance of 3.687(8) Å ($2\times$). Four other Sn2 atoms exhibit even longer distances of 4.663 Å.

The Sn3 atoms have a coordination environment similar to that in metallic tin. In β -Sn the atoms lie in sheets parallel to the xz and xy planes, composed of parallelograms with angles of 74.8 and 105.2° (Figure 1 a). The Sn–Sn bond lengths are 7 and 13 % longer than those of α -tin. Bond lengths and angles are given in Scheme 1 and Table 1. The planar networks in NaSn_5 are constructed from quadratic units. The distances between the network atoms are 12 % greater than the corresponding distances in α -tin. If Sn3 is described with an electron lone pair that is regarded as a pseudoligand according to the VSEPR rules, the resulting environment about the Sn3 atom is analogous to that in β -tin. The axial positions (see Scheme 1) 5 and 6 in **B**, and 5 and an electron lone pair in **C**, are distorted from an ideal octahedral arrangement in the direction of position 2 and the bisector of the angle Sn(2)–Sn–Sn(4), respectively.

The chemical bonding in NaSn_5 is interesting in two distinct ways. First, the title compound exhibits a topological transition from the coordination in β -tin to pentagonal-dodecahedral units; such units are present in the clathrate I structure, K_6Sn_{25} , and $\text{K}_6\text{Sn}_{23}\text{Bi}_2$. The latter two phases crystallize in the $\text{Ba}_6\text{In}_4\text{Ge}_{21}$ ^[6a, 14] structural type and contain distorted pentagonal dodecahedra of the elements Sn^[3b, 15] and Sn/Bi^[15] in place of In/Ge. These pentagonal dodecahedra form three-dimensional zeolite-like networks in which each shares three faces and has one exo bond.^[14, 16] The development of such polyhedra from the β -Sn structure is especially striking in the NaSn_5 structure. In Scheme 2 the transformation of the C_{2v} -symmetric hemisphere (comprising $12 + 8 = 20$ Sn atoms) to a pentagonal dodecahedron is shown. The distortion of the quadratic network of eight Sn atoms (**D**), which borders the fragment **H**, passes through the intermediates **E** and **F** to form two edge-sharing five-membered rings (**G**, pentalene analogue). One of these supplements the fragment **H** to create a pentagonal dodecahedron (**I**). Furthermore, NaSn_5 contains both localized bonds between tetravalent atoms, as in α -tin and the Zintl phases, and delocalized bonds like those of β -tin. The structural findings discussed above were verified with band structure calculations.

LMTO-ASA calculations^[18] predicted NaSn_5 to be an anisotropic conductor. The density of states at the Fermi level E_F can be attributed predominantly to contributions from the Sn3 atoms (Figure 2, right). The fat-band analysis, in which the atomic orbital character is represented as a function



Scheme 2. The topological transformation from eight atoms of a quadratic network and a unit of four five-membered rings to a pentagonal dodecahedron. In **D**, a section from a quadratic network, a connection along the diagonal, as shown in **E**, is effected. Opening of the dashed lines in **F** with a concomitant distancing of the centers 3 and 3a leads to two edge-sharing five-membered rings (**G**). The fragments **G** and **H** combine to form a pentagonal dodecahedron **I**.

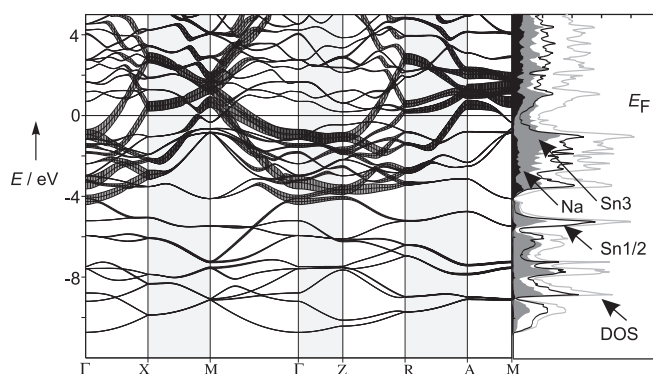


Figure 2. Band structure showing p_x and p_y orbital character (fat-band analysis),^[18] density of states (DOS), and the atomic contributions to the DOS.

of the band width, shows that the bands crossing the Fermi level are characterized almost completely by contributions from the p_x and p_y orbitals of Sn3; that is, metallic conductivity propagates predominantly over states with Sn3 orbital contributions. The presence of structural regions with delocalized bonds, the localized bonds of the tetravalent Sn1 and Sn2 atoms, and the electron lone pairs on the Sn3 atoms (see Scheme 1) is further supported by analysis of the quantum-mechanical results with the help of the electron localization function (ELF).^[19]

Cross-sectional plots of the ELF in two planes parallel to the z direction and through the Sn2–Sn2 bond a (along [110])

and the Sn3–Sn3 bond b ([100]) are shown as contour diagrams in Figures 1e and 1f. Regions with ELF greater than 0.8 characteristic of 2c–2e bonds can be clearly recognized between the atom pairs Sn2–Sn2 and Sn2–Sn3. The ELF region along the Sn2–Sn3 bond is typical of a polar bond.^[19c] Not depicted are the regions of higher ELF values, which show another 2c–2e bond along the Sn1–Sn2 interaction vector. The localization is clearly poorer (ELF < 0.6) between the Sn3 atoms, and the ELF shows no local maximum (attractor^[19d]) on the nucleus–nucleus connecting line (Figure 1f). A electron lone pair on the Sn3 atom is clearly apparent (Figure 1e); it is directed toward the electropositive Na atoms and together with the five other bound Sn atoms builds a distorted octahedral coordination polyhedron about Sn3. The comparison with the coordination of the Sn atoms in metallic tin is highlighted in Scheme 1. When the electrons in NaSn₅ are distributed according to the ZKB concept, the formula Na₂(Sn1)₂(Sn2)₄(Sn3)₄ results with a partial charge of –0.5 on Sn3.^[20] Since two electrons are considered to form the lone pair, 0.75 electrons per shortest Sn3–Sn3 distance remain for the bonds of the quadratic network. This is consistent with 4c–3e bonds between the atoms of the planar network. BaAl₄, in which Al atoms cap quadratic nets of Al atoms, has 6e–5c bonds between the network and apical atoms, and the ELF values between the atoms of the Al networks are also small (ELF < 0.6).^[21]

NaSn₅ represents a new, unusual three-dimensional network in which metallic layers analogous to those in β-tin alternate with tetravalent tin atoms. The compound shows the beginning of the formation of pentagonal-dodecahedral units (which frequently occur in Zintl phases) from the β-Sn modification. Like the recently reported stannide BaSn₃, the title compound lies on the border between Zintl phases and intermetallic compounds. Interesting physical properties are predicted on the basis of theoretical calculations.^[6b] The determination of the electronic properties and a more thorough quantitative analysis of the chemical bonding with the aid of the ELF (electronic domains)^[21b] are the subject of further investigations.

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Small Potassium Clusters**

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The investigation of ligand-free atomic clusters presents an ideal opportunity for studying the transition from a single atom to a macroscopic particle. Moreover, the basic properties of small metallic clusters are believed to be an important link in the understanding of the fundamental mechanisms of catalysis and numerous chemical transformations.^[1] Despite considerable recent effort, the structures of small atomic metal clusters remain largely unknown.^[2, 3] This attests to the intrinsic difficulties associated with experimental work in this field. Even the generation and isolation of the smallest species requires an extensive experimental setup.^[4] On the other hand, the number of theoretical calculations and predictions has increased explosively during this decade due to the increasing computer capacity available. Alkali metal clusters are one of the main subjects for theoretical work, but even the diatomic species have yet to be isolated experimentally.

A simplified method for the generation of diatomic potassium molecules was developed during experiments for the simulation of stratospheric phenomena. The apparatus consists of a regular low-pressure plasma tube which is connected to a cryostat with a copper cold surface (15 K).^[5]

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The metal sample is sputtered by a microwave-induced low-pressure krypton plasma, and the material stream is frozen immediately on the cold surface. After one hour of deposition time, a blue layer of solid krypton and potassium molecules was formed. Figure 1 shows the Raman spectrum of the

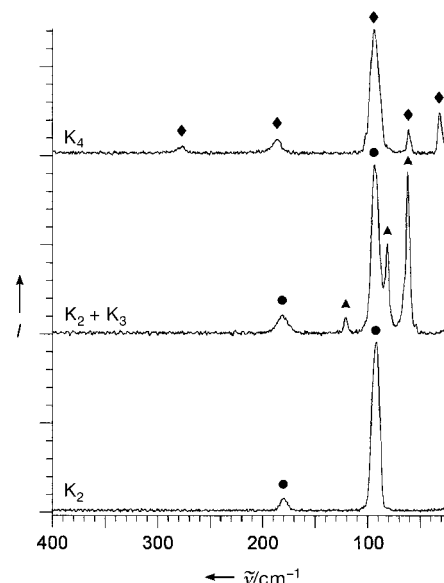


Figure 1. Raman matrix spectra of K_2 , K_4 , and a mixture of K_2 and K_3 in krypton at 15 K (experimental conditions: 100 μ m layer, laser wavelength 514.5 nm, laser power 125 mW, resolution 0.6 cm^{-1}). I = intensity. ●: lines from K_2 , ▲: from K_3 , ◆: from K_4 .

krypton matrix with diatomic potassium molecules. The fundamental frequency of 91.0 cm^{-1} is in excellent agreement with the value obtained from gas-phase experiments (92.0 cm^{-1}), and from density functional theory (DFT) calculations (see Table 1).^[6] The surprising result of the microwave sputtering experiment is the efficient formation of the diatomic species. Thermal evaporation under similar conditions (ca. 80 °C) would yield more than 99 % potassium atoms.^[7] This was verified by thermal evaporation experiments which yielded red matrices of potassium atoms without any detectable molecular species. These experiments also confirm that the blue color of the krypton matrix is due to the

Table 1. Experimental and calculated (DFT) Raman frequencies [cm^{-1}], and vibration modes for K_2 , K_3 , and K_4 .

K_n	DFT ^[a]	Exp.	Assignment
K_2	90.0	91.0	$\nu(K_2)$ Σ_g
		181.5	$2\nu(K_2)$ Σ_g
K_3	57.2	(61.0)	$\delta(K_3)$ A_1
	58.9	61.0	$\delta(K_3)$ B_2
	83.0	81.5	$\nu(K_3)$ A_1
		120.0	$2\delta(K_3)$ A_1
K_4	31.2	30.0	$\delta(K_4)$ A_g
	60.0	61.5	$\delta(K_4)$ B_{3g}
	92.4	93.0	$\nu(K_4)$ A_g
		185.0	$2\nu(K_4)$ A_g
		276.0	$3\nu(K_4)$ A_g

[a] DFT calculations with the Slater exchange function and the local spin density correlation function of Vosko, Wilk, and Nusair (SVWN5)^[10] and the basis set LANL2DZ^[11] performed with the Gaussian 94 package.^[16]

diatomic potassium, and does not result from solvated electrons, as observed in solutions of alkali metals in aprotic solvents.

The blue color of the potassium molecules is the first visible difference in the transition from potassium atoms to metallic material. Investigation of diffusion-controlled clustering processes,^[8] which occur during warm-up cycles of the krypton layers above their diffusion temperature, revealed that two relatively stable clusters exist. The first one is the diatomic potassium cluster, which reacts relatively slowly to form the second stable species, a tetraatomic potassium cluster (Figure 1). Further annealing results in spontaneous deposition of silvery metallic potassium. To obtain the elusive triatomic species, which has already been detected by ESR spectroscopy,^[9] a mixture of mono- and diatomic potassium was prepared and annealed. During the clustering process, we first observed an increase in the intensity of the K_2 lines in the Raman spectra and the appearance of three additional lines (Figure 1), which we assigned to the trimer. Two of these lines disappeared completely (the third line overlaps with a line from K_4 cluster) after further warm-up cycles. The final Raman spectrum shows only lines for the K_4 cluster, and there are no indications for larger clusters.

The vibrational data provide a reliable way to determine the cluster geometry from quantum mechanical calculations. To choose the appropriate theoretical method for the clusters, we compared results from Hartree–Fock (HF), Moeller–Plesset (MP2), and two DFT calculations (B3LYP and SVWN5) with different basis sets for alkali metal dimers. The HF and MP2 calculations yielded frequencies which deviated widely (up to 10%) from the experimental gas-phase data. Finally, the SVWN5 method, with the LANL2DZ basis set augmented with polarization and diffuse functions, produced data with deviations of less than 1–2% from the experimental values.^[10, 11] The careful choice of a theoretical method at this stage is of great importance, since the discrepancies are carried over to the larger clusters and can lead to somewhat erratic results, as discussed in the literature.^[12] The observed frequencies and the symmetry (derived from spectroscopic selection rules) of the clusters agree well with the calculated data summarized in Table 1 (Figure 2).

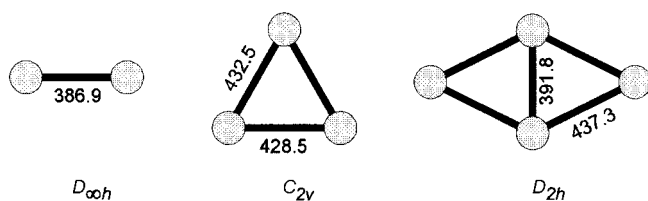


Figure 2. Symmetry and bond lengths of K_2 , K_3 , and K_4 .

The vibrational frequency and the bond length of K_2 (386.9 pm), which is 15% shorter than the atomic distance in the body-centered cubic lattice of potassium (454.4 pm),^[13] indicates the presence of a single σ bond. Therefore the nature of the bonding in dipotassium should be similar to that of diatomic nonmetal molecules. This is to be expected based on classical valence bond theory (overlap of two 4s orbitals), but

earlier theoretical investigations have predicted that this kind of bonding would be influenced by the core electrons.^[14] A comparison of the results from different theoretical methods enabled us to confirm earlier predictions that core electron polarization (CVP) causes additional contraction of the single bond (Figure 3).^[14] The contribution of this effect to a classical

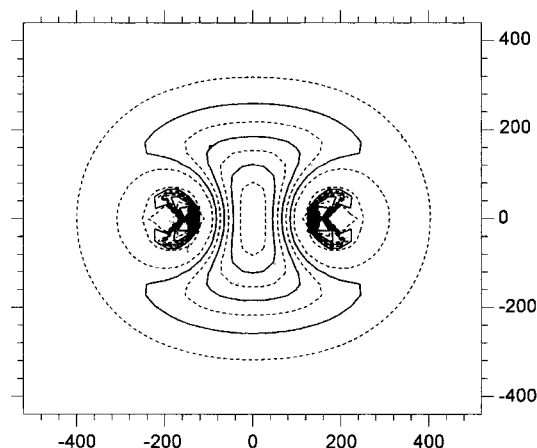


Figure 3. Contour-line diagram of the electron density $\rho(r)$ of K_2 in the ground state ($1\Sigma_g^+$). Scale in pm.

single bond is already in the range of 8% for diatomic potassium, and it persists for the K_3 and K_4 clusters. Therefore, the tri- and tetraatomic potassium clusters do exist, in contrast to predictions made on the basis of valence-only (without CVP) calculations.^[15] When all the experimental observations and theoretical calculations are summarized, it appears at this stage, that bond strengthening due to CVP plays a significant role in the formation of clusters.

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The First Specific Ti^{IV} –Protein Complex: Potential Relevance to Anticancer Activity of Titanocenes**

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Biological interest in titanium complexes arises from current clinical trials of two anticancer agents $[\text{Ti}^{\text{IV}}(\text{bzac})_2(\text{OEt})_2]$ ($\text{Hbzac} = 1,3\text{-diphenyl-1,3-propanedione}$) and $[\text{Ti}^{\text{IV}}\text{Cp}_2\text{Cl}_2]$,^[1, 2] and the potential radiopharmaceutical use of compounds containing ^{45}Ti isotopes.^[3] Moreover, since enormous amounts of titanium occur in a wide variety of materials, especially TiO_2 , there are abundant opportunities for Ti ions to enter into biochemical pathways in living systems. However, very little is known about the biological chemistry of Ti compounds. There appear to be no reports of specific binding of Ti ions to proteins, and the mode of action of Ti anticancer complexes is poorly understood. We chose to study the binding of Ti^{IV} ions to the blood plasma protein transferrin since this protein has been implicated in the transport and delivery of metal ions such as Ga^{III} (as ^{67}Ga) and Ru^{III} to cancer cells.^[4, 5] We show here that Ti^{IV} forms a strong complex with human serum transferrin (hTF) by binding to the specific Fe^{III} binding sites in this protein. This appears to be the first characterization of a specific Ti–protein complex, one which may play a role in the mechanism of action of the titanium anticancer drugs.

Our initial experiments focussed on the reaction of titanium(IV) citrate^[6] with human serum apotransferrin.^[7] When titanium(IV) citrate was added to an aqueous solution of apo-transferrin (apo-hTF), three new bands gradually appeared in the UV difference spectrum and increased in intensity over a period of 12 h, Figure 1. The wavelengths of the two sharp bands at 241 and 295 nm are typical of

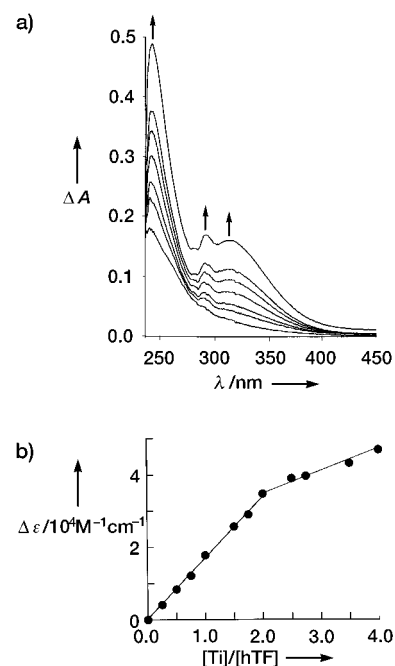


Figure 1. a) UV difference spectra of apo-hTF ($13 \mu\text{M}$ in 10 mM Hepes, 5 mM HCO_3^- , pH 7.4, 310 K) after addition of 2 molequiv titanium(IV) citrate. Reaction times (from bottom to top): 1, 5, 10, 20, 40, 150, and 720 min. b) Titration curve for addition of titanium(IV) citrate to apo-hTF (conditions as above). Each solution was left $> 12 \text{ h}$ to reach equilibrium. $\Delta\epsilon$ is the absorbance at 241 nm divided by the transferrin concentration.

phenolate groups generated by the binding of metal ions to Tyr residues (Tyr95 and Tyr188 in the N-lobe, Tyr426 and Tyr517 in the C-lobe) in the specific iron binding sites.^[8] The third, broader band at 315 nm ($\Delta\epsilon = 4700 \pm 300 \text{ M}^{-1} \text{ cm}^{-1}$) is likely to be a ligand-to-metal charge-transfer (LMCT) band. However, we could find no reports of such LMCT bands for titanium(IV) phenolate complexes in the literature. To confirm this assignment, titanium(IV) citrate was titrated into a solution of the model ligand ethylenebis(*o*-hydroxyphenylglycine) (EHPG, pH 7.4, 10 mM Hepes buffer), a ligand used previously for mimicking Fe^{III} binding.^[9] The UV difference spectra were almost identical to those from reaction of titanium(IV) citrate with transferrin and ^1H NMR shifts of the aromatic protons of EHPG induced by titanium(IV) citrate are consistent with the binding of Ti^{IV} ions to phenolate groups on the ligand.

Analysis of the titration curve for reaction of apo-hTF with titanium(IV) citrate (Figure 1b) suggests that two Ti^{IV} ions bind strongly to transferrin (i.e. one in each lobe). A similar stoichiometry of $\text{Ti}:\text{hTF} = 1.9 (\pm 0.1):1$ was obtained from the measurement of the titanium content of purified titanium transferrin by inductively coupled plasma atomic emission spectroscopy (ICP-AES). The value of the extinction coefficient for the first step of Ti^{IV} binding to transferrin (occupation of one lobe), $\Delta\epsilon_1$, is $17000 \pm 400 \text{ M}^{-1} \text{ cm}^{-1}$ at 241 nm , which is the same as the value determined for Ti^{IV} binding to ethylenebis(*o*-hydroxyphenylglycine) ($\Delta\epsilon \approx 17000 \text{ M}^{-1} \text{ cm}^{-1}$), suggesting that two tyrosines are involved in binding Ti^{IV} in both the N- and C-lobes (linear increase in $\Delta\epsilon$ with occupation of sites, see Figure 1b). The resulting yellow $\text{Ti}_2\text{-hTF}$ solution was stable at ambient temperature.

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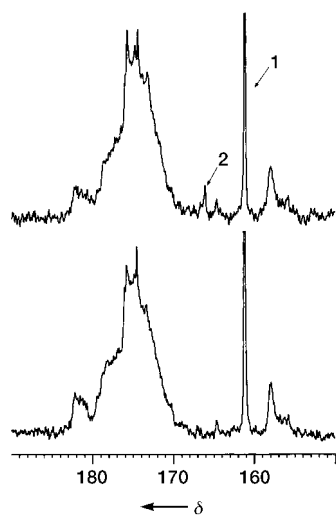


Figure 2. ^{13}C NMR spectra (125 MHz) of apo-hTF. Top: 1.6 mM, 10 mM $\text{H}^{13}\text{CO}_3^-$, 100 mM KCl, 70% $\text{H}_2\text{O}/30\%$ D_2O , pH 7.5. Bottom: Same solution treated with 2 molequiv Ti^{IV} (10 mM aqueous solution of $[\text{TiCp}_2\text{Cl}_2]$ solubilized by addition of 1.2 molequiv sodium citrate). A similar signal for bound $^{13}\text{CO}_3^{2-}$ was also seen on reaction of hTF with titanium(IV) citrate. This peak is weaker than that of, for example $\text{Bi}_2\text{-hTF}$,^[14] suggesting a difference in the extent of lobe closure and anion exchange rate. Labels 1 and 2 refer to signals of free HCO_3^- and bound CO_3^{2-} , respectively.

complexes.^[10] In the ^{13}C NMR spectrum a new signal assigned to bound $^{13}\text{CO}_3^{2-}$ appeared at $\delta = 166.1$ (Figure 2), almost identical to signals observed on reaction of hTF with titanium(IV) citrate in the presence of $\text{H}^{13}\text{CO}_3^-$. The chemical shift of this bound anion is close to that observed previously for other metallothioneins ($\delta = 165.4$ for Al^{III} , $\delta = 166.5$ for Ga^{III} , $\delta = 166/166.2$ for Ti^{III} ,^[11, 12] $\delta = 166.8/167.2$ for Sc^{III} ,^[13] and $\delta = 165.8$ for Bi^{III}).^[14]

Even though ^1H NMR spectra of hTF are complicated by the overlap of a large number of resonances, it was clear that Ti^{IV} binding caused characteristic changes in certain regions, for example new peaks appeared in the *N*-acetyl region ($\delta = 2.066$ and 2.055 due to glycan chains), and in the high-field region ($\delta = 0.284, 0.050, -0.073$, Figure 3). Resonances due to bound Cp ($\delta \approx 6.2\text{--}7.0$) disappeared and new peaks at approximately $\delta = 6.0$ can be assigned to displaced Cp ligands.

The apparently strong binding of Ti^{IV} ions to transferrin is consistent with predictions based on metal ion acidity: the most acidic metal ions bind the most strongly.^[15] In view of the pK_a values of Ti^{IV} and Fe^{III} ions (< 1 and 2.7 , respectively),^[16] Ti^{IV} might be expected to bind to transferrin even more strongly than Fe^{III} (although in practice this may be influenced by other hydrolytic equilibria). We found that Fe^{III} ions can displace Ti^{IV} ions from transferrin but only slowly. Upon addition of 2 molequiv $[\text{Fe}^{\text{III}}(\text{nta})_2]$ (nta = nitrilotriacetate) to $\text{Ti}_2\text{-hTF}$ (pH 7.4) a band appeared at approximately 465 nm, which is characteristic of iron transferrin. This reaction seems

Attempts to determine by UV spectroscopy whether the anticancer drug $[\text{TiCp}_2\text{Cl}_2]$ can transfer Ti ions to hTF were hampered by the absorption of the drug itself. Therefore ^1H and ^{13}C NMR spectroscopy were used to establish this interaction. We reasoned that in blood plasma $[\text{TiCp}_2\text{Cl}_2]$ may be present as a citrate adduct in view of the high concentration of plasma citrate (ca. $100\ \mu\text{M}$). Therefore reactions were carried out with the drug solubilized by approximately 1 molequiv citrate. The exact nature of this complex was not established and we refer to it as $\{\text{TiCp}_2\}^{2+}$. It is clear from ^1H NMR spectra that the Cp ligands remain bound and citrate probably displaces the Cl^- ligands by analogy to recently reported amino acid com-

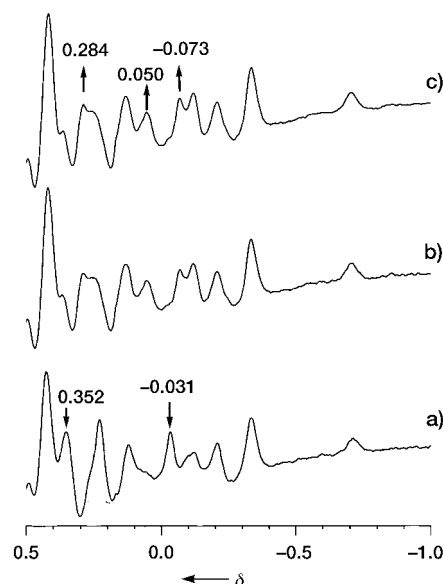


Figure 3. a) High-field region of the ^1H NMR spectrum (500 MHz) of apo-hTF and changes induced by added b) titanium(IV) citrate, and c) $\{\text{TiCp}_2\}^{2+}$ (2 molequiv, pH* 7.4, 0.1 M KCl, 10 mM bicarbonate). The signals in this region are largely from methyl groups situated over aromatic rings in the protein. The spectra are complicated by the broadness of the signals from this 80 kDa protein and by peak overlap, but it is clear that Ti^{IV} binds similarly in both cases with displacement of the citrate and Cp ligands.

to proceed in two steps, the first lasting about 20 min and the second lasting over 5 h.

Since hTF in blood plasma is only about 30% saturated with Fe^{III} ions,^[17] Ti^{IV} ions entering the blood, for example from anticancer complexes, could readily be taken up by this protein. Transferrin could serve to deliver Ti^{IV} to cancer cells and release it inside cells (at low pH), as is well-documented for Ga^{III} and Ru^{III} ions.^[4, 5] Biological investigations of titanium transferrin would therefore appear to be warranted.

Experimental Section

Apo-hTF was purchased from Sigma (Catalog No. T0519) and was washed three times with 0.1 M KCl using Centricon 30 ultrafilters (Amicon) to remove low molecular mass impurities. Protein concentrations were determined by means of the extinction coefficient $\epsilon_{280} = 93\,000\ \text{M}^{-1}\ \text{cm}^{-1}$.^[18] Ethylenebis(*o*-hydroxyphenylglycine) (Sigma), $\text{Ti}^{\text{III}}\text{Cl}_3$ (Sigma), sodium citrate (Sigma), titanocene dichloride (Aldrich), NaHCO_3 (Sigma), and $\text{NaH}^{13}\text{CO}_3$ (MSD isotopes, $> 99\%$ enriched) were used without further purification.

Measurements of pH were made using a Corning 145 pH meter equipped with an Aldrich microcombination electrode calibrated with Aldrich buffer solutions of pH 4, 7, and 10. Meter readings for D_2O solutions are designated as pH*.

A 200 mM fresh purple solution of $[\text{Ti}^{\text{III}}(\text{cit})_{1.25}]$ (cit = citrate) was prepared under N_2 by adding sodium citrate (1 mL of a 250 mM solution) to a known amount of $\text{Ti}^{\text{III}}\text{Cl}_3$, and the pH was adjusted to approximately 6.0 by addition of solid NaHCO_3 .^[19] After bubbling with O_2 , a colorless solution of titanium(IV) citrate was obtained, which was then diluted to roughly 3.3 mM for UV experiments. UV spectra were recorded on a computer-controlled Perkin Elmer lambda 16 spectrometer; the temperature of the cell (1 cm) was maintained at 310 K.

A 10 mM yellow titanocene solution was prepared by dissolving a known amount of $[\text{TiCp}_2\text{Cl}_2]$ in a sodium citrate solution (Ti:cit = 1:1.2), and the pH was adjusted to 4.5 (1 M NaOH).

^1H and ^{13}C NMR spectra were recorded on a Bruker DMX500 NMR spectrometer at 500 and 125 MHz, respectively. The experimental conditions were similar to those reported previously.^[14] The ^1H NMR reference was endogenous formate ($\delta = 8.465$ at $\text{pH}^* > 7.0$ relative to trimethylsilyl propionate (TSP)), which was always present in transferrin samples as a minor impurity. The ^{13}C NMR reference was added dioxane ($\delta = 67.4$ relative to TSP).

The titanium content of transferrin was measured using inductively coupled plasma atomic emission spectroscopy (ICP-AES; Thermo Jarrell Ash IRIS, at 323.40 nm). The Ti_2 -hTF samples for ICP-AES were prepared as follows: titanium(IV) citrate (2.2 molequiv) was added to apo-hTF (in 10 mM HEPES buffer, pH 7.4, 10 mM bicarbonate) and left to equilibrate for over 24 h at 310 K. The protein was then purified by ultrafiltration (Centricon 30, Amicon), washing four times with 0.1 M KCl and twice with water. An aliquot of the final solution was diluted with concentrated HNO_3 (ca. 6 M) and the titanium content was measured without any digestion of the sample.^[20] The transferrin concentration in this sample was determined by titrating with Fe^{III} ions (added as $[\text{Fe}(\text{NTA})_2]$) by measuring the absorbance at 465 nm ($\Delta\epsilon = 4950 \text{ M}^{-1} \text{ cm}^{-1}$ for diferric transferrin).^[21]

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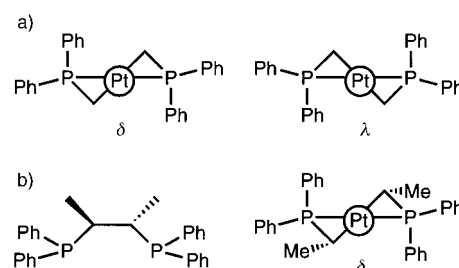
Keywords: antitumor agents • bioinorganic chemistry • titanium • transferrin

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Platinum(II) Complexes with Constructive and Destructive Interaction of Diphosphane and Binaphthol Ligands**

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(*S,S*)-2,3-Bis(diphenylphosphanyl)butane ((*S,S*)-Chiraphos) and its achiral analogue 1,2-bis(diphenylphosphanyl)ethane (dppe) belong to a class of chelating diphosphanes that form five-membered rings with late transition metals. These diphosphanes usually adopt a δ - or λ -skew conformation (Scheme 1a).^[1] With the achiral dppe, the two conformers are



Scheme 1. a) skew conformations of dppe in platinum complexes. b) (*S,S*)-Chiraphos and its preferred δ conformation in the complex.

equally favorable; however, backbone modification of chiral diphosphanes makes one conformer more stable than the other.^[2] For example, the *trans*-methyl substituents of (*S,S*)-Chiraphos favor the δ conformer (pseudoequatorial versus

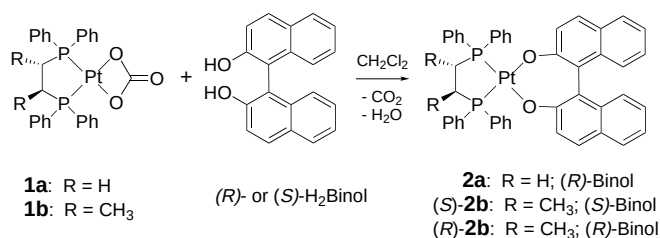
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pseudoaxial methyl groups, Scheme 1b).^[3] Because of this conformational preference, (*S,S*)-Chiraphos and similar ligands have been used extensively in asymmetric catalysis.^[4] The chelate ring fixes the positions of the phenyl groups of the phosphane such that their stereochemistry influences other bound ligands.^[2, 5] Although the effect of diphosphane conformation on the stereoselectivity with which ligands are bound has been studied in detail, the reciprocal effect of coordinating ligands on the conformation of the diphosphane has received little attention.

To investigate the magnitude of this type of interaction, the square-planar platinum(II) complex [(dppe)Pt{(R)-Binol}] (**2a**) was synthesized by the method of Andrews et al. (Scheme 2, H₂Binol = 1,1'-bi-2-naphthol).^[6] The single-crystal



Scheme 2. Synthesis of **2**.

X-ray structure of **2a** indicates that the chelating diphosphane adopts only the λ -skew conformation in the solid state.^[7] Since dppe has no inherent conformational preference, the λ conformation must be imposed on the diphosphane by the bulky (*R*)-Binol ligand, which interacts with the phenyl groups of dppe.

The strength of the Binol–diphosphane interaction was further probed by replacing dppe with the chiral diphosphane (*S,S*)-Chiraphos. Incorporation of two chiral ligands into a complex forces them to interact either constructively (matched) or destructively (mismatched).^[8] (*S,S*)-Chiraphos prefers the δ conformation. Since the structure of **2a** indicates that (*R*)-Binol favors the λ chelate, it and (*S,S*)-Chiraphos are mismatched, whereas (*S,S*)-Chiraphos and (*S*)-Binol are matched.

The matched ((*S*)-**2b**) and mismatched ((*R*)-**2b**) complexes were prepared in the same way as **2a** (Scheme 2).^[9] The X-ray structure of (*S*)-**2b** confirms that the diphosphane adopts the δ conformation that is favored by both (*S,S*)-Chiraphos and (*S*)-Binol (Figure 1).^[10] The structure is otherwise unexceptional.^[1, 3, 11] The unit cell of the mismatched complex, on the other hand, contains eight molecules of (*R*)-**2b** that differ in conformation.^[12] Superposition of the conformers shows the significant conformational variability of both the Chiraphos and Binol ligands (Figure 2). Differences in the Pt–P bond lengths and P–Pt–P angles of the eight (*R*)-**2b** conformers are generally smaller than the differences in the Pt–O bond lengths and O–Pt–O angles (Table 1), but all bond lengths and angles are similar to those of related compounds.^[11, 13, 14]

The extent of Binol distortion in each of the ten molecules (**2a**, (*S*)-**2b**, and eight (*R*)-**2b**) was quantified in terms of the distance ξ of the binaphthyl centroid from the P–Pt–P plane

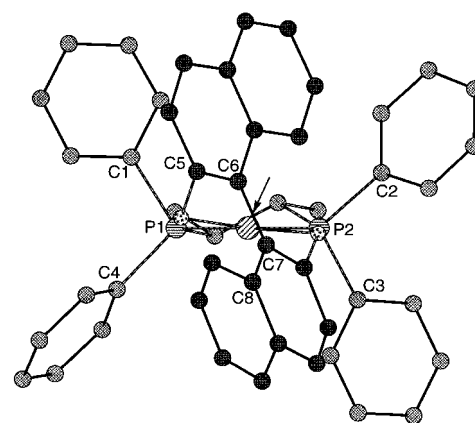


Figure 1. X-ray structure of (*S*)-**2b**. The arrow shows the center of the Binol 1,1' bond: the distance from this point to the P–Pt–P plane is ξ (see Table 1).

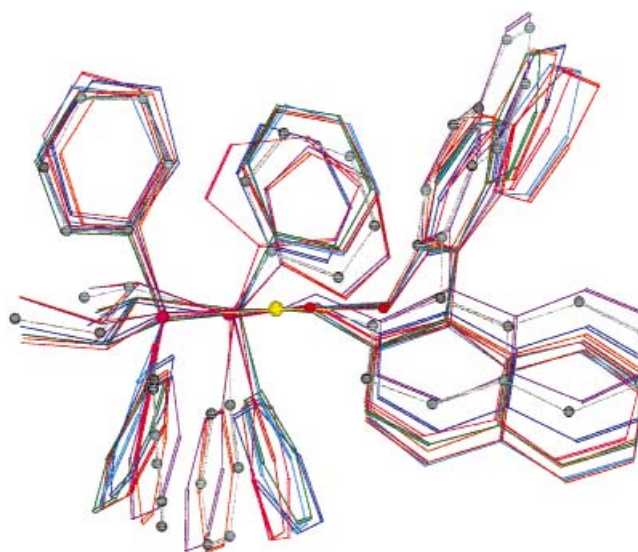


Figure 2. Superposition of the eight molecules of the unit cell of (*R*)-**2b**. The P–Pt–P planes are superimposed, and ξ is positive (the Binol units are skewed above the square plane).

Table 1. Bond lengths [Å] as well as bond and dihedral angles [°] of **2a**, (*S*)-**2b**, and (*R*)-**2b**.

	2a	(<i>S</i>)- 2b	(R)- 2b	
			median	range
Pt–O	2.071(5)	2.072(6)	2.058	2.021(9)–2.091(8)
Pt–P	2.212(2)	2.203(3)	2.210	2.200(3)–2.222(4)
O–Pt–O	89.0(2)	90.3(3)	90.5	89.8(3)–92.6(3)
P–Pt–P	85.5(1)	87.3(9)	86.7	86.1(1)–87.2(1)
C ₅ –C ₆ –C ₇ –C ₈	–62.9(1)	62.8(1)	–61.9	–58.6(2)–(–70.0)(2)
–(P ₂ –Pt–P ₁ –C ₁)	142.5(6)	103.1(6)	106.7	98.2(8)–115.5(8)
P ₁ –Pt–P ₂ –C ₂	113.5(6)	127.3(6)	131.8	125.6(9)–143.6(8)
–(P ₁ –Pt–P ₂ –C ₃)	120.1(5)	111.0(6)	105.1	91.1(8)–113.0(9)
P ₂ –Pt–P ₁ –C ₄	94.0(5)	135.2(6)	133.4	123.1(8)–138.7(9)
ξ	0.328	0.316	0.435	0.225–0.689

(Figure 1, Table 1). In an ideal *C*₂-symmetric molecule, $\xi = 0$ (the two naphthylene groups are symmetrically arranged above and below the square coordination plane of the Pt center). Nonzero values of ξ reflect twisting of Binol due to steric conflict with the phenyl groups of the phosphane.

Variations in diphosphane conformation were quantified by means of the four P-Pt-P- C_{ipso} torsional angles (Figure 1). These angles describe the degree to which each phenyl ring is pseudoaxial (ideal value: 90°) or pseudoequatorial (ideal value: 135°); together they define the λ and δ conformations (Scheme 1).^[13] From the values in Table 1 it is apparent that all of the molecules deviate slightly from the ideal C_2 symmetry. The variation of ξ in the (*R*)-**2b** molecules (compared to $\xi_{2a} \approx \xi_{(S)-2b}$) shows the flexibility of the Binol unit in these complexes. The range of torsional angles in (*R*)-**2b** is also impressive, although **2a** and other Chiraphos compounds show similarly large deviations from ideal geometry.^[11, 15] The most significant conclusion drawn from the torsional angle data is that each of the eight (*R*)-**2b** molecules adopts the δ conformation.^[16] Comparison of the diphosphane conformations of **2a**, (*S*)-**2b**, and a representative molecule of (*R*)-**2b** reveals that (*R*)-**2b** more closely resembles (*S*)-**2b** than **2a** (Figure 3). Thus the *trans*-methyl groups of (*S,S*)-Chiraphos have a stronger influence on the diphosphane conformation than the Binol ligand.

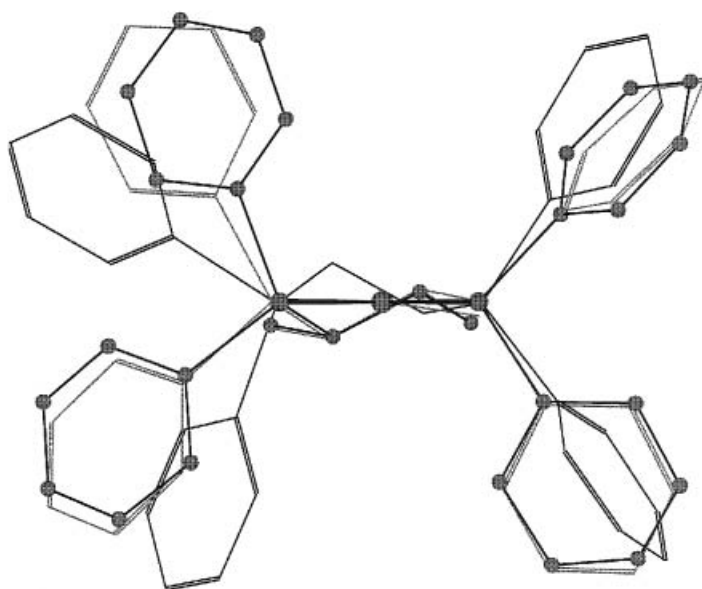
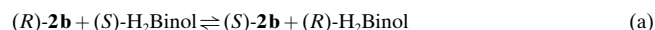


Figure 3. Comparison of the phosphane conformations of **2a** (black), (*S*)-**2b** (gray), and a typical molecule of (*R*)-**2b** (black, with atoms shown).

The influence of stereochemically matched and mismatched ligand pairs on the kinetics of complex formation was assessed by UV/Vis spectroscopy. Reactions with an excess of Binol (80 equiv) generated reproducible pseudo-first-order kinetic plots. Surprisingly, k_{obs} for the formation of the mismatched diastereomer (*R*)-**2b** is twice that of the matched diastereomer (*S*)-**2b** ($5.2(1) \times 10^{-3} s^{-1}$ versus $2.6(1) \times 10^{-3} s^{-1}$).^[17]

The relative ground-state energies of the two diastereomers were determined by means of an exchange reaction of the binaphtholate ligands [Eq. (a)]. Integration of the ^{31}P NMR signals of the diastereomers at equilibrium afforded an



equilibrium constant K_{eq} of 3.6 ± 0.3 at $25^\circ C$ [$\Delta G^\circ = 0.76 \text{ kcal mol}^{-1}$ (3.18 kJ mol^{-1})]. As expected, the matched diastereomer (*S*)-**2b** is slightly more thermodynamically stable than the mismatched (*R*)-**2b**.

The interaction of (*S,S*)-Chiraphos and Binol across the square coordination plane of the Pt^{II} center clearly has significant structural, kinetic, and thermodynamic consequences. Although the interactions observed are small, they are relevant, since high selectivities in asymmetric catalysis can be achieved with energy differences $\Delta\Delta G^\ddagger$ of only 2–3 kcal mol^{-1} for diastereomeric transition states. The conformational flexibilities of (*S,S*)-Chiraphos and Binol are noteworthy, as both ligands are widely used in asymmetric catalysis. This mobility is undoubtedly a general phenomenon that should not be dismissed when correlating ground-state structural data with stereochemical models for reaction selectivities.^[13]

Experimental Section

Racemic H_2 Binol (Aldrich) was resolved into the enantiomers (>95% *ee*) with *N*-benzylcinchonidinium chloride.^[18a] The starting materials [(dppe) $PtCl_2$], [(cod) $PtCl_2$], [(*S,S*)-Chiraphos] $PtCl_2$, **1a**, and **1b** were prepared according to literature procedures.^[1a, 18b–d] A representative synthesis of a binaphtholate complex follows:^[6]

(*S*)-**2b**: To a solution of [(*S,S*)-Chiraphos] $PtCO_3$ (125 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) was added (*S*)-Binol (53 mg, 0.19 mmol). The reaction mixture immediately turned yellow, and the reaction was complete after 2 h according to ^{31}P NMR spectra. The solvent was evaporated in vacuo, and the yellow product was recrystallized from CH_2Cl_2/Et_2O to give 163 mg of (*S*)-**2b** (94% yield).

UV/Vis spectra for the kinetic investigation were collected on an OLIS Cary-14 spectrometer interfaced to a computer for data collection. Reaction mixtures contained 0.16 mM **1a** or **1b** and 13.3 mM (*R*)- or (*S*)-Binol; k_{obs} is the average value from at least three experiments. Custom-made glass UV/Vis cells with screw-cap lids lined with PTFE-faced septa were used to prevent evaporative loss of CH_2Cl_2 . The program Kaleidograph was used to determine k_{obs} by fitting a plot of absorbance ($\lambda = 410 \text{ nm}$) versus time to the equation $A_t = A_\infty - A_\infty[\exp(-k_{obs}t)]$.

Equilibrium experiments were carried out in dry CH_2Cl_2 . One equivalent of (*R*)- or (*S*)-Binol was added to an NMR tube containing 15 mg (16 μmol) of (*S*)-**2b** or (*R*)-**2b**, respectively. The same equilibrium was reached from either side of Equation (a).

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- (1 equiv CH_2Cl_2 of crystallization also observed); $[\alpha]_{\text{D}}^{25.4} = -1.03$ ($c = 1.01$ in CH_2Cl_2); elemental analysis calcd for $\text{C}_{46}\text{H}_{36}\text{O}_2\text{P}_2\text{Pt} \cdot \text{CH}_2\text{Cl}_2$: C 58.6, H 4.0; found: C 58.2, H 4.0.
- [7] Crystal data for **2a**: $a = 12.5114(7)$, $b = 17.0838(10)$, $c = 18.3107(10)$ Å, $V = 3913.8(4)$ Å³, orthorhombic, space group $P2_12_12_1$, crystal dimensions $0.05 \times 0.05 \times 0.40$ mm, $\rho_{\text{calc}} = 1.634 \text{ Mg m}^{-3}$, $Z = 4$, $2\theta_{\text{max}} = 50.0^\circ$. X-ray data were collected at -100°C on a Siemens SMART diffractometer with CCD detection and MoK_α radiation ($\lambda = 0.71073$ Å) in the ω scan mode. Of 20439 reflections collected, 6903 were unique and 5370 were included in subsequent calculations. Correction of the intensity data by using the SADABS program gave a range of relative corrections of 0.733–1.76 and an absorption correction of $\mu = 3.83 \text{ mm}^{-1}$. The structure was solved by direct methods. In the final least-squares refinement cycle, non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included with a riding model. The quantity minimized was $\text{SwD}|F|^2$. The model converged at $R = 0.042$, $wR = 0.042$, and $\text{GOF} = 1.15$ for 5335 reflections with $I_{\text{net}} > 2.5\sigma(I_{\text{net}})$ and 487 parameters. Calculations were performed with the program NRCVAX. 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-101092. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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- [9] (S)-**2b**: ^{31}P NMR (121.5 MHz, CD_2Cl_2): $\delta = 30.3$, $^1J_{\text{PPt}} = 3547 \text{ Hz}$; ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 7.86$ (m, 8H), 7.66 (m, 4H), 7.51 (m, 12H), 7.05 (dd, $J = 7.7, 6.9 \text{ Hz}$, 2H), 6.95 (dd, $J = 8.3, 6.8 \text{ Hz}$, 2H), 6.79 (d, $J = 8.5 \text{ Hz}$, 2H), 6.59 (d, $J = 8.8 \text{ Hz}$, 2H), 2.28 (m, 2H, CH), 1.05 (m, 2H, CH_3) (0.5 equiv Et_2O of crystallization also observed); $[\alpha]_{\text{D}}^{24.7} = -151.6$ ($c = 1.02$ in CH_2Cl_2); elemental analysis calcd for $\text{C}_{48}\text{H}_{40}\text{O}_2\text{P}_2\text{Pt} \cdot 0.5 \text{ C}_4\text{H}_{10}\text{O}$: C 63.7, H 4.8; found: C 63.9, H 4.9. (R)-**2b**: ^{31}P NMR (121.5 MHz, CDCl_3): $\delta = 31.8$, $^1J_{\text{PPt}} = 3562 \text{ Hz}$; ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 7.92$ (m, 4H), 7.83 (m, 4H), 7.74 (d, $J = 6.1 \text{ Hz}$), 7.66 (m, 6H), 7.53 (m, 2H), 7.46 (m, 4H), 7.35 (d, $J = 8.8 \text{ Hz}$, 2H), 7.03 (t, 2H), 6.90 (t, $J = 7.0 \text{ Hz}$, 2H), 6.71 (d, $J = 8.6 \text{ Hz}$, 2H), 6.00 (d, $J = 8.8 \text{ Hz}$, 2H), 2.22 (m, 2H, CH), 1.04 (m, 6H, CH_3) (H_2O and Et_2O of crystallization also observed); $[\alpha]_{\text{D}}^{24.0} = +110.6$ ($c = 1.02$ in CH_2Cl_2); elemental analysis calcd for $\text{C}_{48}\text{H}_{40}\text{O}_2\text{P}_2\text{Pt} \cdot \text{H}_2\text{O} \cdot 0.375 \text{ C}_4\text{H}_{10}\text{O}$: C 62.5, H 4.85; found: C 61.9, H 4.55.
- [10] The crystal structure analysis of (s)-**2b** was carried out as described in ref. [7]. Crystal data: $a = 13.4508(6)$, $b = 17.5011(8)$, $c = 19.0202(9)$ Å, $V = 4477.4(4)$ Å³, orthorhombic, space group $P2_22_1$, crystal dimensions $0.20 \times 0.20 \times 0.08$ mm, $\rho_{\text{calc}} = 1.399 \text{ Mg m}^{-3}$, $Z = 4$, $2\theta_{\text{max}} = 55.0^\circ$. Of 36189 reflections collected, 10236 were unique and 9052 were included in the refinement. Correction of the intensity data by using the program SADABS gave a range of relative corrections of 0.816–1.136 and an absorption correction $\mu = 3.23 \text{ mm}^{-1}$. In the final least-squares cycle, the model converged at $R = 0.050$, $wR = 0.059$, and $\text{GOF} = 2.47$ for 9031 reflections with $I_{\text{net}} > 2.5\sigma(I_{\text{net}})$ and 538 parameters.
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The Hexanitridodimanganate(IV) $\text{Li}_6\text{Ca}_2[\text{Mn}_2\text{N}_6]$: Preparation, Crystal Structure, and Chemical Bonding**

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While the ternary nitrides $\text{Li}_7[\text{V}^{\text{V}}\text{N}_4]$ ^[1, 2] and $\text{Li}_6[\text{Cr}^{\text{V}}\text{N}_4]$ ^[3] contain the 3d metals in their highest oxidation states, only the oxidation state +5 is attained by manganese in $\text{Li}_7[\text{Mn}^{\text{V}}\text{N}_4]$ ^[1]. In the ternary systems $\text{Ca}/(\text{V}, \text{Cr}, \text{Mn})/\text{N}$, only intermediate transition metal(III) compounds occur: $\text{Ca}_3[\text{V}^{\text{III}}\text{N}_3]$ ^[4], $\text{Ca}_3[\text{Cr}^{\text{III}}\text{N}_3]$ ^[5], $\text{Ca}_3[\text{Mn}^{\text{III}}\text{N}_3]$ ^[6] and $(\text{Ca}_3\text{N})_2[\text{Mn}^{\text{III}}\text{N}_3]$ ^[7]. In the quaternary system $\text{Li}/\text{Ca}/\text{Mn}/\text{N}$, we have now obtained $\text{Li}_6\text{Ca}_2[\text{Mn}_2\text{N}_6]$, a hexanitridodimanganate(IV). This is the first nitridometalate of a transition metal with an unbridged

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metal–metal bond within a complex anion.^[8] It is also the first example of a Mn–Mn bond between manganese centers in the high oxidation state +4. The currently known compounds with unbridged Mn–Mn bonds contain Mn⁰ and Mn^{−1} centers (e.g., [Mn₂(CO)₁₀]^[9] and (AsPh₄)[Mn₃(CO)₁₄]^[10]).

For the synthesis of Li₆Ca₂[Mn₂N₆], a mixture of lithium, calcium, and manganese in a molar ratio of 6:1:1 was heated in a tantalum crucible to 900 °C over 2 h and subsequently treated with a stream of nitrogen at this temperature. After a reaction time of 60 h, the reaction mixture was cooled to room temperature over 6 h. Li₆Ca₂[Mn₂N₆] was obtained as the main product together with some other phases that were not further investigated. The preparation of the quaternary compound also succeeds with a Li:Ca:Mn molar ratio of 3:1:1 under the same conditions, but the yield is considerably lower. Li₆Ca₂[Mn₂N₆] forms platelike crystals with a silver-metallic luster and layer cleavage parallel to (001).

The crystal structure of Li₆Ca₂[Mn₂N₆]^[11] is shown in Figure 1. The nitrogen atoms are arranged according to the motif of hexagonal close packing (stacking sequence AB); the

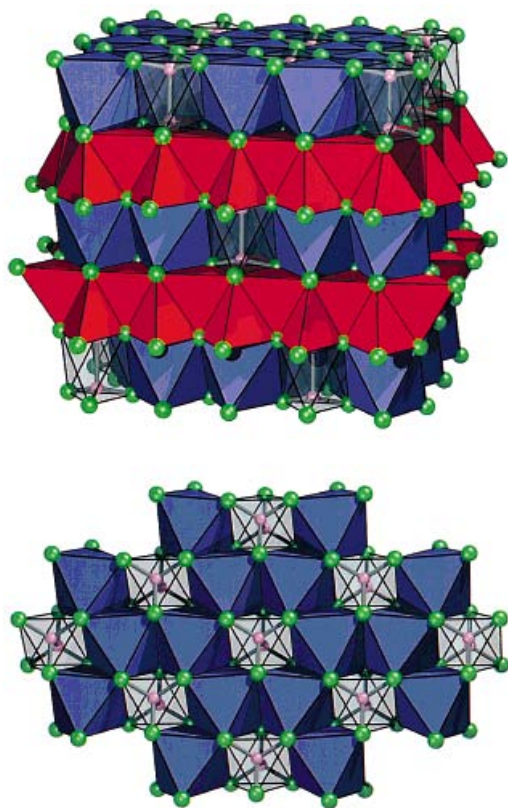


Figure 1. Section of the crystal structure of Li₆Ca₂[Mn₂N₆] (top) and a section of the octahedral layer (bottom). Green spheres: nitrogen; blue octahedra: (N₆Ca); transparent octahedra: (N₆Mn₂); red tetrahedra: (N₄Li).

octahedral holes of every second double layer are occupied by an ordered arrangement of calcium ions and Mn₂ dumbbells in a ratio of 2:1. This Ca₂[Mn₂N₆]^{6−} partial structure is closely related to that of the hexaselenodiphosphate(IV) Mg₂[P₂Se₆] (space group *R*3̄, noncentrosymmetric variant^[12]) and is an isotype of CuAl[P₂Se₆] (space group *R*3̄, statistical distribu-

tion of Cu and Al^[13]). The negative charges of the anionic layer structure are compensated by Li⁺ ions, which occupy all the tetrahedral holes between the octahedral layers filled by calcium and Mn₂ dumbbells.^[14] The interatomic distances in the Li₆Ca₂[Mn₂N₆] structure resemble those of known nitridomanganates,^[15] with the exception of the Mn–Mn bond found here for the first time.

A special feature of the Li₆Ca₂[Mn₂N₆] structure is the hexanitridodimanganate(IV) anion (Figure 2) with a short Mn–Mn bond of 235.8(1) pm. Unbridged Mn–Mn bonds were formerly known only for Mn⁰ and Mn^{−1} compounds, which exhibit Mn–Mn bond lengths of 289.5 pm (Mn₂(CO)₁₀)^[9] and 288.3 and 290.6 pm ((AsPh₄)[Mn₃(CO)₁₄])^[10]. The Mn–Mn distances in α-Mn lie between 224 and 291 pm.^[16] The close relationship between the crystal chemistry of hexaselenodiphosphates(IV)^[12, 13] and the hexanitridodimanganate(IV) has already been mentioned; the complex anions show identical conformations (staggered arrangement), but strictly speaking are not isosteric ([P₂Se₆]^{4−}: 50 e[−]; [Mn₂N₆]^{10−}: 54 e[−]).

The electronic structure of Li₆Ca₂[Mn₂N₆] was calculated by means of the TD-LMTO program (LDA approximation).^[17] For the interpretation of the bonding situation, the electron localization function (ELF)^[18] was evaluated. The ELF values are restricted by definition to the range between 0 and 1. High ELF values are characteristic of regions of high localization, such as in bonds or lone pairs. Specific details were obtained from the ELF by an analytical procedure that is also applied to the investigation of electron density.^[19] By topological analysis, the total ELF field is partitioned into the basins of the core or bond attractors as well as the basins of the attractors of the lone pairs. The integration of the electron density in these regions yields the number of electrons belonging to them. For the bonding attractor, this procedure also provides information about bond order.^[20–24]

The ELF for the crystal structure of Li₆Ca₂[Mn₂N₆] is characterized by three symmetrically independent maxima in the unit cell (Figure 3). The highest ELF value (0.866) is exhibited by the lone pairs of the nitrido groups of the [Mn₂N₆] units (Figure 3a). The deformation of these regions is caused by the repulsive interaction between the neighboring nitrido groups and by the polarizing influence of the coordinating cations. The next lower maximum, with an ELF value of 0.785 and a small basin, extends from the nitrido ligand towards the Mn center (Figure 3b). This attractor is located very close to the nitrogen atom and is thus representative of the pronounced polar character of the Mn–N bond. The third and most interesting type of local ELF maximum is found on the Mn–Mn connecting line (Figure 3c) and can

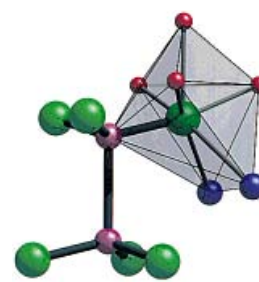


Figure 2. Complex anion [Mn₂N₆]^{10−} (staggered conformation) with cation coordination polyhedron around one nitrido position. Green spheres: nitrogen; violet spheres: manganese; red spheres: calcium; gray spheres: lithium. Selected interatomic distances [pm]: Li–N 200–221, Ca–N 252–264, Mn–N 178, Mn–Mn 236.^[15]

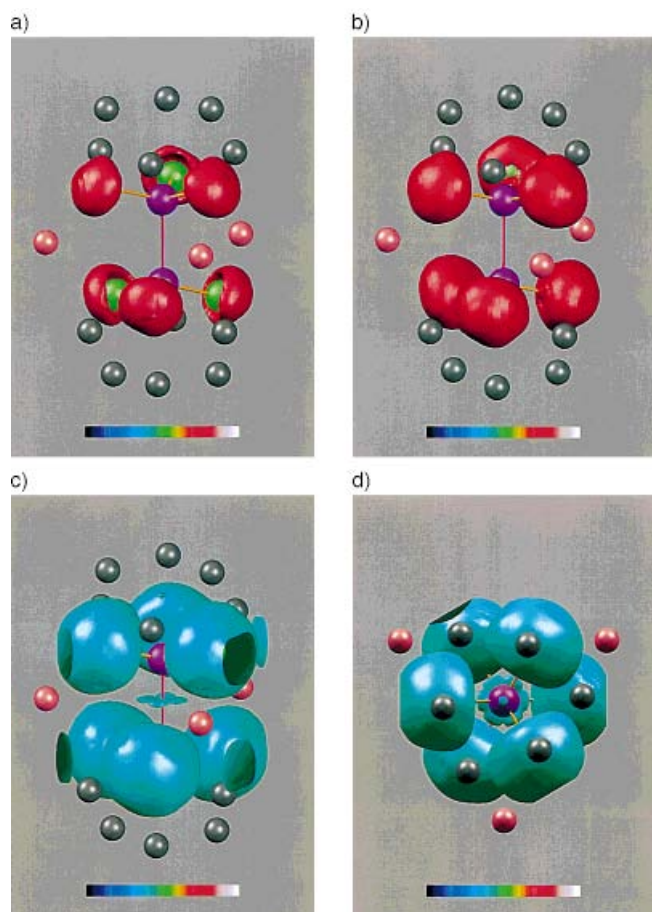


Figure 3. Isosurfaces of the electron localization function for $\text{Li}_6\text{Ca}_2[\text{Mn}_2\text{N}_6]$. Green spheres: nitrogen; violet spheres: manganese; red spheres: calcium, gray spheres: lithium. The connecting lines Mn–Mn and Mn–N are shown in red and orange, respectively. The colors of the ELF isosurfaces correspond to the ELF scale in the lower part of the figure. a) Attractors of the lone pairs at the nitrido positions ($\text{ELF} = 0.866$). b) Bonding attractors ($\text{ELF} = 0.785$) on the Mn–N connecting line (polar character of the Mn–N bonds). c) Bonding attractor Mn–Mn with the low ELF value of 0.392 (d character of the electron density^[25]); two-electron, two-center bond (see text). View approximately perpendicular to the Mn–Mn bond. d) Bonding attractor Mn–Mn; view along the Mn–Mn bond.

assigned to a covalent interaction. The putative fourfold symmetry of this attractor evident in Figure 3c is in fact consistent with the threefold axis (space group $R\bar{3}$), as can be seen in Figure 3d with a view along the connecting line Mn–Mn. The relatively low ELF value in this maximum (0.392) is consistent with the predominant d character of the electron density in this region.^[25] The integration of the electron density in the basin of this attractor gives 2.0 electrons; hence, the Mn–Mn bond should be regarded as a two-electron, two-center bond.

Till now investigations of the magnetic properties of $\text{Li}_6\text{Ca}_2[\text{Mn}_2\text{N}_6]$ have been affected by magnetically active impurities in the samples. Nevertheless, the measurements already indicate a weak temperature-dependent paramagnetism of the quaternary compound, presumably resulting from the electrons that do not participate in the bonds of the complex anion.

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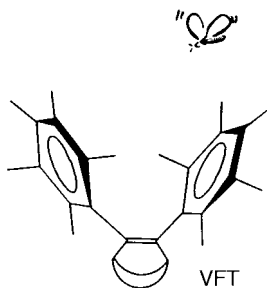
An Efficient Venus Flytrap for the Reversible Binding of Nitric Oxide**

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Intermolecular noncovalent binding of guest molecules by synthetic macromolecular hosts has been a rapidly growing field of research^[1] since the first discovery of crown ethers by Pedersen.^[2] The unique chemical and physical properties of these novel host–guest structures are the key to the future development of nanomolecular devices, chemosensors, etc.^[3] Here we describe the synthesis of a novel *cis*-stilbenoid hydrocarbon ligand which strongly binds a neutral diatomic molecule such as nitric oxide (NO), which is of significant biological interest.^[4]

The hydrocarbon ligand 1,2-bis(pentamethylphenyl)bicyclo[2.2.2]oct-2-ene (Venus flytrap, VFT)^[5] possesses a unique molecular structure in which a pair of pentamethylphenyl moieties are forced to be closely juxtaposed in a cofacial manner by the very rigid bicyclooctene framework, as established by X-ray crystallography.^[6]

The activation of VFT by oxidation in dichloromethane readily generates the persistent cation radical VFT^{•+},^[7] which upon exposure to gaseous nitric oxide leads immediately to a bright blue solution. Quantitative IR spectroscopic analysis of the blue solution indicates the complete uptake of nitric oxide, as judged by observing



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the characteristic absorption at 1885 cm⁻¹ for a single N–O stretching frequency.^[8] The high stability of blue [VFT·NO]⁺ allows the ready isolation of a single crystal from a mixture of dichloromethane and toluene at –23 °C. X-ray crystallography established its molecular structure to be made up of a single molecule of nitric oxide trapped between two cofacial phenyl rings. The diatomic nitric oxide fits neatly within the cavity of VFT, where it lies parallel to one of the phenyl rings, as shown by the space-filling representation in Figure 1.

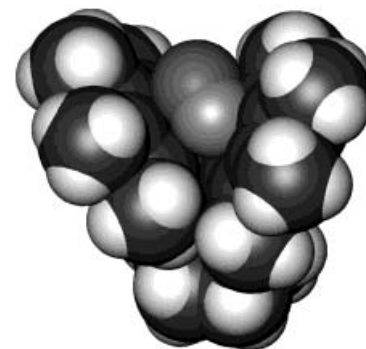


Figure 1. Space-filling representation of NO tightly entrapped within the VFT cleft.

The N–O bond distance of 1.12 Å in [VFT·NO]⁺ is consistent with a noncovalently bonded nitric oxide molecule,^[9] especially since the separation between the nitrogen atom and any aromatic carbon atom (av 2.5 Å) is much greater than the covalent N–C bonding distance.^[10] Moreover, most of the positive charge resides on the aromatic and olefinic carbon atoms, as judged by the significant lengthening of the average C_{arene}–C_{arene} distance (1.42 Å) with respect to that in the neutral stilbenoid ligand.^[11] Thus, VFT acts as a molecular tweezer for neutral NO. This is readily apparent upon inspection of the phenyl rings, which are significantly arched in an attempt to encapsulate the NO molecule. The distortion of the pentamethylphenyl groups is shown in Figure 2.^[12]

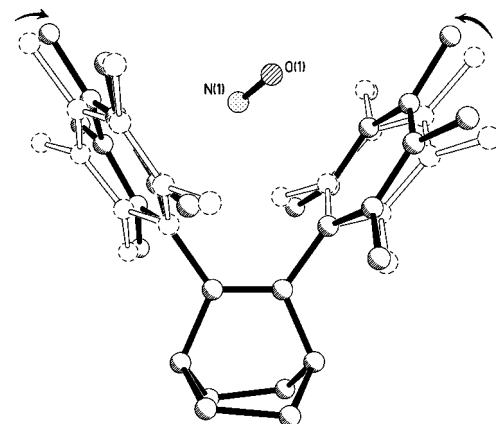
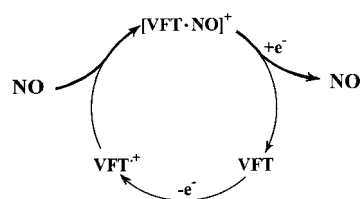


Figure 2. The superimposed molecular structures of the neutral stilbenoid ligand VFT (dashed line) and [VFT·NO]⁺ (solid line); hydrogen atoms have been omitted for clarity.^[12]

The tight binding of nitric oxide in $[\text{VFT} \cdot \text{NO}]^+$ is also evident from the very high value of the binding constant K ($> 3 \times 10^6 \text{ M}^{-1}$) estimated by an electrochemical method;^[13] this value is unprecedented for nitric oxide incarceration. Furthermore, the unusual stability is further reflected in the fact that NO cannot be extricated, even upon prolonged pumping in vacuo.

The same blue $[\text{VFT} \cdot \text{NO}]^+$ is also obtained by mixing the neutral VFT ligand with the nitrosonium cation (NO^+) in dichloromethane at 25°C .^[14] Indeed, the two possibilities for the synthesis of $[\text{VFT} \cdot \text{NO}]^+$ by treatment of either VFT^{++} with gaseous NO or the neutral hydrocarbon (VFT) with the cationic NO^+ suggests the construction of a redox-controlled molecular pump for nitric oxide. The electrochemical (one-electron) reduction^[13] of blue $[\text{VFT} \cdot \text{NO}]^+$ rapidly leads to the neutral VFT and nitric oxide.^[15] Scheme 1 presents the catalytic cycle for the reversible uptake and release of NO, which can be repeated indefinitely.^[16]



Scheme 1. Reversible binding of NO by VFT.

We have successfully demonstrated the redox-controlled and exceptionally effective binding of neutral diatomic NO by the stilbenoid hydrocarbon ligand VFT. The nature of the unusually strong intermolecular binding in $[\text{VFT} \cdot \text{NO}]^+$ is currently under investigation.

Experimental Section

2,3-Bis(pentamethylphenyl)bicyclo[2.2.2]oct-2-ene (VFT) was synthesized by the reaction of pentamethylphenylmagnesium bromide with 2,3-dibromobicyclo[2.2.2]oct-2-ene in the presence of a palladium catalyst according to a known general procedure.^[17] Yield: 94%; m.p. $239-240^\circ\text{C}$ (EtOH); ^1H NMR (CDCl_3): $\delta = 1.77$ (brd, $J = 7.4$ Hz, 4H), 1.91 (brd, $J = 7.4$ Hz, 4H), 2.14 (s, 12H), 2.18 (s, 6H), 2.19 (s, 12H), 2.63 (brs, 2H); ^{13}C NMR (CDCl_3): $\delta = 16.63$, 16.81, 19.83, 27.28, 37.79, 131.96, 132.08, 132.54, 139.45, 142.71; GC-MS: $m/z = 400$ (M^+), calcd for $\text{C}_{30}\text{H}_{40}$: 400; elemental analysis calcd for $\text{C}_{30}\text{H}_{40}$: C 89.94, H 10.06; found: C 89.77, H 10.01. Crystal data for $[\text{VFT} \cdot \text{NO}]^+$: ($\text{C}_{30}\text{H}_{40}$) NOSbCl_6 . A suitable crystal ($0.2 \times 0.2 \times 0.1$ mm) was obtained by slow diffusion of toluene into a solution of blue $[\text{VFT} \cdot \text{NO}]^+$ in dichloromethane at -23°C . $M_r = 765.08$, monoclinic, space group $P2_1/n$, $a = 11.260(2)$, $b = 20.084(2)$, $c = 15.322(3)$ Å, $\rho_{\text{calcd}} = 1.549 \text{ mg m}^{-3}$, $V = 3280.9(11)$ Å³, $Z = 4$. The data were collected on a Siemens SMART diffractometer equipped with a CCD detector using $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å) at -150°C . A total of 40937 reflections were measured, of which 14952 were symmetrically nonequivalent. The structure was solved by direct methods and refined by the full-matrix least-squares procedure. Final residuals were $R_1 = 0.0496$ and $wR_2 = 0.0838$ for 14952 reflections with $I > 2\sigma(I)$. The X-ray structure of dichloromethane monosolvate $[\text{VFT} \cdot \text{NO}^+\text{SbCl}_6 \cdot \text{CH}_2\text{Cl}_2]$ was also determined, and the details of the investigation can also be obtained from the Cambridge Crystallographic Data Centre. Crystal data for 1,2-bis(pentamethylphenyl)bicyclo[2.2.2]oct-2-ene: $\text{C}_{30}\text{H}_{40}$. A crop of well-formed crystals was obtained from ethanol/dichloromethane after three days at -23°C . A colorless crystal of dimensions $0.3 \times 0.2 \times 0.1$ mm was used for the X-ray study. $M_r = 400.62$, monoclinic, space group $P2_1/n$, $a = 8.6608(7)$, $b = 13.2230(10)$, $c = 20.401(2)$ Å, $\rho_{\text{calcd}} = 1.139 \text{ mg m}^{-3}$, $V = 2335.6(3)$ Å³, $Z = 4$.

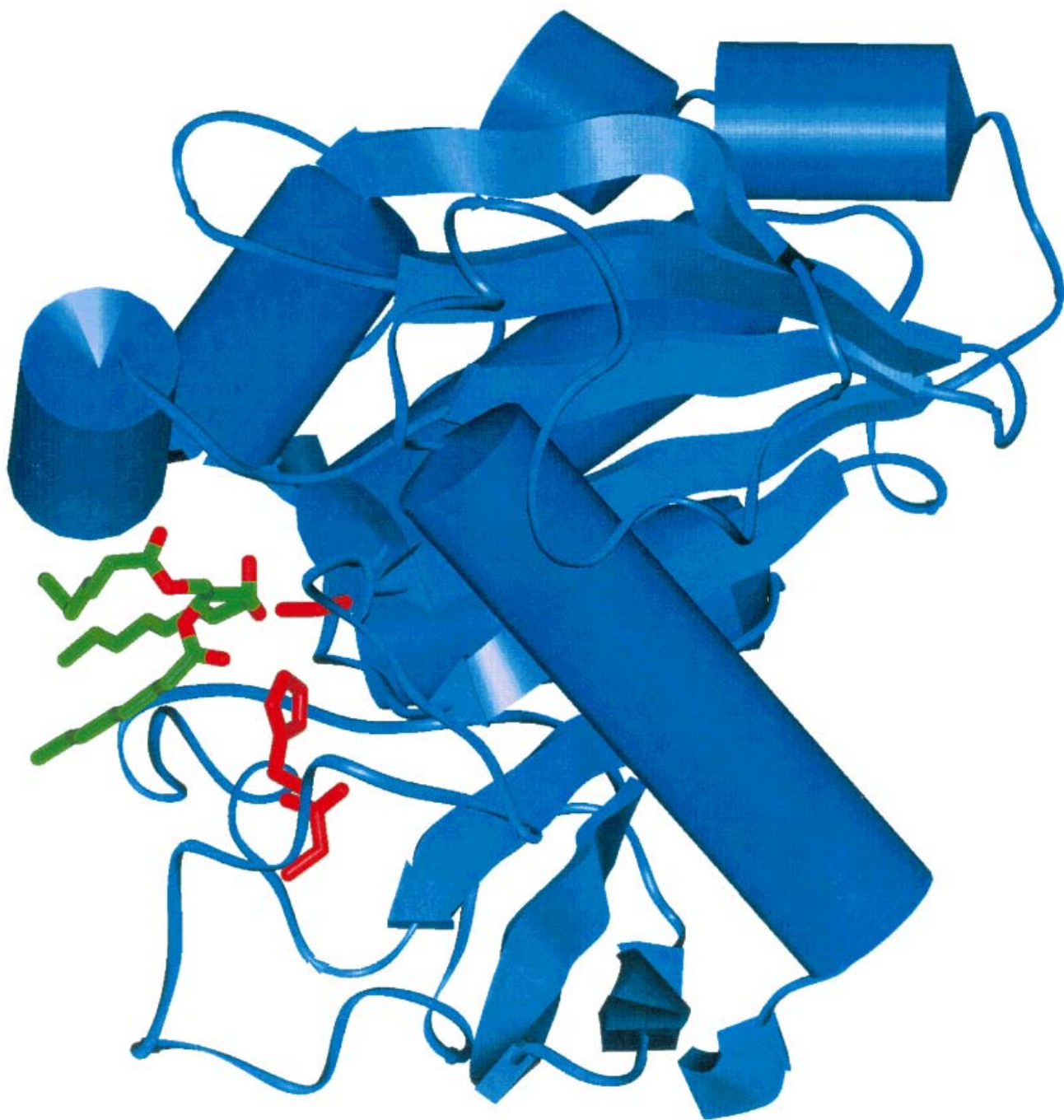
The data were collected as described above. A total of 8416 reflections were measured, of which 3237 were symmetrically nonequivalent. The structure was solved by direct methods and refined by the full-matrix least-squares procedure. Final residuals were $R_1 = 0.073$ and $wR_2 = 0.126$ for 3073 reflections with $I > 2\sigma(I)$. 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-101552, -101553, and -101554. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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- [12] The distortion of the phenyl rings in $[\text{VFT} \cdot \text{NO}]^+$ is judged by the decrease in the dihedral angle between the mean planes of the phenyl rings from about 71.8° to 61.1° (or to 64.5° in the dichloromethane solvate) as well as a decrease in the interplanar separation between the centers of the phenyl rings from about 4.94 Å (4.89 and 4.99 Å for the two disordered positions in VFT) to 4.74 Å in $[\text{VFT} \cdot \text{NO}]^+$ and 4.64 Å in the dichloromethane solvate. Furthermore, the *para* carbon atoms in the phenyl rings are bent outwards in neutral VFT, whereas in $[\text{VFT} \cdot \text{NO}]^+$ they are bent towards each other.

- [13] The binding constant for $[\text{VFT} \cdot \text{NO}]^+$ was estimated from the electrochemical reduction potential of $E_{\text{red}}^{\circ} = 0.58 \text{ V}$ versus SCE (obtained by cyclic voltammetry in dichloromethane containing 0.2 M *n*-tetrabutylammonium hexafluorophosphate as supporting electrolyte) in comparison to that of $E_{\text{red}}^{\circ} = 1.49 \text{ V}$ versus SCE for the uncomplexed NO^+ cation by applying the procedure described for the $[\text{hexamethylbenzene} \cdot \text{NO}]^+$ complex; see K. Y. Lee, D. J. Kuchynka, J. K. Kochi, *Inorg. Chem.* **1990**, 29, 4196.
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- [15] The neutral hydrocarbon ligand VFT and NO do not interact, as shown by the absence of any color change upon saturation of a solution of VFT in dichloromethane with gaseous nitric oxide.
- [16] In Scheme 1, $+e^-$ indicates the cathodic reduction of $[\text{VFT} \cdot \text{NO}^+]$ at $E_{\text{red}}^{\circ} = 0.6 \text{ V}$ versus SCE, which leads to the release of nitric oxide and neutral VFT, whereas $-e^-$ indicates anodic oxidation at $E_{\text{ox}}^{\circ} = 1.27 \text{ V}$ versus SCE of VFT to the green cation radical followed by the uptake of NO to yield $[\text{VFT} \cdot \text{NO}]^+$ as a bright blue solution ($\lambda_{\text{max}} = 349, 581 \text{ nm}$). To our knowledge, there are no other nonbiological systems for the reversible binding of nitric oxide.
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Structure of the *Mucor miehei* lipase in the open form. As with all lipases whose structures have been investigated, this lipase shows the “ α/β -hydrolyse fold” motive known from serine proteases. When the “lid” is open, the catalytic triad at the active center (red) becomes accessible for a substrate (normally triglycerides).

Lipases: Interfacial Enzymes with Attractive Applications

Rolf D. Schmid* and Robert Verger

Lipases not only hydrolyze fat in the digestion tract or interesterify triglycerides on a technical scale, but are surprisingly flexible biocatalysts for the acylation or deacylation of a wide range of unnatural substrates. Lipase-catalyzed transformations of racemic and prostereogenic compounds usually proceed with high enantioselectivity. If several functional groups amenable to lipase catalysis are present, the reaction is mostly regioselective. Lipases are quite stable and can be obtained from animals and plants as well as from

natural and recombinant microorganisms in good yields. Therefore, they are used industrially as detergent enzymes, in paper and food technology, in the preparation of specialty fats, and as biocatalysts for the synthesis of organic intermediates. From an enzymological point of view, lipases exhibit a unique tertiary structure that exposes the catalytically active site only in the presence of a lipid phase or, presumably, in an organic solvent. Recently, a large-scale European research project has led to an explosion in information

about the structure and function of lipases. As a result, these interesting enzymes have become a preferred object for industrial optimization through the modern methods of genetic engineering. Finally, lipases play an important physiological role in the digestion of fat by mammals and humans, and lipase inhibitors may have a potential as antiobesity drugs.

Keywords: acylations • enzyme catalysis • industrial chemistry • lipases • metabolism

1. Introduction

Lipids are key elements in the chemistry of life. Most organisms use the supramolecular chemistry inherent to phospholipids to form their exterior and compartmental membranes. Many plants and animals store chemical energy in the form of triglycerides, which are sparingly soluble in water. For the metabolic turnover of these and other biochemicals, they produce esterases, enzymes which can hydrolyze bonds of water-soluble esters. Esterases which can hydrolyze triglycerides at the water/oil boundary are termed lipases or, more systematically, triacylglycerol hydrolases [EC 3.1.1.3], and those which attack phospholipids are termed phospholipases (various entries under [EC 3.1.x]).^[1]

Both types of enzymes have recently received considerable attention.^[2–13] Whereas phospholipases are involved in key metabolic events such as membrane turnover and signal

transduction (which will not be further discussed here), lipases have diverse functions in the degradation of food and fat; they have qualified as valuable drugs against digestive disorders and diseases of the pancreas. They also find applications in biotechnology (in particular as detergent additives) and as catalysts for the manufacture of specialty (oleo)chemicals and for organic synthesis. Their broad synthetic potential is largely due to the fact that lipases, in contrast to most other enzymes, accept a wide range of substrates, are quite stable in nonaqueous organic solvents, and thus, depending on the solvent system used, can be applied to hydrolysis reactions or ester synthesis (Scheme 1).

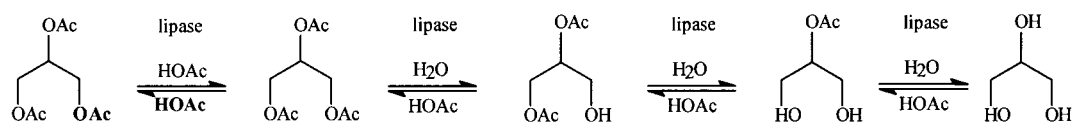
In addition, lipases can accommodate a wide range of substrates other than triglycerides such as aliphatic, alicyclic, bicyclic, and aromatic esters and even esters based on organometallic sandwich compounds. With respect to racemic esters or substrates with several hydroxyl groups, lipases react with high enantio- and regioselectivity.^[14] Finally, the acyl enzyme intermediate in lipase-catalyzed reactions is not only formed from carboxylic esters but from a wide range of other substrates such as thioesters or activated amines, which expands the synthetic potential of lipases considerably.^[15] As a result, chemists have long studied how to exploit these properties of lipases for the synthesis of useful intermediates. Today, they may choose their preferred lipase from a great variety of commercially available preparations or even explore a range of different lipases and esterases marketed as a kit.

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Scheme 1. Hydrolysis and ester synthesis with lipases.

2. Occurrence, Preparation, and Analysis

2.1. Occurrence and Preparation

Lipases are ubiquitous enzymes and have been found in most organisms from the microbial,^[16–18] plant,^[19, 20] and animal kingdom.^[21, 22] They are prepared either by extraction from animal or plant tissue, or by cultivation of microorganisms.^[2] Commercially available lipases are usually derived from microorganisms. Since the advent of genetic engineering techniques, an increasing number of lipases is being commer-

cially manufactured from recombinant bacteria and yeasts. As an example, the “detergent lipase” from the fungus *Humicola lanuginosa* is commercially produced in large scale (several 100 tons per year) through fermentation of *Aspergillus oryzae* into which the gene coding for *Humicola lanuginosa* lipase was cloned.^[23]

Usually, lipases are just one member of a “hydrolytic enzyme cocktail” elaborated by an organism with the objective to sustain its growth. Often, the lipase of interest must be separated from other esterases and proteases occurring in the crude enzyme preparation (Table 1).^[24, 25]

Table 1. Purity of commercial lipases; many are impure.

Lipase source	Portion of protein [%]	Lipase activity ^[a] [U mg ⁻¹]	Major SDS-PAGE bands [kDa]	Number of major SDS-PAGE bands	Number of esterase bands ^[b]	Protease activity ^[c] [%]
<i>Rhizomucor miehei</i>	3.5	16	25	5	2	1
<i>Rhizopus spec.</i>	4.8	32	43, 67	10	4	3
<i>Humicola lanuginosa</i>	2.9	10	20, 30	4	2	20
<i>Candida rugosa I</i>	4.2	11	20, 30, 43, 67, 90	13	2	< 1
<i>Candida rugosa II</i>	6.4	14	43, 67	11	2	< 1
<i>Geotrichum candidum</i>	4.3	8	67	3	0	< 1
<i>Pseudomonas fluorescens</i>	1.2	30	14, 25, 40, 43	6	3	< 1
<i>Chromobacterium viscosum I</i>	1.1	45	17, 30, 40	3	1	0
<i>Chromobacterium viscosum II</i>	9.5	154	17, 30, 40	2	1	12

[a] Towards triolein (pH 7.5, 37 °C). [b] Hydrolysis in the presence of α -naphthyl acetate and activity staining with FastRed. [c] As a percentage of proteinase K activity on azoalbumin.

Rolf D. Schmid was born 1942 in Salzburg, Austria, and studied chemistry from 1961 at the Universität München, Germany, and later in Freiburg, where he obtained his Ph.D. in 1970 for thesis work done in Hans Grisebach's laboratory. After postdoctoral studies in France and the USA, he joined the research laboratories of Henkel KGaA in Düsseldorf in 1972, where he became Director of the Biotechnology Laboratories. In 1987 he moved to the Gesellschaft für Biotechnologische Forschung (GBF) in Braunschweig, where he headed the Division of Enzyme Technology and Natural Products Research. In 1993 he accepted an invitation to build up the newly founded Institute for Technical Biochemistry at the Universität Stuttgart. He is also in charge of the Department of Molecular Biotechnology of the Fraunhofer Institute for Membrane Science and Biotechnology in Stuttgart, and he is chairman of the IUPAC Commission of Biotechnology.



R. Verger

R. D. Schmid

Robert Verger was born 1944 in Maison Carrée, Algeria. He started to study chemistry at the University of Aix-Marseille, where in 1970 he obtained his Doctorat d'Etat in physics for a thesis under the guidance of Pierre Desnuelle. After a postdoctoral stay at the University of Utrecht, The Netherlands, he returned to Marseille and started his scientific career at the Centre National de la Recherche Scientifique (CNRS) in Marseille. Since 1990 he has held the title of “Directeur de Recherche 1^{ère} classe” and has received the bronze and silver medals of the CNRS.

Purification protocols are often laborious as the affinity of lipases is high not only to the oil/water boundary, but to any interphase of lower polarity than water (e.g. water-immiscible organic solvents, glass and plastic surfaces, and air bubbles); lipases may irreversibly adsorb and denature at such interphases.^[26, 27]

The critical discussion of experiments on lipase catalysis reach even beyond such difficulties, as many organisms produce mixtures of lipase isoforms which differ only marginally, for example by their glycosylation pattern.^[28] Limited proteolysis during maturation of a prolipase or during recovery in the presence of protease impurities may result in a heterogenous mixture of enzymes with lipolytic activity, and ambiguities may exist in the taxonomic classification of the producing microorganism (Table 2).

Thus, quite a few results from the application of “lipases” to oleochemistry and organic synthesis may have originated from the use of a poorly defined enzyme cocktail which, among other activities, also included a lipase. Any result obtained with a commercial lipase should be scrutinized in view of potential masking effects from unrelated enzymes or other additives contained in the sample. Fortunately, many pure lipases, often obtained by recombinant technology, can now be purchased from enzyme suppliers. Table 3 summarizes commercially available lipases and their abbreviation codes used throughout this review.

Table 2. Some of the ambiguities concerning commercially available lipases.

Lipase source	Remarks
<i>Candida rugosa</i> (CRL)	An organism that was formerly classified as <i>Candida cylindracea</i> . Protein purification and cloning of the enzyme revealed that the organism produces at least five related lipase isoforms.
<i>Geotrichum candidum</i> (GCL)	Contains two isoforms differing in specificity towards Δ^9 -unsaturated fatty acids.
<i>Rhizopus</i> (RAL, ROL, RDL, RNL)	Although literature data suggest different specificities of the lipases from <i>R. arrhizus</i> , <i>R. oryzae</i> , <i>R. delemar</i> , and <i>R. niveus</i> , cloning and sequencing revealed nearly complete identity of all four enzymes.
<i>Penicillium camembertii</i> (PeCL)	Classified as lipase from <i>P. cyclopium</i> until 1990. Contains four lipase isoforms which differ in their glycosylation pattern.
<i>Pseudomonas glumae</i> (PGL)	Cloning and sequencing revealed identity with lipase from <i>Chromobacterium viscosum</i> (CVL).
<i>Pseudomonas cepacia</i> (PCL)	Reclassified in 1995 as <i>Burkholderia cepacia</i> . Cloning and sequencing revealed identity with lipase from <i>P. sp.</i> ATCC21808 (PSL).

2.2. Analytical Determination

Lipases are often analyzed by their hydrolytic action on triglycerides in a heterogeneous reaction medium of water and oil. The greatest caution must be exercised both when

Table 3. Important commercially available lipases.

Origin	Code ^[a]	<i>M</i> [kDa] (rounded)	Specificity (remarks)	Applications
of mammalian origin				
human pancreatic lipase	HPL	50	<i>sn</i> -1,3	organic synthesis, digestive aid
human gastric lipase	HGL	50	<i>sn</i> -3 (acid-stable)	
porcine pancreatic lipase	PPL	50	<i>sn</i> -1,3	
guinea pig pancreatic lipase	GPL-RP2	48	<i>sn</i> -1,3 (phospholipase A1 activity)	
of fungal origin				
<i>Candida rugosa</i>	CRL	60	nonspecific	organic synthesis
<i>Candida antarctica B</i>	CAL	60	<i>sn</i> -1,3	organic synthesis
<i>Geotrichum candidum</i>	GCL	60	cis-Δ ⁹ (unsaturated fatty acids)	oleochemistry
<i>Humicola lanuginosa</i>	HLL	30	nonspecific	detergents
<i>Rhizomucor miehei</i>	RML	30	<i>sn</i> -1,3	cheese manufacturing
<i>Aspergillus oryzae</i>	AOL			cheese manufacturing
<i>Penicillium camembertii</i>	PEL	30	<i>sn</i> -1,3	monoglycerides
<i>Rhizopus delemar</i>	RDL	41	<i>sn</i> -1,3 (phospholipase A1 activity)	oleochemistry
<i>Rhizopus oryzae</i>	ROL	41	<i>sn</i> -1,3 (phospholipase A1 activity)	oleochemistry
<i>Rhizopus arrhizus</i>	RAL	41	<i>sn</i> -1,3 (phospholipase A1 activity)	oleochemistry
of bacterial origin				
<i>Pseudomonas glumae</i>	PGL	33	nonspecific	detergent enzyme, organic synthesis
<i>Burkholderia cepacia</i>	PCL/BCL	33	nonspecific	organic synthesis
<i>Pseudomonas pseudoalcaligenes</i>	PPL	33	<i>sn</i> -1,3	detergents
<i>Pseudomonas mendocina</i>	PML	33	<i>sn</i> -1,3	detergents
<i>Chromobacterium viscosum</i>	CVL	33	<i>sn</i> -1,3	organic synthesis
<i>Bacillus thermocatenulatus</i>	BTL-2	43	<i>sn</i> -1,3 (thermoalkalophilic)	
<i>Fusarium solani</i> (hydrolyzes cutin)	FSL	22		detergents

[a] Other abbreviations for lipases used in this article: PSL (*Pseudomonas species* lipase), PFL (*Pseudomonas fluorescens* lipase), HLL (human lipoprotein lipase), LPL (lipoprotein lipase). Lipases can be obtained commercially from many suppliers. Important original producers are Novo-Nordisk (Baegsvard, Denmark), Genencor International B. V. (Delft, The Netherlands), Boehringer-Mannheim (Mannheim, Germany), and Amano Co. (Nagoya, Japan).

performing and interpreting kinetic measurements. Since the medium is heterogeneous, the addition of any amphiphilic compound to the system will have effects on the interface and often on the enzyme itself. Some lipases, such as gastric lipases, rapidly become denatured at an interface with pure tributyrin emulsion, and it is therefore impossible to assess the interfacial activation with substrates of this kind. Esters which are partly soluble in water may form monomolecular adsorption films on the surface of the air bubbles which are produced upon stirring the reaction mixture. This phenomenon is responsible for a great disparity between initial velocity measurements, depending on whether or not mechanical stirring methods are used. It has in fact been established that the “quality” of the lipid/water interface—in terms of the orientation and conformation of the film-forming molecules, the molecular and charge surface densities, the interfacial water structure, the surface viscosity, etc.—is one of the most decisive parameters when working with lipolytic enzymes.^[29–31] This unfortunately means that valid comparisons can be made only between data obtained under strictly identical conditions, preferably within the same laboratory. Data on lipase activity obtained from different commercial manufacturers usually cannot be compared. For practical purposes, Table 4 gives an overview of the major procedures used in lipase analysis.

2.3. Interaction of Lipases with Lipids

As lipase catalytic action is strictly dependent upon the presence of a lipid interface, lipolytic enzymes provide a valuable model for studying protein–lipid interactions.^[34–37] Most data dealing with the surface properties of lipases were obtained with the monolayer technique, by recording (either independently or simultaneously) the lipolytic activity, the amount of protein adsorbed to the lipid monolayer, and the variations in surface pressure following protein adsorption (Figure 1). Several non-enzymatic proteins were used as controls in order to determine how lipase behavior differs from that of other proteins. With zwitterionic monolayers, the amount of pancreatic lipase binding to the monolayer decreased with increasing initial surface pressure, as observed

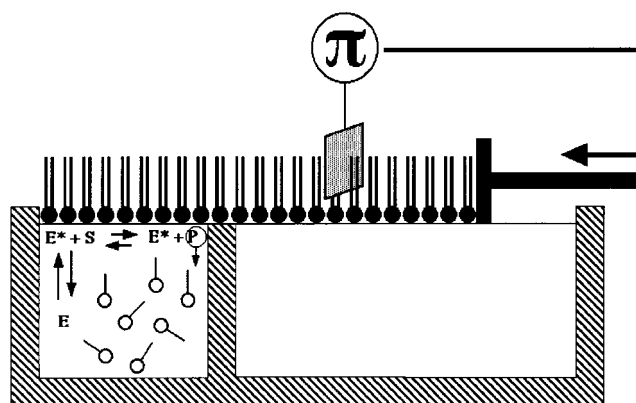


Figure 1. Drawing of a zero-order trough (a Langmuir–Blodgett film balance) composed of a substrate reservoir and a reaction compartment containing the enzyme solution. The two compartments, each covered with a monomolecular lipid film, are connected to each other by a narrow surface canal made in etched glass. The surface pressure of the film can be maintained constant automatically by the surface barostat method.^[32] Fully automated monolayer systems of this kind are now commercially available (KSV, Helsinki, Finland) and have been found to have many advantages: a) With very little amount of lipid, it is possible to monitor one of several physicochemical parameters characteristic of the monolayer film (surface pressure, potential, area, etc). b) In contrast to bulk methods, it is possible to transfer the monomolecular film from one aqueous subphase to another. c) It is possible to obtain accurate pre-steady-state kinetic measurements with minimal perturbation caused by increasing amounts of reaction products. d) Inhibition of lipase by water-insoluble analogues can be precisely estimated using a zero order trough and mixed monomolecular films in the absence of any synthetic, non-physiological detergent.^[33]

with control proteins such as bovine serum albumin and β -lactoglobulin A. However, pancreatic lipase as well as control proteins adsorbed to neutral lipid monolayers in a similar manner and independent from surface pressure. Lipase activity in the presence of various proteins was investigated with monomolecular films of glycerol didecanoate, either at constant surface area or at constant surface pressure. Depending upon the nature of the lipase and the protein, inhibition of lipase activity was either observed or not. Inhibition was correlated with a decrease in lipase surface concentration. The ability of the various proteins to inhibit lipolysis is a) a function of their concentration in comparison to the concen-

Table 4. Analytical methods for determining lipases.^[16]

Method	Principle	Advantages	Disadvantages
pH stat	potentiometric determination of fatty acids liberated upon hydrolysis	continuous kinetic methods for the determination of initial rates	- expensive equipment - added emulsifiers often modify reaction conditions - not applicable under acidic pH conditions
back titration	titration of liberated fatty acids after defined exposure to lipase action	simple	no continuous kinetic data
colorimetry	liberation of a reporter group from a synthetic ester (e.g. <i>p</i> -nitrophenyl palmitate or dilauryl glycerol resorufin ester)	fast and automatic kinetic measurements	unnatural substrates
determining the hydrolysis of lipid films spread at the air/water interface	hydrolysis of a lipid monolayer at constant surface pressure with continuous supply of substrate (zero-order trough)	kinetic measurements in the absence of added emulsifier and under controlled “interfacial quality”	- expensive equipment - time-consuming - trained experimentalist necessary

tration of lipase in the bulk phase and b) correlated with their penetration capacity (i.e., the initial rate of increase in surface pressure of a glycerol didecanoate monolayer having an initial surface pressure of 20 dyn cm⁻¹ after the injection of the protein). Since lipase inhibition was observed with low surface densities of inhibitory proteins, a long-range effect is probably involved in the mechanism of interfacial lipase inhibition.^[34] It is hypothesized that a lack of lipase adsorption to, or desorption from, the lipid monolayer results from a change in the organization of the hydrocarbon moiety of the lipid.

3. Structure and Mechanism

What exactly is a lipase? In 1958 Sarda and Desnuelle defined lipases in kinetic terms, based on the phenomenon of interfacial activation.^[38] It amounts to the fact that the activity of lipases is low on monomeric substrates but strongly enhanced once an aggregated “supersubstrate” (such as an emulsion or a micellar solution for instance) is formed above its saturation limit. This property is quite different from that of the usual esterases acting on water-soluble carboxylic ester molecules, and for a long time lipases were considered as a special category of esterases which are highly efficient at hydrolyzing molecules aggregated in water.

The protein structure underlying these observations remained a mystery until a few years ago. Only in 1990 were the first two lipase structures solved by X-ray crystallography. They revealed a unique mechanism, unlike that of any other enzyme: Their three-dimensional structures suggested that interfacial activation might be due to the presence of an amphiphilic peptidic loop covering the active site of the enzyme in solution, just like a lid or flap.^[39, 40] From the X-ray structure of cocrystals between lipases and substrate analogues, there is strong indirect evidence that, when contact occurs with a lipid/water interface, this lid undergoes a conformational rearrangement which renders the active site accessible to the substrate (Figure 2).^[41]

However, within the framework of the European Lipase Project, carried out from 1990 to 1994 by 24 laboratories in 8 nations, structural and numerous biochemical data on highly purified lipases provided evidence that not all lipases

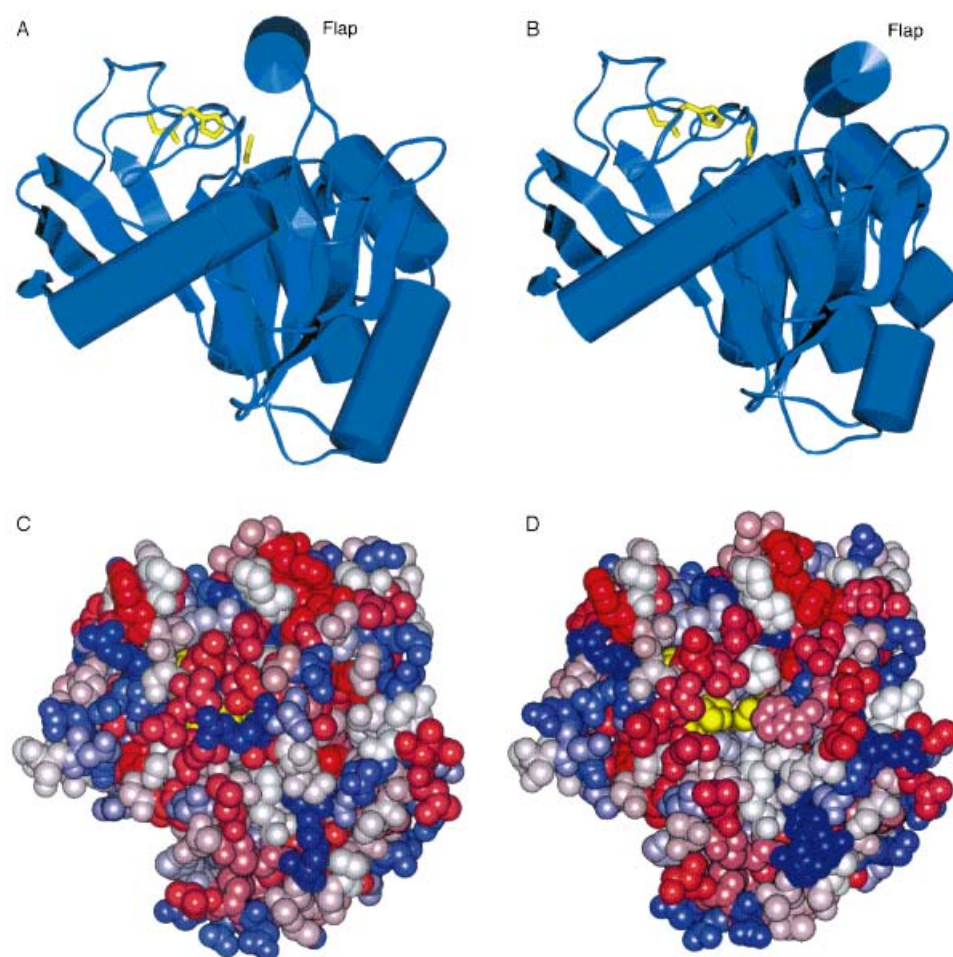


Figure 2. Structure of *Mucor miehei* lipase in closed (A, C) and open form (B, D). A and B (side view): the catalytic triad (yellow) and secondary structure elements showing the α/β -hydrolase fold common to all lipases. C and D (top view): space-filling model, colored by decreasing polarity (dark blue – light blue – white – light red – dark red). Upon opening of the lid, the catalytic triad (yellow) becomes accessible (D), and the region binding to the interphase becomes significantly more apolar.

subscribe to the phenomenon of interfacial activation.^[42] Thus, the lipases from *Pseudomonas glumae*^[43] and *Candida antarctica* (type B),^[44] whose tertiary structure is known, both have an amphiphilic lid covering the active site but do not show interfacial activation. Among the pancreatic lipases whose tertiary structures have been solved, human pancreatic lipase contains a lid with 23 amino acid residues and shows interfacial activation,^[45] whereas coypu lipase does not, although it has a lid of homologous size.^[46] The lipase of the guinea pig, an enzyme which shows no interfacial activation, features a “mini-lid” composed of only five amino acid residues.^[47] Thus, neither the phenomenon of interfacial activation nor the presence of a lid domain are appropriate criteria to classify an esterase into the lipase subfamily. For classifying an esterase as a lipase, the safest experimental evidence remains to be, as in the early days of research on this enzyme, whether or not it can hydrolyze long-chain acyl glycerols.^[29]

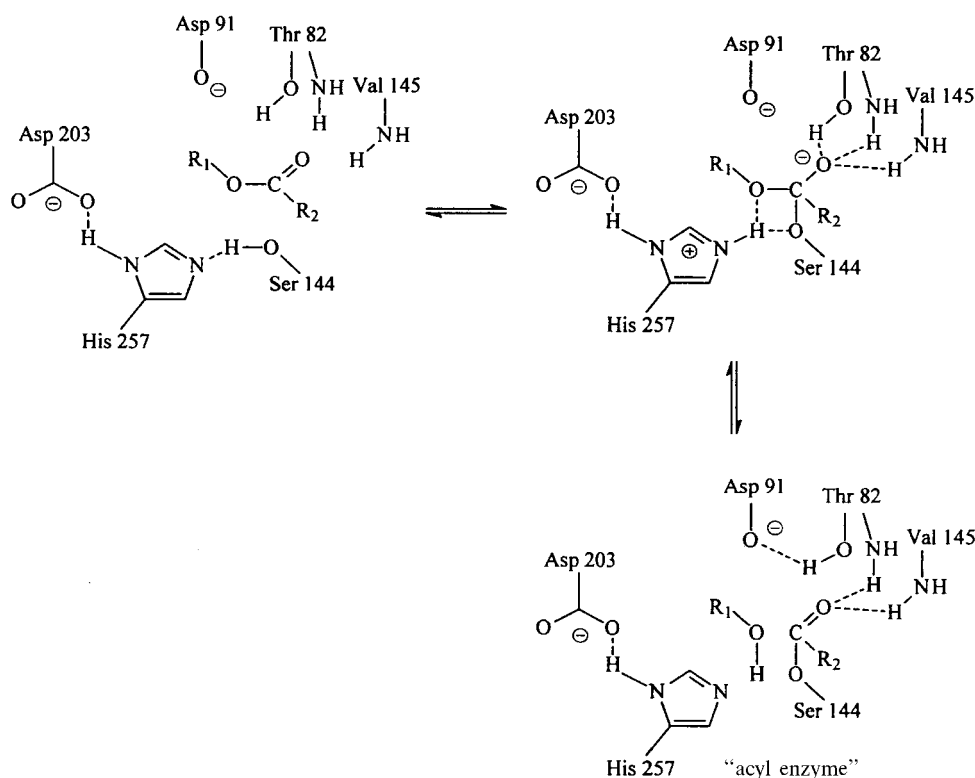
All 12 lipases whose structure has hitherto been elucidated are members of the “ α/β -hydrolase fold” family with a common architecture composed of a specific sequence of α helices and β strands.^[39, 40, 43, 44, 48–53] They hydrolyze ester

bonds by means of a “catalytic triad”, composed of a nucleophilic serine residue activated by a hydrogen bond in relay with histidine and aspartate or glutamate (Scheme 2). Serine proteases (“detergent proteases”) follow essentially the same mechanism.

As pointed out already, a unique structural feature common to most lipases is a lid or flap composed of an amphiphilic α helix peptide sequence, which in its closed conformation (i.e., in the absence of an interphase or organic solvent) prevents access of the substrate to the catalytic triad. After the lid has opened, a large hydrophobic surface is created to which the hydrophobic super-substrate (usually the oil drop) binds. This presumed mechanism is supported by the X-ray structures of lipases covalently complexed with hydrophobic inhibitors such as alkyl phosphonates, cycloalkyl phosphonates, or alkyl sulfonates. They reveal an open lid, suggesting that the phosphonates mimic the transition state for acylation and the sulfonates for deacylation of natural triacyl glycerol ester substrates.^[54, 55]

To summarize these findings, all lipases investigated so far exhibit a surprising degree of structural and functional similarity, regardless of the organism from which they were isolated and even if the observed amino acid sequence homologies are low. The coherent features of lipases are summarized in Table 5.

In spite of these similarities, subtle variations in the architecture of the substrate binding site may have a strong



Scheme 2. Catalytic mechanism of lipases based on a “catalytic triad” of serine (nucleophile), histidine, and aspartate or glutamate (connected through a hydrogen bond). The tetrahedral intermediate is stabilized by an “oxyanion hole”. The numbering of amino acids in this example refers to lipase from *Rhizopus oryzae*.

effect on the catalytic properties, the temperature, and stability of a lipase in a solvent. As these differences are of paramount importance for the selection of an individual lipase for a desired application, recent research has emphasized this aspect, as further described in Section 6.

4. Function and Structure of Digestive Lipases

Human pancreatic lipase (HPL) is the major lipolytic enzyme involved in the digestion of dietary triglycerides,^[56] and it amounts to around 3 % of the total proteins secreted by

Table 5. Important features of lipases.^[54, 55]

Feature	Details	Remarks
Mechanism based on a “catalytic triad” made up of nucleophilic serine, histidine, and aspartate/ glutamate	Found in over 30 lipases, including those from psychrophilic or thermophilic microorganisms; the only exception is replacement of aspartate for glutamate. Substitution of serine for cysteine by site-directed mutagenesis led to strongly reduced activity.	Related hydrolases show much greater variability in catalytic mechanism. In the case of proteases, the amide bond can be hydrolyzed through nucleophilic attack by hydroxyl (serine, threonine) or thiol groups (cysteine), or through electrophilic attack by a carboxyl group (aspartate/glutamate) or a metal ion (Zn^{2+}).
Consensus sequence at the active serine residue	The consensus sequence for over 30 cloned lipases is a “nucleophilic elbow” at the end of a σ sheet and is composed of -Gly/Ala-X-Ser-X-Gly-.	Other hydrolases show greater variability.
Most lipases feature a lid structure	A lid composed of an amphiphilic peptide loop covers the active site of the enzyme in the inactive state.	No lid was observed in esterases or proteases, but some lipases have no lid or just a small lid.
All lipases are members of the “ α/β -hydrolase fold” family	The structure is composed of a core of predominantly parallel β strands surrounded by α helices. The active nucleophilic serine residue rests at a hairpin turn between a β strand and an α helix.	Many other hydrolases (esterases, acetylcholine esterases, serine proteases, carboxypeptidases, dehydrogenases) and even a haloperoxidase show a similar structural motive, which suggests evolutionary relationships.

the exocrine pancreas.^[57] Pancreatic lipase hydrolyzes primary ester bonds of tri- and diglycerides to generate 2-monoglycerides and fatty acids, which are adsorbed through the intestinal barrier in the form of mixed micelles with bile salts. In contrast to most of the other pancreatic enzymes, which are secreted as proenzymes and further activated by proteolytic cleavage in the small intestine, pancreatic lipase is directly secreted as an active enzyme with 449 amino acid residues and a molecular weight of 50 kDa.

Surprisingly, pancreatic lipase is inactive with respect to an emulsified triglyceride substrate in the presence of micellar concentrations of bile salts, such as those found in the small intestine during digestion. Bile salts are amphiphilic molecules which are mainly found adsorbed to the lipid/water interface or dispersed as micelles in solution. Experimental evidence supports the notion that the negatively charged surface of triglyceride globules coated by bile salts inhibits the adsorption and activation of pancreatic lipase. To counteract this effect, a specific lipase-anchoring protein, colipase, is present in the exocrine pancreatic juice. It forms a 1:1 complex with the lipase, which facilitates its adsorption to lipid/water interfaces covered with bile salts.^[45] Thus, through the concerted action of colipase, HPL displays a high specificity towards insoluble triglycerides. Lipases have a key function in the catabolism of fat. Low levels of pancreatic lipase have been described in diseases such as pancreatitis and cystic fibrosis. As a consequence, preparations of lipases from porcine pancreas and other origins are offered, and have been for a long time, as substitutes in enzyme therapy. On the other hand, the excessive intake of dietary fat in the industrialized countries may lead to overweight, which constitutes a risk factor for health. Intact, nonhydrolyzed long-chain triglycerides cannot be absorbed through the gastrointestinal tract and therefore do not contribute to the energy balance of an organism. Lipase inhibitors might thus constitute a principle to prevent obesity in spite of normal dietary fat intake. We will discuss the application of lipase and lipase inhibitors to pharmacology further in Section 7.

4.1. Mechanism of Action of Human Pancreatic Lipase

The general features of the interfacial catalysis by the pancreatic lipase–colipase complex have been particularly well investigated and refined at a molecular level. X-ray studies of the three-dimensional structure of HPL by Winkler et al. confirmed the existence of two distinct domains in pancreatic lipase: a larger N-terminal domain comprising residues 1–335, and a smaller C-terminal domain made up of residues 336–449 (Figure 3).^[39]

The large N-terminal domain is a typical α/β hydrolase fold dominated by a central parallel β sheet.^[39] It contains the active site with a catalytic triad formed by Ser152, Asp176, and His263, all of which are conserved in other members of the mammalian lipase family (e.g. in lipoprotein lipase and hepatic lipase). The active site is covered by a surface loop between the disulfide bridge Cys237 and 261. This surface loop includes a short one-turn α helix with a tryptophan residue in position 252, which is completely buried inside the

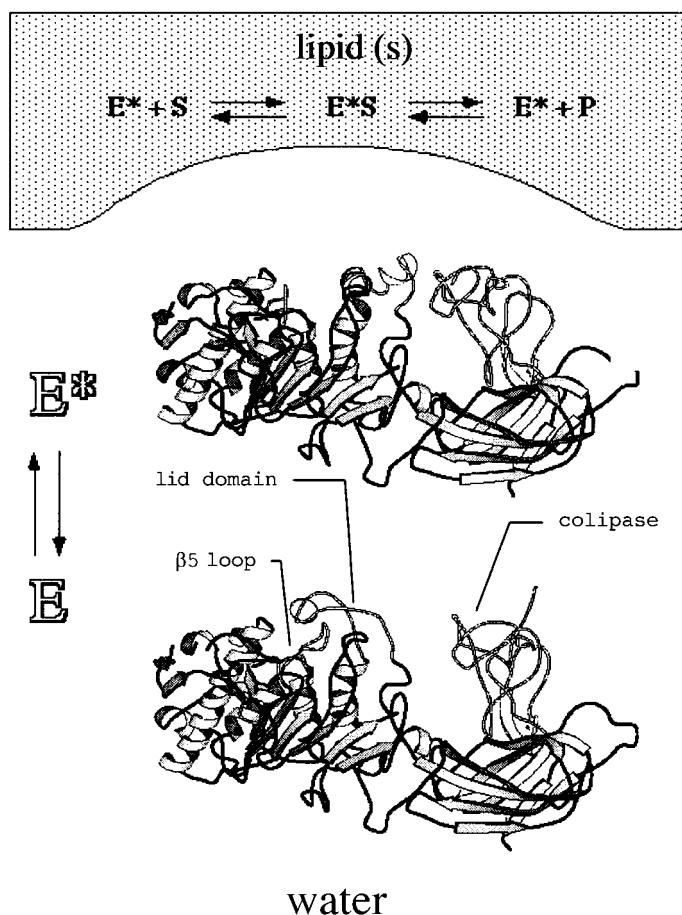


Figure 3. Structure of the HPL–procolipase complex in the closed (E) and open conformation (E*S). These two figures show the conformational changes in the lid—that is, in the $\beta 5$ loop—and the colipase during interfacial activation.

protein and sitting directly on top of the active site Ser152. Under this closed conformation, the lid prevents the substrate from having access to the active site. Spectroscopic studies of tryptophan fluorescence with HPL have shown that large spectral changes are induced by acylation of pancreatic lipase with the inhibitor tetrahydrolipstatin (**16**, see Scheme 18) in the presence of bile salt micelles.^[58] The X-ray crystal structure analyses of cocrystals of the pancreatic lipase–procolipase complex in the presence of mixed bile salt/phospholipid micelles^[45] as well as in the presence of a monoalkyl phosphonate inhibitor^[59] showed that the lid was shifted to one side, exposing both the active site and a larger hydrophobic surface. This motion is induced when binding of the enzyme to the lipidic interface occurs and is probably the structural basis for interfacial activation of pancreatic lipase.

The open structure of the lipase–procolipase complex illustrates how colipase might anchor the lipase at the interface in the presence of bile salts: Colipase binds to the noncatalytic β sheet of the C-terminal domain of HPL and exposes the hydrophobic tips of its fingers at the opposite side of its lipase-binding domain. This hydrophobic surface, along with the hydrophobic back side of the lid as well as the $\beta 9$ loop, helps to bring the catalytic N-terminal domain of HPL into close contact with the lipid/water interface.

Apart from the apolipoprotein CII activating lipoprotein lipase, no colipase has been found in other organs or organisms. Thus, the mechanism discussed above seems to be special to the specific case of the pancreatic lipase/colipase system.

5. Applications of Lipases in Oleochemistry, in Detergents, and in the Paper and Food Industry

5.1. Lipases in Oleochemistry

5.1.1. Soaps and Fatty Acids

While the bulk of the 60 million tons of fats and oils produced every year are directly used in food, over five million tons are a renewable chemical feedstock for non-food-related applications (“oleochemistry”). One major chemical application of triglycerides is in the preparation of soap: Today's preferred chemical processes (Monsavom, Sharples, or De Laval – Centriput processes) operate continuously and provide quantitative yields within minutes at 100 °C, independent from the origin of the fat or oil. Energy consumption is further minimized by energy recycling.^[60]

At present, about two million tons of soap are produced every year by these processes. As early as 1902, however, Connstein described the use of lipase extracted from *Ricinus* seed for the preparation of pure fatty acids from tallow and plant oils.^[61] The process took 34 hours at 30 °C, and yields were between 60 and 95 %, depending on the triglyceride used. While this is hardly competitive to today's chemical processes, points in favor of lipase-catalyzed soap production are the lower depreciation costs incurred (as the equipment is limited to a stirred reactor), the better color of the soap, and the generation of 20 % glycerol water as a by-product (instead of more dilute glycerol in the steam splitting process). Miyoshi Yushi, a company in Nagoya, Japan, seems to be the only company in the world which produces sizable amounts of soap through lipase-based hydrolysis of oils and fats with *Candida rugosa* lipase. They use stirred reactors at around 40 °C, in a batch mode lasting less than 48 hours.

Another key chemical intermediate produced from triglycerides are fatty alcohols, which are prepared from the fatty acid methyl esters (obtained by interesterification of the parent triglycerides), by hydrogenation in fixed-bed reactors at 200–300 bar and 200–300 °C.^[60, 62] Yields of the process are nearly quantitative, regardless of the fat or oil used, and energy recycling has been optimized. However, raffination steps may be necessary to remove products of thermal degradation, and heat-sensitive oils such as fish oils have to be processed separately. Companies specialized in oleochemistry—such as Unilever, Henkel, Procter & Gamble, and others—have therefore explored lipase-based fat splitting as an alternative to generate the raw material for production of fatty alcohols. These studies revealed major drawbacks; for example a) the reaction time depends strongly on the type of fat or oil used (the rate of hydrolysis at 40 °C decreases in the following order for oils from olive > soya = sunflower > palm > coconut > tallow), b) the space-time yields compare

poorly with those for chemical process and necessitate the construction of expensive multistage reactors, c) expensive techniques are required for the separation of the glycerol water from the oil/lipase phase, and d) continuous use of the expensive lipase catalyst is limited by its inherent instability. At present, Nippon Oils & Fats, a medium-sized company in Tokyo, seems to be the only firm which operates with an enzyme-based process for the preparation of highly pure unsaturated fatty acids (oleic, linoleic, linolenic, etc.); they use lipase from *Candida rugosa*.^[63] However, even these speciality products, which are sold only on the kilogram scale, compete with the highly pure fatty acids available today from the oils obtained from genetically modified plants.

5.1.2. Transesterified Triglycerides

Many lipases exhibit *sn*-1,3 specificity, and can therefore be used to regioselectively interesterify positions 1 and 3 of a natural triglyceride; however, the tendency towards acyl migration from the *sn*-2 to the *sn*-1 or *sn*-3 positions must be suppressed. So far, three types of modified triglycerides have gained in commercial importance: a) fats with improved spreadability, b) cocoa-butter equivalents, and c) highly digestive triglycerides.

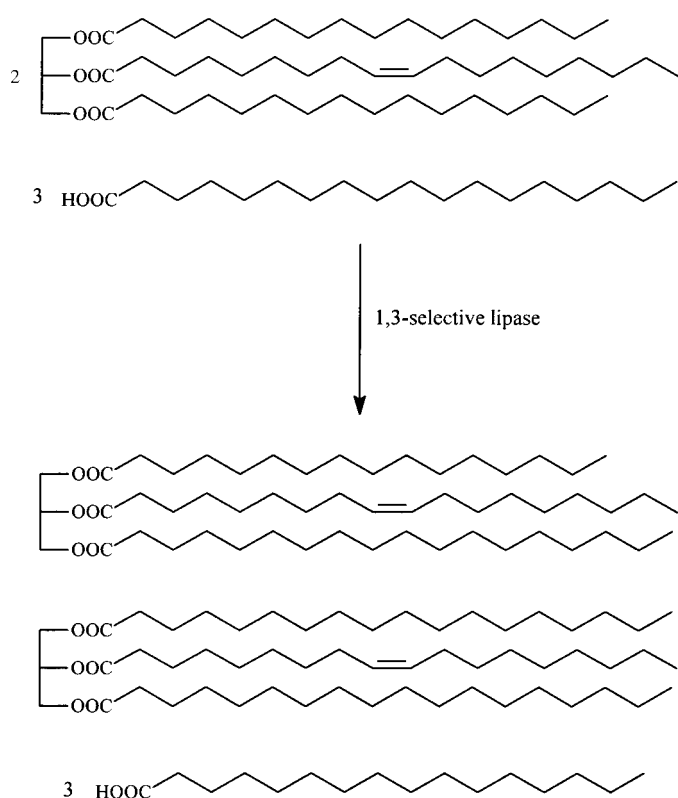
5.1.2.1. Fats with Improved Spreadability

The melting point of an oil can be modulated by the degree of catalytic hydrogenation of double bonds in unsaturated fatty acids. This is done on a large scale for the preparation of margarines and shortenings from plant oils. Alternatively, the desired melting behavior can be achieved through interesterification of suitable triglyceride mixtures with the use of *sn*-1,3-specific lipases or a combination of both procedures.^[64, 65]

5.1.2.2. Cocoa-Butter Equivalents

In 1995 several 100 000 tons of cocoa butter were imported from tropical countries, mainly Kenya and Malaysia. Since its melting point is around human body temperature (37 °C), cocoa butter is well suited as a matrix for suppositories. The main application, however, is in the production of chocolates, where the rapid melting conveys a desirable “mouth feel”. The predominant triglycerides of cocoa butter are glycerols with oleic acid in the *sn*-2-position and stearic and palmitic acids in the *sn*-1- and *sn*-3-positions (SOS and SOP). Cocoa-butter equivalents can be prepared either chemically or by lipase catalysis through the interesterification of suitable natural triglycerides, for example, the middle fraction of palm oil (POP) or sunflower oil with a high content of oleic acid (high-oleic sunflower oil; OOO) with stearic acid or tristearin (SSS; Scheme 3).^[66, 67]

Since the primary hydroxyl groups of glycerol in positions *sn*-1 and *sn*-3 are more reactive than the secondary hydroxyl group in *sn*-2, triglycerides of the type SOP or SOS are predominantly formed. From the standpoint of food regulation, enzyme-catalyzed transesterifications of natural oils are “natural processes” and therefore do not require labeling of the triglyceride. The lipase-catalyzed preparation of cocoa-butter equivalents has been investigated by many companies.



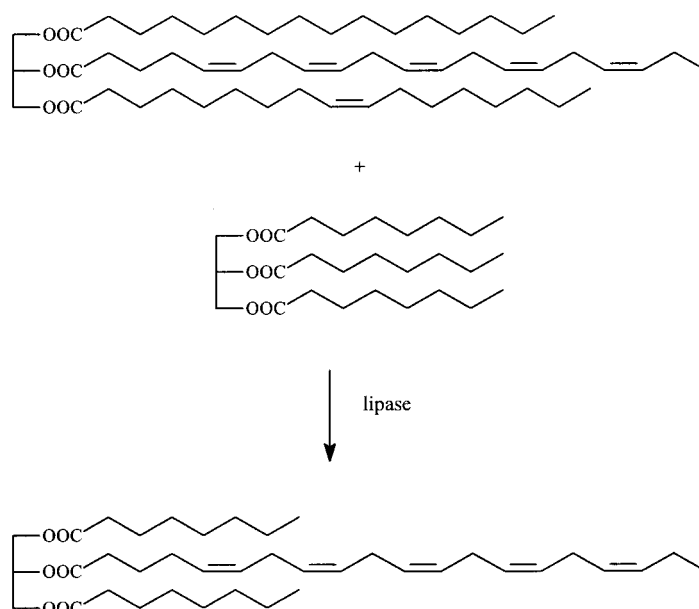
Scheme 3. Interesterification of a natural triglyceride substrate with a *sn*-1,3-regioselective lipase.

At present, Unichema, which is a former subsidiary of the Unilever group and was recently acquired by ICI, produces several hundred tons of “chocolate fat” (SOS) by transesterification of high-oleic sunflower oil with stearic acid in a solvent-free packed-bed reactor; the immobilized lipase from *Rhizomucor miehei* is used as a catalyst.^[68] In Japan, Fuji Oil has established a production capacity of several thousand tons per year for SOS.^[69] The process is similar to the Unichema procedure, but *Rhizopus* lipase is used as a catalyst.

5.1.2.3. Highly Digestive Triglycerides

The absorption of triglycerides from the small intestine strongly depends on the structure of the triglyceride. Thus, triglycerides containing palmitic acid are well adsorbed only when this fatty acid is located in the *sn*-2-position, like in human milk. A commercial product of this type is Unichema's Betapol (OPO), a diet additive for premature infants. It is prepared by interesterification of tripalmitin with oleic acid with use of immobilized *Rhizomucor miehei* lipase. Alternatively, triglycerides of the type MLM, with long-chain saturated or unsaturated fatty acids (L) in the *sn*-2-position and medium-chain fatty acids (M) in positions *sn*-1 and *sn*-3, provide a rapid delivery of energy through enhanced hydrolysis and resorption; pancreatic lipase hydrolyzes medium-chain triglycerides preferentially, and the resulting monoglycerides are efficiently absorbed from the large intestine. Several products of this type are commercially available (e.g. Caprenin (C₆-C_{22:0}-C₈) from Procter & Gamble), but are synthesized by chemical interesterification. Triglycerides of

the MLM type containing essential fatty acids, for example eicosapentaenoic or docosahexaenoic acid, have shown beneficial effects against cardiovascular and inflammatory diseases. Functional triglycerides of this composition are preferentially prepared by means of *sn*-1,3-specific lipases (Scheme 4), as chemical interesterification of highly unsaturated triglycerides (e.g. fish oil) promotes side reactions such as oxidation, *cis*-*trans* isomerization, or migration of the double bond.^[70, 71]



Scheme 4. Preparation of a functional triglyceride with a *sn*-1,3-specific lipase.

5.1.3. Monoglycerides

In 1993 about 120000 tons of monoglycerides and mixtures of mono- and diglycerides were manufactured through glycerolysis of triglycerides. After short-path distillation, monoglycerides of greater than 90 % purity are obtained. Monoglycerides are mild emulsifiers (HLB value 3.4, HLB = hydrophilic lipophilic balance) permitted for use as food additives. Industrial applications include emulsification in food, cosmetics, and drug preparations.^[62, 72, 73] Many reports deal with the preparation of monoglycerides through lipase catalysis, but the key problem remains that mixtures of mono- and diglycerides are formed.^[74, 75] Table 6 offers a survey of enzymatic preparation procedures.

Under commercial aspects, none of these procedures has been able to compete with the chemical manufacture of monoglycerides outlined above. Even when a lipase obtained from *Penicillium roquefortii* providing greater than 90 % monoglycerides in a one-step glycerolysis reaction was used, the economic data were unsatisfactory. The use of lipases has proven advantageous, however, for the synthesis of partial glycerides containing labile substituents such as 8'-apo- β -carotinoic acid, which would not withstand chemical procedures.^[76]

Table 6. Lipase-catalyzed synthesis of monoglycerides.

Procedure	Details	Results and comments
Hydrolysis or alcoholysis	1,3-Specific lipases	Acyl migration from <i>sn</i> -2 to <i>sn</i> -1/ <i>sn</i> -3 may lead to total hydrolysis.
Esterification	a) With glycerol and fatty acid and use of any type of lipase b) With isopropylidene-protected glycerol	a) Since monoglycerides are better nucleophiles than glycerol, mixtures of mono- and diglycerides are formed. b) Leads to pure monoglycerides, but necessitates additional protection and deprotection.
Highly selective lipase	The use of lipase from <i>Penicillium roquefortii</i> allows the production of up to 90% monoglycerides from triglycerides.	
Glycerolysis and improved process engineering	The use of an enzyme membrane reactor with counter-current extraction allows the removal of monoglycerides from the reaction mixture. Alternatively, monoglycerides are precipitated or cryoprecipitated.	Provides the best results, but process engineering is more complex than a chemical procedure.

5.2. Lipases in Detergents

The addition of lipases to detergent formulations has been investigated in the context of removal of fat stains^[77–80] and in situ generation of peracid bleach by perhydrolysis.^[81]

5.2.1. Removal of Fat Stains

After the great commercial success of proteases as detergent additives, the enzyme industry undertook major efforts to introduce lipases as a second group of detergent enzymes. It was hoped that lipases could compete with chemical surfactants in the detergent formulation, and thus respond to changing detergent formula in view of lower wash temperatures and ecologically benign components. Standard wash liquids contain anionic and nonionic surfactants, oxidants, and complexing agents at a pH of about 10 and temperatures around 50 °C, which is a rather hostile environment for enzymes. As a result, major screening programs for lipases stable under such conditions were initiated. Early systematic studies with the then available lipases showed that the marginal effect of lipases could be substituted, at lower price, by the addition of suitable chemical surfactants to the formulation.^[82] It later turned out, however, that suitable lipases can prevent redeposition of fat material on washed textiles, thus exerting a secondary effect on laundry cleaning. In various experiments based on the removal of dyed soils from textiles, detergent formulations including lipase showed an improved performance in the elimination of stains such as lipstick. Novo-Nordisk was the first company to commercialize these results. The product Lipolase, a recombinant fungal lipase from *Humicola lanuginosa* expressed in a host strain of *Aspergillus oryzae*, was produced on an industrial scale in Hokkaido, Japan, and later exported to North America and Europe.^[23] This was probably the first genetically engineered protein to obtain permission by regulatory bodies in Europe to be used in consumer products and be discharged, after use, into the environment. Today, lipases are used in most detergent formulations. The major commercial products are summarized in Table 7.

All the lipases mentioned above show a good secondary washing behavior. However, cutinase, a long-chain cleaving esterase, has an outstanding performance in the removal of wax esters, which are found in lipstick.

Table 7. Commercial detergent lipases.

Brand name	Company	Origin of lipase	pH optimum	T optimum
Lipolase	Novo-Nordisk	<i>Humicola lanuginosa</i> , cloned and expressed in <i>Aspergillus oryzae</i>	10.0	40 °C
Lipomax	Gist-Brocades ^[a]	<i>Pseudomonas pseudoalcaligenes</i> , recloned and expressed in the same organism	11.0	45 °C
Lumafast	Genencor ^[a]	<i>Pseudomonas mendocina</i> , cloned and expressed in <i>Bacillus spec.</i>	10.5	40 °C

[a] The enzyme business of Gist-Brocades was acquired in 1995 by Genencor International B. V. (Delft, The Netherlands).

5.2.2. Production of Peracid Bleach by Perhydrolysis

Peracids of a chain length C₈–C₁₂ are excellent oxidants under the slightly alkaline conditions of washing and thus have potential as a low-temperature bleach. Owing to their limited stability, they cannot easily be mixed into a detergent formulation. The in situ lipase-catalyzed generation of peracids has been investigated as an alternative. However, native lipases show only a marginal tendency to perhydrolyze esters in the presence of water/hydrogen peroxide, probably because hydrolysis of the initial “peracid-acyl” enzyme is much faster at alkaline pH than its formation.^[81]

5.3. Lipases in Paper Manufacture

Nihon Seishi Co., a Japanese paper manufacturer, has developed a process by which the triglycerides contained in raw lumber are hydrolyzed by the addition of lipase. This results in better “pitch control”, that is, an easier processing of the lumber to low-grade paper. The process is carried out at a scale of several hundred tons of lumber per day, and two other Japanese paper manufacturers are using the same procedure.^[83]

5.4. Lipases in the Dairy Industry

Rennet paste, isolated from the stomach of ruminant animals such as cows or goats, is an enzyme mixture traditionally used for the preparation of cheese.^[84] The active

component of rennet is chymosin, an aspartate protease involved in the clotting of milk through the hydrolysis of κ -casein; however, lipases and esterases contained in rennet also contribute to cheese ripening. In 1955 the US Food and Drug Administration issued a ban on further import of calf rennet pastes from Europe because of their poor quality. Since then, proteases and lipases from other sources have increasingly been used in cheese making. Depending on the chain-length specificity of a given lipase, its addition to a milk product may enhance the flavor of the cheese, accelerate the cheese ripening, or assist in the preparation of “enzyme-modified cheeses” (EMC), an important commercial flavor used in the USA for the manufacture of dips, sauces, dressings, crackers, etc. EMC is produced from cheese curd by the addition of lipases at elevated temperatures, increasing the content of free fatty acids about tenfold. Table 8 contains some examples of lipases presently used in cheese making and in accelerated cheese ripening.

Table 8. Examples of lipases used in cheese making and ripening.

Cheese type	Lipase
romano, domiati, feta	pregastric lipase from lamb or goat, <i>Mucor miehei</i>
mozzarella, parmesan, provolone	pregastric lipase from lamb or goat
fontina, ras, romi	<i>Mucor miehei</i>
cheddar, manchego, blue	<i>Aspergillus oryzae</i> , <i>Aspergillus niger</i>

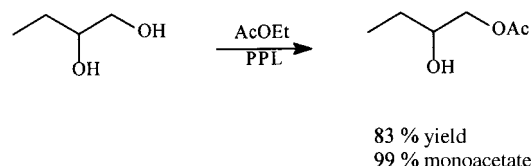
Depending on the chain-length specificity of the lipases used, there is either predominant liberation of short-chain fatty acids (C_4 – C_6)—which results in a sharp, tangy flavor—or of medium- and long-chain fatty acids ($>C_{12}$)—which convey a soapy taste and are readily metabolized by the microbial consortia found in cheese to other flavor ingredients such as acetoacetate, β -keto acids, methyl ketones, and flavor esters and lactones. Addition of lipases to pasteurized cow's milk can generate flavors similar to goat, sheep, or raw milk if used with the appropriate microbial consortia.

6. Lipases as Biocatalysts in Organic Synthesis

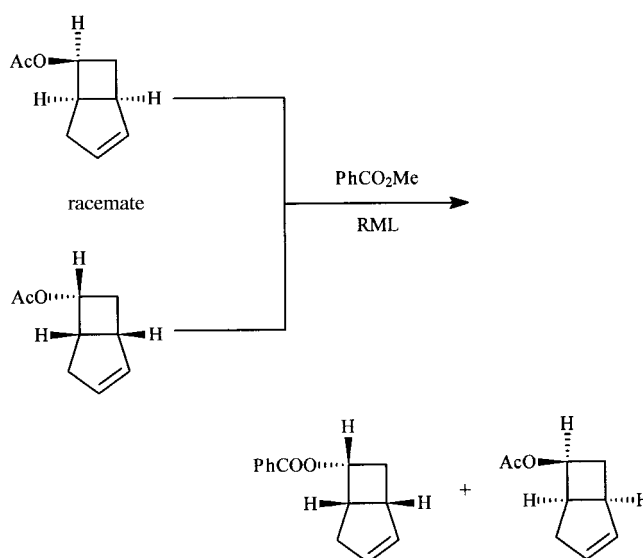
In view of their specific and limited function in metabolism, one should expect lipases to be of limited interest for the organic chemist. However, the opposite is true: Chemists have discovered lipases to be one of the most versatile classes of biocatalysts in organic synthesis^[15, 85–90] for a few simple reasons:

- Owing to the large enzyme domains required for acyl group binding and the unpronounced structural features of acyl chains, lipases can accommodate a wide variety of synthetic substrates, while still showing regioselectivity or chiral recognition.
- Lipases act at the water/lipid boundary, which exhibits high interfacial energy. To withstand the denaturing effect of the interface, lipases have evolved unusually stable structures that may survive even the effect of organic solvents.
- The free energy of fat hydrolysis is close to 0 kJ mol^{-1} .^[91, 92] As a result, thermodynamic equilibria are largely governed by reactant concentrations, and lipase-catalyzed ester hydrolysis in water can easily be reversed, in nonaqueous media, into ester synthesis or interesterification.
- The acyl lipase formed in the first step of the enzymatic reaction can formally be considered as an acylating agent. The wide substrate specificity of this enzyme class allows acylation of nucleophiles other than those with hydroxyl groups, for example hydroperoxides, amines, and thiols.

As a result of this unique combination of properties, chemists have used lipases for a plethora of synthetic reactions.^[93–103] In a recent comprehensive monograph on biotransformations in organic synthesis, almost one-third of all reactions were carried out with lipases.^[85, 89] When polyfunctional compounds, isomers, or racemic or prostereogenic substrates are used, lipases usually exhibit regio- and/or stereoselectivity. Thus, PPL (for abbreviations, see Table 3)—designed by nature to adhere to an oil drop in the presence of bile salts and hydrolyze triglycerides—was found to carry out the regioselective reaction shown in Scheme 5,^[104] and RML catalyzes enantioselective transesterifications in high yields (Scheme 6).^[105]



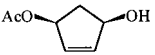
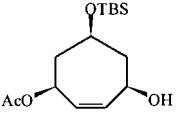
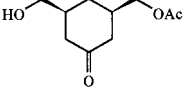
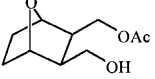
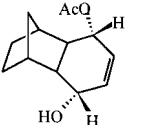
Scheme 5. Regioselective esterification by PPL.



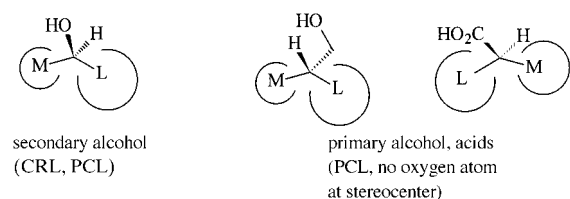
Scheme 6. Example of an enantioselective transesterification by RML; $E = 206$ (acylation), $E = 8$ (hydrolysis).

The only major drawback of lipase selectivity is, in fact, their somewhat restricted specificity towards the acyl group of esters: Most lipases accept linear aliphatic moieties much better than bulky aromatic groups.

Table 9. Lipase-catalyzed asymmetrization of *meso*-diesters.

Product	Lipase/solvent	Yield [%]	<i>ee</i> [%]	Ref.
	pancreatin/ vinyl acetate, THF/Et ₃ N	65	> 99	[132]
	PSL/ isopropenyl acetate	81	> 99	[133]
	PCL	80	70	[134]
	PPL/ vinyl acetate, MeCN	92	> 99	[135]
	PPL/ vinyl acetate	92	> 99	[136]

on the reagent. These rules are often dubbed “Kazlauskas rules”;^[111] the basics are presented in Scheme 10. Experience has shown that the rule is highly predictive for lipase action on secondary alcohols, but less accurate for lipase-catalyzed transformations of primary alcohols and acids.



Scheme 10. The “Kazlauskas rules” (M = medium-sized substituent, L = large substituent).

Recently, the Kazlauskas model was supported by crystallographic evidence. Cygler et al. cocrystallized two complexes of CRL inhibited by the two enantiomers of a menthyl phosphonate inhibitor (CRL is able to discriminate between enantiomeric menthyl esters and prefers the *R* enantiomer).^[112] The preferred binding of the *R* inhibitor was attributed to the higher number of hydrogen bonds (Figure 5).

6.2. Lipases as Acylating Agents

The enzymatic mechanism of lipases (see Scheme 2) leads to the acylation of a serine residue in the catalytic triad of the enzyme. The subsequent reactions can formally be viewed as acylation of water (hydrolysis) or an alcohol (esterification). In the following, we will discuss acylation of oxygen-containing and other nucleophiles as well as unusual acyl donors. We will show that lipases are not only acylated when they hydrolyze carboxyl esters, but also upon reaction with

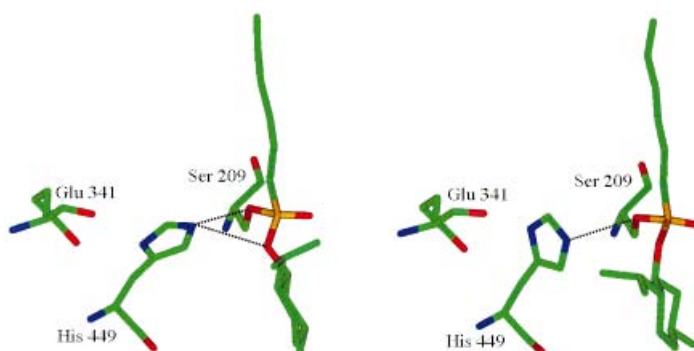


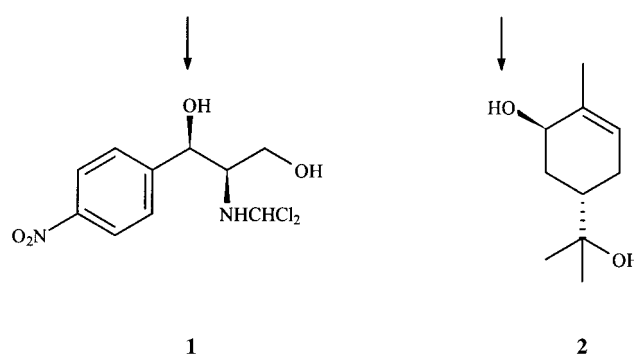
Figure 5. Binding of (*R*)- (left) and (*S*)-menthyl phosphonate esters (right) to the active site of *Candida rugosa* lipase. In the complex with the *R* enantiomer, catalytic His449 forms two hydrogen bonds (dashed lines), one to catalytic Ser209 and another to the alcohol group of menthol, while in the complex with the *S* enantiomer, His449 rotates out of the plane and thus loses its capacity to bind to menthol.

carbonates and other substrates. Finally, some examples for lipase-catalyzed reactions of industrial relevance will be summarized.

6.2.1. Acylation of Hydroxyl or Alcohol Groups

6.2.1.1. Selective Esterification of Hydroxyl Compounds

Hydroxyl compounds such as chloramphenicol (**1**), sobrerol (**2**), or oligopeptide esters were selectively acylated with PPL (Scheme 11).^[85, 113–115] As sugars are the most important



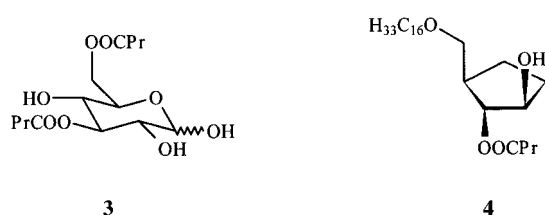
Scheme 11. Position of the regioselective acylation of chloramphenicol (**1**) and sobrerol (**2**).

examples of polyhydroxyl compounds, many studies have been devoted to their regioselective acylation or deacylation by means of lipases.^[115–117] The major focus was on the elaboration of protection and deprotection in carbohydrate chemistry and, in the industrial domain, the preparation of sugar esters, a class of detergents based on renewable resources.

6.2.1.2. Protection and Deprotection of Sugars

Unprotected mono- or disaccharides in polar organic solvents (e.g. DMF, 2-methyl-2-butanol) and in the presence of a lipase such as PPL,^[118] CAL,^[119] or RML^[120] react readily

with long- or short-chain fatty acids or their esters to form the 6-*O*-acylated sugars; the regioselectivities are higher than 70 %, and the conversions between 40 and 100 %. The yields could be increased by protecting the secondary hydroxyl groups (as isopropylidene derivatives or phenyl borates) or by working in the solid or molten phase, thus circumventing the large difference in solubility of the reaction partners. Protection of the primary hydroxyl group (at C6) by acylation allowed for the esterification of the secondary hydroxyl functionalities, and various lipases differed in their regiopreference. Thus, butyroylation of 6-*O*-butyroylglucose with trichloroethyl butyrate in THF by CVL led to 3,6-di-*O*-butyroylglucose (**3**, 98 % regioselectivity),^[121] whereas a lipase from *Rhizopus japonicus* (similar to CRL) catalyzed butyroylation of 1,4-anhydro-5-*O*-hexadecyl-D-arabinitol (**4**) with trichloroethyl butyrate in benzene at C3 in 79 % yield (Scheme 12).^[122]



Scheme 12. Esters **3** and **4** obtained by lipase-catalyzed butyroylation of sugars and sugar esters.

6.2.1.3. Sugar Ester Detergents

Sugar esters are chemically prepared on a scale of several thousand tons per year by the acid-catalyzed esterification of sorbitans and fatty acids (Span, if ethoxylated Tween). They are widely used as chemical emulsifiers, and the extent of acylation and ethoxylation determines the detergency of the products. Some of them have been registered as food additives, but lipases seem better suited to assist in the preparation of food-grade sugar esters. As a consequence, lipase-catalyzed synthesis of sugar esters has been explored by many researchers; a few examples are given in Table 10. In view of the different solution properties of the two reaction partners, however, it proved quite difficult to achieve high reaction rates that were competitive with chemical procedures

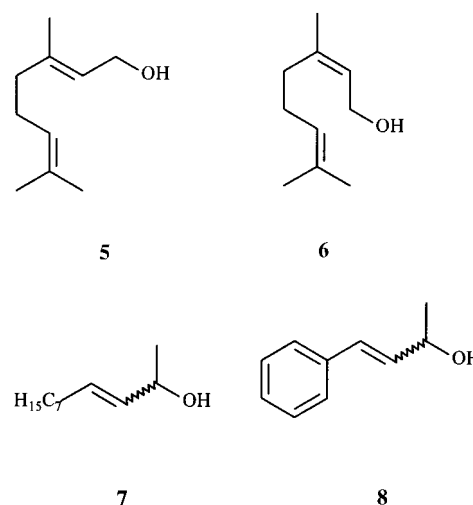
Table 10. Lipase-catalyzed synthesis of sugar esters (examples); ν = reaction rate.

Sugar	Acyl donor	Solvent	Lipase	ν [mmol g ⁻¹ h ⁻¹]	Ref.
glucose	fatty acid trichloro ethyl ester	pyridine	PPL	0.015	[118]
mannose	fatty acid oxime ester	pyridine	PCL	0.028	[123]
sorbitol	fatty acid	2-pyrrolidone	CVL	1.4	[124]
fructose	fatty acid	2-methyl-2-butanol	RML	0.048	[120]
			CAL-B		
glucose	fatty acid	acetone	CAL-B	0.2–0.4	[125]
ethyl glycoside	lauryl and octanoic acid	<i>tert</i> -butanol	CAL-B	undisclosed	

using nonderivatized sugar reagents in food-grade solvents. Further competition arose from chemically prepared alkyl glucosides, which are now being produced on a large industrial scale for nonfood applications and have properties similar to the sugar esters. Lipase-catalyzed production of monoesters of ethylglycoside has been commercialized on the 100-kg scale by Unichema, a company of the ICI group.

6.2.1.4. Stereoisomers

The *E/Z* stereoisomers of allylic alcohols were resolved by acylation in the presence of lipases (PPL, PSL), and the *E* isomer was always preferred. In most cases, however, selectivities were rather modest. Thus, a mixture of (*E*)-geraniol (**5**) and (*Z*)-nerol (**6**) was separated by acylation with trifluoroethyl butyrate or hexanoic anhydride in diethyl ether in the presence of PPL; **5** was acylated faster at a ratio of 4:1 (Scheme 13).

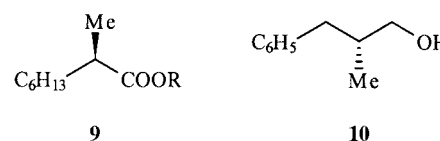


Scheme 13. Alcohols **5**–**8** used for enzymatic transesterifications.

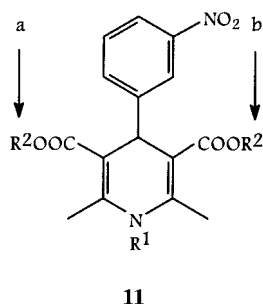
The *E* isomers of secondary allylic alcohols such as 3-undecen-2-ol (**7**) or 4-phenyl-3-buten-2-ol (**8**), however, reacted 20–40 times faster than the *Z* isomers under the same reaction conditions. The *S* enantiomer of the *E* isomer did not participate in the reaction, due to the high enantioselectivity of this enzymatic transesterification ($E > 100$ for the *E* isomers, see Scheme 13).^[126]

6.2.1.5. Resolution of Racemic Alcohols and Acids

Most publications on lipase catalysis deal with this type of reaction. Two examples in which the enantiomers **9** and **10** were obtained in high kinetic resolution and good yields are given in Scheme 14. Further examples will be discussed in Section 6.3.4, which deals with industrial applications.

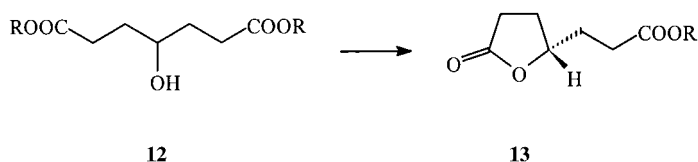


Scheme 14. Enantiopure substances **9** (ROH = 1-icosanol, 1-dodecanol; CRL, 42 % conversion, $ee = 97\%$ ^[127]) and **10** (PFL, 45 % conversion, $ee = 97\%$ ^[128]) obtained by resolution of racemic compounds.



Scheme 15. Asymmetrization of prostereogenic diester 1,4-dihydro-4-(3-nitrophenyl)-2,6-dimethyl-pyridinedicarboxylate (**11**, $R^2 = \text{CH}_2\text{OCOCH}_3$): a) $R^1 = \text{CH}_2\text{OCH}_3$, lipase AK, 63 % (*S*)-monoester, 95 % *ee*; b) $R^1 = \text{CH}_2\text{Ph}$, *Candida* OF-360, 24 % (*R*)-monoester, 73 % *ee*.^[129]

tomer, much work has been done in this area. As an example, the transesterification of various cyclic *meso-cis*-diols is indicated in Table 9.



Scheme 16. Asymmetrization of diester **12** with lipase for the formation of the γ -lactone **13** ($R = \text{Et}$, PPL, hexane: 100 % conversion, > 98 % *ee*; $R = \text{Et}$, PFL, hexane: 100 % conversion, 32 % *ee*; $R = \text{Bn}$, PPL, hexane: 100 % conversion, > 95 % *ee*).

6.3.2. Acylation of Other Nucleophiles

Lipases not only form ester bonds, but acylate a wide range of nucleophiles such as ROOH or RNH_2 . Table 11 gives a survey.

6.3.3. Acylations with Unusual Acyl Groups

Apart from unusual acyl acceptors, unusual acyl donors generating the catalytically active acyl serine residue in a lipase have been observed. Bulky acylating reagents usually react more slowly, as the natural acylating agent of a lipase is a slim fatty acid. Depending on the configuration of their substrate binding sites, however, different lipases may show quite different enantiopreferences towards bulky acyl groups (Table 12).

These examples illustrate that lipases are unusually versatile biocatalysts. Indeed, some of the lipase-based transformations shown in Table 12 have been optimized in view of application in industry.

6.2.1.6. Asymmetrization of Prostereogenic Alcohols and Esters

Lipases have been shown to catalyze both types of reactions. An example for asymmetrization (the formation of enantiomerically pure compounds) is shown in Scheme 15. Asymmetrization of diesters (**12**) with lipase has also been used for the synthesis of enantiomeric lactones (**13**, Scheme 16).^[130, 131]

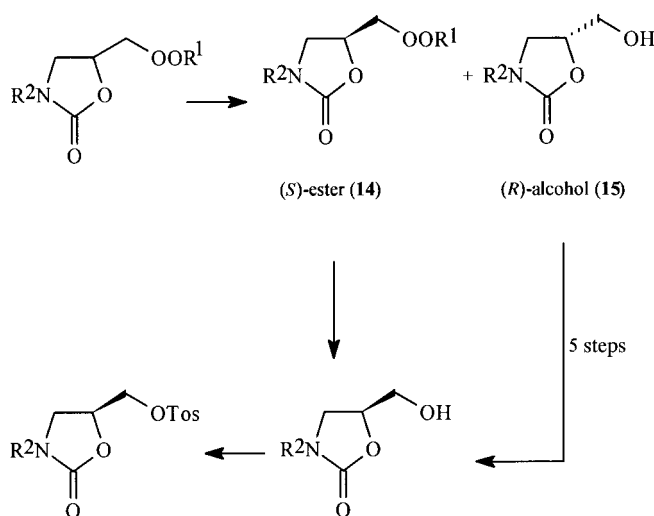
6.2.1.7. Asymmetrization of *meso*-Diols

As this procedure may lead to quantitative conversions of the substrate, preventing racemization of the “wrong” enantiomer,

6.3.4. Examples of the Industrial Relevance of Lipases

In view of the ever-increasing need of the pharmaceutical, agrochemical, and fine-chemical industry for enantiomerically pure products and intermediates, lipases have been extensively studied for their catalytic potential in the preparation of chiral alcohols and acids. Some of the target products, the reagents, and the chiral intermediates are listed in Table 13. However, few of these processes have found industrial applications. This is due to several important reasons:

1. In many cases (e.g. pyrethroids, β -blockers) often no undesirable side effect has been found for the wrong enantiomer, and the racemic product can therefore be marketed as it is.
2. In other cases chemical methods such as preferential crystallization (naproxen, L-menthol), catalytic asymmetric synthesis (Diltiazem), or procedures based on fermentation or synthons from the chirality pool (α -phenoxypropionic acid herbicides) are more economical.
3. A major drawback for the industrial use of lipases is the need to racemize the wrong enantiomer. While this is feasible in most cases, it puts an economic burden on the process. For example, (*S*)-ester **14**, a useful enantiomer intermediate for the synthesis of β -blockers, can be industrially prepared by the action of LPL with greater than 99 % *ee*. However, racemization of the unwanted (*R*)-alcohol **15** requires five additional chemical steps (Scheme 17), which renders the economics of the method questionable.^[168]



Scheme 17. Preparation of (*S*)-ester **14** with LPL and racemization of (*R*)-alcohol **15** ($R^1 = \text{hexyl}$, $R^2 = \text{iso-propyl}$). Tos = $\text{H}_3\text{CC}_6\text{H}_4\text{SO}_2$.

While the use of prostereogenic or *meso* precursors within a retrosynthetic symmetrization – asymmetrization concept is a principal solution to this problem, it is often not possible to define such precursors for a given synthetic problem. In spite of these limitations, there are at present at least two processes in which lipase catalysis has been industrialized: the preparation of Diltiazem by Tanabe Seiyaku Co. and the preparation of several chiral amines by BASF AG.

Table 11. Acyl acceptors accessible by lipase catalysis.

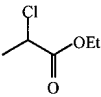
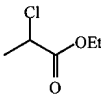
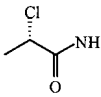
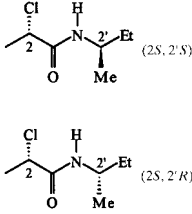
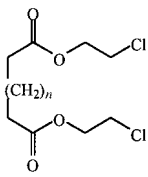
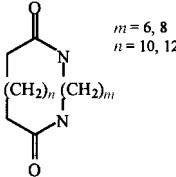
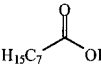
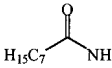
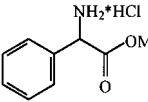
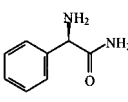
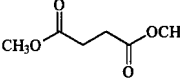
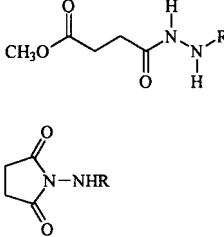
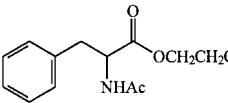
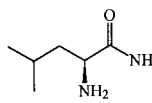
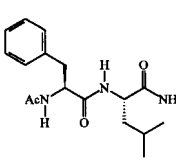
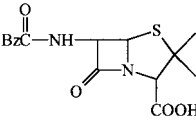
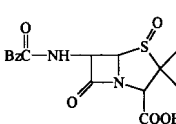
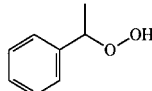
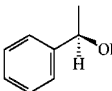
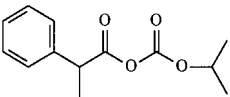
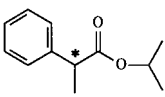
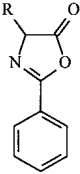
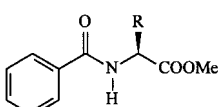
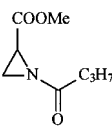
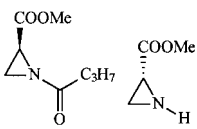
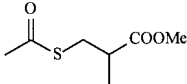
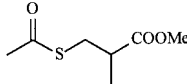
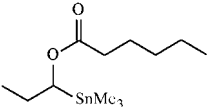
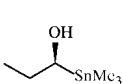
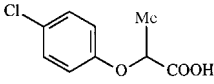
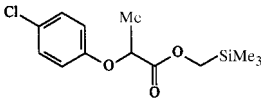
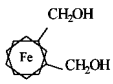
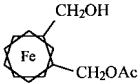
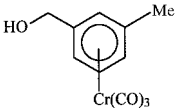
Acyl donor	Acyl acceptor	Product	Conditions	Yield [%]	ee [%]	Ref.
<i>amine as acyl acceptor</i>						
	<i>n</i> -butylamine phenylamine allylamine		CRL hexane or CCl ₄	52–62	80–95	[137]
	<i>rac</i> -2-aminobutane		CAL	45	90	[138]
	1,10-diaminohexane 1,12-diaminododecane		CRL CH ₂ Cl ₂	35–40	–	[139]
<i>ammonia as acyl acceptor</i>						
	NH ₃		CAL, HSL 0.5–2.5 M NH ₃ <i>t</i> BuOH, 40 °C	85–95	–	[140–142]
	NH ₃		CAL <i>t</i> BuOH	39	91 (amide) <i>E</i> = 38	[142]
<i>hydrazine as acyl acceptor</i>						
	substituted hydrazides		PCL, R = CHO a) THF or <i>i</i> Pr ₂ O, RT, 3 d b) 60 °C, 4 d	69–80 20–60	–	[140]
<i>amino acid derivatives as acyl acceptors</i>						
			PPL toluene 45 °C, 3 d	83	–	[137]
<i>hydrogen peroxide and peracids as acyl acceptors</i>						
	H ₂ O ₂		CAL heptanoic acid, 4 °C	74	–	[143]
vinyl acetate			LPL cyclohexane	62	100	[144]

Table 12. Lipase catalysis with unusual acyl donors or acceptors.

Acyl donor	Acyl acceptor	Product	Conditions	Yield [%]	ee [%]	Ref.
<i>carbonates</i>						
	<i>n</i> -propanol		HLL MTBE	55	90	[145]
<i>oxazolidines</i>						
	methanol	 a: R = 4-HOC ₆ H ₄ b: PhCH ₂ SCH ₂	a: PSL b: PCL	52 61	75 90	[146]
<i>amides</i>						
	water		CRL	60	90	[147]
<i>acyl donors or acceptors in structures with unusual heteroatoms</i>						
			PSL PrOH, 25 °C	31	93	[148]
			PPL buffer	40	83	[149]
	Me ₃ SiCH ₂ OH		CRL 19 h	52	96 (acid)	[150]
vinyl acetate			PCL	80	100	[151]
vinyl acetate				47	100	[152]

7. Applications of Lipases in Medicine

We will now briefly discuss the function of lipases in the digestion of normal fat and mention some applications of these enzymes and their inhibitors in human therapy.

7.1. Physiological Function of Lipases in the Digestion of Dietary Fat

Dietary fats are composed of about 95 % triacylglycerols (TG).^[169] Until recently, the hydrolysis of fats was thought to

begin in the intestinal lumen and to be catalyzed entirely by pancreatic lipase. In this view, the stomach was a transient storage organ, whose function was limited to mixing and dispersing lipids with the other nutrients. Although many authors have observed the occurrence of preduodenal lipolysis in humans and other species, gastric lipolysis was assumed to be negligible and even attributed to pancreatic contamination after a gastric reflux in the duodenum.

Today, the picture has changed, and strong experimental evidence supports the view that the gastric and pancreatic lipases act in synergy. Preduodenal lipases have been purified and biochemically characterized, for example rat lingual,^[170] human gastric lipase (HGL),^[171, 172] calf and lamb

Table 13. Examples of industrial relevance.

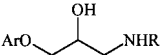
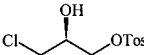
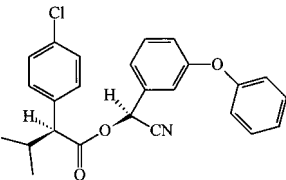
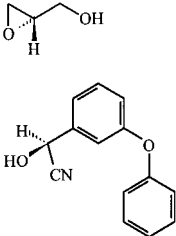
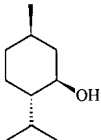
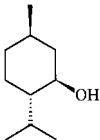
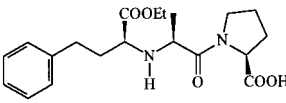
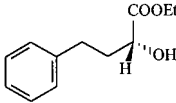
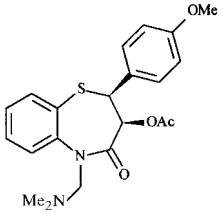
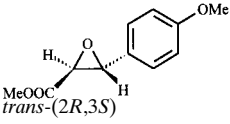
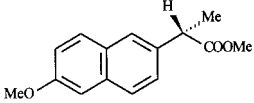
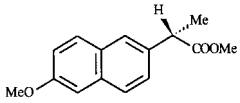
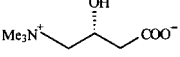
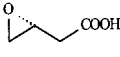
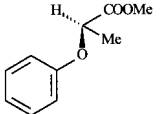
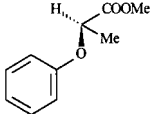
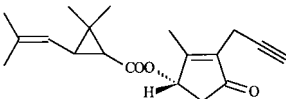
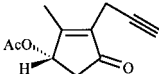
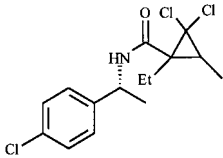
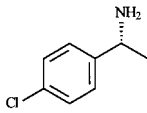
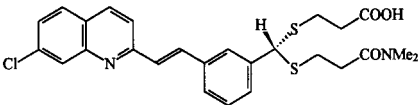
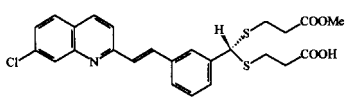
Desired end product	Chiral intermediate or end product	Optimized yields	Ref.
<i>chiral alcohols</i>			
 (S)-beta blocker	 “C ₃ chiron”	LPL/H ₂ O: > 99 % <i>ee</i> ; PPL/BuOH: 97 % <i>ee</i> , 49 % conv.; PCL/vinyl acetate: > 99 % <i>ee</i> , 50 % conv.	[153] [154]
 (S,S)-fenvalerate, a pyrethroid insecticide		PPL/H ₂ O: very high substrate concentration, solvent-free	[155]
 L-menthol		CRL: > 98 % <i>ee</i> , 42 % conv.	[157]
<i>chiral acids</i>			
 enalapril, an ACE inhibitor			[158, 159]
 diltiazem, a calcium antagonist	 <i>Serratia marcescens</i> : 100 % <i>de</i>		[153, 160, 161]
 (S)-naproxen, a nonsteroid inflammatory agent		esterase NP: 98 % <i>ee</i> , 39 % conv.	[162]
 (R)-carnitine, a vitamin-like nutrient		PPL: 95 % <i>ee</i>	[163]
 (R)-α-phenoxypropionic acid, a herbicide		CCL: 95 % <i>ee</i>	[164]

Table 13. Examples of industrial relevance (continued).

Desired end product	Chiral intermediate or end product	Optimized yields	Ref.
 prallethrin, a pyrethroid insecticide		PFL: 99.8% <i>ee</i>	[165]
chiral amines			
 substituted phenethylamines, herbicides		PCL: 99% <i>ee</i> , 43% conv.	[166]
 LTD ₄ antagonist		PCL: 98% <i>ee</i> , 90% yield	[167]

pharyngeal,^[173] rabbit gastric (RGL),^[174] and dog gastric (DGL).^[175]

Recently, investigations on healthy volunteers without any pancreatic or gastric deficiency allowed the definition of the respective physiological contributions of preduodenal and pancreatic lipases in the global hydrolysis of dietary TG. During the digestion of a liquid test meal, gastric and pancreatic lipase hydrolyze 18 and 48% of the meal TG acyl chains, respectively (66% hydrolysis of TG is sufficient for complete absorption). In other words, of the four acyl chains of two TG molecules which must be hydrolyzed for complete intestinal absorption, pancreatic lipase hydrolyzes three, and preduodenal lipase(s) one acyl chain.

It is now well established that the gastric lipolysis of long-chain triacylglycerols is of paramount importance in the physiological absorption of dietary fat, especially in patients suffering from exocrine pancreatic insufficiency, where it could partially compensate for the absence of the pancreatic lipase.^[176] Furthermore, it was demonstrated that human and rabbit gastric lipases can potentiate *in vitro* the hydrolysis of triglycerides by human pancreatic lipase.^[177]

7.2. Lipases in Substitution Therapy

Exocrine pancreatic insufficiency, often found in cystic fibrosis patients, results in two major problems: malnutrition and steatorrhea. These problems can be partly solved by the administration of porcine pancreatic lipase extracts as a replacement therapy for these patients. In the past, such preparations were far from satisfactory, since a large proportion of the enzymes administered were denatured in the stomach due to the extreme acidity of the gastric juice. The coadministration of a lipase which could hydrolyze dietary

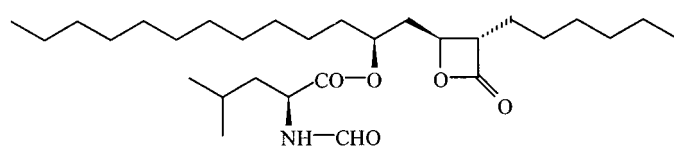
lipids under acidic conditions would probably help in improving some of the problems of malabsorption and steatorrhea. Various clinical studies have been conducted both in animals and humans to assess the efficacy of acid-resistant lipases of fungal origin as enzymatic replacement therapy in exocrine pancreatic insufficiency.^[178] Although some significant effects were observed in weight gain and reduction of steatorrhea, the use of such enzymes is limited as a result of their sensitivity to the proteolytic action of gastric pepsin.

With the advent of genetic engineering techniques, human gastric lipase (HGL) cDNA was synthesized, amplified, and cloned into a baculovirus transfer vector. This vector was cotransfected with a baculovirus which had been deleted from essential parts of the virus genome. High Five cells were used to express recombinant HGL; the level of HGL secretion was about 32 mg l⁻¹ of culture medium. The protein migrated with an apparent molecular mass of 45 kDa as determined by sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS/PAGE) analysis (50 kDa in the case of native HGL), which indicates that the level of the glycosylation was lower for the insect cells than for human gastric chief cells. The maximum specific activities of the recombinant lipase were 434 U mg⁻¹ on long-chain triacylglycerols (Intralipid) and slightly higher on medium-chain and short-chain triglycerides.^[179]

In contrast to the human enzyme, which preferentially hydrolyzes short-chain triacylglycerols, dog gastric lipase has an exceptionally high specific activity on long-chain triacylglycerols, which represent the majority of dietary fat in humans.^[180] Dog gastric lipase would probably facilitate the absorption of lipids when given as an enzyme supplement to cystic fibrosis patients together with classical pancreatic extracts.^[181]

7.3. Lipase Inhibitors as Antiobesity Agents

Conventional treatment for obesity has focused largely on strategies to control energy intake. Under clinical circumstances, the use of an inhibitor of digestive lipases which reduces dietary fat adsorption holds great promise as an antiobesity agent. Tetrahydrolipstatin (THL, **16**; Scheme 18), derived from lipstatin produced by *Streptomyces toxytricini*, acts in vitro and in vitro as a potent inhibitor of pancreatic and gastric lipases as well as of cholesterol ester hydrolase.^[182, 183]



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Scheme 18. Tetrahydrolipstatin (THL, **16**) as a potent inhibitor of pancreatic and gastric lipases as well as of cholesterol ester hydrolase.

It has been suggested that a stoichiometric enzyme–inhibitor complex in the form of an acyl enzyme is produced, which is slowly hydrolyzed (with water as the final acceptor) to leave an intact enzyme and the inactive form of THL.^[184] A reactivation of inactivated HPL was observed, as evidenced by kinetics showing a lag phase; this is probably due to a slow deacylation in the pH-stat assay system of the inhibited enzyme.

Therefore, THL is an amphiphilic inhibitor that reacts with the essential serine residue of the lipase active site. While micellar partitioning of lipases in the presence of bile salts renders many amphiphilic inhibitors inefficient, THL is mostly associated with the triacylglycerol phase, even in the presence of sodium taurodeoxycholate. This property is probably prerequisite for a lipase inhibitor to be effective under physiological conditions, that is, in the presence of bile and lipids.^[185]

As THL inhibits hydrolysis and thus adsorption of triacylglycerols in the duodenum, it is being developed by Hoffmann–La Roche as an antiobesity agent. In one set of experiments, the effect of THL on the secretion and activity of pancreatic lipase and on the hydrolysis of fat in duodenal aspirates of human volunteers (with polyethyleneglycol 4000 as a nonabsorbable recovery marker) was measured. THL was infused in an oil/egg emulsion in parallel with ingestion of a meal, and duodenal juice was aspirated at the ligament of Treitz for determination of exocrine pancreatic enzymes as well as triglycerides that remained intact and their hydrolysis products. It could be demonstrated that an intraduodenal infusion of THL in humans strongly reduced the activity of pancreatic lipase, both by reducing its catalytic activity and pancreatic secretion.^[186]

8. The Future: Highly Pure and Genetically Engineered Lipases

8.1. Highly Pure Lipases

Lipases hold considerable promise in synthetic organic chemistry and have found practical applications already in detergents, oleochemistry, cheese production, medical therapy, and industrial synthesis of specialty chemicals. By now, lipases from over 30 biological sources have been cloned, sequenced, and expressed in host organisms. Pure recombinant lipases from *Humicola lanuginosa*, *Pseudomonas pseudocataligenes*, *Pseudomonas aeruginosa*, *Mucor miehei*, *Candida antarctica* (type B), *Bacillus thermocatenuatus*, and other sources are now commercially available in free or immobilized form, or as part of a screening set (e.g. Chirazyme from Boehringer Mannheim). Even cross-linked crystals of *Candida rugosa* and of *Pseudomonas cepacia* lipase (ChiroCLEC) are commercially available from Altus (Cambridge, MA). The tertiary structures of twelve lipases have been resolved, and due to their application potential, this number will grow rapidly. As a result, a more rational approach for how to modify lipases for detergents, oleochemical applications, and organic synthesis is emerging.

8.2. Protein Engineering of Lipases

With our increasing knowledge on lipase structure and function, it has become clear that substrate binding domains vary greatly from one lipase to another, providing a more rational explanation for their varying substrate specificities. In Figure 6, the substrate binding sites of four different lipases are shown in their activated (open-lid) conformation. While these drawings are based on homology modeling of lipase–inhibitor complexes and molecular dynamics calculations and not strictly proven by X-ray crystallography, they clearly suggest the different steric and electronic environment prevailing in lipases of different origin. As an example, the distance of the active serine residue from the surface varies between 5 Å (ROL) and 16 Å (PCL) in the three examples shown. Information on genetically engineered lipases (mostly taken from the patent literature) is summarized in Table 14.

As detergents are still the commercially most important field of lipase applications, most pertinent patents deal with enhancing lipase stability and activity in a household detergent matrix.^[78] The scientific literature on modified lipases for oleochemistry and organic synthesis is still scarce. One case deals with the chain-length specificity observed in *Rhizopus delemar* lipase, which may be related to steric effects involved in the binding of acyl groups. Indeed, site-directed mutagenesis of F95, F112, V206, and V209, sterically demanding points of acyl chain interaction in this lipase, led to a significant shift in the preference of the mutant lipase for the hydrolysis of medium-chain triglycerides.^[196]

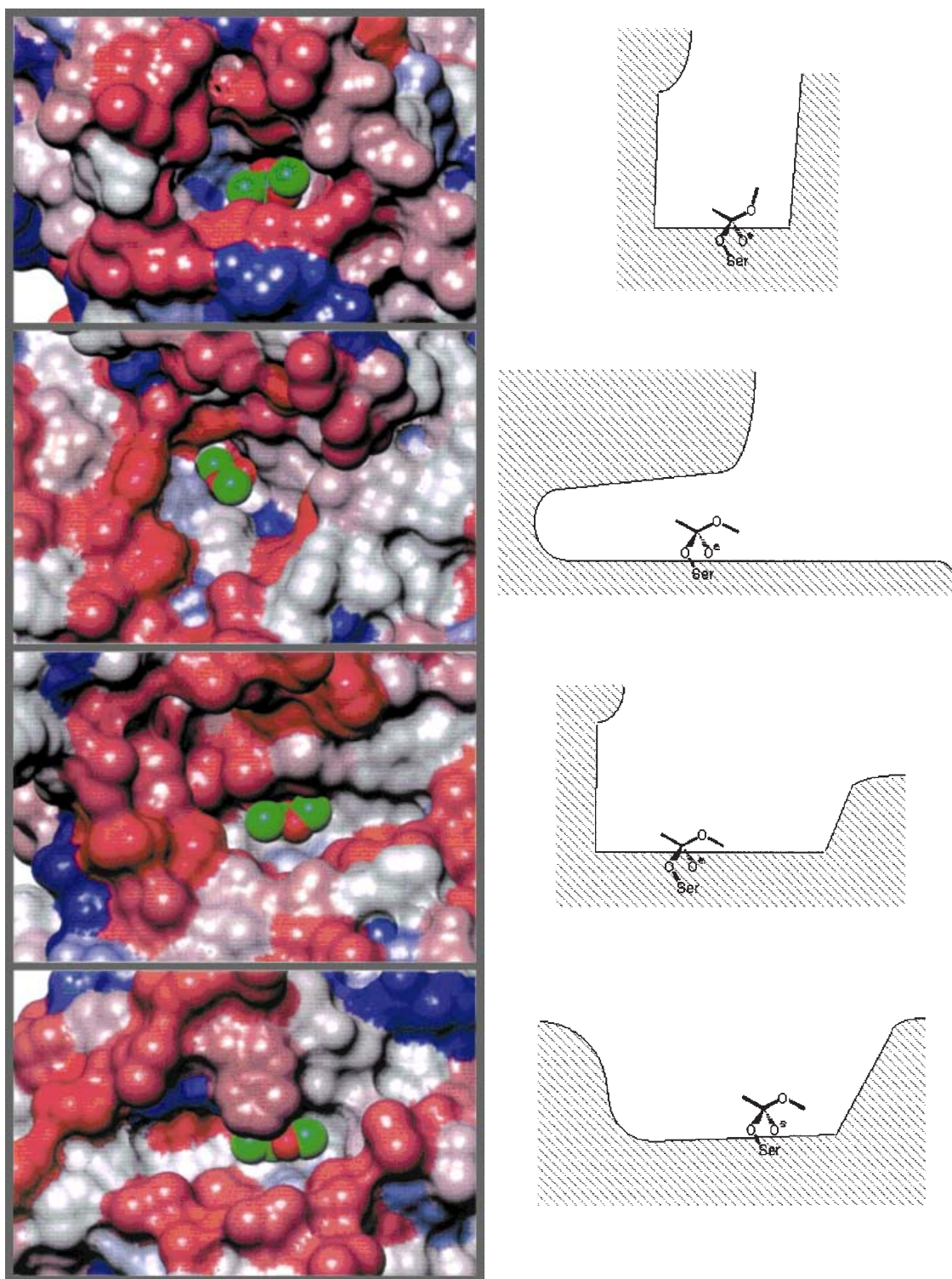


Figure 6. Polarity and geometry of the binding sites of four lipases differ significantly. From the top: *Candida antarctica* lipase (type B), *Candida rugosa* lipase, *Pseudomonas cepacia* (renamed *Burkholderia cepacia* lipase), *Rhizomucor miehei* lipase. Left: space-filling models (plan view), colored as for Figure 2. For comparison, the tetrahedral intermediate of ethyl acetate was docked into the active sites, guided by the experimental structures with substrate analogous covalent inhibitors. Right: sketch of the two dimensional cross-sections (side view) close to the active serine residues ("Conolly surface").

8.2.1. Combinatorial Design

In view of their broad applications and the rapidly advancing knowledge about their structure and function, lipases are interesting candidates for combinatorial ap-

proaches to modify their stability and substrate specificity. The esterase activity of *Rhizomucor miehei* lipase could already be enhanced with this technique.^[198] Recently, proteases have been subjected to an evolutionary screening,

Table 14. Engineered lipases.

Strain	Application	Effect of mutations	Ref.
<i>Humicola lanuginosa</i>	detergent additive	improvement of washing performance increase in thermostability improvement of resistance to proteolytic degradation increase in specific activity	[187] [188] [189]
<i>Pseudomonas glumae</i>	detergent additive	improvement of resistance to oxidative degradation improvement of proteolytic resistance	[190] [191]
<i>Pseudomonas mendocina/putida</i> ATCC 53552	detergent additive in peracid bleaching systems	alteration of substrate specificity	[192]
<i>Pseudomonas pseudoalcaligenes</i>	detergent additive	improvement of perhydrolysis to hydrolysis ratio improvement of washing performance enhanced stability towards anionic surfactants	[193] [194] [195]
<i>Rhizopus delemar</i>	biocatalysis	alteration of chain length selectivity	[196]
<i>Pseudomonas mendocina</i> SD702	detergents, food, and paper	increase of thermostability	[197]

resulting in enhanced solvent stability^[199] and modified substrate specificity.^[198, 201] It is safe to predict that before long lipases will become an eminent example of those enzymes which have been modified by rational and combinatorial design for use in industrial processes.

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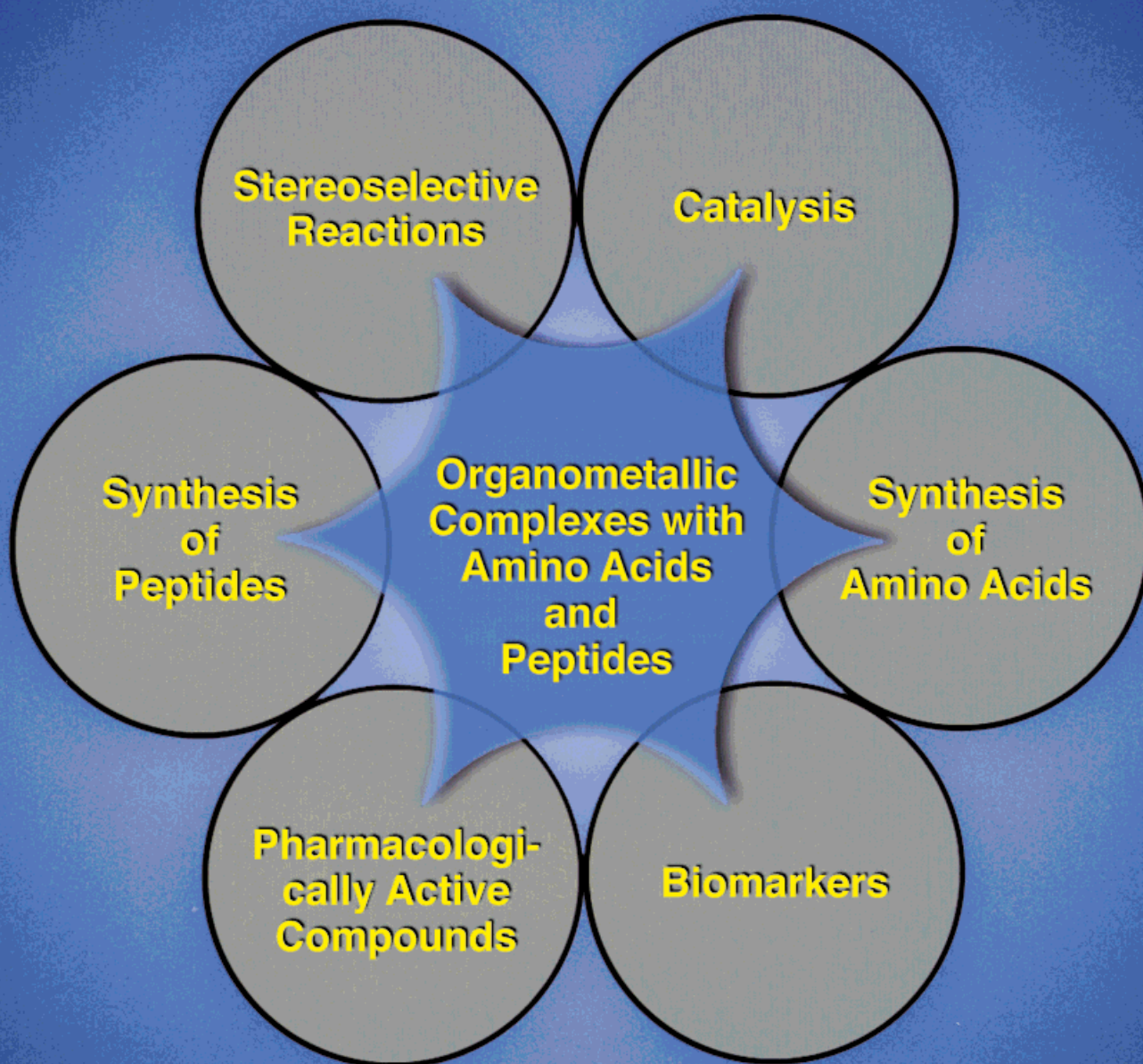
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Bioorganometallic Chemistry–Transition Metal Complexes with α -Amino Acids and Peptides**

Kay Severin, Ralph Bergs, and Wolfgang Beck*

Dedicated to Professor Heribert Offermanns on the occasion of his 60th birthday

One of the characteristic developments in the science of the last decade has been the gradual merging of what were once separate research disciplines. Bioorganometallic chemistry is the relatively recent result of such a fusion. Here, organometallic compounds are coupled with biomolecules (sugars, DNA and its constituents, steroids, etc.). The theme of this review article is organometallic complexes of the transition metals with α -amino acids and peptides. This branch of biorganometallic chemistry may be viewed as the logical next step in the

classical coordination chemistry of α -amino acid and peptide ligands. On the other hand the special physicochemical properties of these compounds also permit some completely new applications, the potential of interdisciplinary research being reflected in the diversity of these applications: α -amino acids and peptides and their derivatives can not only be synthesized, labeled, and stabilized by organometallic complexes, they can also be activated. This is exploited, for example, in the synthesis of α -amino acids with unusual side chains and has led to

the development of an immunoassay based on carbonyl complexes as well as to a template-controlled synthesis of peptides on chiral half-sandwich complexes (synthetic ribosomes). α -Amino acid and peptide ligands also find extended use in enantioselective catalysis. As a consequence of their modular character peptides are of particular interest as ligands for catalyst libraries.

Keywords: α -amino acids • bioorganometallic chemistry • coordination modes • peptides • transition metals

1. Introduction

On the border area between biochemistry and organometallic chemistry a new research field has emerged in recent years: bioorganometallic chemistry. The main features of this new research area are the synthesis, reactions, and applications of organometallic complexes with biogenic ligands. Behind this development a two-way learning process has been underway: on the one hand biologists and biochemists have “discovered” that certain organometallic compounds are stable in the absence of high-purity inert gas atmospheres, often even under physiological conditions, on the other hand, organometallic chemists have recognized the attractiveness and potential of biologically relevant ligands.

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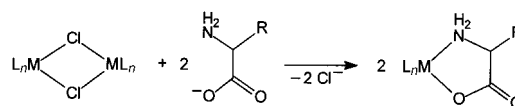
This article focuses on organometallic complexes of transition metals with α -amino acids and peptides, a branch of bioorganometallic chemistry.^[1] Section 2 gives an overview of the synthesis, structure, and reactivity of the classes of compounds known to date, with the emphasis on α -amino-carboxylate complexes. Compounds with unusual structures and/or patterns of reactivity are discussed, for example α -amino acids with organometallic side chains or protecting groups, macrobicyclic peptide complexes, and pharmacologically active compounds. The following sections deal with the applications of these complexes. The multifaceted character of bioorganometallic chemistry is illustrated here in a series of different themes: α -amino acids and peptide syntheses, stereoselective reactions, immunological assays and other analytical methods, as well as catalytic reactions using α -amino acids and peptides as ligands or as substrates.

2. Synthesis, Structure, and Reactivity

As chiral multifunctional compounds, α -amino acids and peptides are highly versatile ligands in the field of organo-transition metal chemistry with its wealth of unusual structures. The compounds described in this section can be divided

into two classes: A: complexes in which α -amino acids or peptide ligands are coordinated to a suitable organometallic complex fragment through functional group donor atoms (e.g. amino, carboxylato, or sulfanyl groups), and B: complexes in which the amino acid is bound to the metal atom through one (or more) metal–carbon bonds. Compounds belonging to class A show a range of typical coordination modes. With α -amino acid anions N,O-chelates are generally observed. α -Amino acids with coordinating side chains (e.g. cysteine, histidine) can, on the other hand, act as tridentate ligands. The complexation behavior of simple peptides and α -amino acid derivatives is likewise determined by their free functional groups. Amide groups undergo coordination in the presence of strongly Lewis acidic metal centers or on addition of excess base.

Methodologically, classical, *non*-organometallic complex chemistry, that is simple substitution reactions as the primary method of synthesis can be applied. This is especially true for compounds in which the organometallic coligands (Cp^* ($\eta^5\text{-C}_5\text{Me}_5$), CO, η^6 -arene, etc.) function solely as spectator ligands. Ideal starting compounds for this have proven to be chloro-bridged complexes (Scheme 1). One of the first examples was described by Hieber et al., in which reaction of the chloro-bridged nitrosyl complex $[(\text{ON})_2\text{MCl}]_2$ ($\text{M} = \text{Fe}, \text{Co}$) with α -aminocarboxylates gave the corresponding N,O-chelate complexes.^[2] In some cases, however, the phy-



Scheme 1. Synthesis of N,O-chelates by reaction of chloro-bridged complexes with α -amino acid ions

sicochemical idiosyncrasies of the chosen system necessitate and/or facilitate alternative synthetic strategies. This applies in particular to complexes in which the organometallic fragment is anchored to the amino acid side chain through σ or π coordination (see Section 2.4) and to complexes such as the hydrido phosphane complex **19**, formed by the oxidative addition of α -amino acids to $[\text{Ru}(\text{CO})_3(\text{PPh}_3)_2]$ (see Section 2.1).

2.1. Carbonyl Complexes

The first evidence of an α -aminocarboxylate carbonyl complex— $[\text{Fe}(\text{CysO})_2(\text{CO})_2]$ —was obtained as long ago as 1929.^[3a] Four years later the precise synthesis of the compound was reported;^[3b] this was the first isolated and characterized organometallic α -amino acid complex. On the basis of IR spectroscopic data an N,S-chelate with *cis*-oriented carbonyl ligands was proposed.^[4] Interestingly, the active

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K. Severin

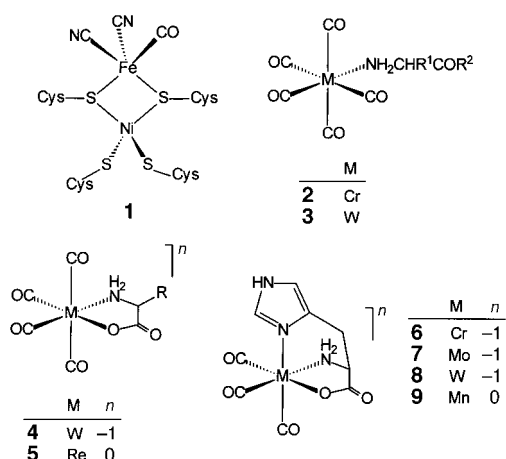
W. Beck

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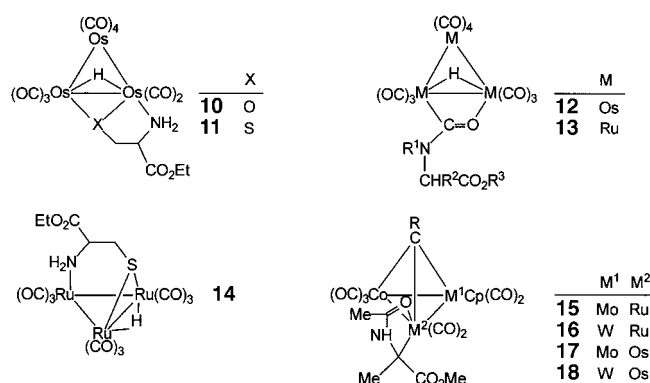
Ralph Bergs, born in 1966, studied chemistry at the LMU in München, and was awarded his Ph.D in 1994 for a dissertation on organometallic compounds of α -amino acids and peptides under the supervision of Prof. W. Beck, after which he spent one year engaged in postdoctoral research with Prof. J. Vicente at the University of Murcia. Since 1995 he has held the post of section leader at Conica Technik AG.

center of Ni/Fe hydrogenases has likewise recently been shown to contain an iron carbonyl complex (**1**).^[5]



Today numerous α -aminocarboxylate carbonyl complexes are known, among them complexes of Cr, Mo, W, Mn, Re, Fe, Ru, Os, and Rh.^[6] The photochemical reaction of $[\text{Cr}(\text{CO})_6]$ or $[\text{W}(\text{CO})_6]$ with α -amino acid or peptide esters leads to the η^1 -amine complexes **2** and **3**,^[7] which are relatively unstable in solution. By contrast, the reaction of $[\text{W}(\text{CO})_5(\text{thf})]$ with alkali metal α -aminocarboxylates affords the N,O-chelate **4**,^[8] which exhibits intermolecular hydrogen bonding in the crystal between the amine protons and neighboring carboxylate groups. The corresponding neutral Re N,O-chelate **5** is synthesized from the organometallic Lewis acid $[\text{Re}(\text{CO})_4(\text{OEt}_2)]\text{BF}_4$.^[9] Tricarbonyl complexes of type **6–9** are obtained with the tridentate ligands L-histidinate and L-cysteine.^[10] The spatial orientation of the donor atoms is fixed here by the configuration at the α -C atom, which means that coordination to the $\text{M}(\text{CO})_3$ group is stereospecific. In its complexation behavior the tridentate histidinate ligand can be likened to the hydridotrispyrazolylborate (Tp) and cyclopentadienide (Cp) ions: by analogy with $[\text{TpM}(\text{CO})_3]$ and $[\text{CpM}(\text{CO})_3]$ ($\text{M} = \text{Mo}, \text{W}$), **6** and **7** react with electrophiles with substitution of a CO ligand.^[10b] Water-soluble tricarbonyldiiminorhenium(i) complexes with histidine ligands have recently been proposed as sensitizers for photochemically induced electron-transfer processes.^[11] Other $\text{Re}(\text{CO})_n$ complexes with α -amino acids and peptides are accessible by reaction with $[\text{Re}(\text{CO})_5\text{Br}]$,^[12] many of which exhibit unusual η^1 - NH_2 coordination with the free acid group.

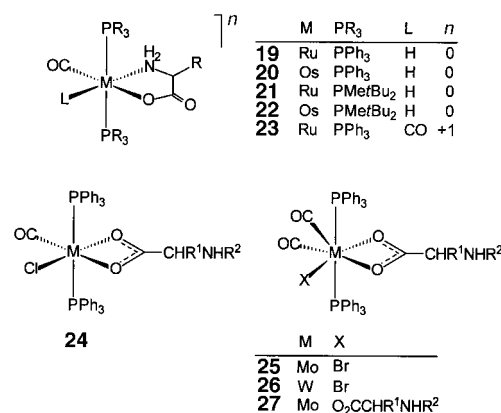
Rare coordination modes are also observed in reactions with metal carbonyl clusters: depending on the reaction conditions the reaction of trinuclear osmium carbonyl clusters with α -amino acid esters can lead either to the alkoxide- and thiolate-bridged complexes **10** and **11** or to carbamoyl hydride complexes of type **12**.^[13] Reaction with $[\text{Ru}_3(\text{CO})_{12}]$ affords the structural analogues **13** and **14**.^[14] Chiral heterotrinuclear hydrido clusters of type $[(\mu\text{-RC})\text{CoM}^1\text{M}^2\text{Cp}(\text{CO})_8\text{H}]$ ($\text{R} = \text{Me}, \text{Ph}$; $\text{M}^1 = \text{Ru}, \text{Os}$; $\text{M}^2 = \text{Mo}, \text{W}$) react with the prochiral alanine precursor methyl acetamidoacrylate with insertion into the $\text{M}-\text{H}$ function and substitution of a CO ligand (**15–18**).^[15] Metalation occurs regioselectively at the α -C atom and is diastereospecific. The CoRuMo compound **15** is the first



fully characterized key intermediate in the enantioselective catalytic hydrogenation of amidoacrylic acid derivatives (other α -metalated amino acid derivatives are described in Section 2.4). Such a hydrogenation is the key reaction in the industrial synthesis of L-dopa from the corresponding dehydroamino acid.

The functionalization of electron-rich, phosphane-substituted carbonyl complexes of the late transition metals with chiral α -aminocarboxylate ligands is of particular interest in its catalytic applications (see Section 6), research to date having focused on octahedral Ru^{II} and Os^{II} and square-planar Rh^{I} complexes.

The reaction of $[\text{MHCl}(\text{CO})(\text{PPh}_3)_3]$ ^[16] or $[\text{MHCl}(\text{CO})(\text{PMe}_2\text{Bu}_2)_2]$ ($\text{M} = \text{Ru}, \text{Os}$)^[17] with α -amino acid anions generates the hydrido complexes **19** and **20** and **21** and **22**, respectively.^[18] The dicarbonyl complexes **23** are accessible

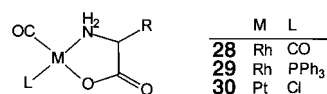


from the organometallic Lewis acid $[\text{Ru}(\text{CO})_2(\text{PPh}_3)_2](\text{BF}_4)_2$. Compounds of type **19** can, alternatively, be obtained through the oxidative addition of α -amino acids to $[\text{Ru}(\text{CO})_3(\text{PPh}_3)_2]$,^[16] in an example of a reaction type described only very rarely to date. In the absence of base, reaction of $[\text{RuHCl}(\text{CO})(\text{PPh}_3)_3]$ with α -amino acids leads to evolution of hydrogen and the formation of the chloro complexes $[\text{RuCl}(\text{NH}_2\text{CHR}(\text{CO}_2)(\text{CO})(\text{PPh}_3)_2)]$, which are unusual in that the two phosphane ligands adopt an unexpected *cis* orientation.

In general, the complexation behavior of *N*-acyl amino acids corresponds to that of simple carboxylic acids; depending on the Lewis acid character of the metal atom this can result in mono- or bidentate coordination of the carboxylate

group. Whereas η^2 coordination is observed for the Ru^{II} , Mo^{II} , and W^{II} complexes **24–26**, the Mo^{II} complex **27** contains both η^1 - and η^2 -coordinated ligands.^[20]

Square-planar α -aminocarboxylate carbonyl complexes are known for rhodium(I) (**28**, **29**)^[21] and platinum(II) (**30**).^[22] Dicarbonyl Rh^{I} complexes of formula



$[\text{Rh}(\text{CO})_2(\text{NH}_2\text{CHRCO}_2)]$ (**28**) were described for the first time in 1976.^[21g] In a subsequent study, however, these compounds were shown to be HCl adducts,^[21c] which exist presumably as oligomers; this study also described an alternative synthetic route to **28**.^[21c] An analogous L-aziridine-2-carboxylate complex has recently been characterized crystallographically.^[21b] Rhodium(I) phosphane complexes of type **29** were obtained by the reaction of the cationic complex $[\text{Rh}(\text{CH}_3\text{CN})(\text{CO})(\text{PPh}_3)_2]\text{BF}_4$ with L-alanine or L-phenylalanine.^[21a] In the crystalline state these compounds exhibit an interesting superstructure with intermolecular hydrogen bonding (as also seen in **3**)^[8].

2.2. η^1 -Alkyl, η^2 -Olefin, and η^3 -Allyl Complexes

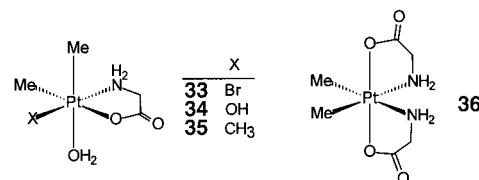
The extremely toxic MeHg^+ ion is formed in the organism by biomethylation of Hg^{2+} . From a physiological point of view the interaction of MeHg^+ with α -amino acids and peptides is interesting because complexation can strongly influence the bioavailability of this heavy metal compound. In addition to numerous studies of their behavior in solution,^[23] α -aminocarboxylate complexes of formula $[\text{MeHg}(\text{NH}_2\text{CHRCO}_2)]$ (**31**)^[24] and the dipeptide complex $[\text{MeHg}(\text{GlyGlyO})]$ ^[25] have been isolated and characterized as model compounds. As can



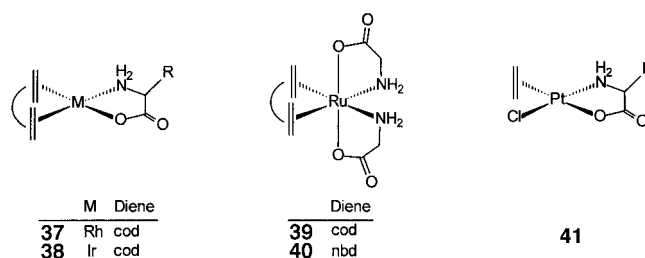
be seen from X-ray crystal structure analyses, in these complexes the MeHg^+ ion is coordinated in a linear fashion to the amino or thiol group. In the crystal intra- and intermolecular interactions are also discernible between the Hg atom and the carboxylate O atoms. Monomeric, light-sensitive dimethylgold(III) complexes (**32**) are obtained by the reaction of $[(\text{H}_3\text{C})_2\text{Au}(\text{OH})_2]\text{NO}_3$ with α -amino acid salts.^[26] With the exception of $[(\text{H}_3\text{C})_2\text{Au}(\text{CysO})]$, N,O-chelates are observed. An S,O-chelate structure has been proposed for $[(\text{H}_3\text{C})_2\text{Au}(\text{CysO})]$.

Owing to the pharmacological importance of cisplatin, studies of the chemistry of platinum amino acid complexes have mostly focused on non-organometallic compounds of oxidation state +II.^[27] The exception are octahedral di- and trimethyl Pt^{IV} complexes, whose synthesis and reactivity have been intensively investigated in recent years.^[28] In aqueous solution these chelate complexes are present as a series of stereoisomers, differing in the orientation of the α -amino acid

carboxylate ligands relative to the methyl ligands which are locked into a *cis* configuration. The glycinate complexes **33–36** serve as representatives of this class. Chelate complexes with Pd–aryl bonds of type $[(\text{tol}_3\text{P})(\eta^1\text{-aryl})\text{Pd}(\text{NH}_2\text{CHRCO}_2)]$ are formed from the chloro-bridged complex $[(\text{tol}_3\text{P})(\eta^1\text{-aryl})\text{PdCl}]_2$ by reaction with α -amino-carboxylates.^[29]



The reaction of the chloro-bridged complex $[(\text{cod})\text{MCl}]_2$ ($\text{M} = \text{Rh}, \text{Ir}$; $\text{cod} = 1,5$ -cyclooctadiene) with glycinate and proline was first reported in 1975,^[30] and affords the N,O-chelates **37** and **38**. The same study also described complexes

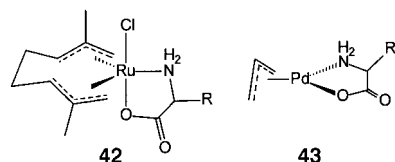


of formula $[(\text{diene})\text{Ru}(\text{GlyO})_2] \cdot x\text{H}_2\text{O}$ ($\text{diene} = \text{norbornadiene, nbd, cod}$) (**39**, **40**), formed from the reaction of polymeric $[(\text{diene})\text{RuCl}_2]_n$ with glycinate. The reaction of $[(\text{diene})\text{RuCl}_2]_n$ with α -amino acids has since been extensively investigated by Sheldrick et al.^[31] Insoluble complexes of formula $[(\text{diene})\text{RuCl}(\text{NH}_2\text{CHRCO}_2)]_n$ are formed in methanol, whereas reaction in water affords the known complexes **39** and **40**. IR spectroscopic data indicate that the α -amino acid anions function in these polymeric compounds as tridentate ligands with bridging carboxylate groups. This comparatively unusual mode of coordination was confirmed for the tetrameric complex $[(\text{cod})\text{RuCl}(\text{D,L-PheO})]_4$ by an X-ray crystal structure analysis.^[31c] Reaction with histidinate or with the anions of sulfur-containing α -amino acids yields compounds in which the α -aminocarboxylate anions are present as bi-, tri-, or tetradentate ligands with S,N-, S,N,O-, N,N,O-, and S,S,N,O-coordination.^[31a, b]

Among the best studied α -aminocarboxylate olefin complexes are Pt^{II} complexes of general formula $[\text{PtCl}(\text{NH}_2\text{CHRCO}_2)(\text{olefin})]$ (**41**).^[22, 32] These compounds are known to exist in two stable isomeric forms: *trans*-(N,olefin) and *cis*-(N,olefin). However, depending on the reaction sequence chosen—making use of the differing *trans*-effects of ethylene and chloride as ligands—either isomer can be synthesized selectively: reaction of Zeise's salt with α -amino acid anions generates the *trans*-(N,olefin) isomer, whereas substitution of a chloride ligand in $[\text{PtCl}_3(\text{NH}_2\text{CHRCO}_2\text{H})]^-$ with ethylene and subsequent elimination of HCl gives the thermodynamically favored *cis*-(N,olefin) isomer. The diastereoselectivity of the coordination

of prochiral olefins has been systematically investigated.^[33] For *trans*-(*N*,olefin) complexes selectivity is low. For *cis*-(*N*,olefin) complexes on the other hand, particularly with *N*-alkyl amino acids such as sarcosine or proline and functionalized olefins, remarkable selectivities are observed in some cases; this is attributed to the selective stabilization of one isomer by intramolecular hydrogen bonding.

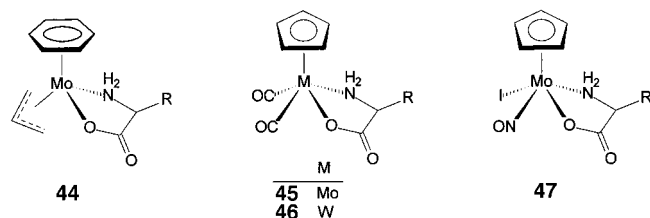
The complex $[(\eta^3:\eta^3\text{-C}_{10}\text{H}_{16})\text{RuCl}_2]_2$ is unusual for two reasons: on the one hand the Ru atom is in the formal oxidation state +IV, and on the other the $(\eta^3:\eta^3\text{-C}_{10}\text{H}_{16})\text{Ru}$ fragment is chiral. Its reaction with salts of α -amino acids results in the neutral, trigonal-bipyramidal Ru^{IV} complexes **42**.^[34] Use of α -amino acid esters with coordinating side chains



led to the isolation of a cationic chelate complex with N,S-coordination (*L*-CysOMe) and a dinuclear complex with an N,N-bridging ester (*L*-HisOMe). Allyl complexes of Pd^{II} with α -aminocarboxylate ligands (**43**) have been known for some time already.^[21b, 35] Such complexes can be prepared from $[(\eta^3\text{-allyl})\text{PdCl}]_2$ and show dynamic behavior in solution. Complexes of similar structure are proposed as intermediates in the asymmetric α -allylation of carbonyl compounds.^[36]

2.3. η^5 -Cyclopentadienyl and η^6 -Arene Complexes

The first half-sandwich complex with an α -aminocarboxylate ligand, a η^6 -benzene, η^3 -allyl complex **44**, was synthesized in 1973.^[37] Since then, a large number of such com-

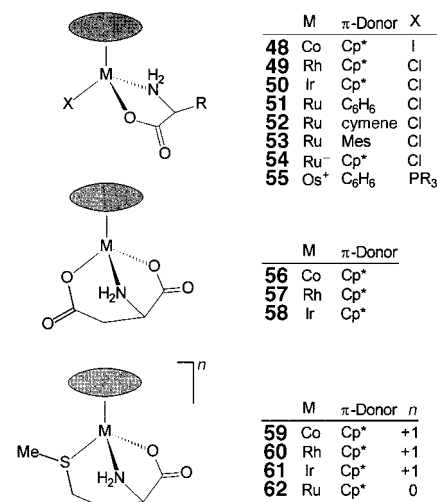


pounds have been characterized. Although certain coordination modes predominate, these complexes exhibit the structural diversity seen with ambidentate α -amino acid and peptides ligands. A particularly interesting feature of these compounds is their stereochemistry, the metal atom functioning here as an additional chiral center, opening up new horizons in stereoselective reactions.

Chiral α -aminocarboxylate complexes of Mo and W (**45**, **46**) have been obtained by the reaction of $[\text{CpM}(\text{CO})_3\text{Cl}]$ ($\text{M} = \text{Mo}, \text{W}$) with the alkali metal salts of various α -amino acids.^[35a, 38] Replacement of the two carbonyl ligands in **45** with a nitrosyl and an iodide ligand affords the isoelectronic derivatives $[\text{CpMoI}(\text{NO})(\text{NH}_2\text{CHRCO}_2)]$ (**47**). This complex can be synthesized from $[\text{CpMo}(\text{NO})\text{I}_2]_2$; corresponding Cp^* complexes were prepared from $[\text{Cp}^*\text{Mo}(\text{NO})\text{I}_2]_2$.^[39]

Complexes **45–47** have four-legged piano-stool geometry. If the α -aminocarboxylate used is optically active, four diastereoisomers are possible for **47**. During the synthesis or upon workup, one isomer is substantially enriched. For the glycinate complex $[\text{CpMoI}(\text{NO})(\text{NH}_2\text{CH}_2\text{RCO}_2)]$ the *cis* and *trans* isomers are obtained in a 7:3 ratio.

η^5 -Cyclopentadienyl complexes of the elements Co, Rh, Ir, and Ru and η^6 -arene complexes of Ru and Os show great similarities in their structure and reactivity. These complexes are generally prepared by the reaction of α -aminocarboxylates or α -amino acid N-glycosides^[32a] with the halogen-bridged complexes $[\text{Cp}^*\text{MX}_2]_2$ ($\text{M} = \text{Co}, \text{Rh}, \text{Ir}, \text{Ru}$; $\text{X} = \text{Cl}, \text{I}$),^[21b, 32a, 35a, 40] $[\{\eta^6\text{-arene}\}\text{RuCl}_2]_2$ (arene = C_6H_6 , C_6Me_6 , mesitylene, *p*-cymene),^[35a, 40g, 41] $[\text{Cp}^*\text{Co}(\mu\text{-Cl})_3\text{Cp}^*]^+$,^[42] or $[\text{Cp}^*\text{Co}(\text{CO})\text{I}_2]$.^[43] Simple α -amino acid anions yield the diastereoisomeric N,O-chelates **48–50**, usually in a 1:1 ratio.



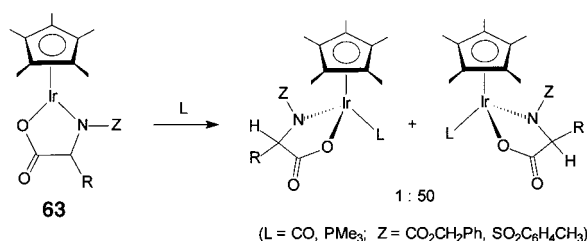
By contrast, high selectivity is observed with *N*-alkylated α -aminocarboxylates such as proline (11:1)^[40f, g] or *N,N*-dimethylvalinate (over 50:1).^[40b] At ambient temperature the Ru, Rh, and Ir complexes are configurationally stable, but at higher temperatures in solution these complexes undergo epimerization at the metal center. This phenomenon is observed even at room temperature for some Co complexes. The metal-halogen bond in **48–54** is relatively labile; substitution reactions allow the introduction of triphenylphosphane^[40f] or alkyne ligands.^[40d] For **49**, abstraction of the chloride ligand with AgBF_4 results in the formation of a trinuclear complex with bridging carboxylate groups. Interestingly, this trimerization proceeds with chiral self-recognition, that is the $S_C, S_C, S_C, S_{\text{Rh}}, S_{\text{Rh}}, S_{\text{Rh}}$ isomer is formed with high selectivity.^[44a, b] A similar trinuclear carboxylate-bridged iridium complex, $[\{\text{Cp}^*\text{Ir}(\text{proline})\}_3]^{3+}$, was recently obtained from $[\text{Cp}^*\text{IrCl}(\text{proline})]$ and $\text{AgOSO}_2\text{CF}_3$.^[44c]

A trinuclear deoxyadenosine-bridged Cp^*Rh complex is able to act as a host for amino acids.^[44d, e]

α -Amino acids with coordinating side chains can function as tridentate ligands, leading to the formation of N,O,N-(histidine^[40g, 42]), N,O,O-(asparagine,^[43] aspartic acid^[40g, 42, 43]) (**56–58**) and N,O,S-chelates (methionine,^[32a, 40c, 42] penicillamine^[42]) (**59–62**). A point of note is the structure of the Cp^*Co asparaginate complexes **56**: these compounds cocrys-

tallize with alkali metal halides; the asparagine dianion is capable of functioning as an up to octadentate ligand.^[42, 43] The phosphane-substituted η^6 -arene Os^{II} complexes [(C₆H₆)Os(NH₂CHRCO₂)(PR₃)X] (**55**) (PR₃ = P*i*Pr₃, P*Me*tBu₂; X = I, SbF₆, PF₆) have been synthesized from [(C₆H₆)Os(PR₃)I₂].^[17] Surprisingly, unlike with the complexes **48–54**, this reaction proceeds stereospecifically. The hydridotrispyrazolylborato Rh^{III} complexes [TpRhCl(NH₂CHRCO₂)] and [Tp^{*}RhCl(NH₂CHRCO₂)] (Tp^{*} = hydridotris-3,5-dimethylpyrazolylborate) are obtained, by analogy with **49**, from the chloro-bridged complexes [{TpRhCl₂]₂] and [{Tp^{*}RhCl₂]₂].^[45]

Dianions of N-functionalized α -amino acids permit the stabilization of the electronically unsaturated 16-electron Cp^{*}Ir^{III} complexes **63**.^[46a–c] These compounds add CO or sterically undemanding phosphanes such as PMe₃ or PMe₂Ph with remarkable diastereoselectivities of over 50:1 (Scheme 2). On addition of a chiral amine, the ¹H NMR spectrum of the adduct formed can be used to determine the



Scheme 2. Stereoselective addition of ligands to unsaturated [Cp^{*}Ir^{III}] complexes.

enantiomeric purity of the amine used.^[46a] Analogous Rh^{III} complexes achieve electronic saturation through dimerization.^[44b] Cp^{*}Ru complexes of prolinates and methioninates were employed for the stereoselective synthesis of planar chiral ruthenocenes.^[46d]

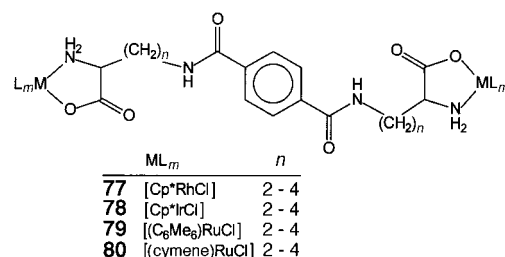
In our research group we have developed an iterative, sequence-specific peptide synthesis using half-sandwich complexes (see Section 4).^[47] In the course of this work we have obtained detailed information about the coordination behavior of α -amino acid esters, α -amino acid amides,^[48d] and di- and oligopeptides.^[47, 48] α -Amino acid or peptide esters form cationic N,O-chelates or η^1 -amine complexes (**64–70**), though in some cases the two forms exist in equilibrium with one another. The coordination of the ester carbonyl group is favored in polar solvents such as methanol and can be forced by abstraction of a halide ligand with silver salts. If the synthesis is carried out in the presence of an additional equivalent of base, the chiral (N^{amine},N^{amide})-chelate complexes **71–74** are obtained. Although these compounds with chiral peptide ester ligands are present as a mixture of two diastereoisomers, at ambient temperature the ¹H NMR spectrum in CD₃OD shows only one, averaged, set of signals, indicating rapid inversion at the metal atom. With dianions of tripeptide esters the N,N',N''-chelates **75, 76** are isolated. The Ru complexes **76** are formed with very high diastereoselectivity. As shown by an X-ray crystal structure analysis, this mode of coordination causes an unusual pyramidalization of the bridgehead amide N atom.

	M	L ¹	L ²	n	π -Donor
64	Co	I	I	0	Cp
65	Rh	Cl	Cl	0	Cp [*]
66	Ir	Cl	Cl	0	Cp [*]
67	Ru	PPh ₃	PPh ₃	+1	Cp
68	Ru	PPh ₃	CO	+1	Cp
69	Ru	Cl	Cl	0	Cp
70	Cr	Br	Br	0	Cp [*]

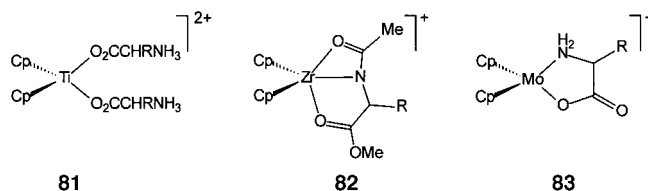
	M	π -Donor
71	Rh	Cp [*]
72	Ir	Cp [*]
73	Ru	C ₆ Me ₆
74	Ru	cymene

	M	π -Donor
75	Rh	Cp [*]
76	Ru	C ₆ Me ₆

Coordination of diaminocarboxylic acids (e.g. lysine) to Cu²⁺ leads to the formation of N,O-chelates bearing a free amino group, which can be selectively functionalized through reaction with electrophiles and subsequent demetalation.^[49] This reaction sequence also allows the synthesis of terephthalamide-bridged α,γ -, α,δ -, and α,ϵ -diaminocarboxylic acids.^[49b] Reaction of these bridged amino acids with chloro-bridged half-sandwich complexes yields—by analogy with **49–52**—compounds **77–80**, as a mixture of two diastereoisomers.^[50]



Bis(cyclopentadienyl) complexes of the early transition metals, titanocene dichloride in particular, attract considerable interest on account of their cytostatic activity. The Ti^{IV} complexes **81** were synthesized and characterized as model compounds for interactions with biologically relevant ligands.^[51] In the crystal these complexes show η^1 coordination



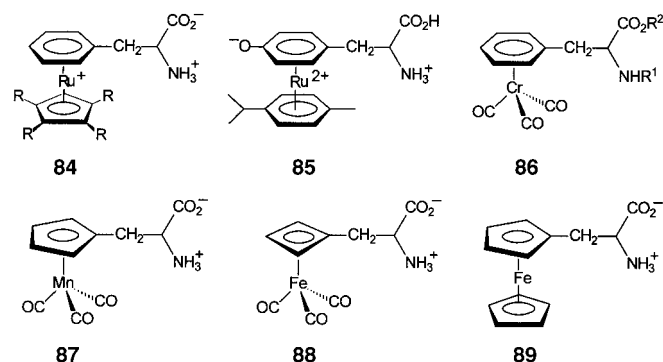
of the carboxylate group along with free, protonated amino groups. In vivo studies have shown that the α -aminocarboxylate complexes **81** also possess antitumor activity.^[52] Unlike [Cp₂TiCl₂], [Cp₂NbCl₂] shows no discernible interaction with α -amino acids in aqueous solution.^[53] Analogues of **81** of formula [Cp₂Ti(O₂CCHR¹NHCOR²)₂] are obtained by reaction of titanocene dichloride with *N*-acyl α -amino acids.^[35a, 54] These complexes can be used as acylation reagents (see Sec-

tion 4).^[54a] The coordination of C,N-protected α -amino acids and peptides to ZrCp₂ fragments is achieved by reaction of [Cp₂ZrMe(thf)]⁺ with OCNCHR¹COR² (**82**).^[55] Cationic compounds of formula [Cp₂Mo(NH₂CHRCO₂)]X (X = Cl, PF₆) (**83**) were synthesized some time ago from [Cp₂MoCl₂].^[56]

2.4. α -Amino Acids and Peptides with Organometallic Side Chains

Replacing α -amino acids with synthetic, non-coded analogues is an effective way of selectively influencing the physical, chemical, and biological properties of peptides. The coordination of organometallic complex fragments to α -amino acid side chains is doubly interesting in this context: not only do the special properties of such α -amino acids (relatively hydrophobic, aromatic character in some cases, unconventional shapes) offer a means of probing the stereo-electronic prerequisites for specific substrate–receptor interactions, the spectroscopic properties of the complex fragments allow them to be used as biomarkers (see Section 5). Moreover, the possibility of extensive functionalization means that α -amino acids with organometallic side chains are also interesting from a synthetic viewpoint (see Section 3).

The π -electron system of aromatic α -amino acid side chains is an obvious target for the introduction of transition metal complex fragments. Starting with [(η^5 -C₅R₅)Ru(CH₃CN)₃]⁺ or [(η^5 -C₅R₅)RuCl₂]₂ (R = Me, H), it is possible to synthesize [(η^5 -C₅R₅)Ru(η^6 -arene)] sandwich complexes with derivatives of phenylalanine (**84**), tryptophan, and tyrosine.^[40c, 57] The (η^5 -C₅R₅)Ru fragment can also be replaced by (η^6 -cymene)Ru, as in **85**.^[58] The analogous chromium tricarbonyl

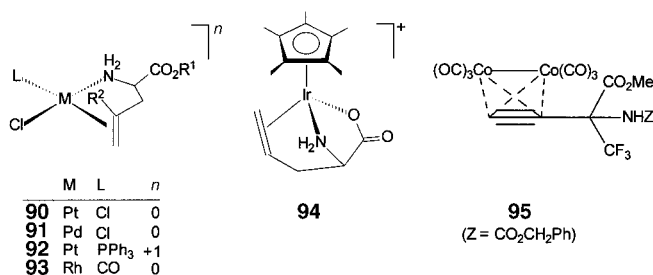


complexes **86** were first obtained by reaction with [Cr(CO)₆].^[59] Carbonyl complexes of the elements Fe and Mn are accessible by the metal-mediated synthesis (and stabilization) of the unnatural amino acids cyclopentadienylalanine and cyclobutadienylalanine (**87**, **88**).^[60] The synthesis of the ferrocene-containing α -amino acids D,L- β -ferrocenylalanine **89** and D,L-*p*-ferrocenylphenylalanine was reported as long ago as 1957 by Schlögl.^[61] The following period saw the introduction of alternative synthetic pathways,^[62] including a synthesis of ferrocenylbis(alanine).^[63] Optically active **89** was obtained by asymmetric hydrogenation of dehydro-*N*-acyl-

amino acids with Rh phosphane catalysts^[64] and by enzymatic resolution of the racemate.^[65]

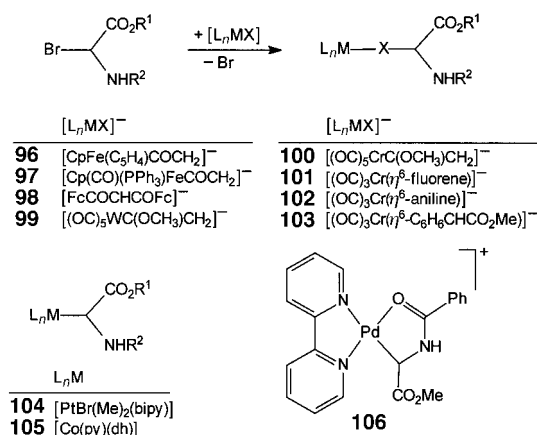
Crucial to the use of organometallic amino acids in biochemical investigations is the possibility of incorporating these compounds into peptides. A Cp^{*}Ru complex of type **84** was used to synthesize dipeptides by the carbodiimide method,^[57a] though the sensitivity to hydrolysis of Cp^{*}Ru sandwich complexes imposes limitations on more extensive use. By contrast, cymantrenyl- and ferrocenylalanine have proven to be particularly stable, allowing even solid-phase peptide syntheses to be carried out (cleavage of the peptide from the resin with HF!).^[66] This was used to synthesize organometallic derivatives of a series of biologically active peptides (e.g. encephalins).^[66b–e] The cymantrenyl compounds are remarkably versatile; photochemical substitution reactions permit the exchange of CO for phosphane ligands,^[66a, b] enabling the size and hydrophobic character of these α -amino acids—and corresponding peptides—to be varied selectively.

With the use of synthetic amino acids such as C-allyl- or C-alkynylglycine, π coordination to organometallic fragments is likewise possible. Chloro-bridged complexes of the elements Ir, Pd, and Pt can be used to obtain the chelate complexes **90**–**94** by reaction with C-allylglycine or C-allylglycine esters.^[67] By analogy with allylamines, the coordinated olefin in the



cationic compound **92** reacts with C-nucleophiles with C–C coupling to form γ -metalated amino acid esters,^[67a] which can then be demetalated. Interesting further chemistry is also shown by the Rh complex **93**: reaction with HCl and P(OMe)₃ generates *N*-acyl complexes by hydrometalation and insertion of CO. After cleavage of the ligand, γ -lactams were obtained.^[68] C-Vinylglycinate can be stabilized as an N,O-chelate coordinated to a [Cp^{*}(Cl)M] fragment (M = Rh, Ir).^[67a] Reaction of the alkynyltrifluoromethyl α -amino acid ZNHC(CF₃)(C $\equiv$ CH)CO₂Me (Z = CO₂CH₂Ph) with [Co₂(CO)₈] resulted in the formation of the metallatetrahydrene **95**.^[69] Complex **95** reacts with norbornene in a [2 + 2 + 1] cycloaddition to give a cyclopentenone-substituted α -trifluoromethyl amino acid derivative.

α -Bromoglycine derivatives (“electrophilic glycine equivalents”) are valuable building blocks for the synthesis of α -amino acids with modified side chains. Reaction with base generates acylimines, which are not isolated, but are allowed to react in situ with nucleophiles such as amines, thiols, silyl enol ethers, Lipshutz cuprates, or Grignard reagents.^[70] Transition metal fragments can be introduced in analogous manner by reaction of methyl α -bromohippurate with organometallic C- and N-nucleophiles (Scheme 3).^[71] Nucleophiles that have been used include acetylferrocene enolates

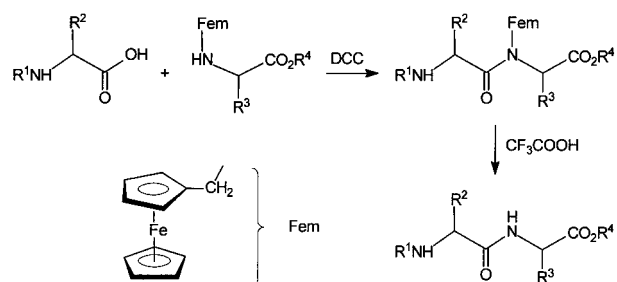


Scheme 3. Synthesis of α -amino acids with organometallic side chains by reaction of electrophilic glycine equivalents with nucleophilic transition metal complexes.

(**96**), $[\text{CpFe}(\text{CO})(\text{PPh}_3)(\text{COCH}_3)]$ (**97**), and a ferrocene-containing acetylacetonate derivative (**98**), as well as anions of Fischer carbene complexes (**99**, **100**) and arenechromium tricarbonyl complexes (**101**, **102**). Analogous chromium complexes had previously been obtained from chlorinated glycine derivatives (**103**) or iodinated alanine derivatives.^[72] Nucleophilic attack can also occur through the metal atom directly: reaction of methyl α -bromohippurate with $[\text{PtMe}_2(\text{bipy})]$ or with $[\text{Co}(\text{py})(\text{dh})]^-$ (bipy = 2,2'-bipyridine, py = pyridine, dh = dimethylglyoxime) affords the complexes **104** and **105**,^[73] which were among the first examples of α -transition metalated amino acid derivatives. The cationic C,O-chelate complex **106** can be obtained by reaction of $[\text{Pd}(\text{dba})_2]$ (dba = dibenzylideneacetone) with methyl α -bromohippurate in the presence of bipyridyl, followed by abstraction of halide with silver salts.^[73b] The oxidative addition of a N-protected aspartic acid anhydride to a Ni^0 complex gives a chiral metallacycle, which can be used for the synthesis of α -amino acids.^[73c]

2.5. α -Amino Acids and Peptides with Organometallic Protecting Groups

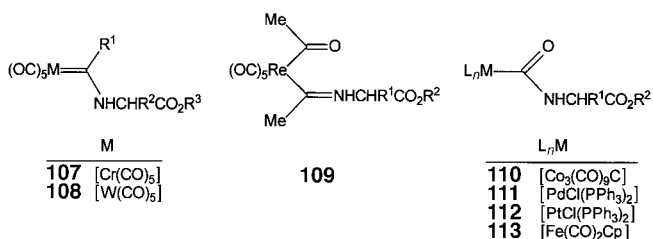
The selective fine-tuning of the solubility and secondary structure of peptides is of great synthetic utility. Use of the chromophoric and lipophilic ferrocenylmethyl residue (Fem)^[74] permits the simple and reversible masking of peptide bonds.^[75] The Fem group can be introduced without racemization by catalytic reductive alkylation of α -amino acids or α -amino acid esters with ferrocenecarboxaldehyde and hydrogen. The resulting N-Fem α -amino acid derivatives can then undergo coupling reactions by the carbodiimide method (Scheme 4). In addition to their strongly lipophilic character, Fem-masked peptides have one further advantage: they are colored (yellow), which simplifies their chromatographic purification. Instead of the ferrocenylmethyl residue, the $[(\eta^4\text{-RC}_6\text{H}_6)\text{Fe}(\text{CO})_3]$ group can be introduced under mild conditions (cf. Section 5).^[76] Following any subsequent trans-



Scheme 4. Reversible masking of peptide bonds with the lipophilic and colored ferrocenylmethyl (Fem) residue. DCC = dicyclohexylcarbodiimide.

formations the complex can then be recovered almost quantitatively through cleavage with trifluoroacetic acid.

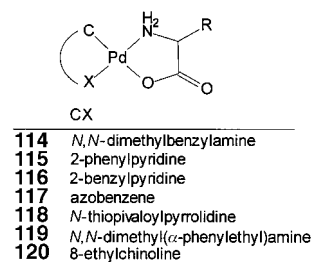
A number of carbonyl complexes have been proposed as amino protecting groups for use in peptide synthesis. Examples include the aminocarbene complexes **107** and **108** formed by the aminolysis of $[(\text{OC})_5\text{M}=\text{CR}(\text{OCH}_3)]$ (M = Cr, W) with α -amino acid esters.^[77] Another organometallic amino pro-



tecting group is based on a carbonylrhenium complex: here α -amino acid esters are condensed with Re acetylacetonate complexes to give the rhenia- β -ketoimine derivatives **109** as a mixture of two isomers.^[78] α -Amino acid or peptide esters can be functionalized with a cobalt carbonyl cluster by reaction with $[(\text{OC})_9\text{Co}_3\text{CCO}]\text{PF}_6$ (**110**).^[79] Analogous carbamoyl complexes are formed by the reaction of $[(\text{Ph}_3\text{P})_2\text{MCl}_2]$ (M = Pd, Pt) with CO in the presence of α -amino acid esters (**111**, **112**)^[80] and by the reaction of $[\text{CpFe}(\text{CO})_3]\text{CF}_3\text{SO}_3$ with α -amino acid esters (**113**).^[8a] α -Amino acid esters can also be added to coordinated olefins.^[81b]

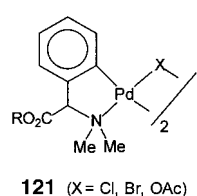
2.6. Other Compounds

Cyclopalladated chloro-bridged complexes of type $[(\text{C}^-\text{N})\text{Pd}(\mu\text{-Cl})_2]$ (also planar chiral ferrocene derivatives) and the corresponding acetylacetonate derivatives have proven suitable starting compounds for the synthesis of square-planar α -aminocarboxylate complexes (**114**–**120**).^[21b, 32a, 35, 82] In these compounds the carboxylate group is generally oriented *trans* to the metalated C atom. Complexes with chiral cyclometalated ligands (**118**–**120**) merit particular attention.^[83a,d] In their reactions with α -amino acids, the



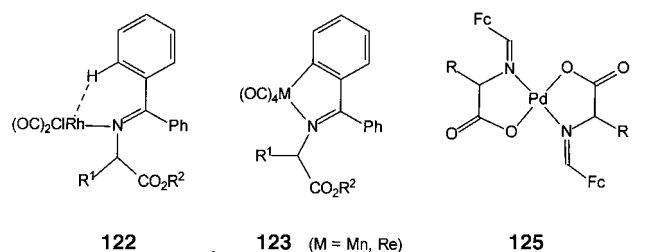
products formed are diastereomeric. Integration of the corresponding ^1H NMR signals allows the enantiomeric ratio of the α -amino acid used to be determined.^[84] If racemic cyclometalated ligands are used (**120**), they can then be obtained in optically active form by diastereomeric separation.^[83a, d]

The orthometalated gold complexes $[\text{AuCl}_2(\text{dmba})]$ and $[\text{Au}(\text{O}_2\text{CCH}_3)_2(\text{dmba})]$ ($\text{dmba} = N,N'$ -dimethyl benzylamine) exhibit antitumor and antibacterial properties. A model used to investigate the interaction between these complexes and sulfur-containing α -amino acids and peptides is their reaction with L-cysteine and glutathione, which afforded square-planar N,S-chelates.^[85] Octahedral, strongly fluorescent Ir^{III} N,O-chelates have been synthesized from the chloro-bridged complex $[\text{Ir}(\text{ppy})_2(\mu\text{-Cl})_2]$ ($\text{ppy} = 2$ -phenylpyridine).^[82a] Cyclometalation of an amino acid protecting group has been observed with a polynuclear Pd complex.^[86] Complexes in which the α -amino acid is itself present as a cyclometalated ligand are comparatively rare; unprotected α -aminocarboxylates form N,O-chelates preferentially. Dinuclear C,N-chelates (**121**) can, however, be isolated from the reaction of N,N' -dimethyl phenylglycine ethyl ester with Pd^{II} salts^[87] and their chemistry was studied.^[87a] An analogous Pt^{II} complex with an orthometalated phenylalanine ligand was formed on heating an aqueous solution of $\text{trans-K}_2[\text{Pt}(\text{PheOH})_2\text{Cl}_2]$.^[88]



121 ($X = \text{Cl}, \text{Br}, \text{OAc}$)

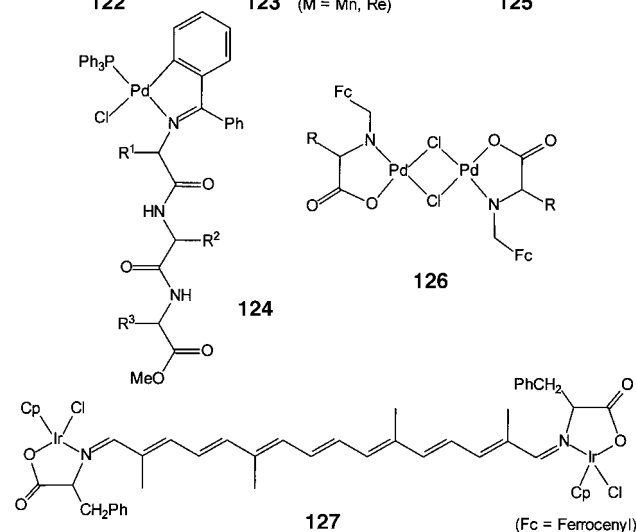
The condensation of benzophenone with α -amino acid esters affords Schiff bases (O'Donnell reagents^[89]). These compounds possess an activated α -carbon atom and are therefore of interest as precursors for the synthesis of non-biogenic α -amino acids (see Section 3).^[89, 90] In organometallic complexes these ligands may be present as monodentate σ -N-donors (**122**),^[91]



122

123 ($M = \text{Mn}, \text{Re}$)

125



124

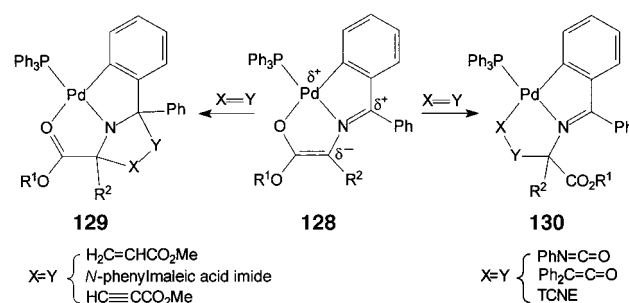
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127

(Fc = Ferrocenyl)

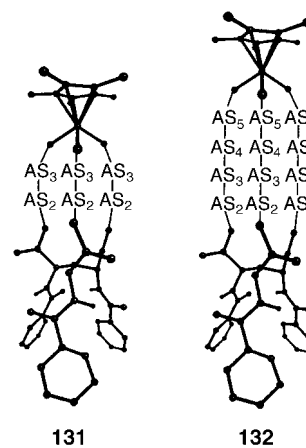
as bidentate C,N-donors (**123**, **124**)^[92] or N,O-donors (**125**),^[93] and as tridentate C,N,O-donors (**128**).^[81, 92b, 95] Reduction of these Schiff bases yields N -alkyl α -amino acids. This route can also be used to synthesize N -ferrocenylmethyl α -amino acids (see also Scheme 4), which react with $[\text{PdCl}_4]^{2-}$ to give the chloro-bridged complexes **126**.^[93] The complexation behavior of Schiff base derivatives of unprotected α -amino acids is comparable to that of the free amino acids, with N,O-chelates generally observed.^[93] Conjugated diimines have been used to synthesize dinuclear complexes bridged by rigid spacer groups (e.g. **127**).^[94]

Particularly striking is the reactivity of enolate phosphane complexes of type **128**. As ambident dipoles they react with various dipolarophiles either with coupling of two C–C bonds (**129**) or with the formation of metallaheterocycles (**130**) (Scheme 5).^[81, 92b, 95] Analogues of **128**, formed from the diphenylmethylene Schiff bases of dipeptides, can undergo addition to unsaturated hydrocarbons coordinated at cationic metal centers.^[96]



Scheme 5. Cycloadditions of Pd complexes with orthometalated α -amino acid Schiff base ligands. TCNE = tetracyanoethylene.

The synthesis of peptides with defined metal binding sites is a first step on the way to synthetic metalloproteins. The necessary preorganization can be achieved through hydrophobic and/or electrostatic interactions as well as through hydrogen bonding, and is often promoted by template effects. Impressive examples are the C_3 -symmetric peptide bundles recently reported by Steglich et al.,^[97] in which the template is a triglycine derivative linked through a nitrogen atom. The complexation behavior of these ligands was probed initially by their reactions with $[\text{Cp}^*\text{TiCl}_3]$, which yielded macrobicyclic, likewise C_3 -symmetric complexes with ring sizes of up to 32 atoms (**131**, **132**).^[98] Ferrocenyl derivatives have also been investigated as a possible way of stabilizing peptide secondary structures. Interest here centers on the β -sheet structures, since the distance between the rings in ferrocene is roughly the same as the N,O-distance between two peptide



131

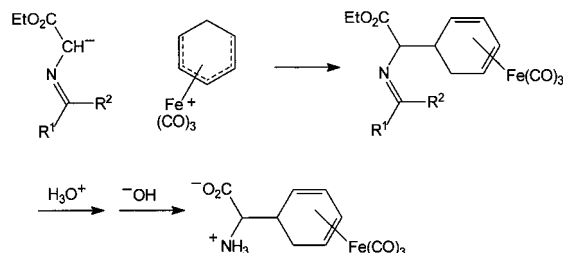
132

chains. Preliminary results suggest that ferrocenyl bridges, supported by intramolecular hydrogen bonds, are able to lock two α -amino acid esters into a defined conformation.^[99, 100]

3. Synthesis of α -Amino Acids

There are few classes of compounds for which so many different synthetic strategies have been developed as α -amino acids and their derivatives. A large proportion of these often stereoselective syntheses are based on traditional organic reactions. Nevertheless, there is also a range of interesting methods based on organometallic transformations. Conceptually, a distinction can be made between two approaches. On the one hand, amino acid side chains can be introduced or modified by reaction with transition metal complexes. Alternatively, the α -amino acid framework can be constructed by organometallic reactions. An overview on this topic is given in a review published in 1995;^[101] thus, in the following only the most important methods are summarized in brief, with reference made to some more recent work.

The addition of nucleophilic glycine or alanine synthons to complexes with π -coordinated unsaturated hydrocarbon ligands is a versatile method for the synthesis of α -amino acid derivatives with unusual or metal-containing side chains. The electrophiles that have been used are cationic carbonyl complexes of iron (Scheme 6),^[102a–c] manganese,^[103] chromium,^[102d] and rhenium,^[102d] as well as allyl palladium com-

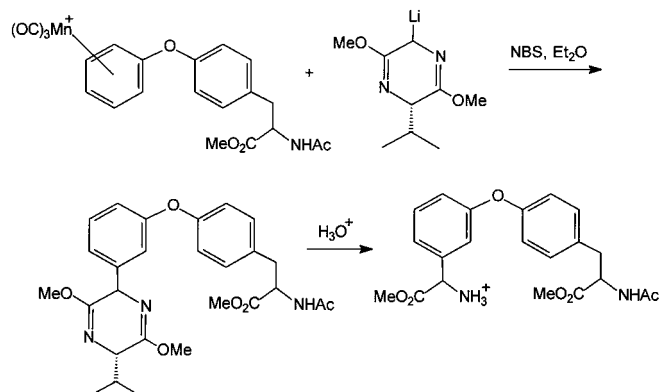


Scheme 6. Synthesis of α -amino acids with cyclohexadienyl side chains by reaction of nucleophilic glycine equivalents with cationic carbonyliron complexes.

plexes.^[102e] This method can be regarded as an “umgepolte” variant of the reaction shown in Scheme 3 (cf. Section 2.4). With the nucleophilic alanine synthetic building block $\text{IZnCH}_2\text{CH}(\text{NHBoc})\text{CO}_2\text{Bn}$ (Boc = *tert*-butoxycarbonyl) direct reactions with organic electrophiles are possible. This organozinc reagent can be obtained in a few steps from serine and reacts in the presence of Cu or Pd compounds with a wide range of electrophiles such as alkenyl, alkynyl, and allyl halides, and acid chlorides.^[104]

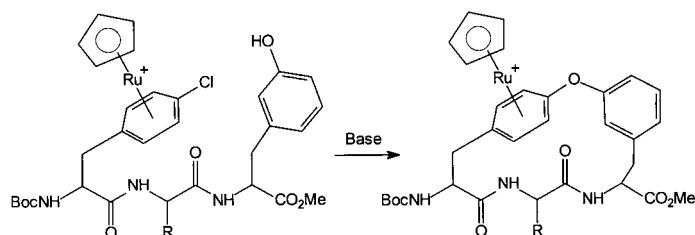
Nucleophilic substitutions with halogenated aryl compounds can be greatly facilitated by η^6 complexation. This method has been used to obtain α -aryl glycines by C_α – C_{aryl} coupling of tricarbonylchromium complexes with anionic glycine equivalents.^[105b–f] The reaction of $[(\text{C}_6\text{H}_5\text{FeCp})^+]$ with α -amino acid esters affords access to iron-containing *N*-acyl amino acids.^[105a] Of particular interest in this context is the activation of chloroaryl compounds by the $\text{Mn}(\text{CO})_3$ frag-

ment. These complexes undergo nucleophilic substitution with aryl alkoxides.^[106] The diaryl complexes thus obtained can be transformed into the corresponding α -aryl glycine derivatives by reaction with Schöllkopf's chiral glycine enolates (Scheme 7).^[106a, b] Diaryl ether-bridged amino acids of this type are of high synthetic value as building blocks for glycoprotein antibiotics such as vancomycin.



Scheme 7. Synthesis of aryl ether bridged phenylglycine derivatives by activation with $[\text{Mn}(\text{CO})_3]^+$ fragments. NBS = *N*-bromosuccinimide.

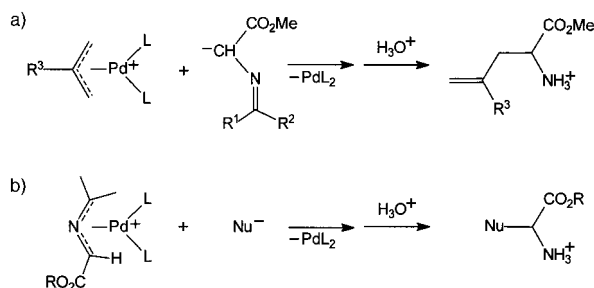
Aryl ether bonds can also be constructed through activation with CpFe and CpRu fragments;^[107] the reagent of choice has proven to be the Ru complex (Scheme 8). The introduction



Scheme 8. Synthesis of cyclic aryl ethers from halogenated $[\text{CpRu}]$ sandwich complexes.

of this group and the coupling reaction proceed under very mild conditions. Furthermore, multiple substitutions are possible. $S_N\text{Ar}$ reactions such as these have been exploited in the formal total syntheses of the protease inhibitors K13 and OF4949III^[108] and in the synthesis of model systems for the antibiotics teicoplanin,^[109] ristocetin,^[110] and vancomycin.^[111]

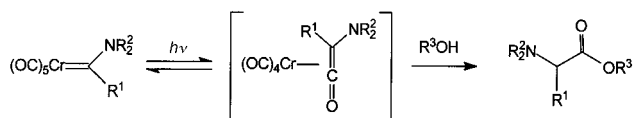
A catalytic version of the type of reaction shown in Scheme 6 is the Pd^0 -catalyzed alkylation of Schiff bases of formula $\text{R}_2\text{C}=\text{NCH}_2\text{CO}_2\text{R}^2$ with allyl esters, allyl halides, or allyl carbonates.^[112] The C–C coupling occurs through nucleophilic attack of the deprotonated Schiff base on a η^3 -allyl Pd complex. The imino ester formed is converted into the corresponding α -amino acid ester on acid hydrolysis (Scheme 9a). Enantioselective alkylations can be achieved with optically active Schiff bases and/or phosphanes.^[113] A variant of this reaction permits the synthesis of α -amino acid esters with 1,3-dienyl or styryl-substituted side chains; allenes are initially coupled with aryl or vinyl halides and then allowed to



Scheme 9. Synthesis of α -amino acids by a) reaction of cationic allyl-Pd complexes with nucleophilic glycine equivalents or by b) reaction of azaallyl-Pd complexes with C-nucleophiles.

react with nucleophilic glycine equivalents.^[114] η^3 -Allyl Pd complexes can also function as α -amino acid building blocks. In the reaction of acetylated Schiff bases with Pd⁰ phosphane complexes the azaallyl Pd complexes formed initially react with C-nucleophiles to give the corresponding α -amino acid derivatives (Scheme 9b).^[115]

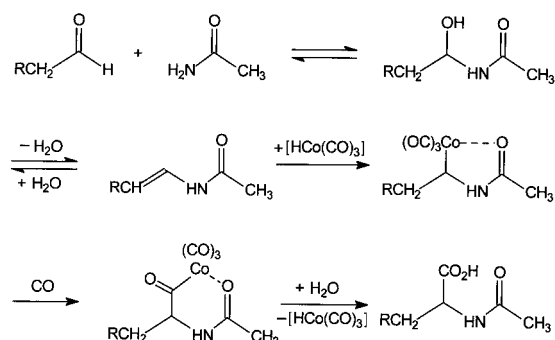
A particularly versatile method for the synthesis of α -amino acids (and peptides: see Section 4) has been developed by Hegedus et al.,^[116] in which the photochemical activation of aminocarbene Cr complexes leads to CO insertion products with ketene-like reactivity; reaction with alkoxides affords α -amino acid esters (Scheme 10). By using chiral auxiliaries,



Scheme 10. Synthesis of α -amino acid esters by photochemically induced reaction of aminocarbene complexes with alcohols.

stereoselective reactions with high optical yields are possible; optically active oxazolidines are particularly suitable. Aminocarbene Cr complexes can also be used to synthesize C-alkyldienamino ketimines, which yield α -amino acid amides on hydrolysis.^[117]

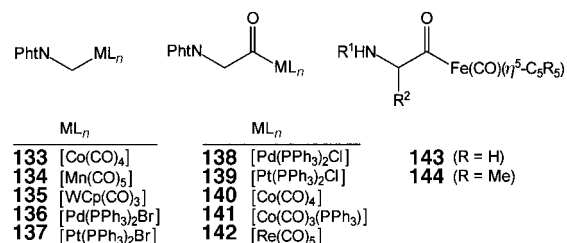
In 1971 Wakamatsu et al. reported the cobalt carbonyl catalyzed amidocarbonylation of aldehydes under the conditions of the oxo synthesis (H₂, CO, [HCo(CO)₄] as catalyst).^[118] This reaction, subsequently named Wakamatsu reaction, leads to *N*-acyl α -amino acids (Scheme 11),^[119] and can be used in combination with other



Scheme 11. Postulated mechanism for the cobalt-catalyzed amidocarbonylation of aldehydes.

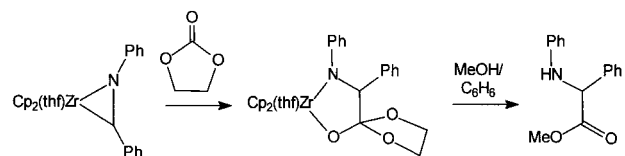
catalytic reactions. Instead of the aldehyde, oxiranes and allyl and homoallyl alcohols can also be used.^[120] These substrates rearrange to the corresponding aldehyde with involvement of a cocatalyst. Because the amidocarbonylation conditions correspond to those used in hydroformylation, olefins^[121] or benzyl chloride^[122] can also be used. In a more recent variant of the amidocarbonylation, Pd catalysts are used in combination with ionic halides.^[123] This procedure can be carried out under relatively mild conditions, does not require hydrogen, and is characterized by its high efficiency. Another Pd-catalyzed reaction, the homogeneously catalyzed hydrocarboxylation of *N*-alkenyl amides, affords access to *N*-protected α -amino acid esters.^[124]

The intermediates in the amidocarbonylation are thought to be aminomethyl and aminoacetyl complexes (Scheme 11). Compounds of this type have been isolated and characterized. Thus, *N*-phthaloylmethyl chloride and *N*-phthaloylglycyl chloride yielded the complexes **133**–**135** and **140**–**141** on reaction with carbonyl metalates,^[125] and complexes **136**–**139** by oxidative addition to Pd⁰ and Pt⁰ compounds.^[126] In



agreement with the postulated mechanism the acetyl compound **140** yields phthaloylglycine with water and dipeptides with α -amino acid esters.^[125b] The reaction of mixed anhydrides of *N*-protected α -amino acids or dipeptides with [CpFe(CO)₂]⁻ (Fp⁻) or [Cp*Fe(CO)₂]⁻ (Fp*⁻) affords the iron acetyl complexes **143** and **144**.^[127] After removal of the *N*-protecting group the relatively stable compounds **144** can be reacted with activated amino acids to give dipeptides.^[127b] Oxidative cleavage of **143** and **144** yields aldehydes, with loss of the amino and acyl groups.^[127a]

The construction of the α -amino acid backbone by connecting a bond between the α -C atom and the carboxylate C atom can also be achieved through reaction of the CO₂ building block ethylene carbonate with zirconocene imine complexes (Scheme 12).^[128] Such an insertion is also possible

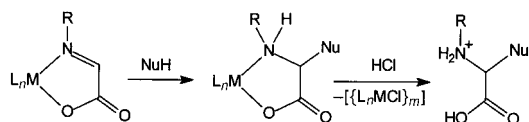


Scheme 12. Construction of α -amino acids at the metal center by reaction of zirconocene imine complexes with the CO₂ building block ethylene carbonate.

with CO₂ directly, though cleavage of the ligand from the metal fragment has proven difficult here. With the use of optically active bridged bicyclopentadienyl ligands this insertion proceeds stereoselectively with over 96% *ee*. A similar

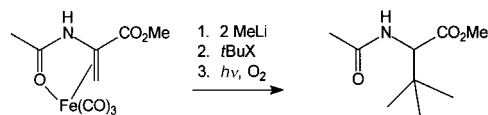
reaction, the coupling of ketimines with CO₂, can be achieved in the presence of ytterbium metal, yielding α -aminocarboxylate Yb complexes.^[129] The free amino acid is then obtained by HCl cleavage.

The addition of nucleophiles to the imino-C atom of α -imino carboxylic acid derivatives is an often used method for the synthesis of α -amino acids. In this reaction, nucleophilic attack is promoted by electron-withdrawing groups. Alternatively, the imino group can be activated by coordination to transition metals. These compounds are generally prepared by the template-directed, metal-mediated condensation of amines with 2-oxocarboxylates or by elimination reactions. Reactions with nucleophiles lead to α -aminocarboxylate complexes; the ligand can then be cleaved off by addition of acid (Scheme 13). Optically active complexes merit particular attention as they allow these C–C couplings to be carried out stereoselectively. In a kind of umpolung reaction, α -imino esters undergo reaction with alkyl halides after coordination to Fe(CO)₄.^[131]



Scheme 13. Synthesis of α -amino acids by reaction of α -iminocarboxylate complexes with nucleophiles.

Iron carbonyl complexes have also been used to synthesize β,β,β -trialkyl- α -amino acids: reaction of acetamidoacrylate–Fe(CO)₃ complexes with two equivalents of methyllithium, a tertiary alkyl chloride, and subsequent oxidative workup affords the corresponding amino acid derivatives in good yield (Scheme 14).^[132]



Scheme 14. Synthesis of α -amino acids with sterically demanding side chains using acetamidoacrylate–Fe(CO)₃ complexes.

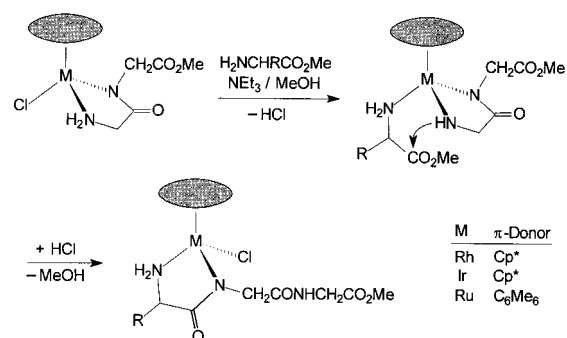
Finally, reference should be made here in brief to some other reactions in which organometallic complexes are present solely as reactive intermediates. One of the best studied methods for the asymmetric synthesis of α -amino acids is the hydrogenation of prochiral dehydroamino acid derivatives. The use of optically active diphosphane–Rh and –Ru complexes allows these reactions to be carried out stereoselectively in excellent optical yield (up to 100% *ee*).^[133] Intermediates in this reaction are α -metalated amino acid derivatives (see also **15**, **105**, **106**).^[133] Transition metal catalyzed reactions have also been used to functionalize amino acid side chains. With the use of α -amino acids with stannylated or halogenated side chains, Pd⁰-catalyzed cross-coupling and, thus, selective lengthening of the side chain is possible.^[134] Metathesis reactions with ruthenium carbene complexes have been used to convert *N*-allyl-, *C*-allyl-, and *C*-vinylalkyl-substituted amino acids or peptides into cyclic,

conformationally rigid compounds.^[135] Simple homoallyl glycine derivatives can also be modified through cross-metathesis reactions.^[136] Conformationally stable phenylalanine derivatives have been obtained by Pd⁰-catalyzed intramolecular C–C couplings.^[137] Chiral ferrocenylphosphane ligands allow β -hydroxy α -amino acids to be synthesized stereoselectively through Au^I- or Ag^I-catalyzed aldol reactions of α -isocyanomethyl esters with aldehydes.^[138] If a planar-chiral tricarbonylchromium benzaldehyde complex is used as the aldehyde, the reaction yields—even without the addition of a further chiral auxiliary—organometallic oxazolines with high diastereoselectivity, which can likewise be transformed into β -hydroxy- α -amino acids.^[139]

4. Synthesis of Peptides

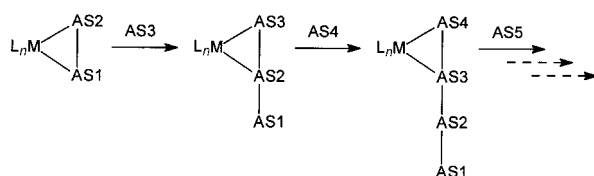
The selective synthesis of peptides in the coordination sphere of transition metals was first reported in 1967.^[140] This type of reaction, which has since been extensively studied, has attained only secondary importance as a synthetic method, though it has been proposed as a possible mechanism for the formation of peptides under prebiotic conditions.^[140e] Organometallic complexes have so far been used relatively rarely for the synthesis or modification of peptides. Nevertheless, there are a number of noteworthy reactions, which are described below.

Half-sandwich complexes of the elements Rh, Ir, and Ru have been used to develop a sequence-specific peptide synthesis,^[47] in which *N,N'*-coordinated peptides undergo selective chain lengthening at the *N*-terminus by reaction with α -amino acid esters. The linking of the peptide bond requires neither activating reagents nor protecting groups; the peptide ester formed can then be cleaved from the metal complex without racemization. Scheme 15 shows the postulated reaction mechanism. This template-directed condensa-



Scheme 15. Sequence-specific peptide synthesis at chiral half-sandwich complexes of the elements Rh, Ir, and Ru.

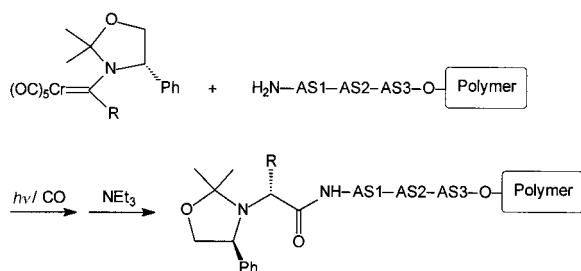
tion proceeds through nucleophilic attack of an amino anion on the carbonyl group of the η^1 -*N*-coordinated amino acid ester. In principle, the mechanism shown in Scheme 15 permits further chain-lengthening as desired; with repeated addition of α -amino acid esters the coordinated peptide is successively lengthened at the *N*-terminus, the half-sandwich complex functioning solely as a catalyst (Scheme 16). Such a



Scheme 16. Metal-catalyzed construction of peptides by successive reaction of α -amino acid esters with coordinated peptide complexes.

reaction sequence has already been used to synthesize peptides with chain lengths of up to nine amino acid residues at the [(*p*-cymene)RuCl] fragment.^[47d] Recently the Ni⁰-catalyzed polymerization of α -amino acid-*N*-carboxyanhydrides (Leuchs anhydrides) was reported; it leads to block copolypeptides with well-defined sequences.^[141a, b] The palladium copolymerization of imines with CO was suggested as a way to polypeptides.^[141c]

In Section 3 a method was described that allows α -amino acid esters to be synthesized by the photochemically induced alcoholysis of aminocarbene chromium complexes (see Scheme 10). If, instead of the alcohol, the reaction partner is an α -amino acid ester or a peptide with an unprotected N-terminus, di- or oligopeptides are formed in good yield (Scheme 17).^[116] This process enables non-biogenic or labeled

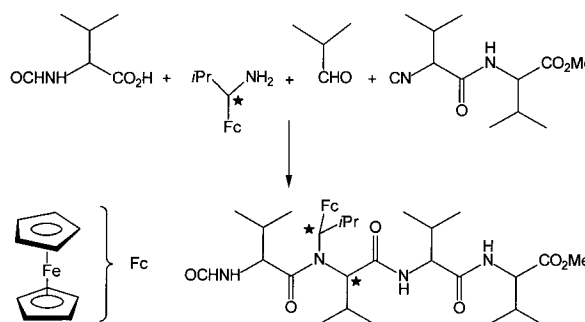


Scheme 17. Diastereoselective incorporation of synthetic α -amino acids in solid-phase peptide syntheses by reaction with chiral aminocarbene complexes.

α -amino acids to be incorporated into peptides selectively. Compared with alternative methods, a number of advantages are apparent; with the appropriate choice of chiral auxiliary the configuration of the incoming amino acid can be determined. Furthermore, the coupling proceeds in good yield even with sterically hindered amino acids and is compatible with the conditions of solid-phase^[142] or polyethyleneglycol-supported^[143] peptide syntheses.

Carboxylate complexes of the early d⁰-transition metals are similar to activated esters in their reactivity, which means they can be used as acylation reagents. The use of organometallic {Cp₂Ti}-*N*-acyl aminocarboxylate complexes in peptide syntheses was first reported in 1990.^[54a] Reaction with methyl L-alaninate under relatively drastic conditions (THF, reflux) affords dipeptide esters in moderate yield. Considerably higher reactivity is shown by carboxylate complexes of type [Cp*TaCl₃(O₂CCHR¹NHR²)],^[144] which react with α -amino acid esters even at low temperatures. The yield and degree of racemization in this condensation reaction are comparable with that of standard systems such as DCC/HOBt (HOBt = hydroxybenzotriazole).

In the work described so far the organometallic complex fragment was directly involved in the formation of the new peptide bond. Another option, however, is to use it as chiral auxiliary. In a series of publications Ugi et al. have described the synthesis of peptides by means of stereoselective four-component reactions,^[145] in which an *N*-protected α -amino acid, a chiral amine, an aldehyde, and an α -isocyanoacyl α -amino acid derivative undergo condensation in a one-pot reaction to give an *N*-substituted tetrapeptide (Scheme 18). With the use of α -ferrocenylalkyl amines as the chiral auxiliary, these Ugi reactions can be carried out almost completely diastereoselectively.

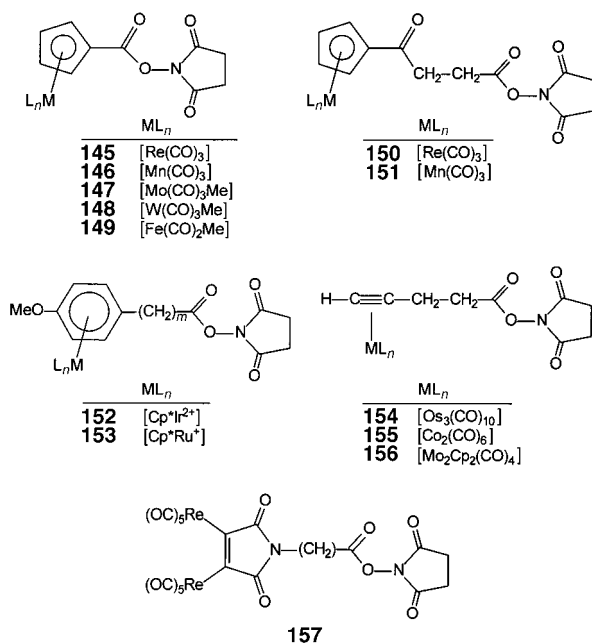


Scheme 18. Ferrocenyl derivatives as chiral auxiliaries in Ugi four-component reactions.

5. Use as Labeling Reagents

The ligands (CO, NO, unsaturated hydrocarbons) and the metal atom offer means by which organometallic complexes can be detected selectively even in small quantities. This has led to the growing use of these compounds as markers in biochemical or biological investigations. Areas of application include immunological assays, X-ray crystallography or electron microscope studies, and the characterization of active centers. Such compounds can also be used as radiopharmaceuticals, provided they are sufficiently stable under physiological conditions and are able to undergo covalent coupling with the appropriate biomolecule in the presence of a suitable coupling reagent. The following section presents the various classes of compound described together with their areas of application.

One of the simplest ways of functionalizing peptides and proteins is by acylation of free amine groups (e.g. lysine side chains). Efficient reagents for this acylation have proven to be succinimidyl esters. Through coupling of this reactive group with transition metal complexes, a range of organometallic markers have been synthesized, such as the cyclopentadienyl complexes **145**–**151**,^[146] the sandwich complexes **152** and **153**,^[147] the alkyne clusters **154**–**156**,^[148] and the bimetallic Re complex **157**.^[149] These compounds are prepared from the corresponding acids by reaction with *N*-hydroxysuccinimide in the presence of DCC. A measure of their reactivity can be obtained from their reaction with α -amino acid esters. Organometallic complex fragments can also be incorporated into peptides by coordination to the π -structures of amino

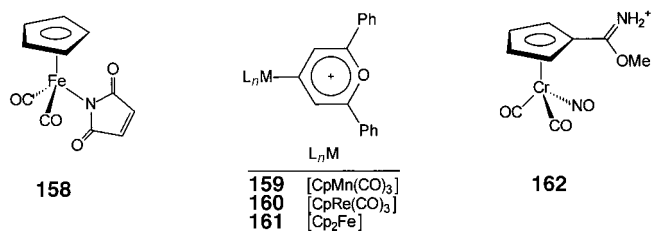


acid side chains, as demonstrated by Sheldrick et al. (see Section 2.4).^[58]

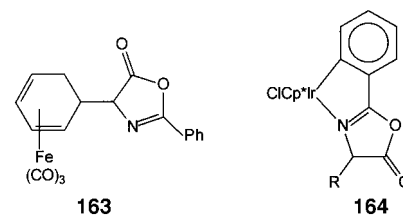
The IR spectra of the carbonyl complexes **145–151** and **157** show extremely intense, characteristic absorption bands in the region between 1900 and 2100 cm⁻¹. Biological molecules, by contrast, have a so-called spectroscopic window in this region, which means that substrates labeled with these complexes can be detected by Fourier transform infrared spectroscopy (FTIR). The detection limit for this is in the picomole region with modern FT spectrometers. This was used by the group of Jaouen as the basis for the development of a carbonylmetal-loimmunoassay (CMIA).^[1c, 150] By means of competitive antigen-antibody reactions with an organometallic hapten, hormones or other pharmacologically relevant substances can be quantitatively detected. CMIA has a number of advantages over classical immunoassays: firstly, no radioactive compounds are necessary,^[151] and secondly, with the use of different markers, several immunoassays can be performed in parallel.^[152] This is possible because different carbonyl complexes can be determined simultaneously by their characteristic absorption bands.

Transition metal complexes of type **145–156**, the metal-rich, and hence electron-rich clusters **154–156** in particular, are of interest not only for their potential CMIA applications, but also as labels for X-ray or electron microscope studies.^[153] As a model system a globular protein (67 kDa) was labeled with **154**;^[148a] here an average of 20 clusters per protein were incorporated.

In addition to the above-mentioned complexes with active ester groups, other electrophilic complexes with potential applications as biomarkers have also been described. The [CpFe(CO)₂] complex **158** reacts with α -amino acids with nucleophilic addition of NH- or SH-functions to the double bond.^[154] Coordination of the [CpFe(CO)₂] fragment (Fp) to tryptophan methyl ester can also be accomplished by direct reaction with FpI under basic conditions.^[155] Labeling with carbonyl or ferrocenyl complexes can be achieved by the



reaction of free amino groups with the pyrilium salts **159–161**,^[156] which yields pyridinium salts. The succinimidyl ester and pyrilium complexes have two drawbacks: they are relatively poorly soluble in water and secondly, this functionalization of the free amino group changes the overall charge on the corresponding protein. Therefore the water-soluble metal carbonyl imido ester **162** was synthesized.^[157] This complex reacts with amino groups to form amidines, which are positively charged under physiological conditions. A disadvantage here, however, has proven to be the low stability of the [CpCr(NO)(CO)₂] fragment. α -Amino acids can also be labeled with tricarbonylchromium complexes by η^6 -complexation of Cr(CO)₃ to *N*-benzoyl protecting groups.^[35a] The oxazolinone complexes **163** and **164** can likewise be regarded as activated esters;^[70a, 158] they react with α -amino acid esters under basic conditions to form transition metal-containing dipeptides.^[159]

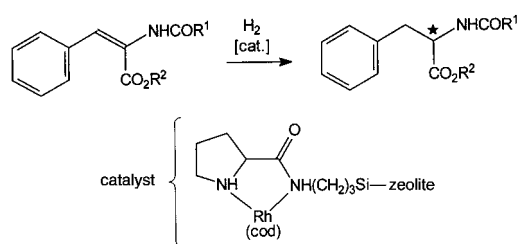


Cationic iron carbonyl complexes of general formula $[(\eta^5\text{-RC}_6\text{H}_6)\text{Fe(CO)}_3]^+$ react with nucleophiles to form neutral diene complexes. In Section 2.4 it was described how this reaction can be used to synthesize α -amino acids with unusual side chains (see Scheme 6). Cationic iron complexes of this type can, however, also be used as a way of selectively labeling peptides and proteins;^[160] a clear preference for cysteine and histidine has been established. In addition to traditional analysis techniques, electrospray mass spectrometry has now emerged as a suitable method for characterizing these adducts.^[161] The functionalization of peptides and proteins with ferrocenyl groups is of interest on account of the electrochemical properties of these complexes,^[162] and can be accomplished by using various derivatives with activated ester groups.

6. Use as Catalysts

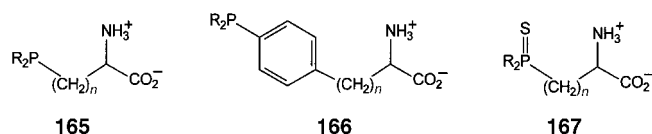
The incorporation of α -amino acids or their derivatives into catalytically active transition metal complexes affords a simple and economical way of accessing chiral compounds with potential applications in enantioselective catalysis.^[163] One such example is the heterogeneous hydrogenation of prochiral olefins with Rh^I proline amide complexes linked to a

modified zeolite through a spacer.^[164] These compounds have proven to be efficient and highly enantioselective catalysts (Scheme 19). Comparable immobilized catalysts have also been used in the hydrogenation of arenes,^[165] in the addition of diethylzinc to enones,^[166] and in cyclopropanations.^[167]



Scheme 19. Enantioselective hydrogenation of acetamidocinnamate esters using immobilized proline-amide-Rh^I complexes.

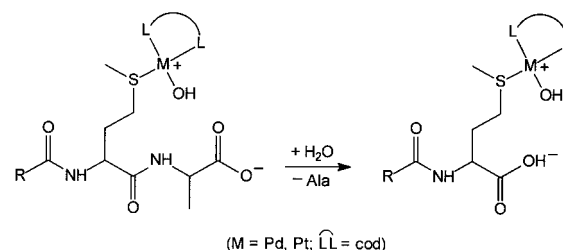
Many homogeneous catalysis processes use electron-rich complexes of the late transition metals, and phosphane ligands have proven particularly useful. For this reason, α -amino acids, particularly the relatively rigid proline, have often been functionalized with phosphane groups.^[163e] An interesting more recent approach is the coupling of alkyl- or arylphosphanes with α -amino acid side chains (**165**, **166**),^[168] which allows the synthesis of peptides with defined binding sites for catalytically active transition metals.^[169] In solid-phase peptide syntheses compounds of the type **167** have proven useful,^[169] since they can subsequently be reduced to the corresponding phosphanes.



The application of the methods and concepts of combinatorial chemistry in the search for new metal-containing catalyst systems may yet lead to the kind of breakthrough in this area seen in recent years in bioorganic and pharmacological chemistry.^[170] Nevertheless, up to now there have been only isolated successes. A first important step in this direction is the assembly of catalyst libraries. An obvious line of approach is the use of ligands with modular structures. α -Amino acids are particularly attractive candidates as building blocks for such ligands; not only are they optically active and commercially available in both enantiomeric forms, they can be used as the basis, using only few fragments, for assembling libraries of great diversity. It is therefore not surprising that many recently published studies on combinatorial catalysis make use of this synthetic concept.^[171]

In organometallic catalysis α -amino acids and peptides are not only used as ligands, but are also the subject of numerous studies in which they are the substrate. Particularly interesting are metal complexes capable of cleaving peptides hydrolytically, and where possible, regioselectively. Such reagents could find use as chemical alternatives to proteolytic enzymes in analytical biochemistry. Pt^{II} and Pd^{II} aqua complexes in particular have proven useful as synthetic metallopeptidases.^[172] These compounds coordinate to the heteroatom of side

chains and catalyze the regioselective hydrolysis of the neighboring amide bond. Such cleavage can also be accomplished with organometallic complexes of type $[M(\text{cod})(\text{D}_2\text{O})_2]^{2+}$ ($M = \text{Pd}, \text{Pt}$) (Scheme 20).^[173]



Scheme 20. Regioselective hydrolysis of peptides.

Because of the long half-life of the hydrolysis of amide bonds under neutral conditions, many studies employ activated esters initially. Thus, *N*-Boc-methionine *p*-nitrophenyl ester has been shown to hydrolyze up to 535 times more rapidly in the presence of orthometalated Pd and Pt complexes than in control experiments without addition of metal complexes.^[174] In these reactions no turnover is observed, as the complexes are coordinated irreversibly to the sulfur-containing methionine side chain. Chloro-bridged half-sandwich complexes of the elements Rh and Ir have proven useful as catalysts for ester exchange reactions with α -amino acid esters.^[48b] Transesterification can then be achieved through nucleophilic attack by the alcohol on the likewise coordinated carbonyl group or through a template reaction with the coordinated alcohol.

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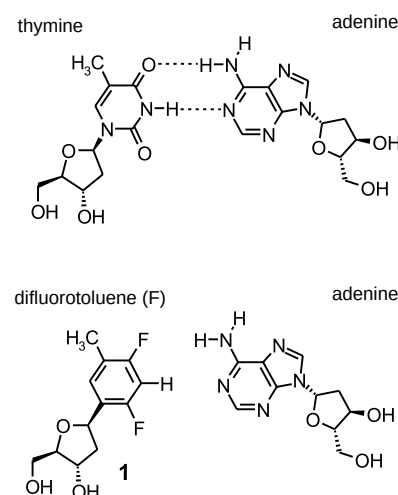
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Selectivity of DNA Replication: The Importance of Base-Pair Geometry over Hydrogen Bonding

Ulf Diederichsen*

Polymerase is the central enzyme of the many proteins involved in DNA replication. It is responsible for the selection and bonding of nucleotides complementary to a template strand as well as the correction of faulty base pairings. A high degree of selectivity is prerequisite for the integrity of the genome over generations.^[1] The hydrogen-bonding recognition between the decoding nucleobase and its complementary nucleotide is an information-transferring interaction and appears initially to be responsible for selectivity. Considering the many combination possibilities in which a nucleobase can produce two or three hydrogen bonds and a mistake percentage in the duplication of a *Escherichia coli* genome of only 10^{-9} – 10^{-10} per base, the selectivity in base pairing alone cannot be the reason for this selectivity. The exonuclease as well as the post-replicative mismatch repair procedures have to be taken into consideration along with the aforementioned transfer fidelity of the applicable assortment of nucleotides. The initial insertion of nucleotides is achieved with only one mutation per 10^3 to 10^5 incorporated nucleotides.^[2] In addition, the following factors must be considered as reasons for high selectivity along with the base pair identification through hydrogen-bonding interactions: 1. Base stacking; 2. polarity of the base and the resulting solvation; 3. geometry of the recognition (pairing mode, the shape and size of the bases); 4. DNA–protein and protein–substrate interactions (dNTP–substrate binding, geometrical selectivity, and phosphate diester bonding structures); 5. enzyme kinetics; 6. sequential factors. The importance of individual factors must be considered, because the mechanism of the selection and incorporation of nucleotides has not yet been established. Publications from E. Kool's group describe *in vitro* replication experiments in which instead of thymine the isoster nucleobase analogue difluorotoluene, which has a much lower hydrogen-bonding capability, was used.^[3–5] The replication fidelity when using the thymine mimetic remains largely intact, which appears to have led to an underestimation of shape recognition, stacking, and solvation as factors for nucleotide selectivity.

The experimental approach is based on nucleoside **1** which contains the pseudobase difluorotoluene (F) instead of thymine.^[6] In peptide chemistry, the use of a fluoroethylene unit as a peptidomimetic and conformational control unit to replace the carboxamide functionality has been established.^[7] Through X-ray crystal structure analysis and NMR spectroscopy, the geometrical and conformational high unanimity between nucleoside **1** and thymidine could actually be determined (Scheme 1).^[6a] The C–F $\cdots$ H–N hydrogen bonding is weaker and a C–H $\cdots$ N interaction can be rated



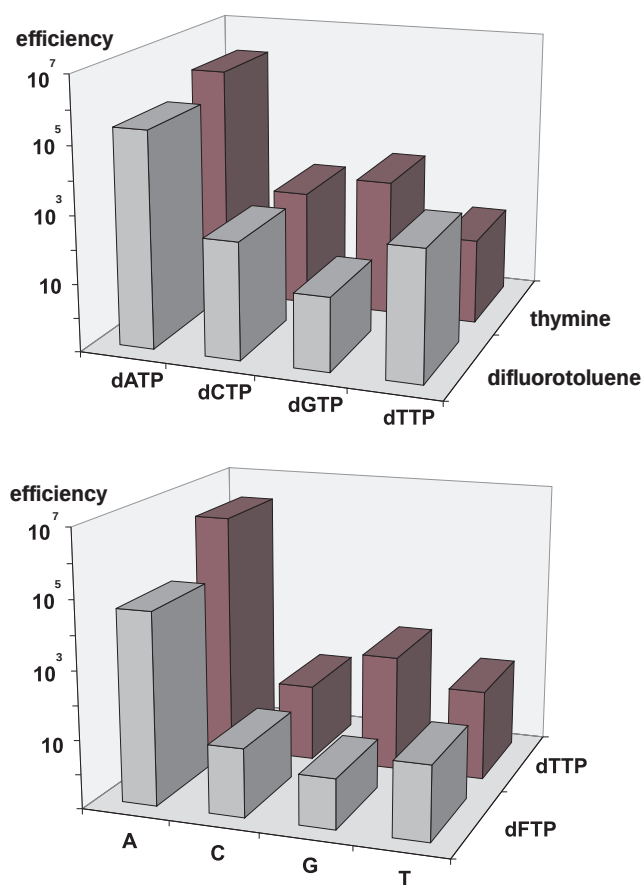
Scheme 1. Difluorotoluene (F) can be substituted for a pyrimidine as a thymine–isoster in Watson–Crick pairing. The ability to form hydrogen bonds is considerably lower for F.

distinctly weaker than the corresponding C=O $\cdots$ H–N and N–H $\cdots$ N hydrogen bonding.^[8] An interaction of difluorotoluene with adenine was not even observed in chloroform.^[4] An A–F mismatch in the center of a dodecamer double strand resulted in destabilization by 18 K relative to the A–T pairing,^[9] which indicates negligible hydrogen bond formation with difluorotoluene. It has to be borne in mind that according to *ab initio* calculations (6-31G**) the charge distribution and electronic density of the aromatic isoster **1** is similar to that of thymine.^[10] Hydrogen bonding, especially in an enzymatic environment in which the orientation of the proton donors and acceptors can be geometrically compelled, cannot be

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excluded. In this instance it is assumed that the contribution of an $F \cdots H-X$ interaction gives almost half of that of an $O \cdots H-X$ bond.^[8c]

The importance of the hydrogen bond formation with the complementary nucleotide triphosphate was investigated by comparing the replication fidelity of a DNA template that contains the pseudo base difluorotoluene instead of thymine.^[3] The replication started with the template-bound primer sequence with the assistance of the Klenow fragment from DNA polymerase I, and the selectivity with regard to insertion of dATP, dGTP, dTTP, or dCTP was studied.^[4] A comparably good selectivity for difluorotoluene and thymine with regard to insertion of dATP was demonstrated (Scheme 2 (top)). In both instances the adenosine nucleotide

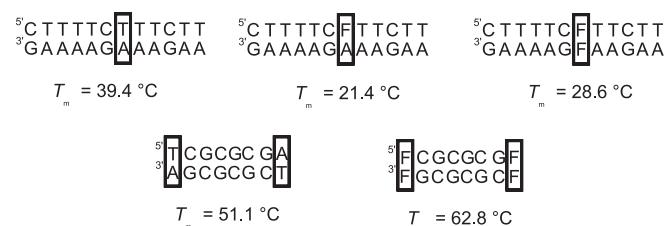


Scheme 2. Top: Efficiency (v_{max}/K_m) of the incorporation of canonical nucleotide triphosphates as complementary for thymine or difluorotoluene.^[4] Bottom: Comparison of the efficiency of incorporation of dTTP and dFTP complementary to A, C, G, or T template bases.^[5]

was inserted as complementary with a more than 1000 times greater efficiency than the other nucleotides. A very similar result is displayed for the selectivity in which the nucleotide triphosphate dTTP and mimetic dFTP are identified and inserted as the template complementary (Scheme 2 (bottom)).^[5] Although difluorotoluene has a much smaller tendency for hydrogen bonding than thymine, the selectivity is surprisingly similar which points to an insignificant contribution of hydrogen bonding for the recognition of the complementary unit. In both instances the aryl units are of

very similar shape and size and a similar preferred conformation and charge distribution appear to be the important selection criteria for the polymerase. These findings are in accord with the suggested “geometrical selection” of Echols and Goodman as the important parameter for insertion specificity.^[11] Hence, the selection criterium is the base pair geometry, which is supplied through the pairing mode and which is reflected in the distances between the anomeric centers and the bonding angles.

What importance does solvation and stacking have for the suitability of nucleoside **1** as an isoster mimetic? The comparison of the stability of regular double strands with duplexes that contain A–F or F–F mismatch positions proves the fundamental influence of both factors (Scheme 3):^[9] The



Scheme 3. Result of difluorotoluene mismatch pairing on the double strand stability of DNA dodecamers (1.5 μM , 100 mM NaCl, 10 mM MgCl_2 , 10 mM Na-PIPES, pH 7) and octamers (6 μM , 1 M NaCl, 10 mM Na-phosphate, pH 7).^[9]

substitution of an A–F mismatch for an A–T base pair severely destabilizes the double strand (the melting point (T_m) is lowered by 18 K) whereas for an F–F mismatch T_m is only 11 K lower than a regular pairing duplex. This tendency is likely to depend on the solvation and stacking contributions. In aqueous solution difluorotoluene is not solvated distinctly, neither in a single nor a double strand. In an A–T base pair the solvation is compensated by the base pairing, whereas adenine in a double strand with A–F mismatch loses its hydrogen bonding without any adequate compensation. The significance of the stacking is indicated by the modifications in the terminal positions of the double strand.^[9] The octamer with two F–F mismatch positions is more stable (T_m increases by 12 K) than the oligomer with terminal A–T pairing: This ordering indicates impressively that difluorotoluene provides a higher stacking contribution than adenine.^[12]

Polymerases appear to rely to a large extent upon shape, polarity of the bases and the Watson–Crick geometry to accomplish selectivity. These results are in full agreement with two recent publications by Doublié et al.^[13] and Kiefer et al.,^[14] who described the X-ray structure of the cocrystallization of DNA polymerase with a DNA-template primer double strand.^[15] On the one hand, the ternary complex could be stabilized in the crystal with a nucleotide triphosphate when the primer is lacking the terminal 3'-hydroxyl group,^[13] while on the other hand, even in the crystal the polymerase–template primer complex retains its catalytic activity and selectivity with respect to the base complementarity.^[14] Without detailing the X-ray structures and the mechanism of the phosphate diester bonding formation, three characteristics which have an impact on selectivity must be emphasized:

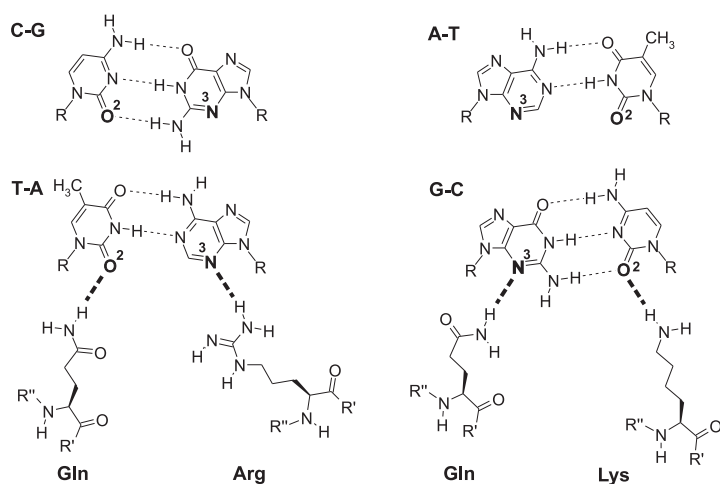
1. The entering nucleotide triphosphate will be held in a tight pocket by stringently conserved amino acids, so that it arrives in a Watson–Crick orientation facing the complementary nucleobase. The template base is fixed through stacking interactions with the adjacent nucleobase and on the other side with a tyrosine residue or through a van der Waals contact with glycine.

2. Apart from the nonspecific recognition of the polyanionic backbone of the DNA double strand another sequence-independent hydrogen-bonding recognition in the minor groove is ascribed to the first four or five base pairs of the active center. Amino acids with proton donor properties recognize the acceptor position N3 in purine and O2 in pyrimidine (Scheme 4). The A–T and G–C pairs both have

As a result the requirement for pseudobases to be incorporated instead of a canonical nucleobase with comparable selectivity is that its corresponding nucleotide phosphate triester analogues are isosters of dNTP with rather similar conformations. Furthermore, it should have an aryl group that shows good stacking interactions, as well as acceptor functionalities in the pseudo N3 and O2 positions, respectively. The difluorotoluene nucleotide **1** fulfills many of these requirements, and it is consequently recognized and incorporated as a Watson–Crick mimetic with high selectivity.

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Keywords: base stacking • DNA replication • geometrical selection • hydrogen bonds • isosteric nucleobases



Scheme 4. O2 in pyrimidines and N3 in purines are proton acceptors and point to the minor groove in the DNA double helix. They are hardly any different in their hydrogen-bonding ability and are aligned quasi-symmetrically in the base pair. The recognition of O2 and N3 by Asn, Gln, Arg, His, or Lys is selective for Watson–Crick pairing.

this double-acceptor pattern, irrespective of whether a purine or pyrimidine is the template.^[16] This interaction can distinguish between the Watson–Crick pairing mode and all other pairing geometries. Analogous hydrogen-bonding interactions of the polymerase in the major groove in which each base pair has its individual donor/acceptor pattern are nonexistent. The nonspecific recognition is a prerequisite for the elongation of the double strand during continuous synthesis in the enzyme pocket.

3. That functional efficiency and selectivity of the polymerase are preserved in the crystal emphasizes how participating molecules have to be aligned.

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Transistors and Light Emitters from Single Nanoclusters

Horst Weller*

What must the perfect transistor be able to do? From a chemist's or physicist's point of view this question can easily be answered: It must be able to operate with a single electron. Recently the groups of Alivisatos and McEuen from Berkeley succeeded in putting into practice such a single-electron transistor (SET) with CdSe semiconductor nanocrystallites of approximately 5 nm in size synthesized by wet chemical methods.^[1] Owing to their size-dependent material properties, the class of substances of these nanoparticles enjoys great popularity in different branches of chemical and physical research.^[2–9] The schematic construction of this SET is shown in Figure 1. It consists of a highly doped, electrically conducting Si substrate, the surface of which is covered with a thin,

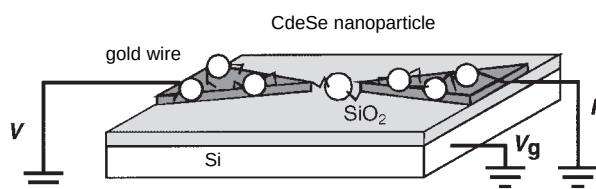


Figure 1. Schematic construction of a single-electron transistor. A CdSe nanoparticle is placed between two gold wires.

electrically insulating layer of SiO₂. By a sophisticated lithographic and evaporating technique two gold wires were applied in a way that their ends were separated by only about 10 nm. With alkane dithiols serving as a kind of molecular adhesive, the CdSe nanoparticles out of the solution were fixed to these wires. Thus, the gold wires are totally covered with nanoparticles, some of which are placed right between the gold wires.

The “trick” is now the following: The tunnel current which can flow from one gold tip over the particles into the other gold tip depends drastically on the tunnel distance. As a result, the electrons choose only one single way through the particle, that with the shortest tunnel barrier, whereas other possible paths of current are practically of no importance. This effect has become known for quite some time from scanning tunnel microscopy.

By means of the construction of Alivisatos and McEuen the current I between the gold contacts can be measured as a function of the applied voltage V and a gate voltage V_g applied over the Si substrate. The authors could show that the charge transport through the nanocrystallite is determined by two effects which are due to the small dimensions of the particles. Let us consider two macroscopic semiconductors or metals in electric contact after adjusting the equilibrium: Both solids

have the same electrochemical potential (Fermi level). A single electron can easily be transmitted from one solid to the other one without any perceptible change in the energetics of the system. Such exchange processes in which the natural fluctuation or the dynamic equilibrium between both solids is expressed occur permanently. Let us imagine that the contact takes place between a macroscopic solid (gold wire) and a nanoparticle. By taking off one single electron from the wire, its energy will not be changed. Owing to the very small surface capacity of the nanoparticle (C) there will be a noticeable charge ΔU according to the capacitor law, which will result in an energy increase of ΔE_C [Eqs. (1), (2)].

$$\Delta U = e/C \quad (1)$$

$$\Delta E_C = e^2/2C \quad (2)$$

The Fermi level of the wire must be augmented by applying a voltage of at least ΔU in order to transfer one electron on the particle. This effect is called the Coulomb blockade. Values typical of a particle with a diameter of a few nanometer are to be found in an area of several 10 meV. This phenomenon is amplified especially in semiconductors by the occurrence of the size-quantization effect (SQE). The nanoparticles represent a state of matter in the transition region between solids and molecules, in which the quasi-continuum of the energy bands has dissolved and an energy diagram with discrete molecular-orbital-like levels already exists.

From a molecular point of view it becomes clear that particular minimum voltages have to be applied to the electric contact in order to fill up gradually levels which are separated by a definite energy difference (ΔE_{SQE} ; comparable with the first and the second oxidation or reduction potentials of a molecule). The difference in the electrochemical potential of a nanoparticle with $N+1$ electrons (μ_{N+1}) and one with N electrons (μ_N) is given by Equation (3).

$$\Delta\mu = \mu_{N+1} - \mu_N = \Delta E_C + \Delta E_{SQE} \quad (3)$$

This transport barrier $\Delta\mu$ can be overcome by applying the grid voltage or a bias voltage, as can be seen from Figure 2. In a situation as that shown in Figure 2a there would be no current flow, as the attainable levels of the nanoparticle are populated by electrons. Only after increasing the potential at one end of the wire—that is, by applying an external voltage—can the electron transport take place as shown in Figure 2b. If the voltage is increased up to the level of the next, non-occupied orbital, the current raises abruptly. From this results a staircaselike current–voltage characteristic.

It is also possible to induce current flow by applying a gate voltage, thus lowering the LUMO (lowest unoccupied molecular orbital) in the particle to a degree that the electrons can jump over (Figure 2c). If the gate voltage is further increased in this direction, the former LUMO is now

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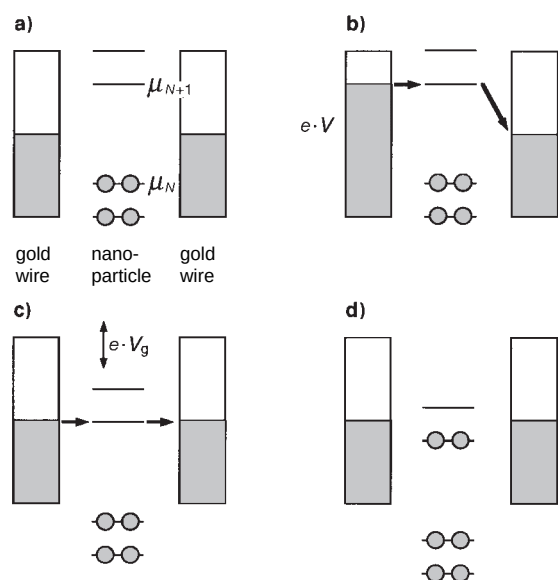


Figure 2. Energy diagram in a single-electron transistor under different conditions of external polarization (see text).

populated by electrons and the current flow breaks down until the next free orbital is brought to the Fermi level of the contact (Figure 2d). The current–voltage curve shows periodical increases and decreases (Coulomb oscillations). Such experiments allow a unique spectroscopy of the electronic states in such nanocrystallites, and they can be considered as an important advance towards molecular electronics.

Same attention should be given to fluorescence spectroscopic investigations on single semiconductor nanoparticles which have also been reported in the recent past.^[10–15] CdS or CdSe particles in extremely thin coating were applied on a quartz sheet which could be moved in the *x,y* plane through a strongly focused laser spot. When the laser beam hits a particle, fluorescence is observed, otherwise there is darkness. Thus, a topography of the sample can be made for which the lateral resolution is not determined by the size of the particles, but by the diameter of the focused laser beam. Then it was possible to approach a position where a particle was detected and to record the focused fluorescence light in spectral decomposition. A fluorescence spectrum of a single CdS particle of approximately 6 nm in size obtained in this way at 15 K is shown in Figure 3.^[14] One can see a very sharp main

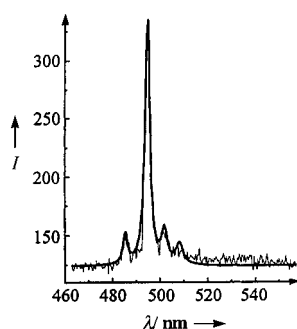


Figure 3. Fluorescence spectrum of a single, 6 nm large CdS particle at 15 K. Intensity *I* is given in arbitrary units.

line and two smaller bands on the long-wavelength side; the distance of the latter exactly conforms to the progression of the LO phonon in CdS. On the short-wavelength side of the main peak there is a further small band which is assigned to the light emission of a biexciton-like state (consisting of two electrons and two holes in one particle).

In such single-particle fluorescence measurements, processes could be detected for

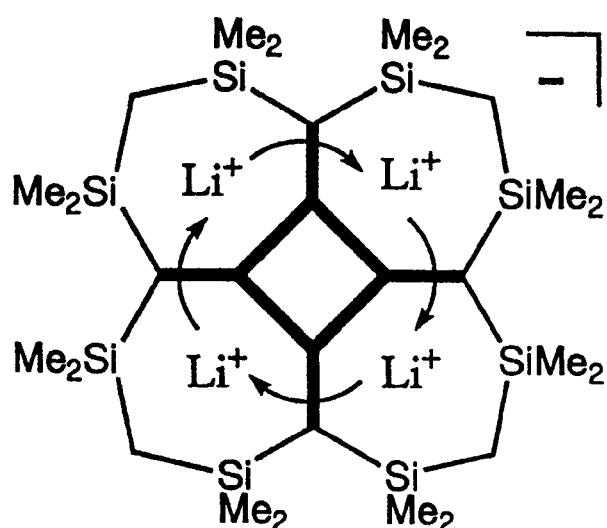
the first time which have been asserted for quite some time to be the explanation for the very complex charge-carrier recombination in such nanoparticles. In accordance with this, there exist “dark states” into which an excited particle can relax and from which no light emission can result. This could be, for instance, an ionized particle or a particle in which the charge carriers are captured in some sort of surface traps. After a certain time the particle can recover from this state, and the radiating recombination with emission of fluorescence quanta starts again. In classical kinetic investigations on an ensemble of particles, this would be observed in a reduced quantum yield and called a competing reaction path. When studying a single particle one can see this competing process in time fluctuations of the fluorescence. For a certain amount of time, the particle is able to fluoresce, then it “switches off” and remains dark for some time then starting again to fluoresce. Thus, one observes the level statistics directly in the time domain. Furthermore, excitation and trapping of electrons can result in the formation of local electric fields which influence the energy of the fluorescence photons. Combined with the mentioned time fluctuations, jumping of the fluorescence bands on the wavelength scale and/or line broadening may be possible. In this connection one may devise interesting modulation experiments on a nanoscopic scale.

These examples show up to which dimensions solids can be diminished and investigated with today’s methods as holders of functions with size-dependent properties. If one thinks of the possibility of ordering nanoparticles in complex superstructures by self-organizing processes,^[16] one recognizes the complexity and the consequences of nanochemistry in modern material research.

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Keywords: clusters • colloids • nanostructures • semiconductors

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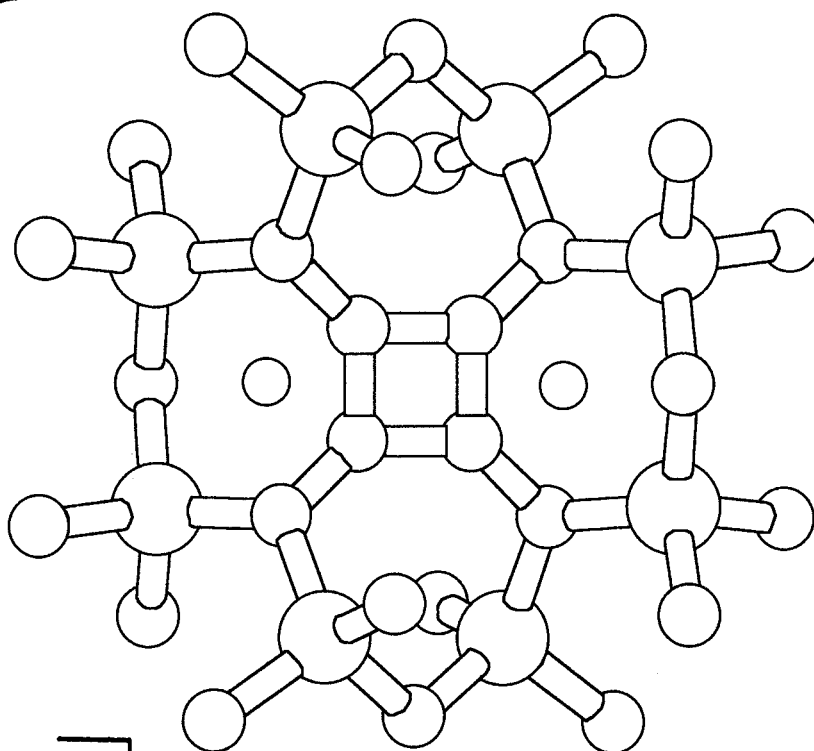


CIP

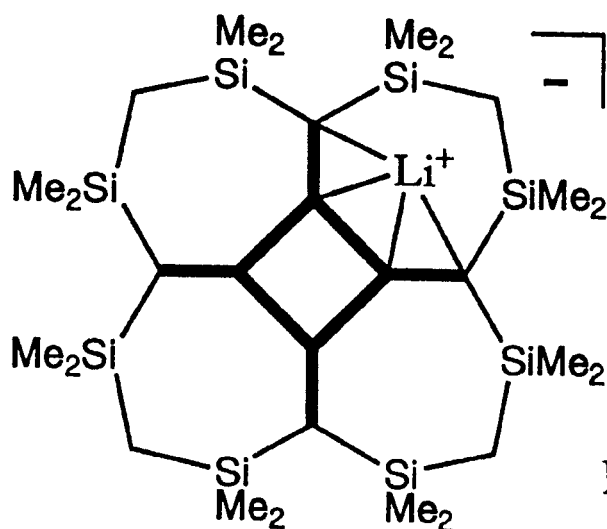
$\text{Li}^+(\text{thf})_n$

SSIP

A novel Li^+ walk (top) on the π -electron system of the dilithium salt of the octasilyl[4]radialene dianion (structure depicted in the center) takes place at 298 K in THF.



The walking Li^+ ion is bound as a contact ion pair (CIP), the other as a solvent-separated ion pair (SSIP).



CIP

$\text{Li}^+(\text{thf})_n$

SSIP

At 173 K the Li^+ walk is suppressed so that Li^+ is fixed at one site on the framework (bottom). Find out more on the following pages.

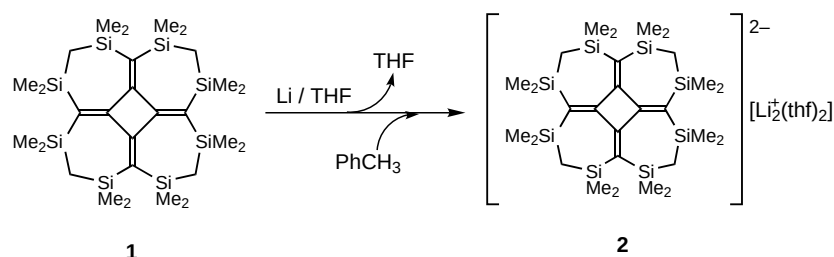
Synthesis and Characterization of the Dilithium Salt of the Octasilyl[4]radialene Dianion: Evidence for a Lithium Walk on the Eight-Center, Ten-Electron π -Electron System**

Akira Sekiguchi,* Tsukasa Matsuo, and Hideki Sakurai

Over the last few years, the structures of various anions in the solid state and in solution have been reported that are either a component of a solvent-separated ion pair (SSIP) or part of a solvent-shared contact ion pair (CIP).^[1] However, in most of these systems, the dynamic behavior of the counteranion in solution has not been appreciably revealed.^[2] We have observed a novel Li^+ ion walk on the π -electron system of the dilithium salt of a [4]radialene dianion. In a solvating medium such as tetrahydrofuran (THF), the two Li^+ ions are not fixed to the π -electron system, and one of the Li^+ ions dissociates to yield an ion pair (CIP and SSIP). Herein, we report the isolation, characterization, and molecular structure of the dilithium salt of the octasilyl[4]radialene dianion, which has as an eight-center, ten-electron π -electron system, on which Li^+ ions undergo a novel walk.

[4]Radialene exhibits a special eight π -electron system. We prepared the [4]radialene dianion from the persilylated [4]radialene (**1**).^[3,4] Reduction of **1** with excess lithium metal in dry oxygen-free THF at room temperature led to the formation of a red solution of the dianion of **1** (Scheme 1).^[5] Crystallization from toluene afforded the air- and moisture-sensitive dark red crystals of the dilithium salt **2**.

The molecular structure of **2** was determined by X-ray diffraction (Figure 1).^[6] The dianion has an inversion center at



Scheme 1. Synthesis of **2**.

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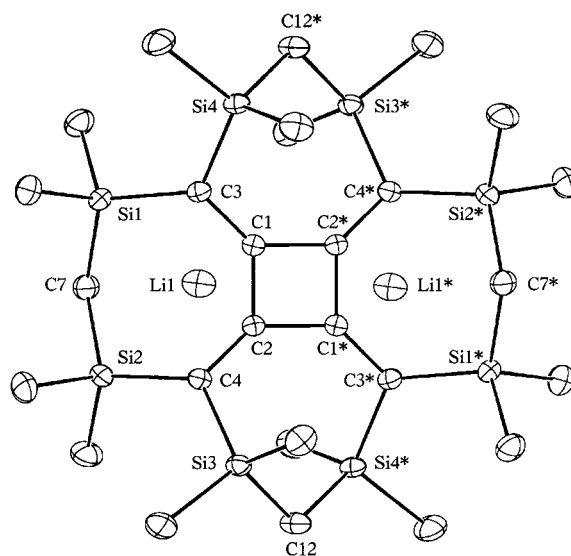


Figure 1. An ORTEP representation of the structure of **2** (THF and hydrogen atoms are omitted for the clarity). Selected bond lengths [Å] and angles [°]: C1–C2 1.473(1), C1–C2* 1.485(1), C1–C3 1.406(1), C2–C4 1.412(1), C3–Si1 1.854(1), C4–Si2 1.851(1), C4–Si3 1.867(1), C3–Si4 1.868(1), Li1–C1 2.246(2), Li1–C2 2.245(2), Li1–C3 2.315(2), Li1–C4 2.309(2); C1–C2–C1* 90.2(1), C2–C1–C2* 89.8(1), C2–C1–C3 134.1(1), C1–C2–C4 133.9(1), C3–C1–C2* 135.0(1), C4–C2–C1* 134.7(1).

the center of the C1–C2–C1*–C2* four-membered ring. The dilithium salt **2** is monomeric and forms bis-contact ion pairs in the crystals. Li1 and Li1* are located above and below the ring, and are bonded to the four carbon atoms of the radialene skeleton as well as to the oxygen atoms of THF molecules. The distances between Li1 and the carbon atoms (C1, C2, C3, and C4) range from 2.245 to 2.315 Å (av 2.279 Å, Figure 2). Two of the seven-membered rings, which lie opposite to each other in the projection shown in Figure 1 and contain the $\text{Me}_2\text{SiCH}_2\text{SiMe}_2$ fragments, exhibit a twist conformation, and the other two exhibit a boat conformation.

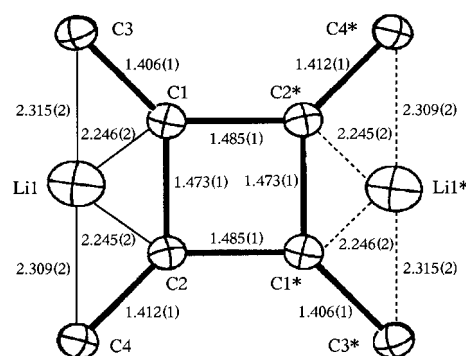


Figure 2. Section from the structure of **2** with selected distances [Å].

The structural features of **2** are quite interesting. The eight carbon atoms that contribute to the π -electron system of the skeleton of **2** are almost coplanar as a consequence of the delocalization of the negative charge. The four-membered ring is planar and almost square, as determined by the internal

bond angles of 89.8 to 90.2° (av 90.0°) and the sum of the bond angles (358.8 to 358.9° for C1, C2, C1*, and C2*). The average length of the exocyclic bonds (C1–C3 and C2–C4) is 1.409 Å and that of the endocyclic bonds (C1–C2 and C1–C2*) is 1.479 Å.

The NMR data on the structure of **2** in [D₈]toluene indicate a very highly symmetric bis-contact ion pair formation in solution. Thus, the ¹H NMR spectrum of **2** in [D₈]toluene shows only one signal for the methyl (δ = 0.32) and methylene (δ = 0.13) groups, respectively, together with the signals for THF. The ⁶Li NMR spectrum of **2** displays only one signal at δ = –0.66, and the ²⁹Si NMR spectrum shows a signal at δ = –11.8, which is shifted upfield relative to that of **1** (δ = –7.8). The ¹³C NMR signal of the exocyclic carbon atoms (δ = 73.2) is shifted significantly upfield relative to that of **1** (δ = 167.5). Thus, the negative charge is largely delocalized on the four exocyclic carbon atoms C3, C4, C3*, and C4*. In contrast, the signal of the endocyclic carbon atoms C1, C2, C1*, and C2* is shifted downfield and appears at δ = 182.8 (δ = 134.7 for **1**). These spectral data suggest that the two Li⁺ ions of **2** are not fixed to the π -electron skeleton, but are fluxional; the two Li⁺ ions are walking on the skeleton on the NMR time scale.^[7]

However, one of the Li⁺ ions dissociates to yield an ion pair in [D₈]THF such that **2** is present as CIP and SSIP. The Li⁺ walk is evidenced in [D₈]THF.^[8] The ⁶Li NMR spectrum of **2** shows two signals with the same intensity at δ = –0.38 and –0.66, and the ratio of the peaks is independent of the concentration (0.03 to 0.13 M). The signal at δ = –0.38 is assigned to the THF-solvated species [Li(thf)_n]⁺, whereas the other signal is assigned to the Li⁺ ion that is bonded to the π -electron system.^[9] The exchange of the two Li⁺ ions was not observed in the temperature range between 173 and 298 K. Thus, one Li⁺ ion of **2** forms a SSIP and the other one forms a CIP in [D₈]THF. Consequently, the skeleton of **2** has a different environment above and below the plane; at room temperature therefore doublets appear in the ¹H NMR spectrum for the methylene protons with a geminal coupling of 12.6 Hz, and two signals for SiMe₂ in the ¹³C NMR spectrum. These spectroscopic data clearly reveal that the Li⁺ of CIP coordinates with one side of the framework and that it can walk freely on the π -electron system of the framework (Figure 3, left).

As the temperature was lowered, the ¹³C NMR signals of the endocyclic and exocyclic carbon atoms broadened and split into two singlets (δ = 185.9, 177.8 and δ = 83.5, 50.2, respectively). The temperature-dependent change of the ¹³C NMR signals of the endocyclic carbon atoms in [D₈]THF must

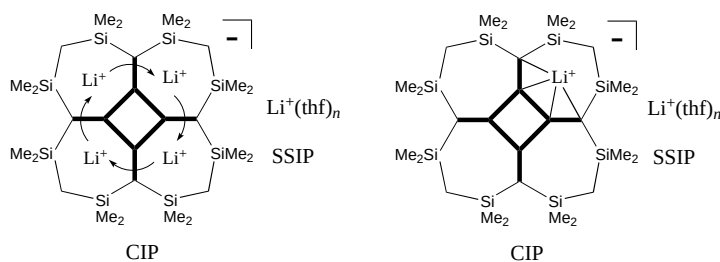


Figure 3. Schematic representation of the Li⁺ walk on the π -electron system of **2** in [D₈]THF at 298 K (left) as well as the position of the Li⁺ ion at 173 K (right).

have resulted from the dynamics of the Li⁺ walk on the [4]radialene framework. Experimental and simulated spectra for the ¹³C NMR signals of the endocyclic carbon atoms are shown in Figure 4. From the Arrhenius and Eyring plots, the

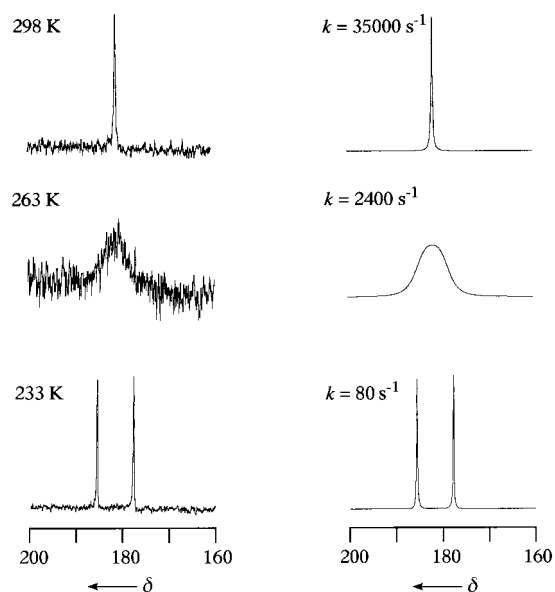


Figure 4. Observed (left) and simulated (right) ¹³C (125 MHz) line shapes of the endocyclic carbon atoms of **2** in [D₈]THF.

values E_a = 13.1 kcal mol^{–1}, $\Delta H^\ddagger$ = 12.6 kcal mol^{–1}, and $\Delta S^\ddagger$ = 4.5 cal mol^{–1} K^{–1} can be estimated for the Li⁺ walk. The present Li⁺ walk is accompanied by the twist-boat interconversion of the two seven-membered rings that contain the Me₂SiCH₂SiMe₂ fragments, which presents a high barrier to internal migrations of the Li⁺ ion. At 173 K, the Li⁺ ion walk of the CIP is suppressed so that Li⁺ is fixed at one site on the framework (Figure 3, right).^[10]

Experimental Section

2: The crystals of **1** (20 mg, 0.03 mmol) and lithium metal (30 mg, 4.3 mmol) were placed in a sealed tube with a magnetic stirrer. After degassing the tube, dry oxygen-free THF (1 mL) was introduced by vacuum transfer and stirred at room temperature to give a red solution of **2** within 1 h. After the solvent was removed in vacuo, degassed toluene was introduced by vacuum transfer. After the lithium metal had been removed from the tube, the solution was cooled to afford dark red crystals of **2** quantitatively. ¹H NMR ([D₈]toluene, 298 K, TMS): δ = 0.13 (s, 8H, CH₂), 0.32 (s, 48H, CH₃), 1.26 (br.s, 8H, THF), 3.46 (br.s, 8H, THF); ¹³C{¹H} NMR ([D₈]toluene, 298 K, TMS): δ = 6.0 (CH₃), 9.5 (CH₂), 25.3 (THF), 69.7 (THF), 73.2 (C), 182.8 (C); ²⁹Si{¹H} NMR ([D₈]toluene, 298 K, TMS): δ = –11.8; ⁶Li{¹H} NMR ([D₈]toluene, 298 K, LiCl in MeOH, external): δ = –0.66.

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- [3] [4]Radialene (**1**) was isolated as yellow crystals in 11% yield by the intramolecular reaction of hexadecamethyl-3,5,8,10,13,15,18,20-octasilacycloicosa-1,6,11,16-tetrayne with $[(C_5H_4Me)Mn(CO)_3]$ (3 molar equiv) by irradiation ($\lambda > 300$ nm) under reflux in THF. However, when one molar equivalent of the manganese complex was used, the octasilyl-substituted trimethylenecyclopentene derivative was obtained in 17% yield. For π -electron systems, such as **1**, derived from silicon-containing macrocyclic polyacetylene, see H. Sakurai, *Pure Appl. Chem.* **1996**, 68, 327. For the trimethylenecyclopentene and its tetraanion tetralithium, see: A. Sekiguchi, T. Matsuo, C. Kabuto, *Angew. Chem.* **1997**, 109, 2572; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2462.
- [4] Spectral data for **1**: m.p. 219–220 °C; ^1H NMR ($[D_1]chloroform$, TMS): $\delta = 0.05$ (s, 8H, CH_2), 0.14 (s, 48H, CH_3); $^{13}C\{^1H\}$ NMR ($[D_1]chloroform$, TMS): $\delta = 2.1$ (CH_3), 10.8 (CH_2), 134.7 (C), 167.5 (C); $^{29}Si\{^1H\}$ NMR ($[D_1]chloroform$, TMS): $\delta = -7.8$.
- [5] The [4]radialene dianion, which was obtained by metalating 1,2-dimethyl-3,4-bismethylenecyclobutene with $nBuLi/KOtBu$ or $nBuLi/N,N,N',N'$ -tetramethylethylenediamine, has been characterized by the quenching experiments, see: W. T. Thorstad, N. S. Mills, D. Q. Buckelew, L. S. Govea, *J. Org. Chem.* **1989**, 54, 773.
- [6] Crystal structure analysis of **2**: A single crystal ($0.35 \times 0.30 \times 0.25$ mm) was sealed in a capillary glass tube for the data collection. Diffraction data were collected at 150 K on a Mac Science DIP2020 Image Plate Diffractometer employing graphite-monochromated MoK_{α} radiation ($\lambda = 0.71073$ Å); $C_{36}H_{72}Li_2O_8Si_8$, $M_r = 767.47$, $a = 9.506(1)$, $b = 22.105(1)$, $c = 11.869(1)$ Å, $\beta = 112.197(1)^\circ$, $V = 2309.20(1)$ Å³, monoclinic, space group = $P2_1/c$, $Z = 2$, $\rho_{calcd} = 1.164$ g cm⁻³. The final R factor was 0.031 ($R_w = 0.038$) for 4208 reflections with $I_o > 2\sigma(I_o)$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101 602. 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] The variable-temperature NMR experiment cannot be conducted in $[D_8]toluene$. When the temperature is lowered, the crystals of the bis-contact ion pair precipitate which hampers the dynamic NMR study.
- [8] Spectral data for **2** in $[D_8]THF$: ^1H NMR ($[D_8]THF$, 298 K, TMS): $\delta = -0.23$ (d, $J = 12.6$ Hz, 4H, CH_2), -0.17 (d, $J = 12.6$ Hz, 4H, CH_2), 0.04 (s, 48H, CH_3); $^{13}C\{^1H\}$ NMR ($[D_8]THF$, 298 K, TMS): $\delta = 6.4$ (CH_3), 6.9 (CH_3), 11.4 (CH_2), 66.8 (C), 180.7 (C); $^{29}Si\{^1H\}$ NMR ($[D_8]THF$, 298 K, TMS): $\delta = -13.5$; $^6Li\{^1H\}$ NMR ($[D_8]THF$, 298 K, LiCl in MeOH, external standard): $\delta = -0.38$, -0.66 .
- [9] The signal at $\delta = -0.38$, which is assigned to the solvated Li^+ ion, becomes more intense on addition of ^6LiBr due to the rapid exchange. However, the intensity of the signal at $\delta = -0.66$ for the Li^+ ion of the CIP remains unchanged because this ion is bound to the π -electron system of the framework.
- [10] The Li^+ ion walk of the CIP is suppressed at 173 K so that Li^+ is fixed at one site of the framework. This gives rise to eight ^{13}C NMR signals for $SiMe_2$ and three methylene groups ($\delta = 9.7$, 10.4, and 11.4), two endocyclic carbons ($\delta = 185.9$ and 177.8), and two exocyclic carbons ($\delta = 83.5$ and 50.2). In the ^{29}Si NMR spectrum, four signals were observed at $\delta = -15.7$, -14.3 , -12.6 , and -11.6 .

$[(CO)_5Cr)_6Ge_6]^{2-}$, A Molecular Organometallic Derivative of the Unknown Zintl Ion $[Ge_6]^{2-}$

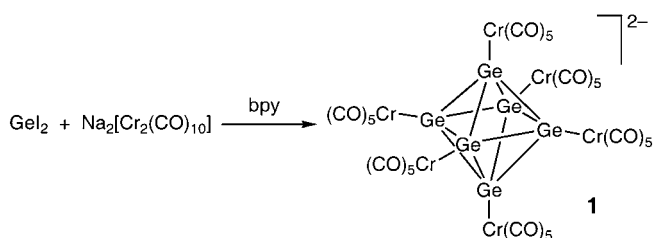
Peter Kircher, Gottfried Huttner,* Katja Heinze, and Gerd Renner

Dedicated to Professor Manfred Weidenbruch on the occasion of his 60th birthday

The synthesis of $[(CO)_5Cr)_6Sn_6]^{2-}$ ^[1] illustrated that clusters composed exclusively of main group elements could be prepared from organometallic precursors; the resulting cluster is embedded in a matrix of organometallic protective groups. At the same time it was shown that octahedral clusters, which obey the usual counting rules^[2] in terms of the structure and the electron count, were not restricted to boron^[3] in main group chemistry. Whereas the $[Sn_6]^{2-}$ ion^[1] protected by organometallic groups was initially the only example for this, in the meantime octahedral clusters that obey the counting rules^[2] have been established as building blocks of solids. Both $[Ga_6]^{8-}$ and $[Ti_6]^{8-}$ exhibit octahedral structures with 14 framework electrons.^[4] Two-dimensional corner-sharing indium octahedra are present in Rb_2In_3 .^[4] The phase KTI contains tetragonally compressed thallium octahedra with 12 framework electrons.^[4] All these octahedral clusters are built from elements of Group 13.^[5, 6] For elements of other groups the only example to date was the $[Sn_6]^{2-}$ ion, which was protected by organometallic groups.^[1]

The reaction principle based on the treatment of pentacarbonylchromate with element halides had with $K_2[Cr(CO)_5]$ and $SnCl_2$ led to the octahedral cluster $[(CO)_5Cr)_6Sn_6]^{2-}$.^[1] The transfer of this principle to other pentacarbonylmetalates and other element halides appeared straightforward; however, numerous attempts proved unsuccessful. We have now found that the reaction of GeI_2 with $Na_2[Cr_2(CO)_{10}]$ leads to the desired anionic cluster $[(CO)_5Cr)_6Ge_6]^{2-}$ (**1**) provided that 2,2'-bipyridine is added to the reaction mixture (Scheme 1).

After the reaction 2,2'-bipyridine (bpy) is mainly contained as ligand in the main product $[(CO)_5Cr)_2Ge_2(bpy)]$.^[7] The role of the 2,2'-bipyridine in the formation of **1** is not clear; however, without it compound **1** is not obtained. Since the



Scheme 1. Synthesis of **1**. bpy = 2,2'-bipyridine.

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reaction of the starting materials to give **1** must involve electron transfer steps, it seems plausible to assume that the ligand functions as a redox mediator. However, 2,2'-bipyridine could also coordinate intermediary precursors as a chelate ligand and thus stabilize those that are required for the construction of the cluster.^[8] The red Ph_4P salt of **1** can be obtained in analytically pure form as single crystals. The positions and the intensities of the CO bands in the IR spectrum resemble those of the analogous $[\text{Sn}_6]^{2-}$ derivative, which indicates that the two compounds have a similar structure; this was subsequently confirmed by an X-ray crystal structure analysis (Figure 1).^[9, 10]

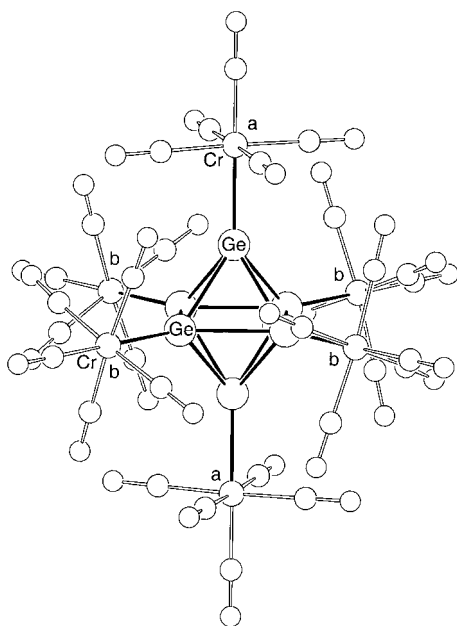


Figure 1. View of the structure of **1** in the crystal. The labeling of the germanium atoms follows the symbolic designation (a, b) of the chromium atoms. The anion has crystallographic D_4 symmetry. The apical building blocks Ge_a and Cr_a lie on the C_4 axis, the equatorial building blocks Ge_b and Cr_b on two of the four C_2 axes in the equatorial plane. Selected distances [pm] and angles [$^\circ$]: $\text{Ge}_a\text{--Cr}_a$ 242.6(2), $\text{Ge}_b\text{--Cr}_b$ 239.5(2), $\text{Ge}_a\text{--Ge}_b$ 254.1(1), $\text{Ge}_b\text{--Ge}_b$ 252.5(2); $\text{Ge}_b\text{--Ge}_a\text{--Cr}_a$ 134.64(3), $\text{Ge}_a\text{--Ge}_b\text{--Cr}_b$ 135.36(3), $\text{Ge}_b\text{--Ge}_b\text{--Cr}_b$ 135.00.

The cluster **1** has crystallographic D_4 symmetry (Figure 1), the $[\text{Ph}_4\text{P}]^+$ ions crystallographic S_4 symmetry. The distances between equatorial and axial germanium atoms are practically equal to the ones between the equatorial germanium atoms (Figure 1). The Ge–Cr distances also do not differ significantly. The Ge–Ge–Cr angles are 135° ; the value that is expected for an ideal octahedral structure with ideal radial orientation of the Ge–Cr bond. In contrast to $[\{(\text{CO})_5\text{Cr}\}_6\text{Sn}_6]^{2-}$ in which the crystallographic C_i symmetry enforces an eclipsed orientation of the equatorial carbonyl groups of the three pairs of $[(\text{CO})_5\text{Cr}]$ entities which are *trans* to each other, these groups adopt a staggered arrangement in **1**. The Ge–Cr distances correspond to those determined for pentacarbonylchromium germylene complexes $[\{(\text{CO})_5\text{Cr}\}\text{--GeR}_2]$ and their base adducts.^[11] The Ge–Ge distances are

similar to those in organogermanium cage compounds (Figure 1): In the prismatic cage of R_6Ge_6 ($\text{R} = \text{CH}(\text{SiMe}_3)_2$), the Ge–Ge distances range between 252 and 258 pm.^[12] Compared with $[\text{Ge}_9]^{4-}$ (Ge–Ge 252–300 pm^[4, 13]), a Zintl ion, which, like the $[\text{Ge}_6]^{2-}$ ion in **1**, obeys the cluster counting rules in terms of its structure and electron count, the Ge–Ge distances in **1** are short. Also in anionic germanium clusters whose electron count deviates from the ideal value, the average Ge–Ge distances are longer than in **1** ($[\text{Ge}_4]^{2-}$: 277–279, $[\text{Ge}_9]^{2-}$: 254–286, $[\text{Ge}_9]^{3-}$: 253–327 and 249–332, $[\text{Ge}_{10}]^{2-}$: 251–295 pm).^[4, 14] Similarly in the heterometallic cluster $[\text{Ge}_9(\mu_{10}\text{--Ge})\text{Ni}(\text{PPh}_3)]^{2-}$, which contains a germanium atom in the center, the distances between the germanium atoms at the surface are longer on average (Ge–Ge 274 pm).^[15]

In accord with the normal to short bond lengths in **1** and the remarkable thermal stability of $[\text{Ph}_4\text{P}]_2[\{(\text{CO})_5\text{Cr}\}_6\text{Ge}_6]$ (decomposition at 105°C), clusters of this kind are intrinsically stable. However, since **1** only forms if 2,2'-bipyridine is present in the reaction mixture, the route according to which such clusters are formed from building blocks protected by organotransition metal groups is so complex that a generalization of this synthetic method is not possible without further detailed investigation.

Experimental Section

All experiments were carried out with Schlenk techniques under an argon atmosphere with exclusion of moisture and oxygen. All solvents were used freshly distilled. NMR: Bruker-Avance-DPX-200, $T = 298\text{ K}$, ^1H NMR (200.13 MHz), $^{13}\text{C}\{^1\text{H}\}$ NMR (50.323 MHz), the solvent was used as internal standard, TMS as external standard: $[\text{D}_6]\text{DMSO}$ ($\delta(^1\text{H}) = 2.49$, $\delta(^{13}\text{C}) = 39.7$), $^{31}\text{P}\{^1\text{H}\}$ NMR (81.015 MHz), external standard 85% H_3PO_4 . IR: Bruker-FT-IR-IFS-66, CaF_2 cells. C,H analysis: Mikroanalytisches Labor, Organisch-chemisches Institut der Universität Heidelberg.

1: GeI_2 (326 mg, 1 mmol) was added in one portion to a stirred solution of $\text{Na}_2[\text{Cr}_2(\text{CO})_{10}]$ (430 mg, 1 mmol) in THF (50 mL). After 5 min, the red solution was treated with 2,2'-bipyridine (156 mg, 1 mmol), and immediately thereafter it was filtered through Kieselgur and concentrated to 3 mL under high vacuum. The dark red residue was purified by chromatography on silica gel (20 cm, $\varnothing = 3\text{ cm}$, diethyl ether). $[\text{Cr}(\text{CO})_6]$, $[(\text{CO})_4\text{Cr}(\text{bpy})]$, and $[\{(\text{CO})_5\text{Cr}\}_2\text{Ge}(\text{bpy})]$ were separated by using diethyl ether and THF as eluent.^[7] The Na salt **1** remained as a dark red band on the column and was subsequently eluted with ethanol. The ethanol solution was treated with solid $[\text{Ph}_4\text{P}]\text{Cl}$ (750 mg, 2 mmol). The Ph_4P salt of **1** precipitated immediately as an orange powder, and was separated from the reaction solution by using a G4 frit. The orange solid was washed with ethanol ($2 \times 5\text{ mL}$) and diethyl ether ($2 \times 5\text{ mL}$), and then dried under high vacuum. The Ph_4P salt of **1** was dissolved on the frit in dimethyl acetamide (DMA; 3 mL) and layered with ethanol (50 mL). This gave analytically pure red single crystals that were suitable for X-ray crystal structure analysis. Yield of crystalline material 250 mg (11%). ^1H NMR: $\delta = 8.01\text{--}7.67$ (m, H_{arom}); ^{13}C NMR: $\delta = 222.2$ (s, CO_{ax}), 217.0 (s, CO_{eq}), 136.2 (s, C_{para}), 135.4 (d, C_{ortho} , $^2J_{\text{C,P}} = 10\text{ Hz}$), 131.3 (d, C_{meta} , $^3J_{\text{C,P}} = 13\text{ Hz}$); ^{31}P NMR: $\delta = 23.5$ (s); IR (DMA): $\tilde{\nu}_{\text{CO}} = 2043\text{ vs.}, 2010\text{ w.}, 1951\text{ vs.}, 1910\text{ s cm}^{-1}$; C,H analysis calcd: C 41.33, H 1.78; found: C 41.27, H 2.01.

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Partially Oxidized Zintl Ions?

The Characterization of

$[(\mu_3\text{-OH})(\mu_3\text{-O})_3(\text{OEt})_3\{(\text{CO})_5\text{W}\}_7\text{Sn}_7]^{2-**}$

Peter Kircher, Gottfried Huttner,* Laszlo Zsolnai, and Alexander Driess

Dedicated to Professor Heribert Offermanns on the occasion of his 60th birthday

The characterization of mixed-valent and subvalent compounds is an important key principle in the search for solid phases with unusual material properties.^[1] Molecular analogues of such subvalent phases are only found in rare cases in the chemistry of main group elements in the homoatomic aggregates $[\text{E}_x]^{m-}$ ^[2] denoted as Zintl ions and in the isopoly-anions $[\text{E}_y]^{n+}$.^[3] Subvalent compounds are also known in the form of partially oxidized derivatives of molecular element modifications (e.g. $\text{P}_4/\text{P}_4\text{S}_3$). A new class of compounds of this type would be generated if Zintl ions $[\text{E}_x]^{m-}$ could be partially oxidized, in which case—as in P_4S_3 —some of the element–element bonds would be retained. However, a direct transformation of Zintl ions in this sense has not been achieved so far.

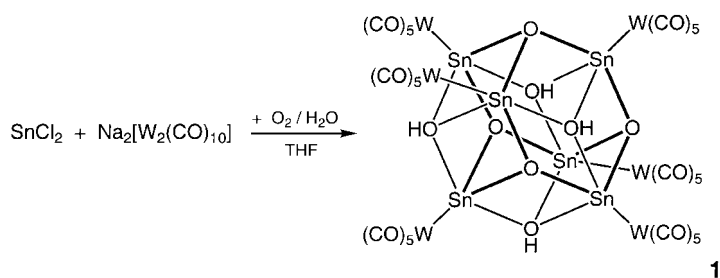
The characterization of $[(\text{CO})_5\text{Cr}]_6\text{Sn}_6]^{2-}$ had shown that a de novo synthesis of Zintl ions from mononuclear precursors may be achieved by using organometallic protective groups.^[4] Furthermore, the preparation of $[(\mu_3\text{-OH})_4(\mu_3\text{-O})_4\{(\text{CO})_5\text{Cr}\}_6\text{Sn}_6]^{5-}$ showed that by analogous syntheses compounds are accessible that can be considered formally as completely oxidized derivatives of Zintl ions. Therefore it seemed appropriate to attempt, under modified conditions, to construct cage compounds that contain within the same molecule building blocks in which the main group elements, as in Zintl ions, are linked directly and building blocks in which the main group elements are bridged by oxygen.

In analogy to the preparation of $[(\mu_3\text{-OH})_4(\mu_3\text{-O})_4\{(\text{CO})_5\text{Cr}\}_6\text{Sn}_6]$ from $\text{K}_2[\text{Cr}(\text{CO})_5]$, SnCl_2 , and H_2O in THF,^[5] SnCl_2 was treated with $\text{Na}_2[\text{W}_2(\text{CO})_{10}]$ in the hope that the $[(\text{CO})_5\text{W}]$ derivatives of the desired cage compounds and clusters would be more stable than their $[(\text{CO})_5\text{Cr}]$ analogues. We finally obtained a few crystals of the compound $[(\mu_3\text{-OH})_4(\mu_3\text{-O})_4\{(\text{CO})_5\text{W}\}_6\text{Sn}_6]$ (**1**), the $[(\text{CO})_5\text{Cr}]$ analogue of which is already known (Scheme 1).^[5]

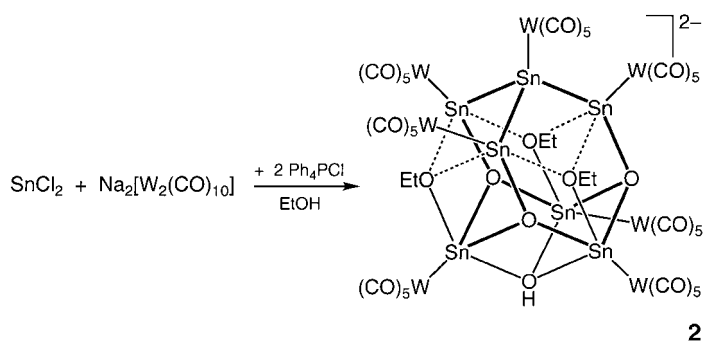
An aggregate, which, unlike the tin(II) compound **1**, also contains tin in a lower oxidation state, was first obtained when the orange solution of $\text{Na}_2[\text{W}_2(\text{CO})_{10}]$ in ethanol was treated with SnCl_2 . This led spontaneously to a red solution, from which, after the addition of a solution of $[\text{Ph}_4\text{P}]\text{Cl}$ in ethanol, the phosphonium salt of $[(\mu_3\text{-OH})(\mu_3\text{-O})_3(\text{OEt})_3\{(\text{CO})_5\text{W}\}_7\text{Sn}_7]^{2-}$ (**2**) precipitated as an orange solid (Scheme 2).

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Scheme 1. Synthesis of **1**.



Scheme 2. Synthesis of **2**.

The structure of **1** closely resembles that of known structures of different derivatives of $[(\mu_3\text{-OR})_4(\mu_3\text{-O})_4\text{Sn}_6]$.^[5–7] The structure of **2**^[6,7] is a modification of that of the known structure of **1**, in which an $\mu_3\text{-O}$ building block is replaced by a $\mu_3\text{-Sn}\{\text{W}(\text{CO})_5\}$ unit. At the same time the charge of the cage **2** is -2 , so that formally the oxygen atom with its six electrons is replaced by the isoelectronic Sn^{2-} ion. Thus, the cage comprises an Sn_4 unit in the top half (Sn_a and Sn_b)^[8] and a $[(\mu_3\text{-OH})(\text{OEt})_3\{\text{Sn}_3\text{O}_3\}]$ unit in the bottom half (Sn_c).

Owing to the different bonding of the tin centers in the cage of **2**, different Sn–W distances are displayed for $\text{Sn}_a\text{--W}_a$ (280 pm) and for $\text{Sn}_b\text{--W}_b/\text{Sn}_c\text{--W}_c$ (272–275 pm, Figure 1). Whereas in cage **1** six chemically equivalent tin(II) centers are present whose electron requirement is compensated by symmetrical $\mu_3\text{-OH}$ and $\mu_3\text{-O}$ bridges, the electron requirement and Lewis acidic character of the three kinds of tin centers in **2** differ because of the different oxidation states. Compound **1** contains four $\mu_3\text{-OH}$ groups, in contrast, **2** contains one $\mu_3\text{-OH}$ and three OEt groups. The $\mu_3\text{-OH}$ group in the bottom half of the cage of **2** symmetrically bridges the three tin centers in this part of the cage. In contrast the OEt groups are almost terminally bound (Figure 1). The interactions to the tin centers in the top half of the compound (Sn_b) can, on the basis of the longer Sn–O distances, be considered as comparatively weak (Figure 1). The frameworks of **1** and **2** are very similar, are drumlike in form^[9] and can, as the formulas show, be delineated to an adamantane structure. On the basis of the Zintl–Klemm concept this is expected for the replacement of $\mu_3\text{-O}$ (**1**) by $\mu_3\text{-Sn}^{2-}$ (**2**).^[10] The mixed-valent aggregate **2** (average oxidation state $+8/7$ for Sn) can be considered as the first in a series of compounds that can be derived by partial oxidation of Zintl ions protected by organometallic groups.

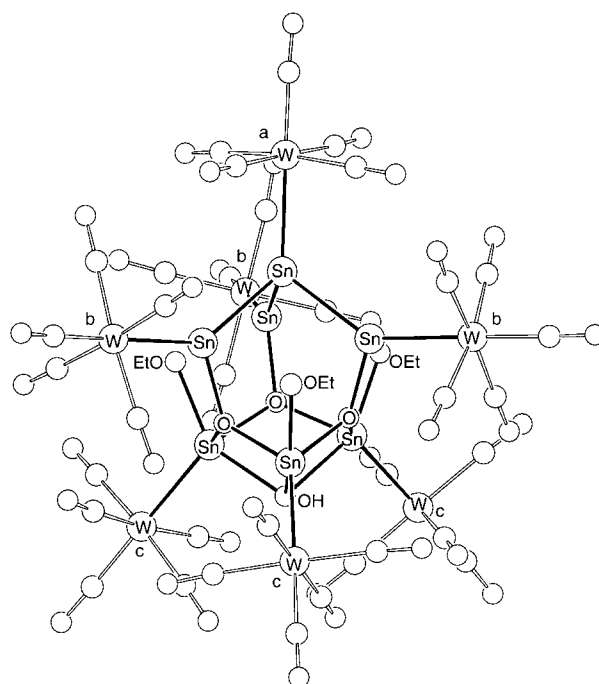


Figure 1. View of the structure of **2** in the crystal. The labeling of the tin centers follows the symbolic designation (a–c) of the tungsten centers. Selected distances [pm]: $\text{Sn}_a\text{--W}_a$ 279.6(1), $\text{Sn}_b\text{--W}_b$ 274.2–275.2(2), $\text{Sn}_c\text{--W}_c$ 271.7–274.0(1), $\text{Sn}_a\text{--Sn}_b$ 279.1–280.1(2), $\text{Sn}_c\text{--}(\mu_3\text{-OH})$ 228.6–234.0(9), $\text{Sn}_b\text{--}(\mu_3\text{-O})$ 205–208(1), $\text{Sn}_c\text{--}(\mu_3\text{-O})$ 203–207(1), $\text{Sn}_b\text{--}(\text{OEt})$ 257–322, $\text{Sn}_c\text{--}(\text{OEt})$ 208–214(1).

Experimental Section

All experiments were carried out with Schlenk techniques under an argon atmosphere with exclusion of moisture and oxygen. NMR: Bruker-Avance-DPX-200, $T = 298\text{ K}$, ^1H NMR (200.13 MHz), $^{13}\text{C}\{^1\text{H}\}$ NMR (50.323 MHz), the solvent was used as internal standard, TMS as external standard: $[\text{D}_6]\text{acetone}$ ($\delta(^1\text{H}) = 2.04$, $\delta(^{13}\text{C}) = 206.18$ and 29.8); $^{31}\text{P}\{^1\text{H}\}$ NMR (81.015 MHz), external standard 85% H_3PO_4 . IR: Bruker-FT-IR-IFS-66, CaF_2 cells. C,H analysis: Mikroanalytisches Labor, Organisch-chemisches Institut der Universität Heidelberg.

1: Compound **1** was prepared analogously to $[(\mu_3\text{-OH})_4(\mu_3\text{-O})_4\{(\text{CO})_5\text{Cr}\}_6\text{Sn}_6]$.^[5a] Single crystals suitable for X-ray structure analysis were obtained only on one occasion. The yield of crystalline material was about 60 mg (2%); IR (THF): $\tilde{\nu}_{\text{CO}} = 2071\text{ m}$, 1953 vs., 1932 vs cm^{-1} .

2: SnCl_2 (190 mg; 1 mmol) was added under stirring to a solution of $\text{Na}_2[\text{W}_2(\text{CO})_{10}]$ (694 mg, 1 mmol) in ethanol (50 mL). The solution spontaneously turned dark red. After 30 min, it was filtered through Kieselgur. Addition of a solution of $[\text{Ph}_4\text{P}]\text{Cl}$ (150 mg, 0.4 mmol) in ethanol (5 mL) to the resulting clear, dark red solution led to the immediate formation of an intense orange precipitate of $\text{2} \cdot [\text{Ph}_4\text{P}]_2$, which was separated on a frit (G4), washed with diethyl ether ($3 \times 10\text{ mL}$), and dried in high vacuum. The Ph_4P salt of **2** was dissolved in THF (3 mL) on the frit and layered with ethanol (50 mL). Orange single crystals were obtained that were suitable for crystal structure analysis. Yield of crystalline material: 360 mg (9%). ^1H NMR: 7.95–7.87 (m, 40H, H_{arom}), 4.27 (q, 6H, OCH_2), 1.56 (t, 9H, CH_3); ^{13}C NMR: 136.52 (s, C_{para}), 135.8 (d, C_{ortho} , $^2J_{\text{C,P}} = 9\text{ Hz}$), 131.5 (d, C_{meta} , $^3J_{\text{C,P}} = 13\text{ Hz}$), 61.9 (s, OCH_2), 19.8 (s, CH_3); ^{31}P NMR: 24.3 (s); IR (THF): $\tilde{\nu}_{\text{CO}} = 2066\text{ w}$, 2054 w, 2044 w, 1941 vs., 1918 vs cm^{-1} ; CH analysis: calcd: C 26.88, H 1.42; found C 25.02, H 1.55.

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A Structural Model for [Fe]-Only Hydrogenases**

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Hydrogenases are enzymes that are capable of catalyzing the reversible oxidation of dihydrogen. They can be divided into two main groups, based on the metals in the enzyme: [Fe]-only hydrogenases and [NiFe]-hydrogenases.^[1] FTIR spectroscopy in combination with a crystal structure determination of the enzyme isolated from *Desulfovibrio gigas* has shown that the active site of [NiFe]-hydrogenases contains the dinuclear unit $[(Cys-S)_2Ni(\mu_2-S-Cys)_2Fe(CO)(CN)_2]$.^[2,3] The publication of the structure of this novel heterodinuclear active site with the biologically uncommon ligands CO and CN^[2,3] has been an incentive for the synthesis of new compounds that could serve as structural models for hydrogenases.^[4] The [Fe]-only hydrogenases contain only iron as the metal constituent. Unfortunately the structure of an [Fe]-only hydrogenase has not yet been determined, and also the composition of the H₂-activating site is still unknown: the reported iron contents vary between three and six Fe atoms per molecule.^[5] Interestingly, a similar architecture has been proposed for the active site of both [NiFe]- and [Fe]-hydrogenases.^[3,5]

We now report the first dinuclear iron(II) compound, which can be regarded as a promising first generation structural model for [Fe]-only hydrogenases. The synthesis and crystallographic characterization of this mixed-spin, dinuclear iron(II) complex, which contains sulfur bridges and terminal carbon monoxide ligands, is described. The compound was synthesized from a mixture of $[Fe^{II}(dsdm)]_2$ ($H_2dsdm = N,N'$ -dimethyl- N,N' -bis(2-sulfanylethyl)ethylenediamine) and $K[HFe(CO)_4]$ in the presence of 2-bis(sulfanylethyl)sulfide (H_2bmes), which was heated under reflux. X-ray quality crystals of the product $[Fe^{II}(dsdm)(bmes)Fe^{II}(CO)_2]$ (**1**) were readily obtained by addition of diethyl ether to a solution of the complex in toluene/ethanol.

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A projection of the structure of the dinuclear iron(II) compound is shown in Figure 1. The structure consists of two octahedrally coordinated iron(II) atoms, each with different

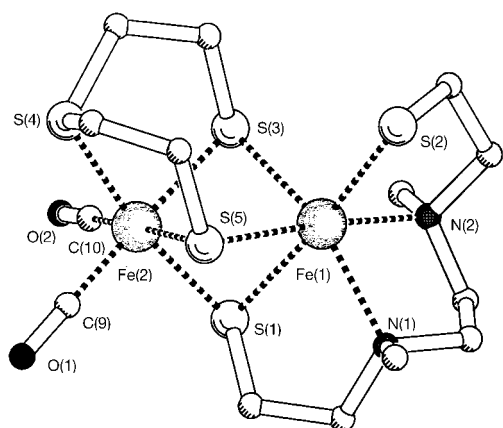


Figure 1. Schematic representation of the structure of **1** in the crystal (hydrogen atoms omitted for clarity). Selected bond lengths[Å] and angles[°]: Fe(1)–S(1) 2.5451(8), Fe(1)–S(2) 2.3658(8), Fe(1)–S(3) 2.5002(8), Fe(1)–S(5) 2.5053(8), Fe(1)–N(1) 2.279(2), Fe(1)–N(2) 2.307(2), Fe(2)–S(1) 2.3158(8), Fe(2)–S(3) 2.3517(8), Fe(2)–S(4) 2.2553(8), Fe(2)–S(5) 2.3387(8), Fe(2)–C(9) 1.772(3), Fe(2)–C(10) 1.771(3), O(1)–C(9) 1.145(4), O(2)–C(10) 1.145(3); S(1)–Fe(1)–S(2) 174.97(3), S(1)–Fe(1)–S(3) 75.32(3), S(1)–Fe(1)–S(5) 78.22(2), S(2)–Fe(1)–S(3) 100.33(3), S(2)–Fe(1)–S(5) 99.16(3), S(3)–Fe(1)–S(5) 86.60(3), S(1)–Fe(2)–S(3) 82.67(3), S(1)–Fe(2)–S(4) 169.21(3), S(1)–Fe(2)–S(5) 86.40(3), S(3)–Fe(2)–C(9) 175.74(10), Fe(2)–C(9)–O(1) 177.9(3), Fe(2)–C(10)–O(2) 178.7(3).

ligand environments. Fe(1) is coordinated to the ligand dsdm and the two thiolate sulfur atoms from bmes, resulting in an FeN₂S₄ chromophore. Fe(2) is bound to the ligand bmes, to two terminally coordinating carbon monoxide groups, and to one of the thiolate sulfur atoms from dsdm, resulting in a FeC₂S₄ chromophore. The two octahedra face-share through three asymmetric μ_2 -thiolato bridges. The dinuclear molecule is electronically neutral, and therefore both irons should be divalent.

The bond lengths of approximately 2.50 Å between the bridging thiolate ligands and Fe(1) are considerably longer than those to Fe(2), which are in the order of 2.35 Å. These differences probably originate from the different spin states of the Fe^{II} atoms: Fe(1) is high-spin and Fe(2) is low-spin. The bond lengths are comparable to those in the trinuclear complex [(OC)₃Fe^{II}(SPh)₃Fe^{II}(SPh)₃Fe^{II}(CO)₃].^[6] The low-spin state of Fe(2) is a result of the influence of the strong CO ligands, which generally invoke a low-spin state. The Fe(1)–Fe(2) distance of 3.0747(7) Å implies no direct metal–metal bonding between the iron atoms,^[7] which is confirmed by magnetic susceptibility measurements.^[8]

Compared to the starting material, the high-spin complex [Fe(dsdm)]₂,^[9] the coordination sphere of Fe(1) in **1** has changed from trigonal bipyramidal to octahedral geometry by addition of an extra bridging dithiolato ligand. The Fe(2)–C distances of 1.771(3) and 1.772(3) Å and the C–O distances of 1.145 Å with Fe–C–O angles of 177.9(3)° and 178.7(3)° are comparable to those found in the octahedral complex [Fe^{II}(CO)₂(tdtt)] (tdtt = 2,3,8,9-dibenzo-1,4,7,10-tetrathia-decane).^[10]

The IR spectrum of the compound in the solid state reveals strong absorption bands for the carbonyl ligands at 2011 and 1957 cm^{−1}, well within the range observed for [Fe]-only hydrogenases. The postulated spin states of the iron(II) atoms were verified by Mössbauer spectroscopy. A Mössbauer spectrum recorded at room temperature showed two doublets of equal intensity but with different isomer shifts and quadrupole splittings, and confirmed the presence of two distinct Fe^{II} atoms (Figure 2). An isomer shift of 0.308 mm s^{−1} ($\Delta E_O = 0.637$ mm s^{−1}) is observed for the low-spin iron(II) atom, while an isomer shift of 1.083 mm s^{−1} ($\Delta E_O = 3.368$ mm s^{−1}) is observed for the high-spin iron(II) atom. Similar results have also been reported for other mixed-spin iron complexes.^[6a, 11]

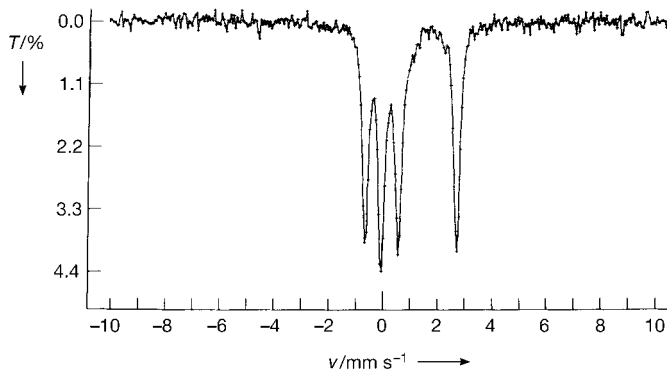


Figure 2. Zero-field Mössbauer spectrum of **1** at room temperature.

In conclusion, the dinuclear iron complex presented here is the first example of a biomimetic iron compound, which can be regarded as a first generation model for the class of [Fe]-only hydrogenases. The complex incorporates both relevant carbon monoxide ligands, and three bridging thiolato ligands which could conceivably be present in the active site of these enzymes. Furthermore, the presence of a histidine group near to one of the iron(II) atoms in the H cluster in [Fe]-only hydrogenases is mimicked in complex **1** by the two amine nitrogen atoms in the dsdm ligand. Finally, the combination of two different, but related ligands might be useful as a new approach for the synthesis of other asymmetric dinuclear active sites, such as those in [NiFe]-hydrogenases, urease, and phosphatases.

Experimental Section

The compound K[HFe(CO)₄] was prepared according to the literature,^[12] the reaction time, however, was extended from 30 min to 16 h.

A solution of K[HFe(CO)₄] (1.92 mmol) in EtOH (10 mL) was added to a suspension of [[Fe(dsdm)]₂] (0.48 mmol) and bis(2-sulfanylethyl)sulfide (0.96 mmol) in toluene (10 mL).^[13] The resulting mixture was then heated under reflux for 4 h. The solution was cooled and filtered to remove any impurities. Diethyl ether was carefully added without disturbing the solution, and the two-layer system was left to stand at room temperature. After several days, hexagonal orange-brown crystals were formed (yield 44 %). Elemental analysis calcd for C₁₄H₂₆Fe₂N₂O₂S₅: C 31.95, H 4.98, N 5.32, S 30.45; found: C 31.32, H 4.98, N 5.23, S 30.93; IR(KBr): $\tilde{\nu}$ = 2011 (C=O), 1957 (C=O) cm^{−1}; Vis-NIR (solid-state; D₂ lamp): λ = 308, 347, 764, 1066 nm.

X-ray structure analysis of **1**: C₁₄H₂₆Fe₂N₂O₂S₅, *M*_r = 526.37, monoclinic, *P*2₁/c, *a* = 12.502(2), *b* = 7.8709(5), *c* = 22.277(4) Å, β = 108.639(13)°, *V* = 2077.1(5) Å³, *Z* = 4, ρ_{calcd} = 1.684 g cm^{−3}, *T* = 150(2) K, ($\sin \theta/\lambda$)_{max} =

0.649 Å⁻¹, orange-brown hexagonal plates (0.25 × 0.5 × 0.5 mm³), 8091 measured reflections, 4746 unique, ($R_{\text{int}} = 0.030$), R values ($I > 2\sigma I$): $R1 = 0.0346$, $wR2 = 0.0640$, all data: $R1 = 0.0588$, $wR2 = 0.0713$. Diffractometer: Enraf-Nonius CAD4T with rotating anode (MoK α , $\lambda = 0.71073$ Å). Structure solution with Patterson methods (DIRDIF-96).^[14] Structure refinement with SHELXL-97 against F^2 ,^[15] 330 parameters, no restraints. Non-hydrogen atoms were refined with anisotropic temperature parameters, hydrogen atoms were refined freely with isotropic temperature parameters. Absorption correction with Psi-scans ($\mu = 1.911$ mm⁻¹, 76–98% transmission). Structure graphics were performed with the program PLATON,^[16] and the symmetry was checked. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101 009. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Differences Between Gas-Phase and Solid-State Molecular Structures of the Simplest Phosphonium Ylide, Me₃P=CH₂**

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Dedicated to Professor Hubert Schmidbaur

There is still no reliable structural determination of the simplest isolable phosphonium ylide Me₃P=CH₂. This is surprising as ylides are very important reagents in chemistry,^[1,2] and Me₃P=CH₂ was first prepared in a pure form by Schmidbaur and Tronich in 1968.^[3] The main focus of structural investigations of ylides has been the coordination at the carbanion center, which is between tetrahedral and trigonal-planar geometries but not necessarily planar. The degree of flattening is dependent on the electronic nature of the substituents.^[2] We have now observed substantial differences between the ab initio calculated geometry of trimethylmethylenephosphorane, Me₃P=CH₂, and the structure determined by gas-phase electron-diffraction (GED) in 1977.^[4] Moreover, a crystal structure determination has resulted in a geometry compatible with neither of these two structures.

The original GED geometry from 1977 was determined under the assumption of local C₃ symmetry for the C=PMe₃ unit, whereas our new calculations employed theory up to the MP2/6-311G* level and consistently show a global minimum having C_s symmetry (Table 1). Assuming this symmetry for the model used in the GED analysis, we have reanalyzed the data collected in 1977^[1] (see Figure 1 and Table 1). A refinement in the lower symmetry of C_s was feasible with our recently developed improved method of GED analysis (SARACEN,^[5] which is a natural extension of Bartell's "predicate value" and Schäfer's MOCED method).^[6] This avoids the use of simplifying, but unjustified fixed constraints, but instead employs information calculated by ab initio methods as flexible restraints. Thus, based on the sum of our experimental and theoretical knowledge, SARACEN provides us with improved geometries and better estimates of errors. The result for Me₃P=CH₂ is a substantially improved fit on the experimental intensities relative to the old refinement,^[1] and the agreement between refined and calculated

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Table 1. Bond lengths [$\text{\AA}$] and angles [$^\circ$] determined by electron diffraction (GED), ab initio calculations,^[a] and single crystal X-ray diffraction (XRD) of $\text{Me}_3\text{P}=\text{CH}_2$.^[b]

Parameter	GED	MP2/6-311G*		XRD
	$r_d/\text{\AA}$	minimum	TS	
P1–C2	1.656(2)	1.677	1.667	1.678(2)
P1–C5	1.837(6)	1.849	1.813	1.791(2)
P1–C9	1.809(3)	1.817	1.832	1.808(1)
C2–P1–C5	122.4(7)	123.9	110.3	110.7(1)
C2–P1–C9	111.4(13)	110.4	117.5	115.69(6)
C5–P1–C9	101.0(20)	101.7	104.8	105.40(7)
C9–P1–C13(C9')108.3(14)	107.4	100.5	102.9(1)	
P1–C2–H3/4	118.2(18)	117.0	119/121.6	111(2)/118(3)
H3–C2–H4	115.7(20)	116.1	119.3	118(3)
C5–P1–C2–H3/4	$\pm 73.9(30)$	± 72.2	180/0.0	180/40.9

[a] Global minimum and transition state of PCH_2 inversion. [b] In all methods the model had C_s symmetry.

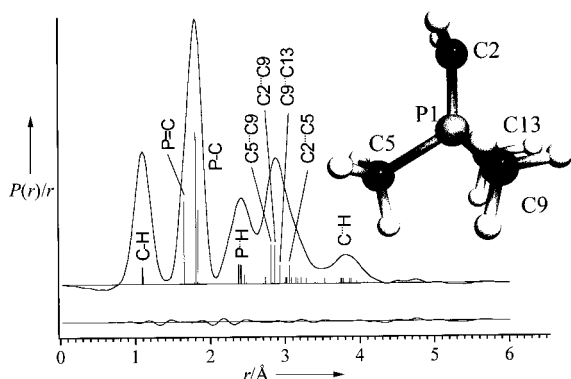


Figure 1. Molecular structure of $\text{Me}_3\text{P}=\text{CH}_2$, and experimental and difference radial distribution and difference curves from the gas-phase electron diffraction refinement. The position of interatomic distances are indicated as vertical lines and assigned.

geometry strongly supports the prediction of the ab initio calculations, justifying the use of calculated restraints.

In the gas phase, the PCH_2 unit is oriented perpendicular to the mirror plane and has a pyramidal geometry, in which the plane of the CH_2 group is at an angle of $27.4(58)^\circ$ to the $\text{P}=\text{C}$ bond.^[8] This compares well with an angle of 26° in $\text{Ph}_3\text{P}=\text{CH}_2$,^[9] which has so far served as the reference structure for phosphonium ylides. The unique $\text{C2}=\text{P}-\text{C5}$ angle is much larger ($122.4(7)$, calcd 123.9°) than the other two $\text{C}=\text{P}-\text{C}$ angles ($111.4(13)$, calcd 110.4°). This discrepancy should be compared to the large differences between the $\text{C}=\text{P}-\text{N}$ angles in $(\text{Me}_2\text{N})_3\text{P}=\text{CH}_2$.^[10] This large deviation from local C_3 symmetry leads to two different $\text{P}-\text{C}_{\text{methyl}}$ bond lengths: $\text{P}-\text{C5}$ is about $0.03 \text{ \AA}$ longer than the two symmetry-equivalent $\text{P}-\text{C}$ bonds.

In the crystal the $\text{Me}_3\text{P}=\text{CH}_2$ molecule adopts a strikingly different geometry^[11] to that in the gas phase (Figures 2 and 3). A crystallographic plane of symmetry passes through the molecules, but one of the ylidic hydrogen atoms is located out of the plane (a disordered position resulting from crystal symmetry, Figure 2c), whereas the other is in the plane. The in-plane angle $\text{C2}=\text{P1}-\text{C5}$ is as much as 11.7° smaller in the crystal ($110.7(1)^\circ$) than in the gas phase, whereas both symmetry-equivalent out-of-plane $\text{C}=\text{P}-\text{C}$ angles ($115.69(6)^\circ$) are

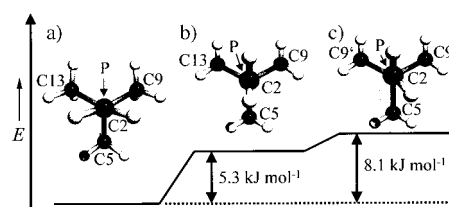


Figure 2. Different orientations of the CH_2 group in $\text{Me}_3\text{P}=\text{CH}_2$ relative to the plane of symmetry (vertical) as shown by a view along the $\text{P}=\text{C}$ bond (the disordered H position is drawn as a faded circle).

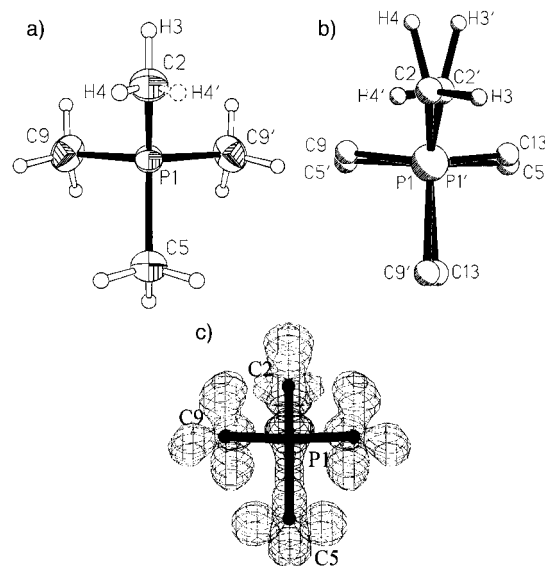


Figure 3. a) Molecular structure of $\text{Me}_3\text{P}=\text{CH}_2$ in the crystal. Labels H4 and H4a mark the positions of the disordered ylidic H atoms. b) One of the rejected disorder models for an alternative interpretation of the crystallographic results.^[12] c) Difference Fourier map as calculated after anisotropic refinement of the P and C positions with contours shown at the $0.43 \text{ e \AA}^{-3}$ level.

larger in the solid state than in the gas phase ($111.4(13)^\circ$). The orientation of the CH_2 group can be taken as a reference for structural comparison: The CH_2 group is bent towards C5 in the gas phase and towards C9 in the solid state (Figure 2). The differences between core angles in the two phases are thus (gas $\rightarrow$ solid) $122.4^\circ \rightarrow 115.7$, $111.4 \rightarrow 115.7$, and $111.4 \rightarrow 110.7$, which represent a pronounced deviation of the solid-state geometry from the ground state. This deviation also affects the $\text{P}-\text{C}-\text{P}$ angles which are 101.0 , 101.0 , and 108.3° in the gas phase, but 105.4 , 105.4 , and 102.9° in the crystal. Hence the whole molecule is distorted. The torsional angles describing the positions of the ylidic H atoms ($\text{C5}-\text{P1}-\text{C2}-\text{H3/4}$: $180/40.9^\circ$), however, are very similar to those found in the crystal structure of $\text{Ph}_3\text{P}=\text{CH}_2$.^[9]

We have also tried to rationalize the unexpected crystal structure in terms of two disordered interpenetrating molecules that are close to the gas-phase geometry but related to one another by reflection or an approximate 120° rotation, as depicted in Figure 3b. However, careful consideration of the anisotropic displacement parameters (ADP) and of the well-determined hydrogen positions make the presence of such disorder improbable, although it cannot be excluded completely at present.^[12]

We were surprised to realize that the geometry of the PC₄ unit in the solid state is very close to that of a transition state computed for rotation–inversion of the ylidic CH₂ group (Table 1); this was obtained by restricting the ylidic H atoms to in-plane positions in C_s symmetry (Figure 2b). This transition state is 5.3 kJ mol^{−1} higher in energy than the calculated ground state. Optimization of the geometry (MP2/6-311G*) with the heavy-atom skeleton angles fixed at the crystal structure values led also to a PCH₂ unit lying in the plane of symmetry, while fixing the torsion angles describing the ylidic H positions to the solid-state values and relaxing the rest of the geometry led to almost the ground-state geometry. Under the action of both constraints (core angles and H-torsion angles as in the crystal) the energy increases by another 2.8 kJ mol^{−1} relative to the transition state, which provides us with an estimate of 8.1 kJ mol^{−1} for the energy difference between a free molecule of Me₃P=CH₂ and one placed in the crystal lattice. This is about the magnitude of deformation energies that can be compensated for by intermolecular forces in crystal lattices.

The crystal structure seems thus to be similar to a transition state (see Table 1 for a comparison of geometries) with ylidic H atoms distorted away from a planar arrangement of the PCH₂ unit. The packing of the molecules does not show any pronounced intermolecular contacts and thus the sum of small interactions must be responsible for the large distortion of the solid-state structure from the ground-state geometry.

The work presented in this paper shows how carefully structural results from one phase (or method) alone need to be interpreted. Only a combination of methods can provide us with realistic pictures of molecular structures. The omnipresent intermolecular forces in crystals should not be underestimated; in this case there are no intermolecular contacts that would normally be described as significant, yet the structural changes on crystallization are profound.

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- [11] A solid–liquid equilibrium was established at 285 K in a sample held in a capillary o.d. 0.16 mm. A single crystal grew on cooling at 1 K h^{−1}. Crystal system monoclinic, space group P2₁/m (the model is essentially unrefinable in the space group P2₁), Z=2, a=6.0864(11), b=7.6153(15), c=6.4565(20) Å, β=92.551(20)°, V=298.96 Å³ at 120 K, cell from 46 reflections (θ range 15–19°). Diffractometer: Stoe-Stadi 4 with Oxford-Cryosystems cryostat, MoK_α-radiation, graphite monochromator, 2θ_{max}=55°, ω scan with on-profile fitting, 739 independent reflections [R_{int}=0.04, 651 with F₀>4σ(F₀)] and solved with direct methods (SIR92, A. Altomare, M. C. Burla, M. Camelli, G. Casciarano, C. Giacovazzo, G. Polidori, and A. Guagliardi, *J. Appl. Cryst.* **1994**, *29*, 435); refinement: CRYSTALS version 10 (D. J. Watkin, C. K. Prout, J. R. Curruthers, P. W. Betteridge, Oxford, 1997) non-hydrogen atoms with anisotropic thermal displacement parameters, hydrogen atoms (located in difference Fourier maps) isotropically. Weighting scheme: Chebyshev polynomial; 55 parameters, R(F) (obs.)=0.030, wR(F)=0.032, maximum residual electron density 0.39 and −0.24 e Å^{−1}. 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-100730. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ (Fax: (+44)(1223)-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [12] For the consideration of possible disorder in the crystal, the GED geometry has been taken as a reference. If the positions C5/C13', C5'/C13 and H3/H3' (see Figure 3b) are averaged to give C5_{av}, C5'_{av} and H3_{av}, the following geometry is obtained: P1=C2_{av} 1.656, P1–C9_{av} 1.791, P1–C5_{av} 1.808 Å, C2–P1–C9_{av} 110.7, C2–P1–C5_{av} 115.7, C9–P1–C5_{av} 105.4, C5–P1–C5_{av} 102.9, H3–C2–H4_{av} 118, H4–C2–H4_{av} 71°. These values are close to those observed in the crystal structure. However, the large distances between the disordered atom positions before averaging (e.g. C5–C13') should be reflected in the experimental ADP's, which should thus be markedly elongated for C5_{av} and C5'_{av}. This is not observed and the direction of this elongation does not coincide with the longest axis of the ADP's. Moreover, TLS (translation, libration, and screw) analysis shows the ADP's to be consistent with molecular libration as a rigid body, thus excluding contamination from alternative atomic positions.
An alternative model was generated from fitting the atom pairs P1/P1', C2/C2', C5/C13', C9/C5', and C13/C9' of two gas phase geometries by a least square procedure (Figure 3b) and averaging the positions of these pairs. The resulting geometry is essentially the same as the above average structure. This model could be rejected on the basis of the well-located hydrogen positions of the CH₂ unit (Figure 3c), as the model suggests both H-positions are clearly off the mirror plane of the disordered heavy-atom skeleton. We are grateful to Prof. R. Boese and the other referees of this paper, who drew our attention to these disorder models, which clearly needed to be considered before drawing the conclusions outlined in this paper.

Diastereoselective Synthesis of Highly Substituted Five-Membered-Ring Oxygen Heterocycles by Zirconocene-Mediated C–C Coupling Reactions**

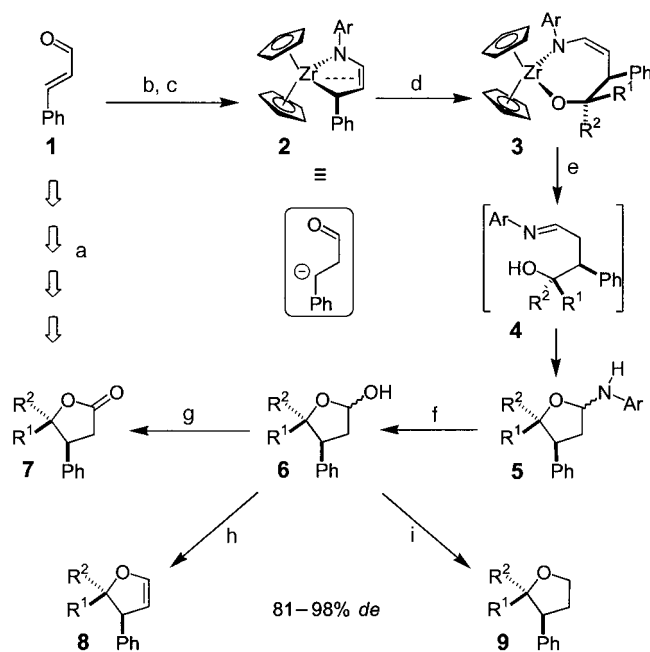
Dieter Enders,* Manfred Kroll, Gerhard Raabe, and Jan Runsink

The synthetic potential of unsaturated compounds has been extended considerably in the last few years by their conversion into the corresponding transition metal complexes.^[1] The use of “Cp₂Zr” (Cp = cyclopentadienyl) as a complexing group has brought forth a number of new synthetic methods during the last ten years,^[2,3] and the chemistry of zirconocene-imine complexes in particular has led to a series of important innovations in this field.^[4]

In this context we present a new synthesis of highly substituted five-membered-ring oxygen heterocycles, with a high degree of diastereoselectivity. Starting from α,β -unsaturated imines and unsymmetrical ketones highly substituted sterically demanding γ -butyrolactols **6** were synthesized. These could be easily converted into the corresponding γ -butyrolactones **7**, dihydrofurans **8**, and tetrahydrofurans **9**. This new practical route to the heterocycles in the title provides building blocks for the synthesis of natural products and biologically active substances such as alkaloids, macrocyclic antibiotics, lignans, pheromones, and fragrances.^[5]

Inspired by the work of Whitby et al.^[6] and Scholz et al.,^[7] we investigated the use of zirconocene-1-aza-1,3-diene complexes as homoenolate equivalents^[8] in stereoselective synthesis. Scholz et al. had shown that acetophenone inserts into the Zr–C σ bond of 2,2-bis(η^5 -cyclopentadienyl)-1-(2-methylphenyl)-3-phenyl-1-aza-2-zircona-4-cyclopentene (**2**). By extending this principle to other substrates and developing a method for the isolation of the β -substituted carbonyl compounds from the corresponding insertion products (**3**), we were able to use complexes **2** as homoenolate equivalents for the first time (Scheme 1).

In the synthesis of the zirconocene-1-aza-1,3-diene complexes (**2**) we used the *n*BuLi-route introduced by Negishi et al.^[9] and further investigated by Dioumaev and Harrod^[10] in order to generate the zirconocene equivalent. Following this method [Cp₂Zr(*n*Bu)₂] is formed in situ by the reaction of two equivalents of *n*BuLi with [Cp₂ZrCl₂] (–78 °C). By warming up the solution the generated Cp₂Zr fragment can form the desired 1-aza-2-zircona-4-cyclopentene **2** through ligand exchange reactions with the α,β -unsaturated imine added to the reaction mixture.^[11]



Scheme 1. Diastereoselective insertion of unsymmetrical ketones into the Zr–C σ bond of zirconocene-1-aza-1,3-diene complexes (**2**) as a new homoenolate equivalent for the synthesis of trisubstituted five-membered-ring oxygen heterocycles (Ar = 2-methylphenyl or 2-methoxyphenyl): a) 16–78 % over six steps; b) ArNH₂, molecular sieves; c) [Cp₂Zr], “*n*BuLi route”, quantitative over two steps; d) R¹COR², toluene, Δ ; e) C₃H₅NO, H₂O; f) HCl/THF, 51–78 % over four steps; g) Ag₂CO₃, toluene, Δ , 94–100 %; h) pyridinium-*p*-toluenesulfonate (PPTS), toluene, 1 h, >90 %; i) BH₃·Me₂S, THF, 69–94 %.

Scholz et al.^[7] emphasized the high degree of *cis*-stereoselectivity achieved in the insertion reaction of acetophenone into the 1-aza-2-zircona-4-cyclopentene (**2**, Ar = 2-methylphenyl), which was also obtained under drastic experimental conditions. In contrast to this, we were only able to reproduce the stereoselective insertion in ether under reflux conditions (85 % *de*); a lower selectivity was observed in boiling toluene (68 % *de*).

Using sterically demanding aliphatic ketones (such as 3,3-dimethyl-2-butanone, 1-acetyladamantane, etc.) we observed a reaction that differed greatly from that mentioned above. When the zirconocene-1-aza-1,3-diene complexes **2** (Ar = 2-methylphenyl or 2-methoxyphenyl) were mixed with 1.05 equivalents of the ketones in boiling toluene, the corresponding 3-aza-1-oxa-2-zircona-4-cycloheptenes **3a–e** (see Table 1) were formed cleanly within 30 to 60 minutes. In contrast to the situation with the aromatic ketone, very high diastereomeric excesses were reached under these conditions (>80 % *de* and in some ones higher than 98%). Additionally NOE experiments and X-ray structural analysis of the resulting products showed that the *trans* insertion products were formed in every aliphatic case (as opposed to *cis* in the aromatic case). This big difference in selectivity can be explained by steric effects for the aliphatic ketones and by attractive π – π interactions for the aromatic ketones. When the symmetric ketones (**g** and **h**) were investigated under these reaction conditions the yields were also nearly quantitative. The zirconocene fragment was removed oxidatively from the insertion products **3** as [Cp₂Zr=O]_{*n*} by the addition of

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pyridinium-*N*-oxide/H₂O. During the course of the reaction an imine–enamine tautomerization took place to yield γ -hydroxyimines (**4**), followed by an intramolecular nucleophilic attack of the hydroxy group on the C=N bond leading to 5,5-disubstituted *N*-aryl(4-phenyltetrahydrofuran-2-yl)-amines (**5**, 1:1 mixture of diastereomers; Figure 1). To obtain

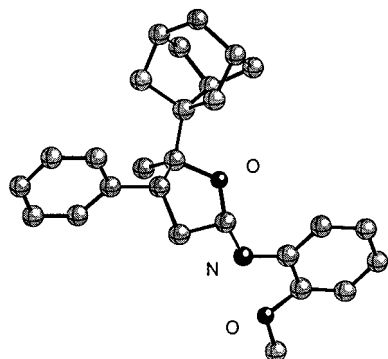


Figure 1. Structure of *N*-(2-methoxyphenyl)(5-methyl-4-phenyl-5-tricyclo[3.3.1.0^{3,7}]non-3-yltetrahydrofuran-2-yl)amine (**5d**).^[14–16]

optimum yields we refrained from the purification of the α -anilinetetrahydrofurans (**5**) as they tended to decompose, even on deactivated silica. Any impurities present had no negative influence on the following steps (cleavage of the aniline unit). If complex **3a** is treated with two equivalents of a freshly prepared ethereal solution of HCl, α -anilinetetrahydrofuran (**5a**) is formed, and the zirconocene fragment is recovered as [Cp₂ZrCl₂]. Nevertheless our less complicated pyridinium-*N*-oxide method was applied in general.

The chemistry of α -anilinetetrahydrofurans **5** is rather unknown apart from their pyrolysis reactions in which the resulting dihydrofurans tend to polymerize.^[12] A method had to be developed, therefore, to cleave the aniline unit from these compounds as efficiently as possible. By reaction with five equivalents of 0.1N HCl we managed to prepare the γ -butyrolactols **6** (Table 1). No spectroscopic evidence for their existence as open-chain γ -hydroxyaldehydes could be found.

The lactols **6** could be quantitatively transformed into lactones **7** by oxidation with Ag₂CO₃^[13] in boiling toluene,

Table 1. Yields and diastereoisomeric excesses of γ -butyrolactols **6**.

6 ^[a]	R ¹	R ²	Yield [%]	<i>de</i> [%] ^[b]
6a	Me	<i>t</i> Bu	64	> 98
6b	Me	cyclohexyl	66	84
6c	Me	1-adamantyl	74	> 96
6d	Me	3-neoadamantyl	72	> 96
6e	Me		78	> 95 ^[c]
6f	Ph	Me	51	> 95 ^[c]
6g	Et	Et	78	–
6h	Ph	Ph	67	–

[a] The data for **6f** and **6h** relate to **2** (Ar = 2-methylphenyl) as the starting material. In all other cases **2** (Ar = 2-methoxyphenyl) was used. Compound **6f** was synthesized according to the procedure of Scholz et al.^[7] [b] The *de* values were determined by ¹H NMR spectroscopy on a Varian Gemini 300 MHz or a Varian Unity 500 MHz spectrometer (**6b–f**: 300 MHz; **6a**: 500 MHz). [c] After flash chromatography (SiO₂, diethyl ether/pentane, 1/4).

whereas their reaction with catalytic amounts of pyridinium-*p*-toluenesulfonate (PPTS) under the same conditions gave the dihydrofurans **8** in very good yield. The series of five-membered-ring oxygen heterocycles could finally be completed by the reduction of the γ -butyrolactols **6** with two equivalents of BH₃·Me₂S to form the corresponding tetrahydrofurans **9** (Table 2).

Table 2. Yields and diastereoisomeric excesses of the resulting five-membered-ring oxygen heterocycles.

7–9	R ¹	R ²	7 yield [%]	8 yield [%]	9 yield [%]	<i>de</i> [%] ^[a]
a	Me	<i>t</i> Bu	64	59	59	> 98
b	Me	cyclohexyl	66 ^[b]	60	57	> 96
c	Me	1-adamantyl	74	69	58	> 96
d	Me	3-neoadamantyl	72	65	68	> 96
e	Me		78	70	54	> 96
f	Ph	Me	51	47 ^[c]	16	> 95
g	Et	Et	78	72	71	–
h	Ph	Ph	67	62	–	–

[a] The *de* values were determined by ¹H NMR spectroscopy with a Varian Gemini 300 MHz spectrometer. [b] 84% *de*. [c] 81% *de*, as the starting material was not enriched.

We have succeeded in using zirconocene-1-aza-1,3-diene complexes **2** as homoenolate equivalents in stereoselective synthesis for the first time. The high degree of flexibility in the range of products as well as the steric demand of the diastereoselectively obtained trisubstituted five-membered-ring oxygen heterocycles must be emphasized. Although they contain quaternary centers adjacent to one another or to tertiary centers, the title compounds could be synthesized in good overall yields and can be broadly used as building blocks for organic synthesis.^[17]

Experimental Section

trans-3a–e and **3g–h**: To a solution of the aza-zirconacyclopentene **2** (Ar = 2-methoxyphenyl; 2-methylphenyl in the case of **3h**) (1.0 mmol) in toluene (20 mL) under an atmosphere of argon was added and the appropriate unsymmetric aliphatic ketone (1.05 equiv), and the mixture heated to reflux. On warming a darkening (red) of the original luminous orange solution took place followed by a further change to yellow. As soon as no further color change was observed the solution was cooled to room temperature (RT) and the solvent evaporated in vacuo. The insertion products were obtained as yellow or orange amorphous solids or oils in greater than 95% purity and were used in this form for the subsequent transformations. A further purification could be achieved by recrystallization from toluene/hexane.

5: Pyridinium-*N*-oxide (0.114 g, 1.2 mmol) was added to solutions of **3** (each 1 mmol) in THF (20 mL). Under vigorous stirring H₂O (1 mL) was added, whereupon an intense clouding caused by the precipitation of [Cp₂Zr=O]_n appeared immediately. After stirring for 8 h at RT the reaction mixture was diluted with ether (40 mL), dried over MgSO₄, and the MgSO₄ filtered off together with the [Cp₂Zr=O]_n. Evaporation of the solvent led to yellow oils or solids that were used in the subsequent manipulations without further purification. Possible impurities do not affect the course of the following steps. In the case of *N*-(2-methoxyphenyl)-*N*-(5-methyl-4-phenyl-5-tricyclo[3.3.1.0^{3,7}]non-3-yltetrahydro-2-furanyl)amine (**5d**) recrystallization (ether/pentane 1/1) resulted in crystals suitable for X-ray structural analysis (see Figure 1).

6: To solutions of the crude α -anilinetetrahydrofurans **5** (1 mmol) in THF (50 mL) was added 0.1N HCl (50 mL) dropwise under vigorous stirring. After completion of the reaction (monitored by TLC, about 6 h) extraction with ether, drying over MgSO_4 , and removal of the solvent in vacuo, the crude product was purified by chromatography (SiO_2 , ether/pentane 1/4). The γ -butyrolactols **6** were obtained as colorless liquids or solids.

8: Lactols **6** were dissolved in toluene (each 20 mL mmol⁻¹) and heated to reflux in the presence of a catalytic amount of pyridinium-*p*-toluenesulfonate (water separator). As soon as no further conversion was detected (as monitored by TLC) the solution was cooled to RT and washed with pH 7 buffer (10 mL). The aqueous phase was extracted with pentane (10 mL), the combined organic layers dried over MgSO_4 , and the solvent evaporated in vacuo. The reddish to orange crude syrups were purified by chromatography (SiO_2 , pentane). Dihydrofurans **9** were obtained as colorless oils.

9: A solution of $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (2N in THF; 1 mL) was added to the appropriate lactol **6** (1 mmol) at 0 °C under an atmosphere of argon. After removal of the cooling bath the mixture was stirred until the evolution of gas ceased and then heated slowly to 60 °C. As soon as no further conversion was detected (monitored by TLC), the solution was cooled to 0 °C. After the addition of methanol (2 mL mmol⁻¹) to hydrolyze any excess borane, the solution was warmed to reflux temperature before removing the volatile components in vacuo. The colorless residue was purified by chromatography (SiO_2 , pentane) to yield the corresponding tetrahydrofurans **9** as colorless liquids or solids.

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Keywords: asymmetric syntheses • heterocycles • homoenolates • insertions • zirconium

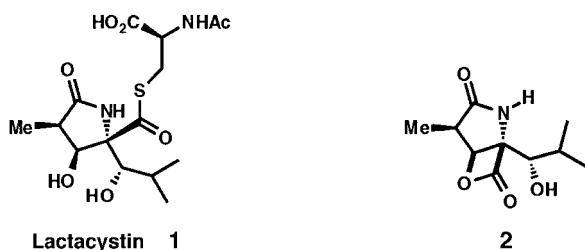
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- [14] Substance **5d** (C₂₇H₃₃NO₂) crystallizes from ether/pentane 1/1 (crystal dimensions ca. 0.3 × 0.3 × 0.3 mm³). Orthorhombic, space group *Pbcn* (No. 60), *a* = 31.362(1), *b* = 10.366(1), *c* = 13.618(2) Å, *V* = 4427.3 Å³, *Z* = 8, *M_r* = 403.57, ρ_{calcd} = 1.211 g cm⁻³. Enraf-Nonius CAD4 diffractometer, CuK α radiation (graphite monochromator, λ = 1.54179 Å). The structure has been solved with direct methods (Gensin, Gentan, from Xtal3.2).^[15] Some of the hydrogen positions could be localized, the remaining have been calculated. Reflections observed [*I* > 2 σ (*I*)] : 2136, parameters refined: 272, *R* = 0.070, *R_w* = 0.049; residual electron density –0.6/ +0.5 e Å⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101110. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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An Efficient and Concise Enantioselective Total Synthesis of Lactacystin**

E. J. Corey,* Weidong Li, and Tohru Nagamitsu

Dedicated to Professor Satoshi Omura

Lactacystin (**1**), a microbial product first reported by Omura et al.,^[1, 2] is a remarkably selective and potent inhibitor of proteasome-mediated degradation of ubiquitin-tagged proteins.^[3, 4] Lactacystin and the equipotent β -lactone **2**^[5] function by acylating a catalytically crucial terminal threonine residue on one of the 28 protein subunits that form



the cylindrical structure of the 20S proteasome (Figure 1).^[3, 4] This was confirmed by X-ray crystallographic studies (at 2.4 Å resolution) of the 20S proteasome inactivated by lactacys-

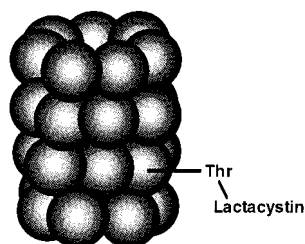
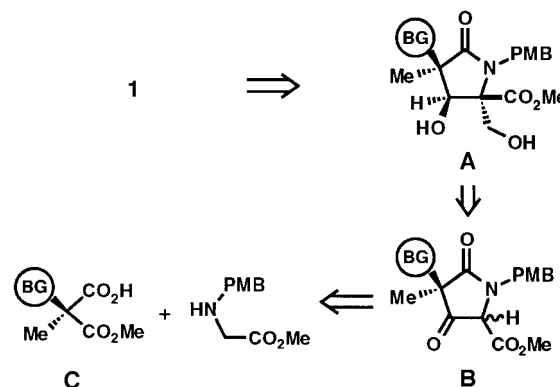


Figure 1. Schematic representation of the 20S proteasome after irreversible inhibition by lactacystin (**1**) or **2**.

tin.^[6, 7] Another interesting finding in the X-ray studies was that the isopropyl group of lactacystin is bound in a hydrophobic pocket of the lactacystin-labeled proteasome subunit.^[6] Because the proteasome system is involved in the degradation of countless proteins, including not only misfolded and denatured molecules^[8] but also proteins involved in cell cycle progression^[9] and regulation of gene transcription,^[10] lactacystin has emerged as a very important new tool for the study of protein biochemistry and cell biology. Lactacystin prepared by the route of the first total synthesis^[5, 11] has been used in numerous biological laboratories. In addition, synthetic **1** has been produced by three other multistep processes.^[12–14] The continuing need for synthetic lactacystin motivated us to develop a shorter synthesis of **1** which is also amenable to the efficient preparation of

structural analogues in which the isopropyl subunit of **1** is replaced by other lipophilic groups. This constraint (which dictates the introduction of the isopropyl group of **1** late in the synthesis) and the use of the γ -lactam α -carbon atom as the initiating stereocenter for the control of subsequent stereochemical elaboration led to the retrosynthetic strategy outlined in Scheme 1. In this plan BG is a blocking group with the



Scheme 1. Retrosynthesis of lactacystin (**1**). PMB = *p*-methoxybenzyl.

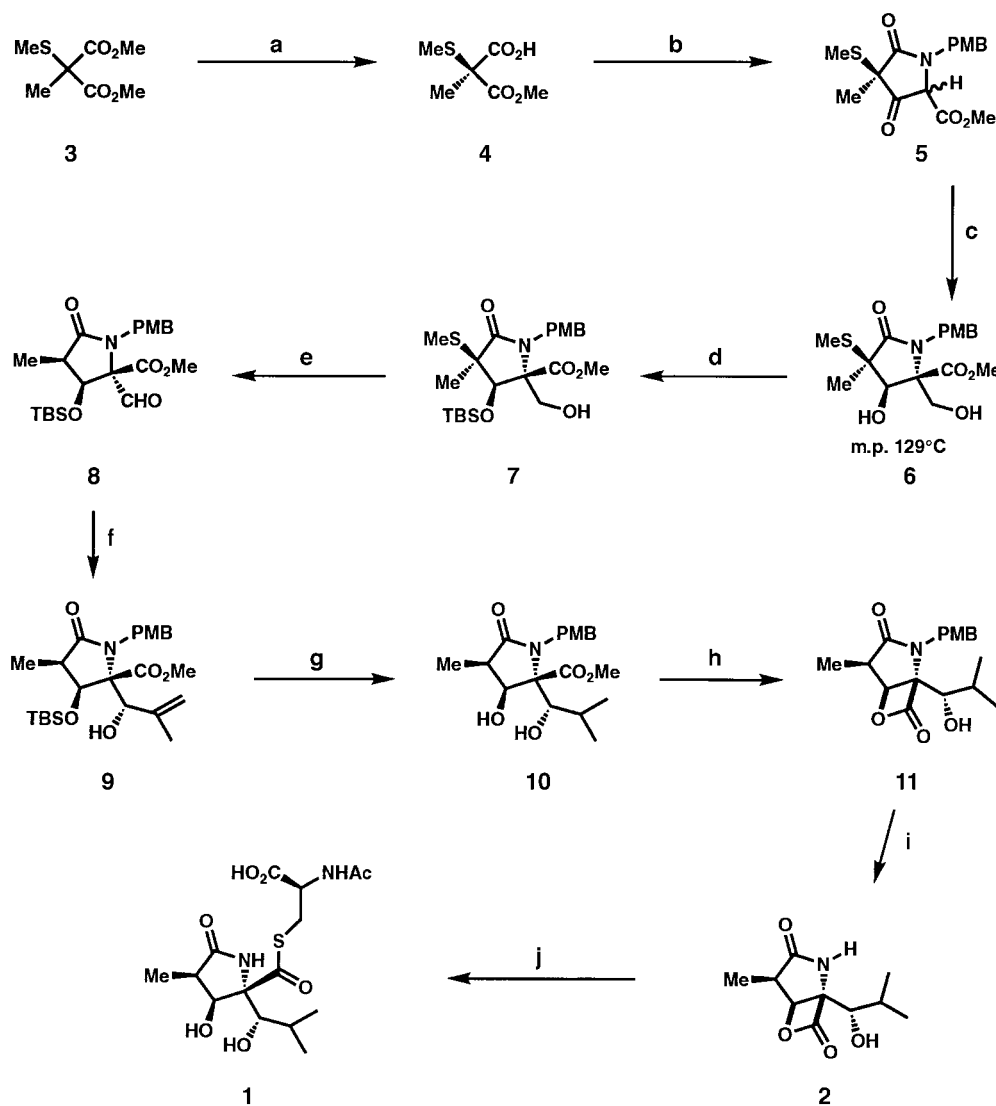
following properties: 1) readily replaceable by hydrogen in intermediate **A**, 2) sufficiently bulky to control the stereochemistry of hydroxymethylation of β -keto ester **B** (i.e., to serve as a controller of diastereoselectivity), and 3) suitable for large-scale enantioselective synthesis of the malonic acid mono ester **C**. The full synthesis is outlined in Scheme 2.

Dimethyl methylmalonate was converted into the achiral α -methylsulfanyl derivative **3** (NaH followed by MeSCl^[15] in THF, 23 °C, 12 h), which was transformed into the chiral mono ester **4** by enantioselective hydrolysis with porcine liver esterase (PLE; see Experimental Section). The crude acid (97% yield) was purified by one recrystallization of the quinine salt from aqueous ethanol to give, after acidification and extractive workup, **4** with 95% enantiomeric excess (*ee*) as a colorless oil.^[16, 17] The acid chloride of **4** was coupled with methyl *N*-*p*-methoxybenzylglycinate (PMB-NHCH₂COOMe), and the resulting amide ester was subjected to Dieckmann cyclization to produce the keto lactam **5** as a 1:1 mixture of diastereomers (with respect to the α -carbon atom of the β -keto ester subunit).

After highly stereoselective (9:1) α -hydroxymethylation of **5** and stereospecific reduction^[18] of the keto group, the crystalline dihydroxy lactam **6** [m.p. 129 °C, $[\alpha]_D^{23} = -41.8$ (*c* = 0.1, CHCl₃)] was obtained in 86% (based on **5**). The stereochemistry of **6** was established by X-ray crystallographic analysis.^[19] The oily mono *tert*-butyldimethylsilyl (TBS) ether **7** was prepared from diol **6** by the following sequence: 1) selective esterification at the primary hydroxyl group by pivaloyl chloride (PivCl), 2) silylation of the secondary hydroxyl group, and 3) cleavage of the pivalate ester. Desulfurization of **7** with Raney nickel proceeded with excellent diastereoselectivity (10:1) to afford aldehyde **8** as a colorless oil in 78% yield after column chromatography and Dess–Martin periodinane oxidation.^[20]

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Addition of organolithium or Grignard reagents to the aldehyde **8** turned out to be problematic, since the formyl group reacted only sluggishly (probably as a consequence of steric screening) and since carbonyl addition was followed by a rapid retro-aldol cleavage reaction. However, this obstacle was overcome by the addition of the 2-propenyl Grignard reagent to a mixture of **8** and trimethylchlorosilane (TMSCl), which afforded the desired addition product **9** stereospecifically and in excellent yield after aqueous workup and isolation. Several factors contributed to the success of this process: 1) TMSCl traps the alkoxide ion resulting from the addition of the 2-propenyl Grignard reagent to the formyl group at a rate that is faster than the retro-aldol reaction; 2) at -40 °C the rate of reaction of the Grignard reagent with TMSCl is slower than that with the aldehyde **8**; 3) the TMS ether of **9** is stable under the reaction conditions, but is rapidly cleaved during aqueous work up; and 4) the stereochemistry of addition of the Grignard reagent to the formyl group of **8** is probably controlled by steric screening within a bidentate complex of Mg^{II} and the ester and formyl carbonyl groups. The reaction of isopropylmagnesium bromide with aldehyde **8** resulted in reduction of the formyl group to CH₂OH (95 %

yield). Isomerically pure **9** was subjected to hydrogenation and desilylation to produce cleanly **10** [m.p. 91–92 °C, $[\alpha]_D^{25} = +12.7$ ($c = 0.06$, CHCl₃)]. Saponification of the ester functionality of **10** and subsequent treatment with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 1.5 equiv) and triethylamine (3 equiv) gave the β -lactone **11** [m.p. 164 °C, $[\alpha]_D^{25} = -84$ ($c = 0.05$, CHCl₃)], the structure of which was fully confirmed by X-ray crystallographic analysis.^[19b, 21] Cleavage of the *N*-*p*-methoxybenzyl protecting group of **11** with ceric ammonium nitrate produced the known β -lactone **2**^[5] [m.p. 185 °C (decomp), $[\alpha]_D^{25} = -94$ ($c = 0.5$, CH₃CN)], which was identical with an authentic sample. Finally, treatment of **2** with *N*-acetylcysteine (1 equiv) and triethylamine (1.5 equiv) afforded pure **1** in 99 % yield; it was identical in all respects to an authentic sample of lactacystin.

The synthesis of lactacystin described here is noteworthy for a number of reasons. The synthesis is direct and simple with regard to reaction procedures and isolation of pure products. It is stereocontrolled and economical in terms of reagents. In addition, the key intermediate **8** allows access to many analogues of lactacystin in which the isopropyl group is replaced by other lipophilic residues. For example, reaction of

8 with vinyl, allyl, and phenylmagnesium halides under the conditions described above for the conversion of **8** into **9** afforded in good yield the corresponding analogues of **9**. These compounds are of special interest in connection with the search for lactacystin analogues that exhibit species selectivity. Finally, the chiral acid ester **4** is a versatile intermediate which serves as a synthetic equivalent of configurationally unstable chiral methylmalonic acid derivatives.

Experimental Section

4: To a stirred suspension of dimethyl methylsulfanylmethylmalonate (19.0 g, 0.10 mol) in 0.1 M phosphate buffer (pH 7.3, 25 mL) and distilled water (300 mL) was added PLE (2.0 g; crude acetonetic powder from *Sigma* L8251). The pH of the resulting mixture was maintained at 7.30 by regular addition of a 2 N aqueous NaOH solution with a syringe pump interfaced with a pH controller. After the mixture was stirred for 15–20 h at 23 °C, one equivalent of NaOH was consumed. The reaction mixture was treated with Celite (20 g) and filtered. The filtrate was acidified to pH 2–3 with 6 N HCl and extracted with Et₂O (3 × 300 mL), and the combined extracts were washed with brine and dried. Evaporation of the solvent in vacuo gave **4** (17.30 g, 98%, 67% ee) as a colorless oil, which was used for optical enrichment with quinine without further purification. A mixture of **4** (15.0 g, 0.08 mol) and quinine (27.3 g, 0.08 mol) in 50% aqueous ethanol (556 mL) was stirred at 70–80 °C for 20 min to give a clear homogeneous solution, which was cooled to 23 °C and allowed to stand for 2 d for crystallization. The resulting crystals were collected, washed with ice-cold 50% aqueous ethanol, and dried in vacuo to give a solid [m.p. 173–174 °C, $[\alpha]_D^{25} = -155$ ($c = 0.35$, 50% EtOH/H₂O)], which was dissolved in 3 N HCl (35 mL). The solution was extracted with Et₂O (3 × 300 mL), and the combined extracts were dried and concentrated in vacuo to give optically enriched **4** (7.80 g, 52%, 95% ee) as a colorless oil. The ee of **4** was determined by ¹H NMR spectroscopy in the presence of one equivalent of (*S*)- α -methylbenzylamine in CDCl₃. The mother liquor was acidified with 6 N HCl to pH 2–3 and extracted with Et₂O (3 × 300 mL). The combined extracts were dried and concentrated in vacuo to give recovered monoacid (3.75 g, <10% ee), which was esterified [(COCl)₂/PhH, DMF (cat.), 23 °C, and then MeOH] to afford **3**, which was subjected to asymmetric enzymatic hydrolysis (PLE). Purification of resulting monoacid with quinine gave additional **4** (1.8 g, total 9.6 g, 64% overall yield). $[\alpha]_D^{25} = -1.2$ ($c = 2.64$, CHCl₃); FT-IR (film): $\nu = 3134$ (brs, OH), 1731, 1713, 1260, 1110 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 1.73$ (s, 3 H, CH₃), 2.24 (s, 3 H, CH₃S), 3.83 (s, 3 H, CH₃O); ¹³C NMR (100 MHz, CDCl₃): $\delta = 14.1$, 21.4, 53.4, 55.6, 169.7, 174.8; HRMS (CI, NH₃) m/z calcd for [C₆H₁₄NO₄S]⁺ 196.0644, found for [M+NH₄]⁺ 196.0640.

Hydroxymethylation of 5: A stirred solution of β -keto ester **5** (6.75 g, 20.0 mmol) in THF (30 mL) was treated with DBU (0.60 mL, 4 mmol) at 0 °C for 15 min, cooled to –78 °C, and treated with a solution of formalin (36 wt %, 12 M aqueous solution, 16.7 mL, 0.20 mol) in THF (10 mL). The reaction mixture was stirred for 0.5 h, quenched with 10% aqueous CuSO₄ solution, and extracted with Et₂O (3 × 30 mL). The Et₂O extracts were washed with brine and dried. Evaporation of the solvent in vacuo gave the crude product, which was purified by flash chromatography on silica gel to afford the desired hydroxymethylation product (6.60 g, 90%) as a colorless oil, $[\alpha]_D^{25} = +94$ ($c = 0.40$, EtOAc); FT-IR (film): $\nu = 3430$ (brs, OH), 1740, 1697, 1513, 1246 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 1.01$ (dd, 1 H, $J = 4.9$, 9.1 Hz, OH), 1.55 (s, 3 H, CH₃), 2.13 (s, 3 H, CH₃S), 3.72 (s, 3 H, CH₃O), 3.79 (s, 3 H, CH₃O), 3.76 (dd, 1 H, $J = 4.9$, 12.5 Hz, CH₂OH), 4.18 (dd, 1 H, $J = 9.1$, 12.5 Hz, CH₂OH), 4.26 (d, 1 H, $J = 15.2$ Hz, CH₂Ph), 5.20 (d, 1 H, $J = 15.2$ Hz, CH₂Ph), 6.87, 7.34 (each d, 2 H, $J = 8.6$ Hz, ArH); ¹³C NMR (100 MHz, CDCl₃): $\delta = 12.3$, 16.8, 44.3, 53.0, 55.4, 61.9, 114.7, 126.1, 129.8, 130.5, 159.3, 165.7, 204.2; HR-MS (FAB, NBA + NaI): m/z calcd for [C₁₇H₂₁NO₆SN₂]⁺ 390.0987, found for [M+Na]⁺ 390.0974.

9: A stirred solution of aldehyde **8** (100 mg, 0.230 mmol) in THF (11 mL) at –40 °C was treated sequentially with TMSCl (0.15 mL, 1.15 mmol) and isopropenylmagnesium bromide (0.5 M in THF, 1.38 mL, 0.69 mmol). After

the mixture was stirred for 0.5 h at –40 °C, the reaction was quenched with saturated aqueous NH₄Cl at that temperature and stirred for an additional 0.5 h. The resulting mixture was extracted with ethyl acetate (3 × 20 mL), and the combined extracts were washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give **9** (106 mg, 97%) as colorless crystals, m.p. 153–154 °C, $[\alpha]_D^{25} = +65.7$ ($c = 0.035$, CHCl₃); FT-IR (film): $\nu = 3389$, 1698, 1683, 1514, 1247 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): $\delta = 0.07$ (s, 3 H, CH₃Si), 0.09 (s, 3 H, CH₃Si), 0.82 (s, 9 H, (CH₃)₃CSi), 1.20 (d, $J = 8.6$ Hz, 3 H, 7-CH₃), 1.59 (brs, 1 H, OH), 1.75 (s, 3 H, C(CH₃)=CH₂), 2.64 (m, 1 H, 7-H), 3.11 (s, 3 H, CO₂CH₃), 3.78 (s, 3 H, CH₂C₆H₄OCH₃), 3.85 (d, $J = 15.0$ Hz, 1 H, CH₂C₆H₄OCH₃), 4.85 (d, $J = 9.2$ Hz, 1 H, 6-H), 4.91 (brs, 1 H, CHOH), 4.92 (d, $J = 15.0$ Hz, 1 H, CH₂C₆H₄OCH₃), 5.12 (brs, 1 H, C(CH₃)=CH₂), 5.20 (brs, 1 H, C(CH₃)=CH₂), 6.81 (d, $J = 8.6$ Hz, 2 H, CH₂C₆H₄OCH₃), 7.21 (d, $J = 8.6$ Hz, 2 H, CH₂C₆H₄OCH₃); ¹³C NMR (100 MHz, CDCl₃): $\delta = 178.0$, 173.2, 158.9, 141.8, 130.5, 130.4, 128.9, 117.4, 113.7, 113.6, 75.2, 73.9, 69.0, 55.3, 51.7, 45.4, 40.8, 25.8, 21.2, 18.0, 11.8, –4.2, –4.6; HR-MS (FAB, NBA + NaI): m/z calcd for C₂₅H₄₀NO₆Si 478.2625, found for [M+H]⁺ 478.2638.

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Structure–Reactivity Relationship in the Reaction of Highly Reactive Zinc with Alkyl Bromides**

Albert Guijarro and Reuben D. Rieke*

The reaction of organic halides with magnesium or lithium in the zerovalent state is the most direct and commonly used method to prepare organometallic compounds containing these metals. However, these reactions do not show much structure selectivity. As has been stated, “the reaction of organic bromides with magnesium is among the least selective of organic reactions”.^[1] The formation of organolithium compounds shows great similarities to that of organomagnesium compounds.^[2] In addition to these metals, zinc has become more important in recent years.^[3] It tolerates a broad range of functionalities, and, since the introduction of highly reactive zinc, virtually any organozinc reagent can be prepared from the corresponding organic bromide.^[4] It is generally accepted that the mechanism of these reactions is similar to those of analogous reactions of magnesium and lithium.^[5] However, few mechanistic studies regarding the formation of organozinc halides are available to date.

To study the rates of reaction of alkyl bromides with highly reactive zinc, we used competitive kinetic methods.^[1] The rate of reaction of organic bromides depends, in principle, on the concentration of the organic halide $[\text{R}^1\text{Br}]$ or $[\text{R}^2\text{Br}]$ and on some undefined physical characteristics of the metal surface

$f(\text{Zn})$ [Eqs. (a) and (b)]. The simultaneous determination of the concentration of two different alkyl bromides in solution that react with the same metallic surface permits a simplification to Equation (c).

$$-d[\text{R}^1\text{Br}]/dt = k_1[\text{R}^1\text{Br}]^x f(\text{Zn}) \quad (\text{a})$$

$$-d[\text{R}^2\text{Br}]/dt = k_2[\text{R}^2\text{Br}]^x f(\text{Zn}) \quad (\text{b})$$

$$d[\text{R}^1\text{Br}]/d[\text{R}^2\text{Br}] = k_1/k_2 ([\text{R}^1\text{Br}]/[\text{R}^2\text{Br}])^x \quad (\text{c})$$

$$\ln([\text{R}^1\text{Br}]_t/[\text{R}^1\text{Br}]_0) = k_1/k_2 \ln([\text{R}^2\text{Br}]_t/[\text{R}^2\text{Br}]_0) \quad (\text{d})$$

Assuming that $x = 1$ (that is, the reactions are first order with respect to the alkyl bromide; this is confirmed below) and integrating Equation (c) leads to Equation (d). The experimental kinetic data fit Equation (d) extremely well (Figure 1). Plots of $\ln([\text{R}^1\text{Br}]_t/[\text{R}^1\text{Br}]_0)$ versus $\ln([\text{R}^2\text{Br}]_t/[\text{R}^2\text{Br}]_0)$ are linear to greater than 95 % consumption of the most reactive halide. Evaluation of the slope by a linear regression analysis yielded k_1/k_2 directly. Every line contains between 8 and 11 points, and the linear regression coefficients are greater than 0.99 in all cases. This confirmed our

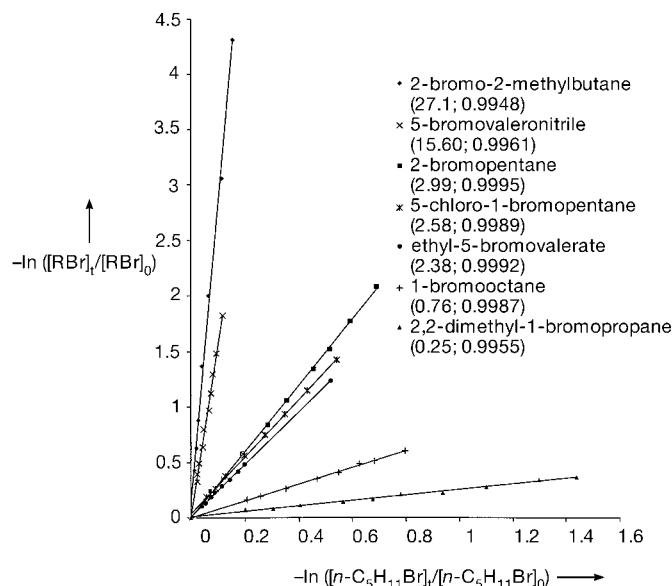


Figure 1. Experimental conformation for the validity of Equation (d) with competition reactions of 1-bromopentane and another bromoalkane with activated zinc. The ratios of the reaction rates, k_1/k_2 , and the regression coefficients are given in parentheses.

hypothesis that the reaction was first order with respect to the alkyl bromide, in agreement with kinetic data reported for magnesium and lithium. Table 1 summarizes the ratio of rate constants (k_1/k_2) determined for all pairs of substrates assayed. Since the yields of organozinc bromides obtained with this procedure are very high,^[4] side reactions perturb the final results only slightly.

The reaction shows selectivity with respect to the nature of the organic moiety (Table 1). The effect of the alkyl halide on the rate of the electron transfer decreases in the order tertiary > secondary > primary; the ratio of the rates is

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

Table 1. Relative reaction rates k_1/k_2 .^[a]

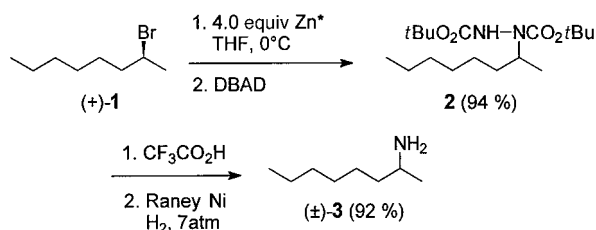
Entry	R ¹ Br	k_1/k_2 ^[b]	
		primary R ² Br ^[c]	secondary
1		1	0.33
2		2.99	1
3		27.1, 28.6	9.58
4		0.25	0.084
5		10.5	3.51
6		2.58	0.86
7		2.38	0.80
8		15.6	5.22
9		0.42	0.17
10		1	0.39
11		2.52	1
12		31.8, 32.8	13.0
13		1.32	0.52

[a] Corresponding to the reaction of two alkyl bromides (R¹Br, R²Br) with highly reactive zinc (in THF at 0 °C). The relative rates were determined by the competitive kinetics technique. [b] Estimated error 5%. The k_1/k_2 values for pairs that were not measured directly are given in italics. [c] R²Br is 1- or 2-bromopentane for entries 1–8, and 1- or 2-bromooctane for entries 9–13.

roughly 30:3:1. Cyclopentyl bromide reacts 3.51 times faster than 2-bromopentane, and 1-adamantyl bromide reacts 5.96 times slower than 2-bromooctane (and 77 times slower than 2-bromo-2-methylheptane). These are consistent with the geometric requirements of radical intermediates. To a certain extent, the reaction also seems to be sensitive to steric factors; neopentyl bromide reacts 4.00 times slower than 1-bromopentane. The effect of a polar group in the chain is to increase the rate of the reaction. In the case of 5-bromovaleronitrile, this change is notable and may be governed by binding interactions of the nitrile group to the metal surface prior to electron transfer.

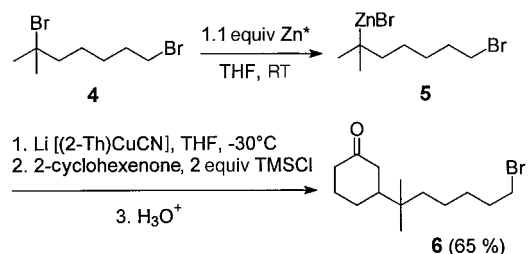
To further explore the existence of radical intermediates, the reaction of highly reactive zinc, Zn*, with an optically active alkyl bromide was studied. (+)-*R*-2-Bromooctane (**1**;^[6] $[\alpha]_D^{25} = +39.7^\circ$, > 95 % *ee*) was prepared and allowed to react with 4.0 equivalents of Zn* at 0 °C. The 2-octylzinc bromide generated was then treated with 1.0 equivalent of di-*tert*-butyl azodicarboxylate (DBAD) at 0 °C.^[7] Deprotection and reduction afforded (±)-2-aminooctane (**3**), as shown by NMR spectroscopy using *S*-(+)-*O*-acetylmandelic acid as a chiral solvating agent.^[8] The configurational stability of the carbon –

zinc bond is well established.^[9] Accordingly, racemization most likely occurred during the formation of the organozinc reagent (Scheme 1).^[10]



Scheme 1. Synthesis of 2-aminooctane (**3**) from optically active 2-bromooctane (**1**). Racemization most likely takes place in the first step upon reaction with active zinc.

These results suggest that by using highly reactive zinc one can take advantage of not only the structure selectivity exhibited but also the high tolerance with respect to functional groups. To test this theory, 1,6-dibromo-6-methylheptane (**4**)^[11] was treated with 1.1 equivalents of Zn* in THF at room temperature to afford the functionalized organozinc bromide **5**, which shows remarkable stability.^[12] Transmetalation with lithium 2-thienylcyanocuprate at –30 °C and reaction with the electrophilic mixture of 2-cyclohexenone and two equivalents of Me₃SiCl (TMSCl) yielded, after quenching, the conjugate addition product **6** (65% yield based on **4**, Scheme 2).^[13] This reaction demonstrates that a tertiary bromide functionality can be elaborated in the presence of primary bromides. The resulting substituted primary bromide is then available for further elaboration.



Scheme 2. Selective formation of a carbon–zinc bond by reaction of the tertiary bromide functionality of **4**, and synthesis of **6**. 2-Th = 2-thienyl.

In conclusion, the oxidative addition of active zinc to alkyl bromides is highly sensitive to structure. Attempts to measure the competitive kinetics of benzylic, allylic, aryl, and vinylic bromides, whose rates of reaction differ largely from those of alkylic bromides, are underway. Additional studies to provide more information on the mechanistic details of the oxidative addition are also in progress.

Experimental Section

6: To a 50-mL centrifuge tube equipped with stirring bar and septum was added under argon active zinc^[6] (2.2 mmol) in dry THF (10 mL) and 1,6-dibromo-6-methylheptane^[11] (544.1 mg, 2.0 mmol). The reaction was stirred at room temperature for about 10 h. Meanwhile, to a two-necked 100-mL flask containing dry THF (10 mL) and copper(I) cyanide (179.2 mg,

2.0 mmol) was added 2-thienyllithium (2 mL, 1.0 M in THF) at -30°C , and the mixture was stirred for 30 min. The organozinc reagent was centrifuged for 2 min (2500 rpm), and the content of the tube was transferred by cannula to the flask containing $\text{Li}(2\text{-Th})\text{CuCN}$ at -30°C . A solution of 2-cyclohexenone (202.4 mg, 2.0 mmol) and TMSCl (439 mg, 4.0 mmol) was then added to the flask. The reaction was allowed to warm slowly to room temperature for one day. An additional aliquot of the electrophilic mixture (0.5 equiv) was added, and the reaction was allowed to stir for two more days. The mixture was then hydrolyzed (2 M HCl) and extracted with diethyl ether ($2 \times 100\text{ mL}$), the organic phases were dried (MgSO_4), and the solvents were removed (15 torr, 30°C). Impure **6** was isolated by column chromatography (Florisil, hexanes/ethyl acetate). By-products were removed by shaking a solution of the impure compound in hexane (50 mL) with a methanolic solution of mercuric(ii) acetate ($\approx 0.25\text{ M}$, 25 mL) for 5 min. Addition of water (50 mL) and extraction with diethyl ether ($2 \times 100\text{ mL}$) afforded, after drying (MgSO_4) and elimination of solvents, pure **6** (375 mg, 65%).

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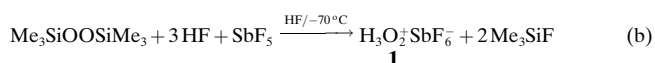
The Crystal Structures of Peroxonium Hexafluoroantimonate $\text{H}_3\text{O}_2\text{SbF}_6$ and Bis(dihydrogenperoxo)hydrogen Hexafluoroantimonate $\text{H}_5\text{O}_4\text{SbF}_6$

Rolf Minkwitz,* Claudia Hirsch, and Hans Hartl

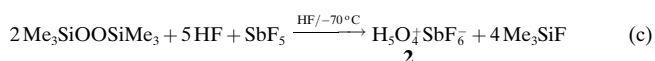
The preparation of peroxonium salts by direct protonation of hydrogen peroxide was accomplished by Christe et al.^[1] in 1979 [Eq. (a)]. These salts were characterized by IR, Raman and NMR spectroscopy. Two O–O stretching vibrations at 876 and 915 cm^{-1} were observed in the IR spectrum of peroxonium hexafluoroantimonate and one vibration at 879 cm^{-1} in the Raman spectrum, although the less intensive vibration at 915 cm^{-1} could not be assigned (Table 1). Therefore we decided to examine this salt more closely.



To avoid the danger of explosion that can arise from the use of highly concentrated hydrogen peroxide, and to ensure that there is no production of $\text{H}_3\text{O}^+\text{SbF}_6^-$ due to traces of water, we decided to use bis(trimethylsilyl)peroxide as the substrate [Eq. (b)]. The crystalline reaction product shows vibrations at 875 and 914 cm^{-1} in the IR spectrum and at 877 and 911 cm^{-1} in the Raman spectrum (Table 1).



Careful examination of the product under a microscope in a stream of cold nitrogen indicated that there were, in addition to crystals^[2] of the expected product **1**, some other crystals with a slightly different habit. The composition of these crystals was determined to be $\text{H}_5\text{O}_4^+\text{SbF}_6^-$ (**2**) by structure elucidation,^[3] and subsequently **2** was prepared in the pure form by the reaction described in Equation (c), in which double the amount of bis(trimethylsilyl)peroxide was used relative to SbF_5 (cf. [Eq. (b)]).



The Raman spectrum of **2** shows no vibration at 879 cm^{-1} but instead one at 908 cm^{-1} . In contrast, the vibration at 874 cm^{-1} in the IR spectrum is retained and no further vibrations were detected in this area (Table 1).

The H_3O_2^+ ion and the SbF_6^- ion in the crystal structure of **1** are donor and acceptor for two short hydrogen bonds ($\text{O1-H}\cdots\text{F2 } 252.1(8)\text{ pm}$ and $\text{O1-H}\cdots\text{F4 } 252.3(8)\text{ pm}$), and for one longer hydrogen bond ($\text{O2-H}\cdots\text{F3 } 270.8(8)\text{ pm}$). The

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Table 1. Vibrational frequencies of the peroxonium salts **1** and **2** [cm⁻¹] at various temperatures.

1		1 ^[1]		2		ν ^[a]
IR <i>T</i> = 223 K	Ra <i>T</i> = 195 K	IR <i>T</i> = 77 K	Ra <i>T</i> = 163 K	IR <i>T</i> = 223 K	Ra <i>T</i> = 195 K	
3453 mw	3462 (2)	3440 sh		3454 m	3459 (4)	$\nu(\text{OH}_2)$
3391 m	3397 (2)	3400–3150 vs		3393 m		$\nu(\text{OH}_2)$
	3262 (1)	3230 vs				$\nu(\text{OH})$
				3201 m		$\nu(\text{OH})$
				3144 m		$\nu(\text{OH})$
				3049 m		$\nu(\text{OH})$
				2829 vw		
				2360 w		
1549 w						$\delta_s(\text{OH}_2)$ ^[b]
1427 m		1421 mw		1422 s	1429 (1)	$\delta(\text{OOH})$
					1409 (1)	$\delta(\text{OOH})$
1267 vw		1280 w		1272 w		$\tau(\text{OH}_2)$
1155 m		1126 mw		1135 s		$\delta_B(\text{OH}_2)$ ^[b]
		1065 sh				$\rho(\text{OH}_2)$
		965 sh				
914 vw	911 (2)	915 w			908 (4)	$\nu(\text{OO})$
875 m	877 (8)	876 mw	879 (8.6)	874 ms		$\nu(\text{OO})$
						$\gamma(\text{OH}_2)$
						$\tau(\text{OOH})$
373 w		375 mw				
	688 (3)		689 (5)			
679 vs	675 (10)		677 (10)		670 (3)	
	663 (5)	666 vs		668 vs	660 (10)	
646 sh	643 (5)		642 (7)	643 m	638 (1)	
	561 (1)	615 s	560 (2)	574 m	561 (1)	
525 sh		571 ms		519 w		
453 sh		514 m				
			326 (1)			} anion
310 m	294 (2)	309 ms		303 m	290 (2)	
280 m	284 (3)		283 (5)	279 s		
	266 (1)		263 (0.9)			
215 m			226 (0.5)			
193 m	201 (1)		200 (1.5)		190 (1)	
	172 (2)		174 (3.2)		165 (1)	
	124 (1)		126 (2.4)			
					107 (1)	

[a] Proposed assignments. [b] δ_s and δ_B are deformation and bending vibrations. vs = very strong, s = strong, ms = medium strong, m = medium, w = weak, mw = medium weak, sh = shoulder.

hydrogen bonds link the cations and anions to form corrugated bands of centrosymmetric ten-membered rings that run parallel to the *ac* plane (Figure 1). Similar linkages exist in the low-temperature structure of oxonium hexafluoroarsenate^[4] and in the structure of oxonium tetrafluoroborate.^[5] None of the other interionic contacts is smaller than the sum of the van der Waals radii. As expected, the Sb–F bonds of the fluorine atoms that participate in short hydrogen bonds (191.3(5) and 191.2(5) pm) in the extremely distorted octahedral SbF₆⁻ ion are significantly longer than the other Sb–F bond lengths (185.5(5)–187.3(5) pm). All three hydrogen atoms of the H₃O₂⁺ ion are linked by hydrogen bonds to the SbF₆⁻ ion. The cation can be assumed to have an antiperiplanar conformation if the hydrogen atoms, only one of which was detected from the difference Fourier map, lie on the connecting line of the O–F contacts. The O–O bond length is 144.3(9) pm and is slightly shorter than the distance in free hydrogen peroxide, as determined by X-ray diffraction (146.1(3) pm) and neutron

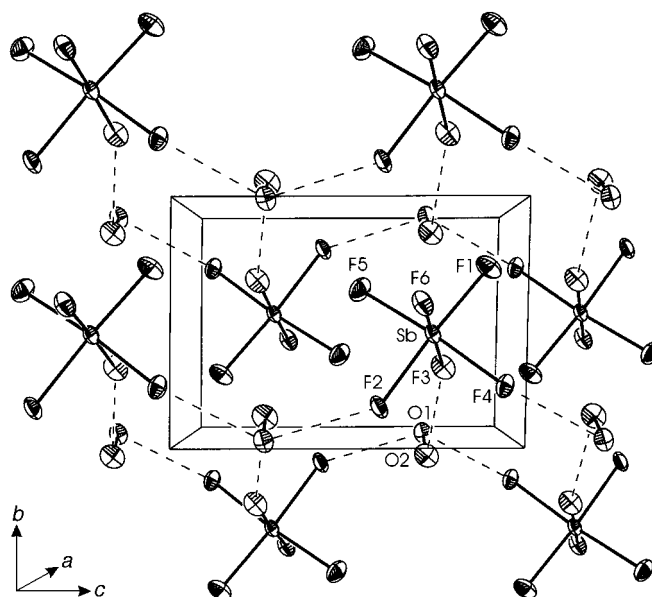


Figure 1. Section of the crystal structure of **1** (50% probability ellipsoids, H atoms are not shown). Distances [pm]: O1–O2 144.3(9), O1–F2 252.1(8), O2–F4 252.3(8), O2–F3 270.8(9).

diffraction (145.8(4) pm).^[6] This indicates that the weak O–O bond in hydrogen peroxide is strengthened by conversion of the lone pair of electrons into a bonding electron pair in **1**.

The triclinic centrosymmetric unit cell of **2** contains, in addition to two crystallographically equivalent SbF₆⁻ ions, two crystallographically independent bis(dihydrogenperoxo)hydrogen cations linked by weak hydrogen bonds (O1–H...O3 287.0(5) pm) to form chains with C_i symmetry. In this case, all the hydrogen atoms were located in a difference Fourier map.

The positional parameters and therefore the O–H bond lengths could only be determined with low accuracy and so, as in **1**, the O–O or O–F bond lengths were used to assess the strength of the hydrogen bond.

Split atomic positions were determined for the bridging hydrogen atoms (Figure 2). The two H₃O₂⁺ ions are shaped

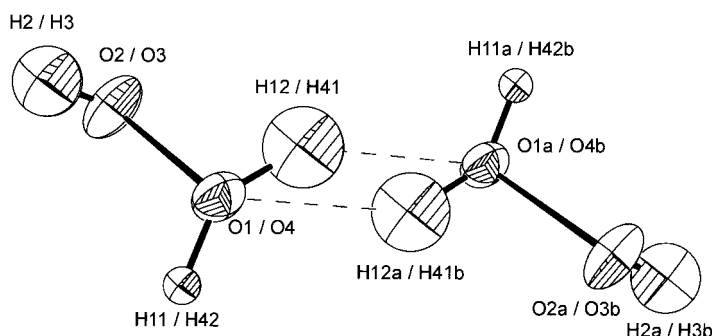


Figure 2. Structure of the H₃O₂⁺ ion (50% probability ellipsoids for the oxygen atoms, 25% probability ellipsoids for the hydrogen atoms, the double atom designation is due to the two crystallographically independent H₃O₂⁺ ions; the hydrogen atom positions H12/H41 and H12a/H41b are each half occupied). Distances [pm]: O1–O2 145.0(7), O3–O4 145.7(5); torsion angles [°]: H2–O2–O1–H12 138(15), H3–O3–O4–H41 90(15), H2–O2–O1–H11 –80(13), H3–O3–O4–H42 –109(8); atoms created by symmetry: a: –x + 1, –y, –z + 1, b: –x, –y, –z.

like the analogous diaquahydrogen H_5O_2^+ ion, and form centrosymmetric units with one unsymmetrical disordered hydrogen bond per unit ($\text{O1-H}\cdots\text{O1a}$ 240.8(5) and $\text{O4-H}\cdots\text{O4b}$ 244.6(6) pm). Similar disorder was observed in the crystal structure of trifluoroacetic acid tetrahydrate.^[7] The O–O bond lengths (145.0(7) and 145.7(5) pm) are slightly longer than in **1** but shorter than in hydrogen peroxide.^[6]

The cation is both a donor and an acceptor of hydrogen bonds and cation-linked ten-membered rings are formed (Figure 3), which are three-dimensionally linked by weaker

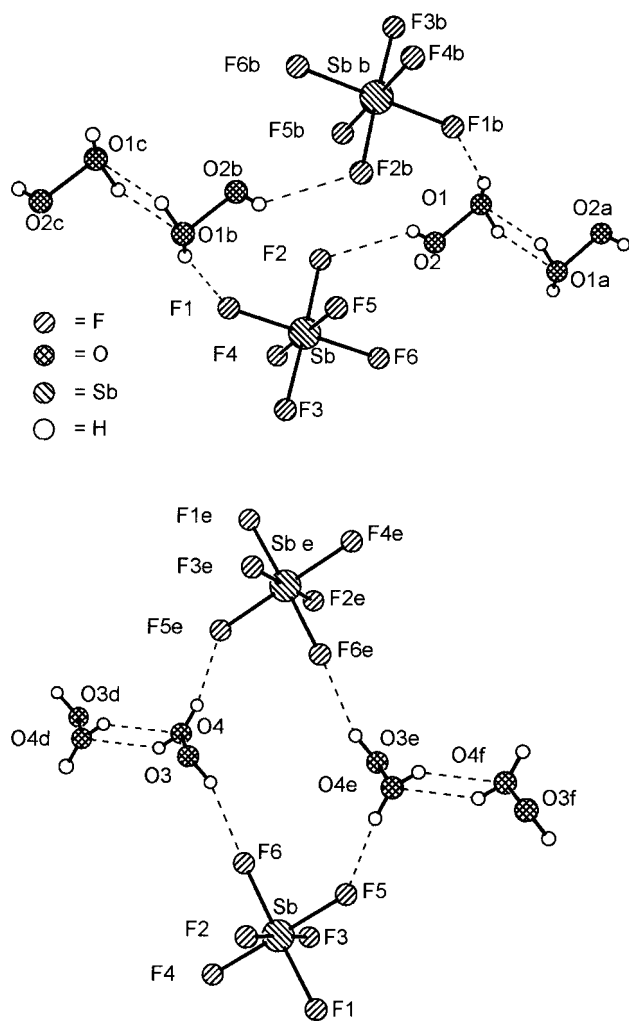


Figure 3. View of the two ten-membered rings in **2**. Distances [pm]: O1b-F1 266.7(6), O2-F2 270.7(6), O3-F6 278.5(5), O4e-F5 270.5(6); atoms created by symmetry: a: $-x+1, -y, -z+1$, b: $-x+1, -y+1, -z+2$, c: $x, y+1, z+1$, d: $-x, -y, -z$, e: $-x, -y, -z+1$, f: $x, y, z+1$.

O–H $\cdots$ O hydrogen bonds (Figure 4). In addition, the O–H $\cdots$ F hydrogen bonds with O–F distances of between 266.7(6) and 296.8(6) pm result in complex cross-linking between the cations and anions. The SbF_6^- ion is a slightly distorted octahedron. The Sb–F bond length (189.9(3) pm) of the F atom that is involved in the shortest hydrogen bond, is only slightly longer than the other Sb–F distances (186.4(3) pm–188.0(3) pm).

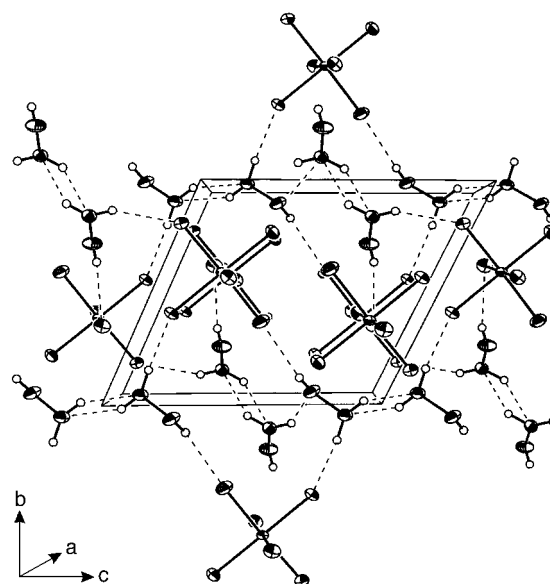


Figure 4. Section of the crystal structure of **2** (50% probability ellipsoids for all atoms except hydrogen).

Experimental Section

Bis(trimethylsilyl)peroxide was prepared from hexamethylene tetramine, hydrogen peroxide, and trimethylchlorosilane.^[8] SbF_5 was distilled several times, and HF was dried with F_2 .

1: SbF_5 (1 mmol) was dissolved in HF (2 g) and placed in a 30-mL-KEL-F-reactor dried with F_2 . After condensation of bis(trimethylsilyl)peroxide (1 mmol) at 77 K, the reaction mixture was warmed slowly to 203 K. The peroxonium salt was formed as a colorless solid. The trimethylfluorosilane and the excess HF were removed at 195 K under dynamic vacuum conditions.

The preparation of **2** was carried out in the same way as the preparation of **1** but with 2 mmol bis(trimethylsilyl)peroxide.

Equipment: Raman: Jobin-Yvon T64000, Ar^+ Laser ($\lambda = 514.5$ nm), Spectra Physics; IR: Bruker IFS 113v.

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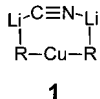
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- [3] a) X-ray data of **2** at 125 K: $M_r = 304.79$, triclinic, space group $P\bar{1}$, $a = 658.0(2)$, $b = 781.3(85)$, $c = 821.6(3)$ pm, $\alpha = 110.51(4)$, $\beta = 95.04(3)$, $\gamma = 113.90(4)^\circ$, $V = 0.34842\text{nm}^3$, $Z = 2$, $\rho_{\text{calc}} = 2.905\text{Mg m}^{-3}$, crystal dimensions $0.67 \times 0.3 \times 0.1\text{mm}^3$, $\mu(\text{Mo K}\alpha) = 4.054\text{mm}^{-1}$, $F(000) = 284$, 2246 measured reflections, 2107 independent reflections, and 2046 with $F_o > 4\sigma(F_o)$, $R_1 = 0.0397$ (all data: 0.0415), $wR_2 = 0.1222$, $S = 0.892$. b) Further details of the crystal structure investigations 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 numbers CSD-40854 (**1**) and CSD-40854 (**2**).

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The Crystal Structures of a Lower Order and a "Higher Order" Cyanocuprate: $[t\text{BuCu}(\text{CN})\text{Li}(\text{OEt}_2)_2]_\infty$ and $[t\text{BuCu}/\text{Bu}\{\text{Li}(\text{thf})(\text{pmdeta})_2\text{CN}\}]^{**}$

Gernot Boche,* Ferdinand Bosold, Michael Marsch, and Klaus Harms

Cyanocuprates are an important class of cuprates because of their significance in organic synthesis.^[1] On the basis of their different composition and reactivity they can be divided into two groups:^[2] lower order cyanocuprates of the type $\text{RCu}(\text{CN})\text{Li}$, with RLi and CuCN units in a 1:1 ratio, and "higher order" cyanocuprates of the type $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$, with RLi and CuCN units in a 2:1 ratio. In recent years the structure of the latter has been the topic of much investigation and controversial discussion.^[3] Do these compounds have a special reactivity due to a bis-anion character? EXAFS,^[4] NMR,^[5] and IR spectroscopic investigations^[6] indicated that the major proportion of the Cu atoms (>90%) is not bonded to the cyanide ion, and thus $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$ more likely exists as " RCuR-Li+LiCN " rather than with a three-coordinate Cu atom. This is consistent with quantum-chemical calculations which show **1** to be the most stable structure.^[4c, 7] Recent cryoscopic investigations in tetrahydrofuran at -108°C demonstrated that lower order cyanocuprates exist as a monomer $[t\text{BuCu}(\text{CN})\text{Li}]$ or as a dimer $[(\text{PhCu}(\text{CN})\text{Li})_2]$. For the higher order cyanocuprates $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$, cryoscopy revealed monomeric species ($\text{R} = \text{Me}, \text{Ph}$); however, in the case of $\text{R} = t\text{Bu}$ there is the possibility of a fast equilibrium between a



higher order and a lower order cyanocuprate.^[8] While only a few solid-state structures of Gilman cuprates containing the free structural element R_2Cu^- exist,^[9] no crystal structures of cyanocuprates have been described yet. Here we report on the crystal structures of $[t\text{BuCu}(\text{CN})\text{Li}(\text{OEt}_2)_2]_\infty$ (**2**), a lower order cyanocuprate, and $[t\text{BuCu}/\text{Bu}\{\text{Li}(\text{thf})(\text{pmdeta})_2\text{CN}\}]$ (**3**, pmdeta = pentamethyldiethylenetriamine), a compound of the type $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$.

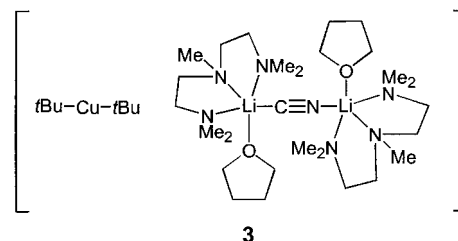
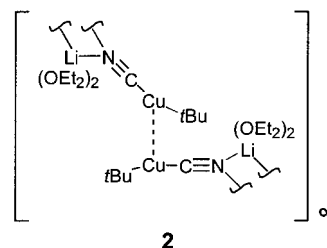


Figure 1 shows a section of the crystal structure of **2**.^[10a] The $t\text{Bu}$ group ($\text{Cu1}-\text{C2}$ 196.9(7) pm) and the cyanide ion ($\text{Cu1}-\text{C1}$ 187.8(8) pm) are bonded to the Cu atom. The N1 atom of the cyanide group ($\text{C1}-\text{N1}$ 115.9(9) pm) is coordinated to two Li cations (Li1 and Li1A), each of which is complexed by two diethyl ether molecules. By the formation of the four-membered ring N1-Li1-N1A-Li1A , an additional molecule

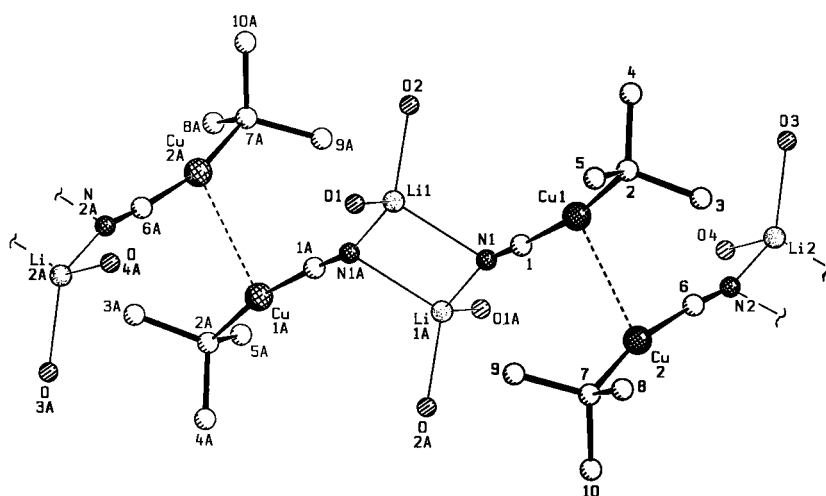


Figure 1. Section of the crystal structure of **2**. The ethyl groups of the diethyl ether molecules have been omitted for clarity.

is bound. The mutual arrangement of the two cyanocuprate units C2-Cu1-C1-N1 and C7-Cu2-C6-N2 is of particular interest. In both cuprates the angles C1-Cu1-C2 and C6-Cu2-C7 ($170.0(3)$ and $168.0(3)^\circ$, respectively) are less than 180° , while the dihedral angles C1-Cu1-Cu2-C6 and C1-Cu1-Cu2-C7 are $84.8(3)$ and $-94.9(3)^\circ$, indicating an almost perpendicular relative arrangement of the two cyanocuprates. The angle C1-Cu1-Cu2 (C6-Cu2-Cu1) amounts to $86.5(2)^\circ$ ($88.4(2)^\circ$), while that involving the $t\text{Bu}$ groups (C7-Cu2-Cu1

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103.5(2)°, C2–Cu1–Cu2 103.4(2)°) is clearly larger than 90°. The cuprate units are thus bent towards one another at the Cu atoms. The Cu1–Cu2 distance is 271.3(1) pm. This raises the question of whether in the case of **2** a Cu(d¹⁰)–Cu(d¹⁰) bond exists even in a free dimer, that is, not in a complex in which the Cu atoms are brought into close proximity through ligand complexation. After earlier quantum-chemical investigations by Hoffmann et al.,^[11] both R. Ahlrichs et al.^[12] and more recently P. Pyykkö et al.^[13] made comprehensive studies of the weak d¹⁰–d¹⁰ interactions of Cu compounds. Pyykkö et al. also compared these with interactions in similar compounds of Ag and Au. As models he used free metal–metal dimers of the type (ClCu(Ag,Au)PH₃)₂ with a perpendicular arrangement of the components, as found experimentally in the gold species.^[14] Although the Cu–Cu interactions (Cu–Cu 313.2 pm) are energetically 48% less favorable than the Au–Au interactions,^[15] they are sufficient for dimer formation. These model calculations thus demonstrate that the structure containing a perpendicular arrangement of two lithium cyanocuprate molecules, as for **2**, provides the first experimental indication for a Cu(d¹⁰)–Cu(d¹⁰) bond in a free dimer.^[16, 17]

A section of the crystal structure of [tBuCuBu{Li(thf)(pmdeta)}₂CN] (**3**)^[10b] is shown in Figure 2. The essential difference between the structures of **2** and **3** is that in **3** the tBuCuBu[–] anion is completely detached from the LiCNLi⁺ cation (Cu1–Li1 747.4, Cu1–Li1A 1062.3 pm). Consequently the cyanide ion also exhibits no contact with the Cu1 atom (C5 and N1 cannot be distinguished from one another in the X-ray crystal structure^[10b]). In the linear cuprate anion (C1–Cu1–C1A 180.0°) the C–Cu1 bonds are 195.7(4) pm long. Both Li1 and Li1A are surrounded by three N atoms of the pmdeta ligand and by the O atom of a THF molecule; they also form bonds with atoms C5 and N1A (210.5(7) pm) of the cyanide ion. The arrangement of the cyanide ion and the two Li⁺ ions is practically linear (C5b–N1–Li1 178.3(6)°). The structural situation in **3** corresponds essentially to that recently observed for a compound of the type [Ar₂Cu(CN)Li₂(thf)₄]_∞ (Ar = C₆H₄–2-CH₂NMe₂).^[18] A Gilman cuprate anion R₂Cu[–] is found also in this structure beside a solvated cation LiCNLi⁺. These solid-state structures are in agreement with most of the findings in solution.^[3–6]

Thus, higher order cyanocuprates R₂Cu(CN)Li₂, or better: cyano–Gilman cuprates,^[19] do not appear to be strongly different from normal Gilman cuprates, at least in the anionic portion. Perhaps it is significant that in the solid-state structures of Gilman cuprates Li⁺ is bonded to R–Cu–R[–] except if Li⁺ is complexed by a crown ether.^[16] Certain differences in reactivity and selectivity between these cuprates might therefore be due to differences in anion–cation interactions as well as different complexing solvents ligands, and the cyanide anion.^[19] From the structure of **3** it can also be seen that enantioselective syntheses with chiral cyano–cuprates should be successful only if the moiety X* that contains the chiral information remains bonded to the Cu atom. If complexes of X* with Li⁺ are formed, or if heterocuprates RCuX*Li are transformed into homocuprates RCuRLi and X*CuX*Li, the distance from X* to the reaction site is rather large.^[20] The fact that cyanocuprates of the type R₂Cu(CN)Li₂ have not been shown to be dimers by both cryoscopic measurements and determinations of solid-state structures could be a result of the smaller tendency of the R₂Cu[–] anion to form Cu–Cu bonds.^[16] The distinctly different reactivities and selectivities of compounds of the types RCu(CN)Li and R₂Cu(CN)Li₂ are consistent with the completely different cuprate structures which have been revealed for **2** and **3**.

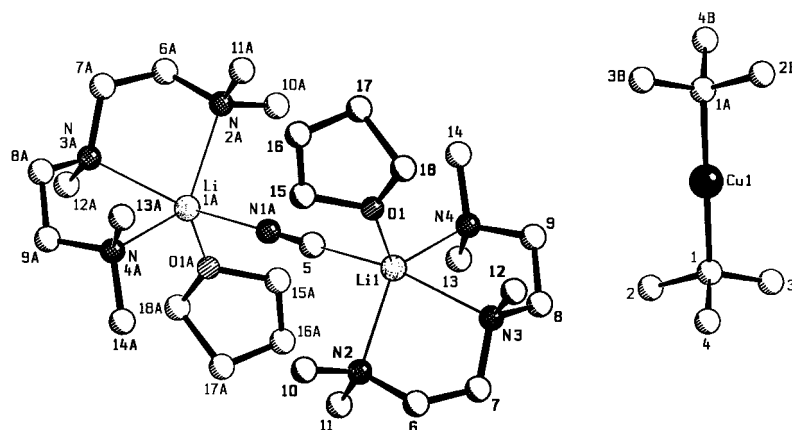
Experimental Section

2: CuCN (45 mg, 0.50 mmol) was heated under high vacuum, purged with argon, and layered with diethyl ether (2.2 mL). At 203 K 1.6 M *tert*-butyllithium in *n*-pentane (0.32 mL, 0.50 mmol) was added, and, while maintaining this temperature, the mixture was shaken vigorously until all CuCN had dissolved. After 24 h at 195 K crystals suitable for X-ray structure analysis had formed; yield: 83 mg (79%).

3: CuCN (45 mg, 0.50 mmol) was heated under high vacuum, purged with argon, and layered with THF (1 mL). At 233 K 1.6 M *tert*-butyllithium in *n*-pentane (0.63 mL, 1.00 mmol) was added, and, while maintaining this temperature, the mixture was shaken vigorously until all CuCN had dissolved. The mixture was warmed to 273 K and pmdeta (0.1 mL, 172 mg, 1.00 mmol) was added. After six days at 195 K crystals suitable for X-ray structural analysis had formed; yield: 290 mg (41%).

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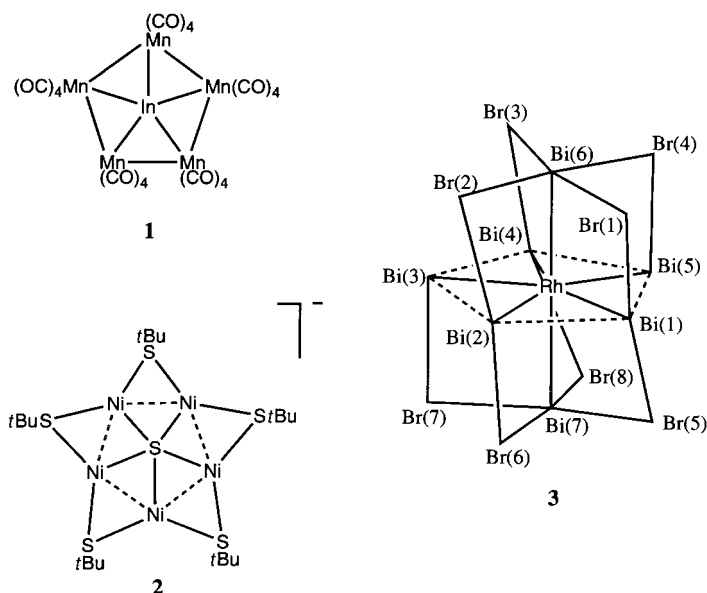
Unusual Five-Center, Four-Electron Bonding in a Rhodium–Bismuth Complex with Pentagonal-Bipyramidal Geometry**

Zhitao Xu and Zhenyang Lin*

Pentagonal coordinated molecules always provide very interesting bonding features. For example, in $[\text{In}(\text{Mn}(\text{CO})_4)_5]^{2-}$ (**1**),^[1] the indium atom and five manganese atoms lie almost in a plane. The bonding was elegantly described as an In^{3+} ion that binds the pentagonal Mn_5 ring.^[2] In the pentagonal ring there are five two-center, two-electron bonds. Each manganese center satisfies the 18-electron rule. In the recently synthesized pentagonal $[\text{Ni}_5(\mu_5\text{-S})(\mu_2\text{-SrBu})_5]^-$ cluster (**2**),^[3] the bonding has been described as having a six-center, ten-electron bond in the central $\text{Ni}_5(\mu_5\text{-S})$ unit.^[4] The cluster has a total of 70 valence electrons and actually conforms to the 16-electron rule. Very recently Ruck reported the synthesis and structural characterization of, and calculations on, a structurally remarkable ternary subhalide of bismuth containing the discrete rhodium–bismuth molecular complex $[\text{RhBi}_7\text{Br}_8]$ (**3**).^[5] In this complex the seven bismuth atoms are bonded to the central rhodium atom in a regular pentagonal-bipyramidal arrangement. The eight bromine atoms bridge the apical and equatorial bismuth atoms in a

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μ_2 -mode in which four are above the equatorial plane and the other four below the plane. In such an arrangement, two of the five equatorial bismuth atoms are coordinated to only one Br atom.

The results of band-structure calculations by Ruck^[5] show that the interactions between the central Rh atom and the coordinated Bi atoms are almost exclusively bonding, the Bi–Bi interactions between the equatorial atoms are all bonding while those between the equatorial and the apical Bi atoms are non-bonding. It was also noted that the Rh–Bi bonds within the equatorial plane are weaker than those along the axis. These weaker Rh–Bi bonds are compensated by an additional, homoatomic bond in the five-membered ring. Indeed, the average Bi–Bi nearest-neighbor distance of 3.22 Å in the Bi₅ ring is longer than the sum of two covalent radii (2.92 Å) but shorter than the recently reviewed closed-shell Bi–Bi interaction distances (3.50–3.80 Å).^[6] This bonding feature is very intriguing. What does this additional homoatomic bond look like? What is the overall electronic structure of this molecular cluster complex? In this communication we attempt to provide a clearer picture of the bonding based on the simple orbital interaction concept to describe the intriguing electronic structure of this molecular complex with the aid of ab initio molecular orbital calculations.

Full geometry optimizations were performed at both the HF and B3LYP levels (see Experimental Section for details). The optimized structural parameters are listed in Table 1, and where reported, experimental values are included for comparison. In view of the size of the metal cluster, the calculated structural parameters agree reasonably well with the experimental values. Overall, it seems that the B3LYP results agree better. The agreement could be improved if we increased the size of the basis sets by adding polarization functions for the Br atoms. It should also be noted that our calculation is for an isolated cluster. The close packing effect, as noted by Ruck,^[5] certainly influences the geometry of the cluster. An exact comparison is therefore not possible. However, our aim is to provide a qualitative bonding picture to understand the intriguing feature of the electronic structure.

Table 1. Selected bond lengths [Å] and bond angles [°] of the $[\text{RhBi}_7]\text{Br}_8$ molecular complex from both calculation and experimental results.

	HF	B3LYP	EXP
Rh–Bi(1)	2.734	2.735	2.732
Rh–Bi(2)	2.734	2.735	2.738
Rh–Bi(3)	2.751	2.743	2.749
Rh–Bi(4)	2.719	2.732	2.742
Rh–Bi(5)	2.751	2.743	2.719
Rh–Bi(6)	2.831	2.793	2.735
Rh–Bi(7)	2.831	2.793	2.719
Bi(1)–Bi(2)	3.256	3.285	3.266
Bi(2)–Bi(3)	3.183	3.171	3.228
Bi(3)–Bi(4)	3.235	3.232	3.191
Bi(4)–Bi(5)	3.235	3.232	3.203
Bi(5)–Bi(1)	3.183	3.171	3.194
Bi(1)–Bi(6)	3.950	3.913	3.813
Bi(1)–Bi(7)	3.934	3.898	3.882
Bi(6)–Br(1)	3.175	3.077	2.897
Bi(6)–Br(2)	2.796	2.871	2.876
Bi(6)–Br(3)	2.900	2.949	2.962
Bi(6)–Br(4)	3.332	3.197	3.010
Bi(1)–Rh–Bi(2)	73.10	73.80	73.32
Bi(2)–Rh–Bi(3)	70.95	70.74	71.08
Bi(3)–Rh–Bi(4)	72.50	72.36	71.05
Bi(4)–Rh–Bi(5)	72.50	72.36	71.81
Bi(5)–Rh–Bi(1)	70.95	70.74	71.73
Bi(6)–Rh–Bi(7)	179.49	179.67	178.91

Before continuing our discussion of the calculation results, we examine the relevant electron count of the complex. In the molecular complex, none of the seven Bi atoms has a terminal ligand. One can assume that each Bi atom has one lone pair of electrons whose maximum electron density is pointing away from the central Rh atom. In other words, each Bi atom has a lone pair (two electrons) that is not involved in the Rh–Bi or Bi–Bi bonding. The assumption should be reasonable in view of the fact that many naked Bi clusters (e.g., Bi₃⁺ and Bi₃²⁺),^[7] which conform to Wade's electron counting rules, have this feature in their electronic structures. Excluding these lone pair electrons and those electrons involved in the metal–bromide bonding, we can immediately have a valence electron count of 22 for the metal complex. These 22 metal electrons are responsible for the Rh–Bi and Bi–Bi interactions.

For a Rh complex in a three-dimensional ligand environment, one would expect it to conform to the 18-electron rule. An 18-electron regular ML₇ pentagonal-bipyramidal transition metal complex would normally have seven metal–ligand bonds (14 electrons) and two non-bonding d electron pairs (4 electrons in the d_{xz} and d_{yz} orbitals if the axis of the pentagonal-bipyramid is defined as the z axis). In the Rh complex, we would expect a similar bonding picture in which fourteen electrons are required to form the seven Rh–Bi σ-bonds (two axial and five equatorial bonds) and four electrons occupy the two non-bonding d_{xz} and d_{yz} orbitals. The remaining four electrons can be considered to be involved in the Bi–Bi interactions. Since the distances between the apical Bi and the equatorial Bi atoms are significantly longer than those between the adjacent Bi atoms in the equatorial plane, the remaining 4 electrons can be assigned to the Bi–Bi bonding among the 5 equatorial Bi atoms. This unprecedented five-center, four-electron bond is thus responsible for the observed Bi–Bi bonding in Ruck's band structure calculations.

At this stage, one would ask how the five-center, four-electron bond is formed. Examining carefully the local coordination environment of each Bi center in the equatorial plane, we find that each Bi atom has one p orbital not used in the Bi–Br and Bi–Rh bonding. This unused p orbital is lying on the equatorial plane and is tangential to the pentagonal ring. The symmetry-adapted linear combinations of five such tangential p orbitals (each Bi atom contributes one) can be easily derived from group theory.^[8] A pictorial illustration of the five symmetry-adapted linear combinations is shown in Figure 1. One can see that there are two bonding and three antibonding orbitals in the five linear combinations. Occupation of the two bonding orbitals (e_2 in a five-fold rotational point group) gives the five-center, four-electron bonding picture.

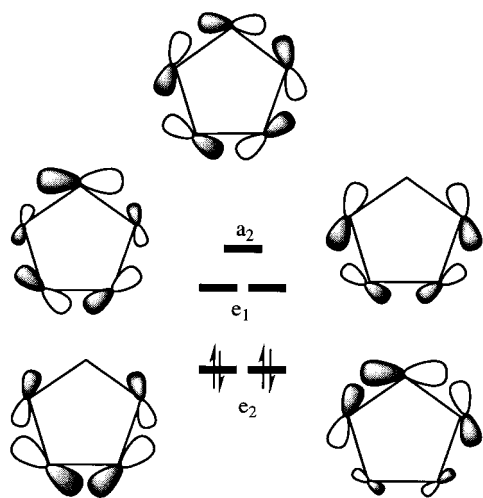


Figure 1. Schematic illustration of the five symmetry-adapted linear combinations based on the five tangential p orbitals of the Bi atoms. The relative locations of the MO energy levels are given.

Indeed, the two tangential Bi–Bi bonding molecular orbitals (e_2 in a five-fold rotational point group) are found from our *ab initio* molecular orbital calculations. Based on the B3LYP results, they are in the region of highest occupied molecular orbitals (HOMOs). Other molecular orbitals in the HOMO region also include those involving the seven Bi lone pairs pointing away from the Rh center. Figure 2 shows the spatial plots^[9] of the two Bi–Bi bonding molecular orbitals obtained from the B3LYP calculations. These two molecular orbitals are mainly derived from the tangential p orbitals of

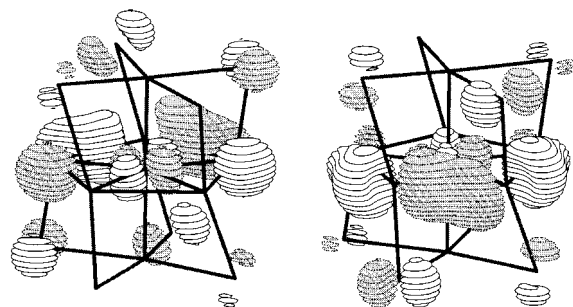


Figure 2. Spatial plots of the two Bi–Bi bonding molecular orbitals of the $[\text{RhBi}_7]\text{Br}_8$ molecular complex obtained from the results of B3LYP calculations.

the five equatorial Bi atoms, and the electron density is maximized between Bi–Bi bonds in the equatorial pentagonal ring. Slight mixings with orbitals from Br atoms and Rh can also be seen. The mixings are desirable, because Br atoms are π -donating ligands and Rh–Bi bonding orbitals (containing metal d orbitals) are low-lying and fully occupied. Ignoring the mixings, the overall features of these two Bi–Bi bonding molecular orbitals resemble the e_2 representations shown in Figure 1.

A preliminary examination of the Laplacian of electron density ($\nabla^2\rho$) on the equatorial plane indicates that all Bi atoms have maximum electron density pointing away from the central Rh atom. This result gives support for the assumption that each Bi atom has one lone pair of electrons not participating in metal–metal bonding. Since the Laplacian plot gives the overall feature of the electron density, it does not correlate directly with the five-center, four-electron bond discussed above.

In summary, the bonding in the $[\text{RhBi}_7]\text{Br}_8$ complex can be described as follows: The complex has 22 valence electrons available for Rh–Bi and Bi–Bi bonding interactions. The Rh center satisfies the 18-electron closed-shell electronic requirement. The remaining four electrons are mainly responsible for the Bi–Bi bonding among the five Bi atoms in the equatorial plane. An unusual five-center, four-electron bond is discovered in this complex. The approach here is to consider the Rh–Bi interactions first. The Bi–Bi bonding interactions are then derived from the available orbitals of individual Bi fragments from their local metal–ligand coordination. This kind of “local metal frontier orbital” approach has proved extremely successful in understanding the metal–metal interactions of transition metal cluster complexes containing mainly π -donating ligands.^[4, 10]

Experimental Section

Quasi-relativistic pseudopotentials of Stuttgart-type^[11] were employed in our *ab initio* calculations. Full geometry optimizations were performed at both HF and B3LYP levels with the Gaussian 94 suite of programs.^[12] The pseudopotential basis sets of the central Rh atom were described with (8s7p6d)/[6s5p3d], corresponding to a triple- ζ representation for the metal d orbitals. For the Bi atoms, basis sets with the polarized functions (4s4p1d)/[2s2p1d] were used, while for the Br atoms, basis sets of (4s5p)/[2s3p] were used. The total number of basis set functions used in the calculations was 215.

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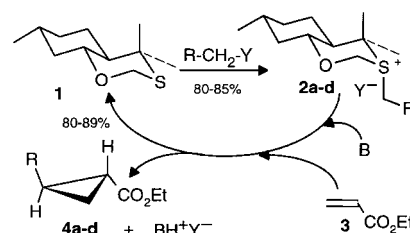
Two-Step Synthesis of *trans*-2-Arylcyclopropane Carboxylates with 98–100 % *ee* by the Use of a Phosphazene Base

Arlette Solladié-Cavallo,* Ahn Diep-Vohuule, and Thomas Isarno

We found recently that oxathiane **1** (see Scheme 1) is a very efficient chiral auxiliary that allows the preparation of various pure *trans*-diarylepoxydes in high yields ($\approx 85\%$) and with high enantiomeric purities (98.5–99.9 %).^[1] We report here the extension of this method to the synthesis of disubstituted cyclopropanes.

Since the first Simmons–Smith reaction in 1958,^[2] extensive work has been devoted to the synthesis of enantiomerically enriched polysubstituted cyclopropanes. Pure *trans*- (or pure *cis*-) disubstituted cyclopropanes with levels of enantioselectivity up to 93 % have been obtained from *trans*- (or *cis*-) olefins by the use of stoichiometric quantities of an external chiral promoter and an excess of the preformed $\text{Zn}(\text{CH}_2\text{I})_2 \cdot \text{DME}$ complex.^[3] However, with catalytic amounts of a chiral promoter only 90 % *ee* could be achieved.^[4] Although styrene was converted into a *trans*-alkoxycarbonyl-substituted cyclo-

propane with 99 % *ee* by adding only 1 mol% of a chiral copper catalyst,^[5] an exotic and very hindered ester had to be used to obtain a *trans/cis* ratio of 94/6. Starting from the inexpensive and commercially available ethyl ester, low *trans/cis* diastereoselectivities (*trans/cis* $\approx 70/30$) are obtained. Further difficulties arise from the fact that diazo reagents have to be used and that they have to be added slowly (over about 16 h for 0.02 mol) to avoid the formation of side products.^[6, 7] Therefore, for large-scale preparations the sulfur ylide method might be more promising, as already stated by Corey.^[8] However, until now the chirality had only been located on the olefinic moiety, and either yields^[9] or diastereomeric excesses^[10] were low. In the method described here the chirality is located at the sulfur center of the reagent, which is recoverable and can thus be reused (Scheme 1).



Scheme 1. Synthesis of cyclopropanes **4a–d**. **2a**: R = Ph, Y = TfO; **2b**: R = *p*-NCC₆H₄, Y = TfO; **2c**: R = *p*-*t*BuC₆H₄, Y = BF₄; **2c'**: R = *p*-*t*BuC₆H₄, Y = TfO; **2d**: R = 2-naphthyl, Y = BF₄; **4a**: R = Ph; **4b**: R = *p*-NCC₆H₄; **4c**: R = *p*-*t*BuC₆H₄; **4d**: R = 2-naphthyl. B = NaH, Et–P₂.^[13]

(Arylmethyl)sulfonium salts **2a–d** were prepared in about 80–85 % yield from RCH₂OH, Tf₂O, and pyridine in CH₂Cl₂^[11] or from RCH₂Br AgBF₄. Only one diastereomer was detected by ¹H and ¹³C NMR spectroscopy, and the axial position was assigned for the arylmethyl group in **2b–d** based on a comparison with spectra of the known **2a**.^[12] The corresponding ylides were generated in situ with either NaH or EtN=P(NMe₂)₂–N=P(NMe₂)₃ (“Et–P₂”)^[13] as base (Tables 1 and 2). With NaH in THF at –30 °C full conversions were achieved, as seen from the ¹H NMR spectra of the crude product, but 24 to 76 hours were required. Whereas cyclopropane **4a** was isolated in high yield (83 %) and with complete enantioselectivity (100 % *ee*), **4b** and **4d** were obtained with slightly lower enantioselectivities ($\approx 96\%$ for **4b** and $\approx 95\%$ for **4d**, Table 1). Only traces of the *cis* isomer of crude **4d** were detected, but about 15 % of the *cis* isomer was observed for **4b**. Surprisingly, in the case of **4c**, although

Table 1. Synthesis of cyclopropanes **4a–d** from **2a–d** in THF at –30 °C with NaH as base.

4	R	<i>c</i> _{ylide} [M]	<i>t</i> [h]	Crude product <i>trans/cis</i> ^[a]	<i>trans</i> - 4 yield [%] ^[b]	<i>ee</i> [%] ^[c]	Reisolat- ed 1 [%]
a	C ₆ H ₅	0.22	24	95/5	83	100	89
b	<i>p</i> -NCC ₆ H ₄	0.23	48	80/20	62	95.8	89
c	<i>p</i> - <i>t</i> BuC ₆ H ₄	0.23	72	$\geq 99/1$	50	60.8	80
d	2-naphthyl	0.19	6	95/5	78	94.8	80

[a] Determined by ¹H NMR spectroscopy (200 MHz). [b] Not optimized. [c] Determined by chromatography on a chiral phase (see ref. [16] and the supporting information).

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the *cis* isomer was not detected, the enantiomeric purity was only 61 %.

In an attempt to improve these results and to shorten the reaction time, we decided to generate more reactive “naked” carbanions by using a phosphazene base. Et–P₂ (p*K*_a ≈ 30),^[14] is potentially able to provide a high concentration of ylide and could be used in CH₂Cl₂. The results are summarized in Table 2. As expected, full conversions were achieved in only

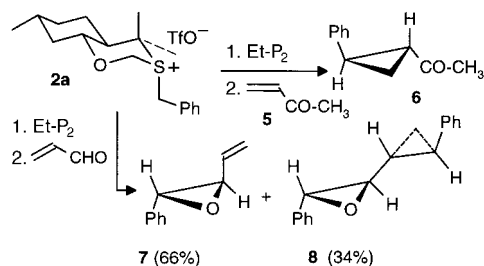
Table 2. Synthesis of cyclopropanes **4a–d** from **2a**, **b**, **c**, **d** in CH₂Cl₂ with Et–P₂ as base.

4	R	<i>t</i> [min]	<i>T</i> [°C]	<i>c</i> _{ylide} [M]	<i>trans/cis</i>	<i>trans-4</i> <i>ee</i> [%] ^[a] [<i>α</i>] _D ^[b]	Config.
a	C ₆ H ₅	15	–30	0.05	95/5	96.7	<i>R,R</i>
		15	–50	0.25	94/6 ^[a]	97.8	
b	<i>p</i> -NCC ₆ H ₄	30	–30	0.05	85/15	99.2	<i>R,R</i>
		30	–50	0.25	94/6 ^[a]	98.8	
c	<i>p</i> - <i>t</i> BuC ₆ H ₄	30	–30	0.05	96/4 ^[a]	98.9	<i>R,R</i>
d	2-naphthyl	30	–30	0.05	93/7	84.4	<i>R,R</i>
		30	–50	0.25	95/5 ^[a]	94.8	

[a] Determined by gas chromatography on CP-Chirasil-DEX CB and by HPLC on Chiralcel OJ for **4a**, and by HPLC on Chiralcel OJ for **4b–d** (see ref. [16] and the supporting information). [b] In ethanol.

15 to 30 minutes. The percentage of the *cis* isomer for **4b** was reduced to 6 %. It is worth noting that in all cases, after chromatographic separation from the starting oxathiane, the *cis* isomers were not detected by ¹H NMR spectroscopy (200 MHz). The enantiomeric purities of **4a–c** ranged from 97.8 to 98.9 %, and reached 94.8 % for **4d**.

The enolizable ketone **5** also reacted smoothly under the same conditions to provide the corresponding cyclopropane **6** in high yield and with high enantioselectivity (98.5 % *ee*, Scheme 2). In an analogous manner acrolein led mainly to the



Scheme 2. Reaction of **2a** with acrolein and **5**. The *trans* configuration at the epoxide ring was proven by the coupling constant for the *trans* protons (**7**: ³*J* = 2.5 Hz;^[11] **8**: ³*J* = 2 Hz); the configuration at the cyclopropane ring in **8** is unclear.

diastereomerically pure *trans*-epoxide **7** (66 %), although the epoxycyclopropane **8** was also observed (34 %) as a single diastereomer. The latter was generated by epoxidation of the already formed cyclopropane.

In all the cases the *trans* structure was assigned to the major compound with the help of ¹H NMR spectroscopy.^[15] The enantiomeric purities were determined by gas chromatography on a CP-Chirasil-DEX CB column in the case of **4a** and **6** or by HPLC on a Chiralcel OJ column in the case of **4a–d**.^[16] The 1*R*,2*R* absolute configurations were assigned to *trans*-

cyclopropanes **4b–d** and **6** on the basis of the *minus* sign of their optical rotations in ethanol; the 1*R*,2*R* isomer of the known **4a** is levorotatory in ethanol according to Walborsky^[17] and Evans.^[18] The *R,R* absolute configurations (obtained in all cases) are reasonably explained by the model already proposed for the syntheses of mono- and diarylepoxydes.^[11, 12] The approach of the Michael acceptor occurs opposite to the *gem*-dimethyl group (Figure 1). The very high *ee* values observed (98–100 %) could well be due to the participation of the salt present (Et–P₂H⁺TfO[–] or BF₄[–]) in a coordinative and/or electrostatic interaction in the transition state leading to the cyclization.

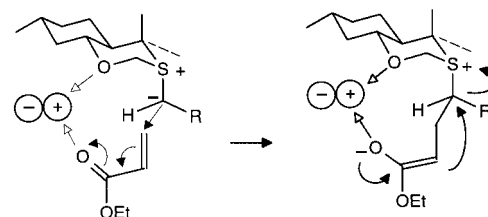


Figure 1. Possible participation of the salt (symbolized by a charge within a circle) in the mechanism of the cyclopropanation.

The chiral sulfur ylide derived from oxathiane **1** provides, in 15 to 30 minutes and with about 90 % conversion, 2-arylcyclopropane carboxylates (**4a–d**, **6**) with high enantioselectivities (98–100 % *ee*, 95 % for **4d**). It is worth noting that these ylides also react smoothly with an enolizable ketone to provide in high yield enantiomerically pure ketocyclopropanes of type **6**, which can then be further derivatized. Although used in stoichiometric amount, the chiral auxiliary is recovered in high yield; we are now searching for a way to avoid the presently necessary chromatographic separation. It is also worth noting that the phosphazene base can be recovered through precipitation of Et–P₂H⁺TfO[–].

Experimental Section

The base (1 equiv) and the Michael acceptor (2 equiv) were successively added (at the desired temperature) to a stirred solution of the sulfonium salt (5 mmol) in anhydrous CH₂Cl₂ (20 mL). The smooth reaction was monitored by thin-layer chromatography (TLC). After the reaction was complete, the mixture was poured into cold water, the aqueous phase was extracted with CH₂Cl₂ (5 × 10 mL), and the organic phases were combined and dried over NaSO₄. The cyclopropane derivative and the chiral auxiliary were then separated by chromatography (silica gel, hexane/ether 95/5), and the chiral auxiliary was reused. All compounds gave correct elemental analyses.

2a: ¹H NMR (200 MHz, CDCl₃, TMS): δ = 7.48 (m, 2H), 7.38 (m, 3H), 5.60 (d, 1H, ²*J* = 12 Hz), 4.80 (d, 1H, ²*J* = 12 Hz), 4.66 (s, 2H), 3.80 (td, 1H, ³*J* = 10.5, 10.5, 4.5 Hz), 2.01 (m, 1H), 1.80 (m, 2H), 1.74 (s, 3H), 1.68 (s, 3H), 1.50 (m, 2H), 1.30 (q, 1H, ³*J* = 11 Hz), 1.10 (m, 2H), 0.95 (d, 3H, ³*J* = 6.5 Hz); ¹³C NMR (50 MHz, CDCl₃, TMS): δ = 130.7, 71.0 (C), 130.1, 129.8, 127.0, 78.0, 43.0, 31.0 (CH), 58.0, 40.0, 36.0, 33.5, 24.0 (CH₂), 23.5, 22.0, 21.0 (CH₃), 120.7 (q, *J*_{CF} = 320 Hz).

2b: ¹H NMR (200 MHz, CDCl₃, TMS): δ = 7.75 (AB system, 4H, ³*J* = 8.5 Hz, Δ*ν* = 15 Hz), 5.53 (d, 1H, ²*J* = 12 Hz), 4.96 (d, 1H, ²*J* = 12 Hz), 4.80 (AB system, ²*J* = 13 Hz, Δ*ν* = 13 Hz), 3.76 (td, 1H, ³*J* = 10.5, 10.5, 4 Hz), all other signals are very similar to those of **2a**.

2c: ¹H NMR (200 MHz, CDCl₃, TMS): δ = 7.45 (brs, 4H), 5.62 (d, 1H, ²*J* = 12 Hz), 4.86 (d, 1H, ²*J* = 12 Hz), 4.57 (s, 2H), 3.80 (td, 1H, ³*J* = 10, 10, 4 Hz), all other signals are similar to those of **2a**. The ¹H and ¹³C NMR

spectra of **2c'** are identical to those of **2c** with the exception of the signal for the carbon atom of the anion CF_3SO_2^- at $\delta = 120.7$ (q, $J = 320$ Hz).

2d: ^1H NMR (200 MHz, CD_2Cl_2 , TMS): $\delta = 7.95$ (m, 4H), 7.56 (m, 3H), 5.43 (d, 1H, $^3J = 12$ Hz), 4.90 (d, 1H, $^3J = 12$), 4.77 (AB system, $^2J = 13$ Hz, $\Delta\nu = 15$ Hz), 3.79 (td, 1H, $^3J = 10.5$, 10.5, 4.5 Hz), 2.10 (m, 1H), 1.90 (m, 2H), 1.76 (s, 3H), 1.74 (s, 3H), 1.6 (m, 2H), 1.4 (q, 1H, $J = 11$ Hz), 1.1 (m, 2H), 1.0 (d, 3H, $^3J = 6.5$ Hz); ^{13}C NMR (50 MHz, CDCl_3 , TMS): $\delta = 134.1$, 133.8, 124.1, 71.5 (C), 131.4, 130.6, 128.5, 128.3, 128.2, 127.7, 127.0, 78.7, 43.7, 31.4 (CH), 58.5, 40.4, 36.9, 34.3, 24.1 (CH_2), 26.2, 22.0, 21.1 (CH_3).

4a: ^1H NMR (200 MHz, CDCl_3 , TMS): $\delta = 7.27$ (m, 3H), 7.13 (m, 2H), 4.18 (q, 2H, $^3J = 7$), 2.53 (ddd, 1H, $J = 9.5$, 6.5, 4 Hz), 1.91 (ddd, 1H, $J = 8.5$, 5.5, 4.5 Hz), 1.61 (ddd, 1H, $J = 9.5$, 5.5, 4.5 Hz), 1.32 (ddd, 1H, $J = 8.5$, 6.5, 4.5 Hz), 1.29 (t, 3H, $^3J = 7$ Hz); ^{13}C NMR (50 MHz, CDCl_3 , TMS): $\delta = 173.5$, 140.2 (C), 128.5, 126.5, 126.2, 26.3, 24.2, (CH), 60.7, 17.1 (CH_2), 14.4 (CH_3).

4b: ^1H NMR (200 MHz, CDCl_3 , TMS): $\delta = 7.50$ (d, 2H, $^3J = 8$ Hz), 7.13 (d, 2H, $^3J = 8$ Hz), 4.15 (q, 2H, $^3J = 7$ Hz), 2.49 (ddd, 1H, $J = 10$, 6.5, 4 Hz), 1.91 (ddd, 1H, $J = 8.5$, 5.5, 4 Hz), 1.62 (ddd, 1H, $J = 10$, 5.5, 4.5 Hz), 1.29 (ddd, 1H, $J = 8.5$, 6.5, 4.5 Hz), 1.22 (t, 3H, $^3J = 7$ Hz).

4c: ^1H NMR (200 MHz, CDCl_3 , TMS): $\delta = 7.33$ (d, 2H, $^3J = 8.5$ Hz), 7.06 (d, 2H, $^3J = 8.5$ Hz), 4.16 (q, 2H, $^3J = 7$ Hz), 2.51 (ddd, 1H, $J = 9.5$, 6.5, 4 Hz), 1.90 (ddd, 1H, $J = 8.5$, 5.5, 4 Hz), 1.60 (ddd, 1H, $J = 9.5$, 5.5, 4 Hz), 1.34 (ddd, 1H, $J = 8.5$, 6.5, 4 Hz), 1.32 (s, 9H), 1.29 (t, 3H, $^3J = 7$ Hz).

4d: ^1H NMR (200 MHz, CDCl_3 , TMS): $\delta = 7.78$ (m, 3H), 7.57 (s, 1H), 7.45 (m, 2H), 7.21 (dd, 1H, $^3J = 8.5$, $^4J = 2$ Hz), 4.19 (q, 2H, $^3J = 7$ Hz), 2.69 (ddd, 1H, $J = 9.5$, 6.5, 4.5 Hz), 2.01 (ddd, 1H, $J = 8.5$, 5.5, 4.5 Hz), 1.67 (ddd, 1H, $J = 9.5$, 5.5, 4.5 Hz), 1.47 (ddd, 1H, $J = 8.5$, 6.5, 4.5 Hz), 1.30 (t, 3H, $^3J = 7$ Hz); ^{13}C NMR (50 MHz, CDCl_3 , TMS): $\delta = 173.5$, 137.6, 133.5, 132.4 (C), 128.3, 127.7, 127.5, 126.4, 125.6, 124.9, 124.6, 26.5, 24.3 (CH), 60.9, 17.2 (CH_2), 14.4 (CH_3).

6: ^1H NMR (200 MHz, CDCl_3 , TMS): $\delta = 7.30$ (m, 3H), 7.10 (m, 2H), 2.53 (ddd, 1H, $J = 9$, 6.5, 4 Hz), 2.32 (s, 3H), 2.23 (ddd, 1H, $J = 8$, 5.5, 4 Hz), 1.70 (ddd, 1H, $J = 9$, 5.5, 4 Hz), 1.39 (ddd, 1H, $J = 8$, 6.5, 4 Hz); ^{13}C NMR (50 MHz, CDCl_3 , TMS): $\delta = 207.0$, 140.4 (C), 127.5, 126.5, 126.1, 33.0, 30.9, 29.1 (CH, CH_3), 19.2 (CH_2).

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Multiple Coordination of Metal Atoms to Arenes: The Coordination of Six Ruthenium Atoms to Naphthalene-1,8-diyl in $[\text{Ru}_6(\mu_6\text{-C}_{10}\text{H}_6)(\mu_3\text{-PPh})(\text{CO})_{14}]^{**}$

Antony J. Deeming* and Caroline M. Martin

Research on the incorporation of arenes into clusters has largely been stimulated by their potential as models for chemisorption on metal surfaces and by a wish to modify arene structure and reactivity.^[1,2] The chemistry of benzene with metal clusters has been developed extensively in recent years,^[3] and dominant modes of coordination are η^6 coordination at a single metal atom, $\mu_3\text{-}\eta^2, \eta^2, \eta^2$ coordination over a triangular cluster face, and combinations of these two modes with $\sigma\text{-M-C}$ bonding, as observed in phenyl and *ortho*-phenylene (1,2-didehydrobenzene) systems. Several of these modes resemble chemisorption of benzene on a (111) metal surface or on step-sites on such surfaces.^[4] In contrast, however, relatively few clusters that contain more complex, polycyclic arenes such as naphthalene and anthracene have been reported. Studies of such compounds are often hindered by the difficulty of introducing the polycyclic arene into the coordination sphere of the cluster, and has, so far, centered on mono- and binuclear species, with interactions through either σ bonds, as in $[\text{Fe}(\text{C}_{10}\text{H}_7)_4][\text{LiOEt}]_2$,^[5] or more commonly by π complexation through η^2 , η^4 , η^6 , or bis-allylic $\eta^3\text{:}\eta^3$ interactions, as in, for example, the compounds $[\text{Rh}_2(\text{C}_5\text{Me}_5)_2(1,2\text{-}\eta^2\text{-}3,4\text{-}\eta^2\text{-C}_{10}\text{H}_8)(\text{PMe}_3)_2]$,^[6] $[\text{RhCp}(\eta^4\text{-C}_{14}\text{H}_{10})]$,^[7] $[\text{Ru}(\eta^4\text{-C}_8\text{H}_{12})(\eta^6\text{-C}_{10}\text{H}_8)]$,^[8] and $[\text{Fe}_2(\text{CO})_6(\mu\text{-}\eta^3\text{:}\eta^3\text{-C}_{14}\text{H}_{10})]$.^[9] One of our recent objectives has therefore been to extend the coordination chemistry of naphthalene and anthracene by the combination of the σ and $\pi\text{-M-C}$ interactions that are present in the above molecules, to allow extensive metalation of each ring of the polycyclic arene.

We have introduced polycyclic arenes into the clusters by the thermal degradation of tertiary phosphanes in the presence of metal compounds. The thermolysis of $[\text{Ru}_3(\text{CO})_{12}]$

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with (1-naphthyl)diphenylphosphane yields a number of cluster derivatives (**1–4**), which generally retain the original P–C(naphthyl) bond (Scheme 1). The crystal structures of compounds $[\text{Ru}_3(\text{C}_{10}\text{H}_5\text{PPh}_2)_2\text{H}_2(\text{CO})_8]$ (**2**), $[\text{Ru}_4(\text{C}_{10}\text{H}_5\text{PPh}_2)(\text{CO})_{11}]$ (**3**), and $[\text{Ru}_5(\text{C}_{10}\text{H}_5\text{PPh}_2)(\text{PPh})(\text{CO})_{12}]$ (**4**) will be reported elsewhere.^[10] Here we present the title compound $[\text{Ru}_6(\mu_6\text{-C}_{10}\text{H}_6)(\mu_3\text{-PPh})(\text{CO})_{14}]$ (**1**), which contains a naphthalene-1,8-diyl moiety. This was formed by C–H cleavage at the 8-position together with P–C(naphthyl) bond activation. Complex **1** is unique in that the naphthalene-1,8-diyl group interacts through five carbon atoms to all six metal centers in the cluster framework in a rather dramatic manner; in addition to two Ru–C σ bonds at the 1 and 8 positions, there are also two η^3 and two η^2 interactions.

Compound **1** was initially identified on the basis of IR and NMR spectroscopy, and mass spectrometry;^[10] the mass spectrum exhibits a parent ion at m/z 1233 (most abundant isotopomer; calculated: m/z 1233), and the ^1H NMR spectrum shows a well-resolved ABC pattern, indicative of a symmetrically 1,8-disubstituted naphthalene group, together with a multiplet attributable to the phenyl protons. The molecular structure of **1** was confirmed by a single-crystal X-ray structure analysis and is shown in Figure 1.^[11]

Complex **1** has a triangular “raftlike” cluster geometry^[12] in which five of the ruthenium atoms are approximately coplanar and the sixth, Ru(1), is out of this plane by 2.367 Å. Hence, the Ru(1)–Ru(2)–Ru(3) triangular face, which is asymmetrically capped by a phosphanidene ligand, is tilted away from the Ru_5 plane with a dihedral angle of 105°. The C_{10} plane of the naphthalene lies at an angle of 42.0 and 63.1° to the Ru_5 and Ru_3 planes, respectively, which enables interaction with all six metal atoms. There are two η^2 interactions between C(1n)–C(2n) and Ru(4), and C(8n)–C(9n) and Ru(6), while the C(1n)–C(10n)–C(9n) unit interacts in an η^3 -allylic manner with both Ru(1) and Ru(5), and there are two σ bonds C(1n)–Ru(2) and C(9n)–Ru(3). Figure 2 shows three views of the Ru_6C_{10} core. Fourteen terminal carbonyl ligands complete the coordination sphere of the cluster.

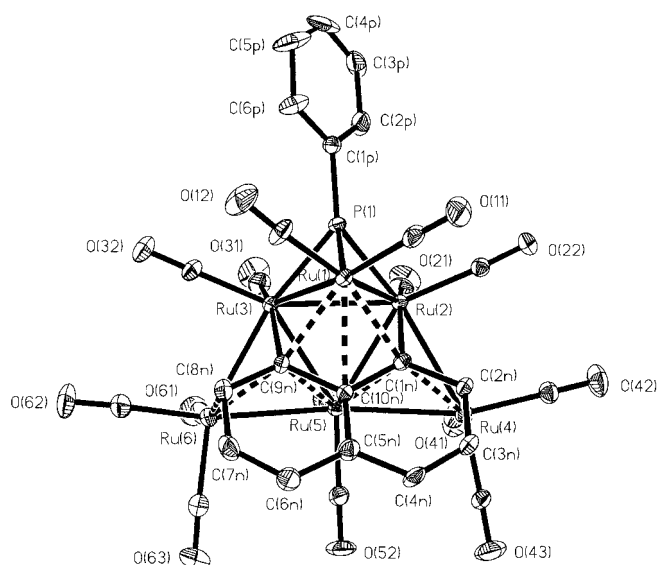
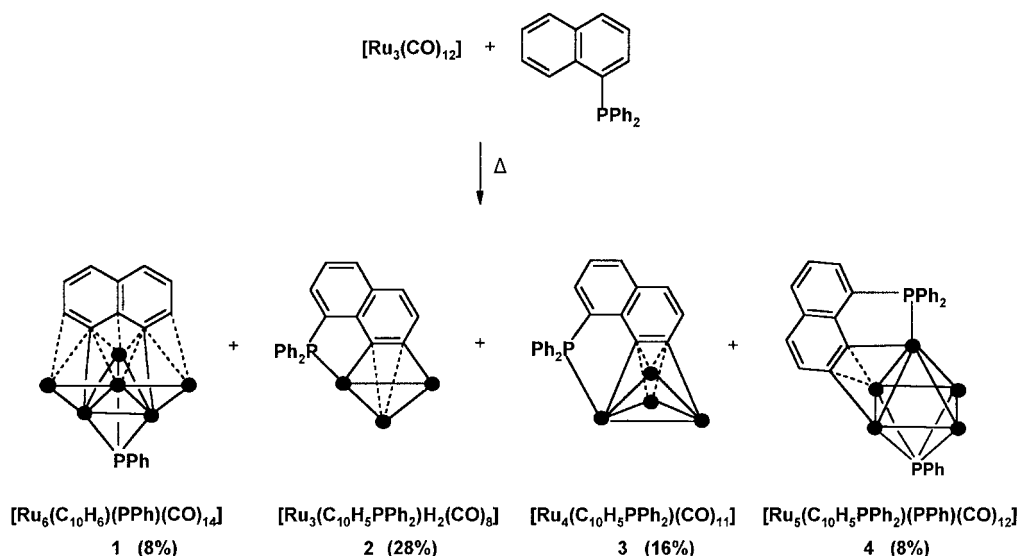


Figure 1. Molecular structure of **1**; the C atoms of the CO groups bear the same numbers as the corresponding O atoms. Selected bond distances [Å] and dihedral angles [°]: Ru(1)–Ru(2) 2.835(1), Ru(1)–Ru(3) 2.815(1), Ru(2)–Ru(3) 2.807(1), Ru(2)–Ru(4) 2.808(1), Ru(2)–Ru(5) 2.702(1), Ru(3)–Ru(5) 2.701(1), Ru(3)–Ru(6) 2.799(1), Ru(4)–Ru(5) 2.772(1), Ru(5)–Ru(6) 2.783(1), Ru(1)–P(1) 2.221(2), Ru(2)–P(1) 2.253(2), Ru(3)–P(1) 2.271(2), Ru(1)–C(1n) 2.267(6), Ru(1)–C(9n) 2.274(7), Ru(1)–C(10n) 2.397(7), Ru(2)–C(1n) 2.154(7), Ru(3)–C(9n) 2.142(7), Ru(4)–C(1n) 2.486(6), Ru(4)–C(2n) 2.266(7), Ru(5)–C(1n) 2.465(7), Ru(5)–C(9n) 2.480(7), Ru(5)–C(10n) 2.310(7), Ru(6)–C(8n) 2.265(8), Ru(6)–C(9n) 2.461(9), C(1n)–C(2n) 1.440(9), C(1n)–C(10n) 1.440(10), C(2n)–C(3n) 1.425(10), C(3n)–C(4n) 1.338(12), C(4n)–C(5n) 1.424(11), C(5n)–C(6n) 1.421(13), C(5n)–C(10n) 1.454(10), C(6n)–C(7n) 1.345(14), C(7n)–C(8n) 1.431(12), C(8n)–C(9n) 1.439(11), C(9n)–C(10n) 1.470(10); Ru(2)Ru(3)Ru(5)–Ru(3)Ru(5)Ru(6) 6.9, Ru(2)Ru(3)Ru(5)–Ru(2)Ru(4)–Ru(5) 7.3, Ru(2)Ru(3)Ru(5)–Ru(1)Ru(2)Ru(3) 105.1, Ru(2)Ru(3)Ru(5)–P(1)Ru(2)Ru(3) 13.9, Ru(2)Ru(3)Ru(5)–C(10n)(naphth) 42.0, Ru(1)Ru(2)–Ru(3)–C(10n)(naphth) 63.1.

The naphthalene-1,8-diyl group in **1** is thought to donate eight electrons to the cluster framework: two through the σ bonds and six through extensive π interactions. The C–C bond lengths within the organic ring are in agreement with this proposition and suggest that C(3n)–C(4n) and C(6n)–C(7n) maintain their double bond character (mean 1.34(1) Å), whilst all other C–C bonds are lengthened (mean 1.44(1) Å). These eight electrons, together with those donated by the PPh and fourteen CO ligands, give a total valence-electron count of 88 for the cluster. This is two fewer, according to simple electron-counting rules, than required for an electron-precise cluster with nine M–M bonds.

Naphthalene is known to form four-membered met-



Scheme 1. Thermolysis of $[\text{Ru}_3(\text{CO})_{12}]$ and (1-naphthyl)diphenylphosphane.

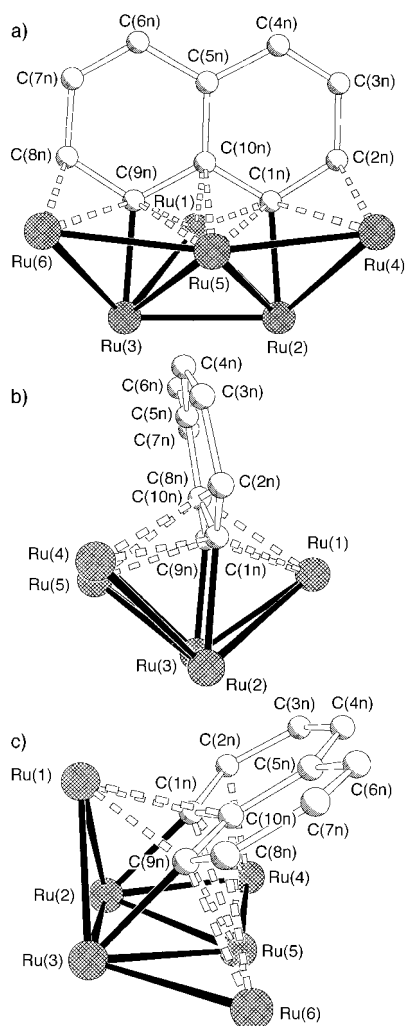


Figure 2. Three projections of the Ru_6C_{10} core of cluster **1**, showing the similarity to a step on a (111) Ru surface (a), the ten Ru–C bonding contacts (b), and the alignment of the C_{10} ligand within the metal cleft (c).

allacycles^[13] with a single metal center, where it is coordinated in a 1,8-diyl fashion. It can also be coordinated as a 1,2-didehydronaphthalene unit as in the clusters $[\text{Ru}_4(\mu_4\text{-C}_{10}\text{H}_6)(\mu_4\text{-AsC}_{10}\text{H}_7)(\text{CO})_{11}]$ and $[\text{Ru}_4(\mu_4\text{-C}_{10}\text{H}_6)(\text{CO})_{12}]$.^[14] However, as far as we are aware, this is the first time such extensive σ and π interactions have been observed between a polycyclic arene and a transition metal cluster. This illustrates, firstly, how it is possible to “load-up” such a simple organic molecule with metal atoms, which gives rise to the potential to construct clusters of higher nuclearity with the polycyclic arene as a convenient stable organic core about which an outer shell of metal atoms could be constructed. Secondly, our example shows how multiple coordination can stabilize an open geometric cluster framework. As the extent of σ and π bonding of the arene to the metal centers develops, one would predict increasing departure from normal arene behavior. Furthermore, one might envisage incorporation of another six Ru atoms on the opposite edge of the arene, to carbon atoms C(3n) to C(7n). In the context of the surface-cluster analogy, complex **1** might relate to the multiple interactions that could develop when naphthalene is chemisorbed at a step-site on a (111) metal surface.

Experimental Section

A solution of $[\text{Ru}_3(\text{CO})_{12}]$ (0.100 g, 0.157 mmol) and $\text{PPh}_2(1\text{-C}_{10}\text{H}_7)$ (0.50 g, 1.60 mmol) in octane (30 mL) was heated to reflux for 4 h. The solvent was removed in vacuo and the mixture separated by thin-layer chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{hexane}$ 3/7). Several products were isolated and characterized: $[\text{Ru}_3(\mu_3\text{-C}_{10}\text{H}_5\text{PPh}_2)(\mu\text{-H})_2(\text{CO})_8]$ (**2**) (yellow, 28%), $[\text{Ru}_4(\mu_4\text{-C}_{10}\text{H}_5\text{PPh}_2)(\text{CO})_{11}]$ (**3**) (purple, 16%), and $[\text{Ru}_5(\mu_5\text{-C}_{10}\text{H}_5\text{PPh}_2)(\mu_4\text{-PPh})(\text{CO})_{12}]$ (**4**) (orange-brown, 8%), each of which contains a didehydronaphthalene group formed by double metalation at the 7,8-positions of the unsubstituted ring. The final product isolated was the title compound $[\text{Ru}_6(\mu_6\text{-C}_{10}\text{H}_6)(\mu_5\text{-PPh})(\text{CO})_{14}]$ (**1**) (purple-black, 8%).

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- Spectroscopic data for **1**: IR (CH_2Cl_2): $\tilde{\nu}$ = 2077 m, 2053 vs, 2029 s, 2018 s, 2004 m, 1974 cm^{-1} w (CO); ^1H NMR (400 MHz, CDCl_2): δ = 8.72, (dd, ^3J = 8.28, 5.96 Hz, 2H, $\text{H}^{3n,7n}$), 7.94 (m, 2H, *o*-Ph), 7.63 (m, 3H, *m*-, *p*-Ph), 7.16 (d, ^3J = 8.30 Hz, 2H, $\text{H}^{4n,6n}$), 4.98 (d, ^3J = 5.92 Hz, 2H, $\text{H}^{2n,8n}$); positive-ion FAB MS: calcd: 1233, found: 1233. Selected data for other products: **2**: $\tilde{\nu}$ = 2081 s, 2049 s, br, 2038 m, sh, 2005 s, br, 1990 cm^{-1} m, sh (CO). **3**: $\tilde{\nu}$ = 2080 m, 2058 vs, 2037 s, sh, 2025 s, 2010 s, 1952 cm^{-1} m, sh (CO). **4**: $\tilde{\nu}$ = 2078 s, 2054 vs, 2042 vs, 2011 m, br, 1890 cm^{-1} m, sh (CO).
- X-ray crystal structure analysis of $[\text{Ru}_6(\mu_6\text{-C}_{10}\text{H}_6)(\mu_5\text{-PPh})(\text{CO})_{14}]$ **1**: black crystal from hexane, $\text{C}_{30}\text{H}_{11}\text{O}_{14}\text{PRu}_6$, $0.45 \times 0.40 \times 0.37 \text{ mm}^3$, M_r = 1232.80, orthorhombic, space group $P2_12_12_1$, a = 11.570(2), b = 16.484(2), c = 18.023(3) Å, V = 3437.3(9) Å³, Z = 4, ρ_{calcd} = 2.38 g cm⁻³, $\lambda(\text{Mo})$ = 0.71073 Å, $\mu(\text{Mo}_{\text{K}\alpha})$ = 135.6 cm⁻¹, $F(000)$ = 2328. Nicolet R3v/m diffractometer, direct methods (SHELXTL-PLUS), 4427 total data and 4399 unique data were collected (corrected for Lorentzian and polarization effects and for absorption by ψ -scans, max./min. transmission factors, 0.966/0.765), $5 \leq 2\theta \leq 55^\circ$. 4120 data with $I_o \geq 1.5\sigma(I_o)$ and 460 parameters (all non-hydrogen atoms anisotropic) were used in the refinement, final R = 0.0286 and wR = 0.0310 where $wR = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$ where $w = 1/[\sigma^2(F_o) + 0.000510 F_o^2]$. Hydrogen atoms added in calculated positions (C–H 0.96 Å) riding on the respective carbon atoms. Maximum peak in final difference Fourier = 0.52 e Å⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100597. Copies of the data can be obtained free of charge on application to CCDC, 12

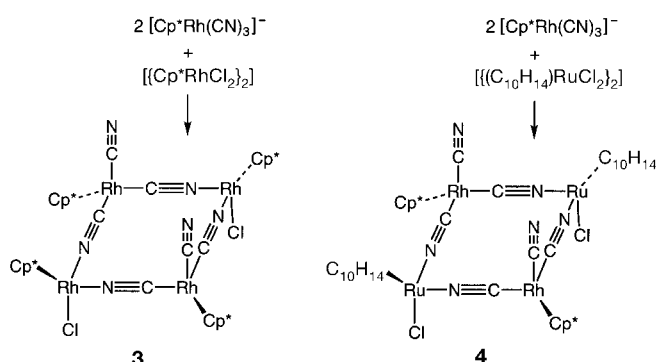
Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Stepwise Assembly of $[(C_5H_5)_4(C_5Me_5)_4Co_4Rh_4(CN)_{12}]^{4+}$, an "Organometallic Box" **

Kevin K. Klausmeyer, Thomas B. Rauchfuss,* and Scott R. Wilson

Solid-state coordination polymers^[1] and molecular coordination ensembles^[2–4] are typically constructed with bifunctional organic ligands such as 4,4'-bipyridine, and the vertices of the compounds are often square-planar or tetrahedral metal centers. An important advance in this area would involve the use of most common geometry for transition metals, the octahedron. Octahedral building blocks would allow the assembly of cube-shaped structures. Here we report the realization of this goal by the synthesis of a cubic array of cyano-linked^[5] metal octahedra, a subunit of the polymeric hexacyanometalates. Prussian Blue complexes^[6] such as $Fe_4[Fe(CN)_6]_3$ are polymeric by virtue of the sixfold bridging of the octahedral $[M(CN)_6]^{n-}$ subunits. In our approach, we have replaced three of these CN groups with a cyclopentadienyl ligand, which blocks one face of the octahedron. Polymerization is thus inhibited, and a family of cages with boxlike architectures results.



Scheme 1. Assembly of $M_2M'_2(CN)_4$ squares.

The tricyanometalates $Et_4N[Cp^*Rh(CN)_3]$ (**1**)^[7] and $K[CpCo(CN)_3]$ (**2**)^[8] were employed to prepare a series of molecular squares ($Cp^* = C_5Me_5$, $Cp = C_5H_5$). Thus, **1** reacts with $[Cp^*RhCl_2]_2$ (CH_2Cl_2 solution, 25 °C, 2 h) to give **3**, which was isolated as orange crystals after purification on Sephadex LH-20 (Scheme 1). The two-line ^1H NMR spectrum of **3** indicates that the Rh–C bonds are retained in the assembly process. Although other $M_4(CN)_4$ squares are known,^[9] the $2M(CN)_2 + 2M'$ route is novel.^[10] The complex [(cymene)- $RuCl_2$]₂ (cymene = 4-isopropyltoluene) reacts with **1** to give **4**. The ^1H NMR signal of C_5Me_5 group in **4** matches one of the signals of **3** and is assigned to the $Cp^*Rh(\mu-CN)_2(CN)$ moiety. A Co_2Rh_2 square **5** was prepared analogously with $[CpCo(CN)_3]^-$; in **5**, the Rh center is bound to the N atom of the cyanide ion. A single-crystal X-ray diffraction study confirmed the structure of **3** (Figure 1).^[11]

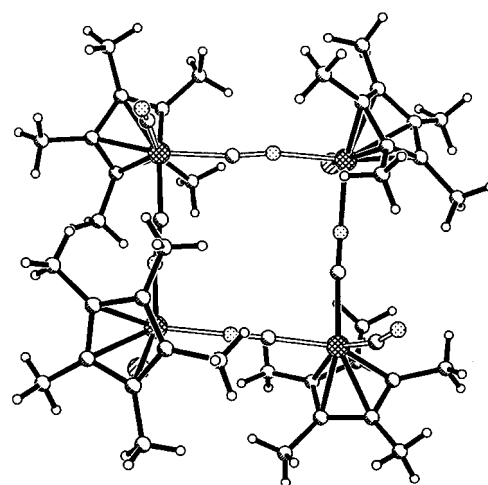


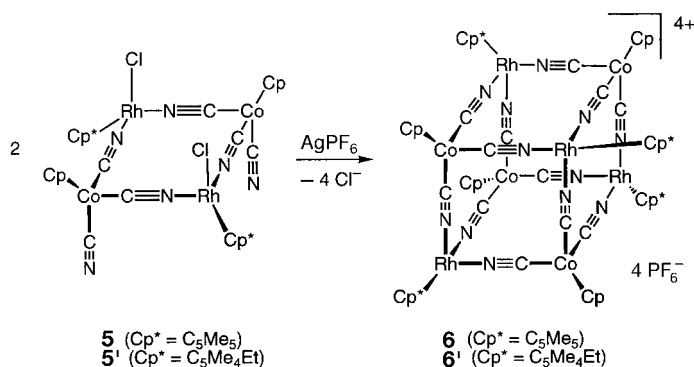
Figure 1. ORTEP plot of the structure of **3** with thermal ellipsoids drawn at the 50% probability level.

It is probable that many kinds of molecular objects could be prepared by using $[(C_5R_5)M(CN)_3]^-$ as metalloligands. Of particular interest are "molecular boxes" of the type $[(C_5R_5)_8M_8(\mu-CN)_{12}]$ in which metal centers occupy all eight corners. Molecular models show that Cp^*-Cp^* steric interactions would inhibit the assembly of the cubic cage $[Cp^*_8M_8(CN)_{12}]$; however, such boxlike architectures could be realized if half of the Cp^* ligands were replaced by the smaller Cp groups.

The synthesis of the box was effected by removal of the chloride ligands from **5** with $AgPF_6$ (Scheme 2; MeCN solution, 25 °C, 12 h). According to NMR measurements, the yield is nearly quantitative. Note that all twelve $\mu-CN$ units are provided by the two $[Co_2Rh_2(CN)_6]$ precursors without the need to break any M–C bonds. The 500 MHz ^1H NMR spectrum of the product is simple: it consists of one signal

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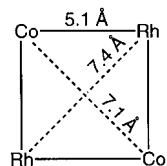
[**] This research was supported by the U.S. Department of Energy.



Scheme 2. Synthesis of **6**-4PF₆ and **6'**-4PF₆.

each for Cp and Cp* in a ratio of 1:3. The simplicity of the ¹H NMR spectrum also indicates that the Co–C bonds are retained, and the cage has idealized T_d symmetry. Compound **6** was also characterized by its electrospray mass spectrum which shows a peak for the molecular ion of [[Cp*Rh]₄][[CpCo(μ-CN)₃]]⁴⁺ (P) at *m/z* = 440.5 [P⁴⁺], as well as signals for the expected ion pairs at 1025 ([P · 2 PF₆]²⁺) and 2195 ([P · 3 PF₆]⁺). We also characterized the closely related and more easily crystallized derivative **6'**, which was obtained from the corresponding square **5'**. We conducted ¹³C NMR measurements on samples of **5'** and **6'** that had been isotopically enriched by using 30 % ¹³CN[−] in the synthesis to investigate the symmetry of the metal centers. In the case of **5'**, we observed CN signals at δ = 130.2 and 120 in an intensity ratio of 2:1, as expected for μ-CN and terminal CN ligands, respectively; for **6'**, we observed one intense CN signal at δ = 132.4.

Crystallographic studies show that the cation in **6'** (Figure 2) is highly symmetrical;^[12] it contains eight octahedral metal centers (alternating Co and Rh positions), which are bridged by twelve CN ligands. The metal–ligand distances and angles indicate an unstrained species, consistent with the facile assembly process. The regularity of the boxlike cage is indicated by the fact that all C–Co–C angles lie in the range 90–95°, and the N–Rh–N angles in the range 85–89°. The differences in these ranges reflect the relative sizes of the two types of cyclopentadienyl ligands. Six molecules of MeCN solvent are located near the six faces of the box but are neither bonded to nor inserted into the cage. The size of the cluster



Scheme 3. Dimensions of the Rh₂Co₂-(CN)₄ faces of **6'**.

can be estimated from the dimensions of the nearly square faces (Scheme 3). If one assumes an ideal cube whose angles are all 90° and whose edges are 5.1 Å long, then the volume of the box is approximately 132 Å³.

We have prepared a family of cubic molecular cages, the boxlike cores of which resemble subunits of an Prussian Blue lattice. The large volume of the box invites a study of the host–guest behavior of these species. It also appears that the synthetic methodology could be adapted to the preparation of related organometallic cyanometallates.

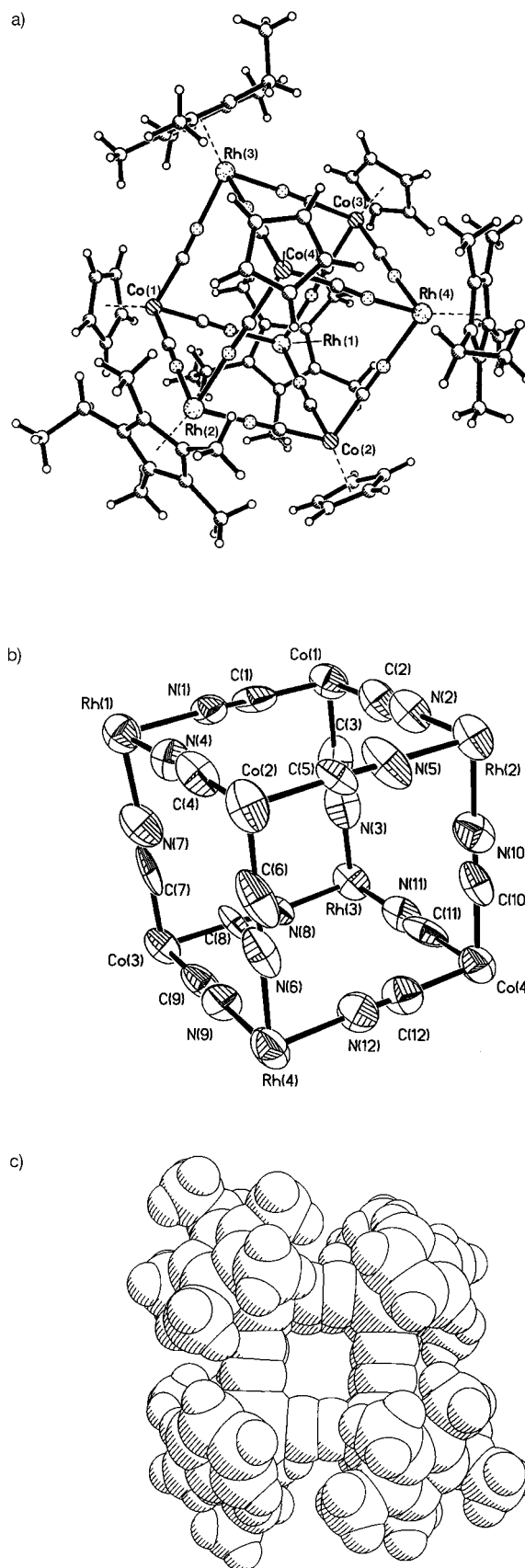


Figure 2. a) ORTEP plot of the Rh₄Co₄(CN)₁₂ framework in **6'** with thermal ellipsoids drawn at the 50% probability level. b) The inner Co₄Rh₄(CN)₁₂ framework; thermal ellipsoids set at the 50% probability level. c) Space-filling model of the cationic cage viewed perpendicular to a square face.

Experimental Section

6': A solution of **5'** (0.105 g, 0.107 mmol) in CH₃CN (20 mL) was added to a solution of AgPF₆ (0.054 g, 0.214 mmol) in CH₃CN (2 mL). After 12 h the slurry was centrifuged for 15 min at 5000 rpm. The supernatant was allowed to stand for a further 24 h, and the solvent was evaporated to give a yellow oil (further AgCl was removed by filtration through Celite). The oil was extracted into $\approx$ 3 mL of CH₃CN. The addition of 50 mL of Et₂O gave 0.078 g of product (60% based on **5'**). ¹H NMR (500 MHz, [D₃]CH₃CN, 22 °C, TMS): δ = 5.71 (s, 20H, C₅H₅), 2.34 (q, 8H, CH₃CH₂), 1.77 (d, 48H, (CH₃)₄C₅), 1.17 (t, 12H, CH₃CH₂); ¹³C NMR (125 MHz, [D₃]CH₃CN, 22 °C, TMS, sample enriched to 30% ¹³C): δ = 132.4 ppm (s, CN); IR (KBr pellet): $\tilde{\nu}$ = 2180 cm⁻¹ (C $\equiv$ N); elemental analysis calcd for C₇₆H₈₈N₁₂Co₄F₂₄P₄Rh₄: C 38.09, H 3.70, N 7.01; found (two independently synthesized batches): batch A: C 37.61, H 3.74, N 6.51; batch B: C 37.75, H 3.75, N 6.40.

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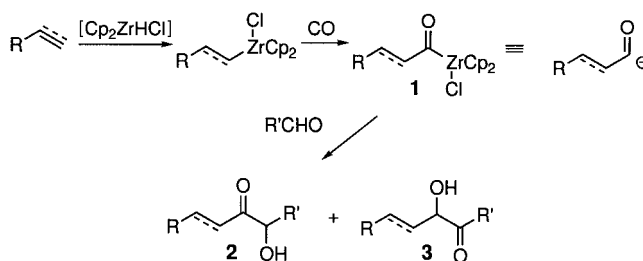
Keywords: cage compounds • cobalt • coordination chemistry • cyanide • rhodium

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Acylzirconocene Chloride as an “Unmasked” Acyl Anion**

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Easy access to stable acylzirconocene chloride derivatives **1** through a sequential treatment of alkenes or alkynes with zirconocene hydrochloride ([Cp₂ZrHCl], Schwartz reagent) and carbon monoxide has brought about the synthetic utility of **1** for the preparation of carboxylic acids and their derivatives.^[1] Extensive structural studies and work on the reactivity of acylzirconocene compounds have been carried out by many research groups^[2] to elucidate the characteristic features of the acylzirconocene derivatives. While the generation of very reactive acylmetals in which the metal species is a main group metal is a very attractive field,^[3] their use as an “unmasked” acyl anion for organic synthesis is limited due to their instability. The transition metal acyl complexes have also long attracted much attention because of their intrinsic usefulness as an acyl anion equivalent in organic synthesis.^[4] To the best of our knowledge, there is no report regarding the carbon–carbon bond forming reactions of **1** with carbonyls in which an acyl group of **1** reacts as an acyl anion to give α -ketol derivatives **2**. We describe here the first reactions of acylzirconocene chloride complexes **1** with aldehydes to give α -ketol derivatives **2** in fair to good yields under mild Lewis acid mediated conditions (Scheme 1).



Scheme 1. Preparation of acylzirconocenes **1** and their reactions with aldehydes.

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Table 1. α -Hydroxyketone derivatives **2** and **3** from acylzirconocene chlorides **1** and aldehydes.

Entry	Alkene or alkyne	Conditions ^[a] starting material	R'	Additive	Yield [%] ^[b]	
					2	3
1	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	A	Ph	AgBF ₄	22 ^[c]	—
2	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	A	Ph	AgAsF ₆	34 ^[c]	—
3	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	B	Ph	BF ₃ ·OEt ₂	79 ^[c]	—
4	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	B	Ph	ZnCl ₂	58 ^[c]	—
5	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	B	Ph	TiCl ₄	60 ^[c]	—
6	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	B	Ph	TiCl ₂ (OiPr) ₂	25 ^[c]	—
7	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	B	Ph	AlCl ₃	9 ^[c]	—
8	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	B	Ph(CH ₂) ₂	BF ₃ ·OEt ₂	49 ^[c]	29 ^[c]
9	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	B	<i>p</i> -MeOC ₆ H ₄	BF ₃ ·OEt ₂	62 ^[c]	18 ^[c]
10	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	B	(<i>E</i>)-PhCH=CH	BF ₃ ·OEt ₂	—	59 ^[c]
11	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	B	(<i>S</i>)-H ₃ CCH(OBn)	BF ₃ ·OEt ₂	53 ^[c,d]	—
12	$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	B	(<i>S</i>)-H ₃ CCH(OTBDMS)	BF ₃ ·OEt ₂	77 ^[c,e]	—
13	BnO(CH ₂) ₂ CH=CH ₂	C	Ph	BF ₃ ·OEt ₂	74 ^[f]	—
14	BnO(CH ₂) ₂ CH=CH ₂	C	(<i>E</i>)-H ₃ CCH=CH	BF ₃ ·OEt ₂	22 ^[f]	53 ^[f]
15	$n\text{-C}_4\text{H}_9\text{C}\equiv\text{CH}$	C	Ph	BF ₃ ·OEt ₂	69 ^[f]	—
16	Ph(CH ₂) ₂ C≡CH	C	Ph	BF ₃ ·OEt ₂	43 ^[f]	—
17	Ph(CH ₂) ₂ C≡CH	C	Et	BF ₃ ·OEt ₂	48 ^[f]	—
18	PhC≡CH	C	Ph	BF ₃ ·OEt ₂	65 ^[f]	—
19	PhC≡CH	C	Ph(CH ₂) ₂	BF ₃ ·OEt ₂	60 ^[f]	—

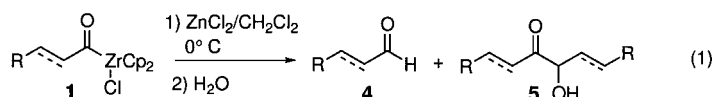
[a] A: See the experimental procedure except the molar ratio of alkene:[Cp₂ZrHCl]:R'CHO:additive = 2:1:1:2. B: Same as A except the ratio of alkene:[Cp₂ZrHCl]:R'CHO:additive = 4:2:1:2. C: Same as A except the ratio of alkene or alkyne:[Cp₂ZrHCl]:R'CHO:additive = 1:1.5:2:2. [b] Yield of isolated product. [c] Based of aldehyde. [d] *syn/anti* = 5.4. [e] *syn/anti* = 3.5. [f] Based on alkene or alkyne. Bn = benzyl. TBDMS = *tert*-butyldimethylsilyl.

Synthetic routes to **2** through the reactions of an “unmasked” acyl anion with carbonyl compounds are not common. Previous reports concerning “unmasked” acyl anions give acyllithium^[3] and/or acylsamarium^[4a] as the reagents of choice for the preparation of **2**. However, the generation and reactions of the acyllithium species with carbonyls require extreme conditions ($\approx -110^\circ\text{C}$). Similarly, the reactions of acylsamarium—generated by treating alkyl halide or acyl halide with a low-valent samarium complex—with carbonyls depend on the nature of the substrate.

The results of the reactions of **1** with aldehydes in the presence of an additive are listed in Table 1.^[5] The Lewis acidic silver ion is known to activate the carbonyl group and to accelerate the nucleophilic reactivity of the organozirconocene chloride complex by abstracting a chlorine atom to form a cationic organozirconocene species.^[6] Treatment of a mixture of **1** and aldehyde in dichloromethane with a silver salt at -20°C gives **2** in modest yields (18–34%) (entries 1–2). In the absence of the silver salt, no **2** could be observed in the reaction mixture. Although the yield of **2** is modest, the preferred silver salt is silver hexafluoroarsenate [AgAsF₆] (entry 2) as judged by the reaction rate and the clearness of the reaction medium.

Replacing the silver salt with a variety of other Lewis acids revealed that the yields of **2** depend largely on the specific Lewis acid employed. Thus, the yield of **2** was significantly improved to 79% when a stoichiometric amount (1 equivalent with respect to **1**) of boron trifluoride etherate (BF₃·OEt₂) was employed at 0°C (entry 3). α,β -Unsaturated acylzirconocene complexes **1** also reacted with aldehydes under the same reaction conditions to give **2** (entries 15–19). Steric bulk in the alkyl group of the aldehyde severely impeded the reaction. Thus, pivalaldehyde failed to react with **1** to give **2**. Furthermore, neither ketones nor acid chlorides react with **1**. In the BF₃·OEt₂-mediated reaction of **1**, isomeric α -ketol **3**

was isolated as a side product (entries 8, 9) or a major product (entries 10, 14), while the reaction of **1** derived from alkyne did not give the isomeric α -ketol product **3** (entries 15–19). The formation of **3** as a side product has also been reported in the reaction of acylsamarium with aldehydes.^[4a] It should be noted that the reactions of α -alkoxy aldehydes with **1** gave a 1,2-*syn* isomer as the major product (a *syn/anti* ratio from 3.5 to 5.4) (entries 11, 12).^[7] The exact role of the added Lewis acid in the present reaction is unclear. However, it is worth mentioning that the reaction of **1** with ZnCl₂ at 0°C without adding aldehyde gave the aldehyde **4** and α -ketol **5** in a 1:1



ratio [Eq. (1)]. This observation suggests that the transmetalation of **1** with ZnCl₂ giving an acylzinc derivative might be partially involved in the present reaction since the easy isomerization of acylzinc to an oxycarbene intermediate and the formation of α -ketol product **5** have been suggested.^[8]

The addition of AlCl₃, which is also reported to give acylaluminum^[9] by the transmetalation of **1**, yielded **2** in 9% yield (entry 7). We must await further study to be able to differentiate between the following mechanisms: a) the nucleophilic addition of the acyl group of **1** to the Lewis acid activated aldehyde, or b) the nucleophilic addition of the acyl group of the cationic species of **1** to aldehyde, or c) the transmetalation of **1** with Lewis acid.

In any event **1** is an excellent candidate as an “unmasked” acyl anion precursor, since the reported procedure in the literature for the generation and the reaction of the “unmasked” acyl anion is usually carried out at extremely low temperature and is hampered by the difficulty of the experimental procedure.

Experimental Section

A typical procedure for the reaction of **1** with benzaldehyde: To a suspension of $[\text{Cp}_2\text{ZrHCl}]$ (507 mg, 2.0 mmol) in CH_2Cl_2 (8 mL) was added 1-octene (0.62 mL, 4.0 mmol), and the resulting mixture was stirred for 30 min at ambient temperature. After the mixture had been stirred under an atmosphere of CO for 2 h, benzaldehyde (0.10 mL, 1.0 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (0.24 mL, 2.0 mmol) were added at -20°C , and the mixture was stirred at 0°C for 1 h. The reaction mixture was treated with aqueous NaHCO_3 and extracted with ether (3×15 mL). The combined ethereal extracts were washed with saturated sodium chloride solution, dried over MgSO_4 , and concentrated under reduced pressure to give a crude oil, which was purified by flash column chromatography (silica gel, hexane:EtOAc = 20:1 $\rightarrow$ 15:1 $\rightarrow$ 10:1) to give 1-hydroxy-1-phenyl-2-decanone (193 mg, 79 %). Spectroscopic data for 1-hydroxy-1-phenyl-2-decanone: mp $33.3\text{--}35.5^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ = 0.84–0.88 (3 H, m), 1.15–1.28 (10 H, m), 1.43–1.55 (2 H, m), 2.29 (1 H, ddd, J = 6.9, 7.9, 16.8 Hz), 2.37 (1 H, ddd, J = 6.5, 8.2, 16.8 Hz), 4.35 (1 H, d, J = 4.2 Hz), 5.08 (1 H, d, J = 4.2 Hz), 7.30–7.40 (5 H, m); ^{13}C NMR (100.6 MHz, CDCl_3): δ = 14.0, 22.5, 23.6, 28.87, 28.94, 29.1, 31.7, 37.7, 79.6, 127.4, 128.6, 128.9, 138.1; IR (KBr) $\tilde{\nu}$ = 3431 (broad), 2917, 1716 cm^{-1} ; EIMS m/z 248 [M^+]. Analysis calcd for $\text{C}_{16}\text{H}_{24}\text{O}_2$: C 77.38, H 9.74; found: C 77.14, H 9.57.

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Highly Enantioselective One-Pot Synthesis of Chiral Tri- and Tetrasubstituted Ferrocenes from 1,1'-Ferrocenedicarbaldehyde**

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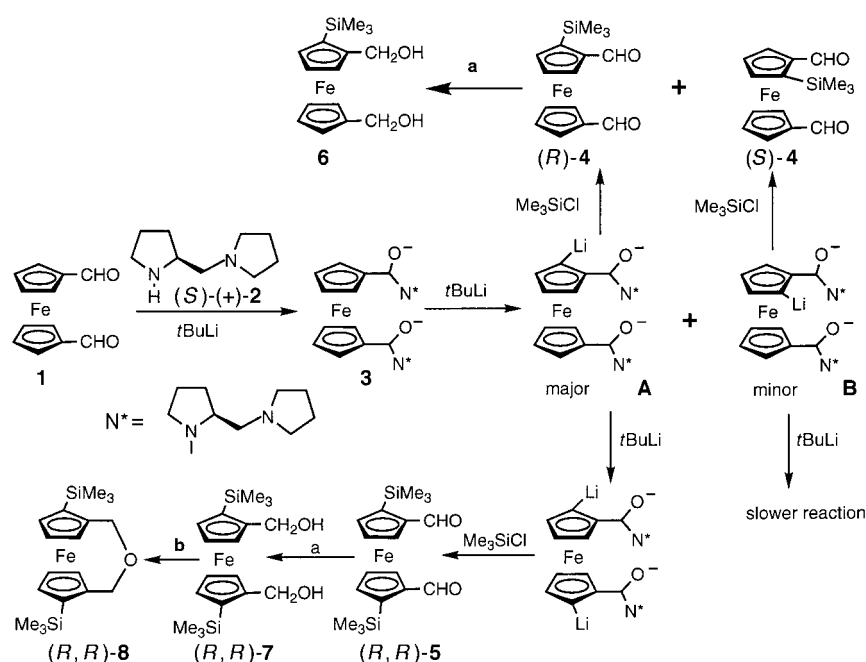
Owing to the increasing involvement of ferrocene derivatives in various fields^[1] such as asymmetric synthesis and catalysis^[2] and materials chemistry (especially for nonlinear optics),^[3] new methods for obtaining pure enantiomers of substituted ferrocenes with planar chirality are of current interest. Several efficient syntheses of chiral disubstituted ferrocenes are based on diastereoselective lithiation of ferrocenyl derivatives in the position *ortho* to substituents that exhibit asymmetric induction, such as tertiary amines,^[4] acetals,^[5] sulfoxides,^[6] and oxazolines.^[7] Recently, enantioselective *ortho* lithiation of nonchiral monosubstituted ferrocenes (direct synthesis)^[8] with chiral tertiary amines as auxiliaries was reported. This led to disubstituted ferrocenes with enantioselectivities of up to 99 % *ee*.^[8b] The enantioselective synthesis of C_2 -symmetric tetrasubstituted ferrocene derivatives with planar chirality has so far received little attention, and all the reported methods followed the diastereoselective *ortho* lithiation strategy.^[9] However, C_2 -symmetric tetrasubstituted ferrocenes are important starting materials for the design of chiral ligands that have given enantiomeric excesses of up to 99 % in asymmetric syntheses.^[10]

In 1981 Comins and Brown described a straightforward method in which the addition of a lithium amide to an aromatic aldehyde produced an amination anion as a temporary protecting/directing group for *ortho* metalation.^[11] Recently, Alexakis et al.^[12] reported the enantioselective *ortho* lithiation of a benzaldehyde complex of tricarbonylchromium by applying the same strategy with chiral amides. We described a new method for the synthesis of 1,1'-disubstituted ferrocenes by a one-pot procedure based on the addition of the lithium salt of *N*-methylpiperazine to ferrocenedicarbaldehyde. This produced an aminoaminal anion that protects the formyl group of one ring while its amino group directs the deprotonation in the other ring.^[13]

Here we report an extension of this procedure to the enantioselective synthesis of C_2 -symmetric tetrasubstituted ferrocenes **5** from 1,1'-ferrocenedicarbaldehyde (**1**) by means of the lithium salt of (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (**2**; Scheme 1). Treatment of the diaminal dianion **3** with *t*BuLi (1.5 equiv) at -78°C followed by reaction with the electrophile trimethylsilyl chloride afforded (*R*)-**4**, which after hydrolysis and purification by flash chromatography was obtained in 29 % yield with an enantiomeric excess^[14] of 96 %

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Scheme 1. Asymmetric synthesis of chiral ferrocenes. a) NaBH₄ (15 equiv)/MeOH/NaOH (2N). b) TsCl (1 equiv)/toluene/4-Å molecular sieve.

(Table 1, entry 1).^[15] No other substituted ferrocenes were detected, but the observation of significant amounts of insoluble brown material indicated partial decomposition of the ferrocene derivatives under these conditions. Increasing the temperature of the deprotonation step (−45 °C) decreases the yield of **4** to 15% without loss of enantioselectivity (entry 2). With an excess of *t*BuLi (3 equiv), bis-metalation occurs in the 2- and 2'-positions to give the C₂-symmetric disilylated compound **5**, which was isolated in 28% yield (entry 4). No other regio- or stereoisomers were detected. The enantiomeric excess of **5** is very high (>99%), and the minor enantiomer could not be detected by NMR spectroscopy.^[14] The molecular structure of **5** was elucidated by X-ray crystallography^[16] (Figure 1), which confirmed that the compound is C₂-symmetric and substituted in the 2- and 2'-positions. The *R,R* configuration of the planar-chiral **5** is consistent with the *R* configuration obtained for **4**.

When the amount of *t*BuLi was sufficient to give the dilithiated precursor of **5**, a lower enantiomeric excess of **4** was obtained (entries 1, 3, and 4). Adding three equivalents of *t*BuLi in one portion (entry 5) or in two portions (entry 6: the

monolithiated intermediate is obtained initially, as in entry 1) gave similar results. With a large excess of *t*BuLi (5 equiv, entry 7) the enantiomeric excess of **4** dropped to 56%. This could be explained by faster conversion of the monolithiated intermediate **A** (Scheme 1) to the dilithiated species, which would give an **A/B** mixture enriched in the (*S*)-configured minor diastereoisomer **B**.

We also report the transformation of the tetrasubstituted ferrocene **5** into the first C₂-symmetric disubstituted ferrocenophane to be obtained as a pure enantiomer.^[17] Reduction of **5** with an excess of NaBH₄ gave the diol **7** (71% yield). By means of a procedure described by Hillman et al. and modified by us,^[18] **7** was dehydrated with tosyl chloride (TsCl) in toluene in the presence of 4 Å molecular sieves at 50 °C.^[19] The (*R,R*)-bis(trimethyl-

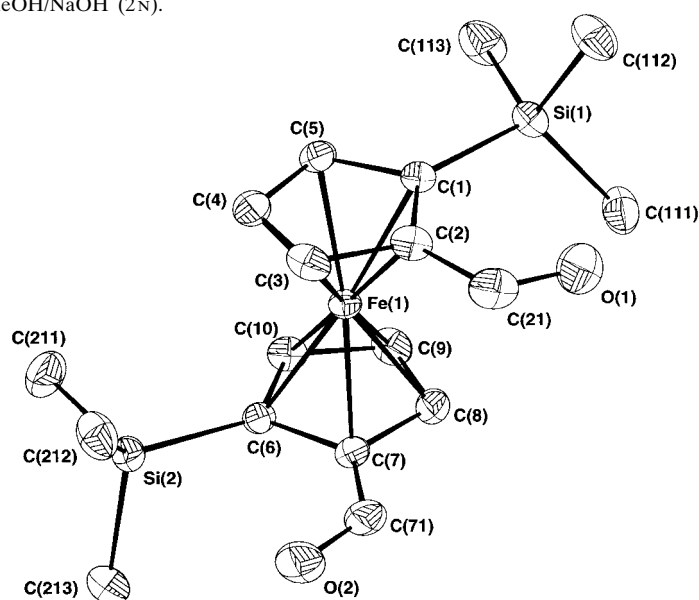


Figure 1. CAMERON representation of the molecular structure of **5** (single-crystal analysis^[16]). The thermal ellipsoids correspond to 30% probability. Selected distances [Å]: C(1)–Si(1) 1.876(2), C(6)–Si(2) 1.866(3), C(2)–C(21) 1.458(4), C(7)–C(71) 1.449(4), C(21)–O(1) 1.193(5), C(71)–O(2) 1.194(3).

Table 1. Direct synthesis of chiral tri- and tetrasubstituted ferrocenes from **1**.

Entry	Equiv <i>t</i> BuLi	Conditions ^[a] <i>T</i> [°C]	<i>t</i> [h]	Conversion [%]	Yield (4) [%] ^[b]	Yield (5) [%] ^[b]	Total yield (1 + 4 + 5) [%] ^[b]	<i>ee</i> (4) [%] ^[c]	<i>ee</i> (5) [%] ^[d]
1	1.5	−78	1	80	29	0	49	96	–
2	1.5	−45	1	85	15	0	30	96	–
3	3.0	−78	0.5	77	13	23	59	78	>99
4	3.0	−78	1	90	25	28	63	60	>99
5	3.0	−78	3	97	19	26	48	66	98
6	1) 1.5 2) 1.5	−78	1	90	21	19	50	65	>99
7	5.0	−78	3	100	13	24	37	56	96

[a] 2.2 equiv **2**, electrophile = ClSiMe₃. [b] Yields of isolated products and recovered starting materials. [c] *R* configuration in all cases. [d] *R,R* configuration in all cases.

silyl)- β -oxatrimethyleneferrocene (**8**) was obtained in 44 % yield (Scheme 1) and characterized by X-ray crystallography^[16] (Figure 2). The geometry of the ferrocenophane unit (tilt angle: 11.4°) is similar to those of other 1,1'- β -oxatrimethyleneferrocenes.^[19]

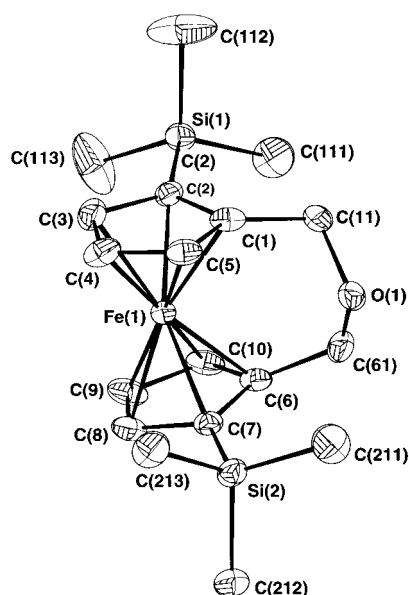


Figure 2. CAMERON representation of the molecular structure of **8** (single-crystal analysis^[16]). The thermal ellipsoids correspond to 30 % probability. Selected distances [Å]: C(2)–Si(1) 1.857(6), C(7)–Si(2) 1.864(6), C(1)–C(11) 1.45(1), C(6)–C(61) 1.52(1), C(11)–O(1) 1.45(1), C(61)–O(1) 1.40(1).

Here we have described the first direct and highly enantioselective synthesis of tri- and tetrasubstituted ferrocenes with exclusively planar chirality by using a chiral aminoamide as a temporary protecting/directing group. This method converts achiral 1,1'-ferrocenedicarbaldehyde into almost enantiomerically pure tetrasubstituted or trisubstituted ferrocenes in a one-pot procedure. We are now attempting to improve the yields and to extend the scope of this method.

Experimental Section

(R)-4: A solution of *t*BuLi in pentane (1.5 M, 575 μ L) was added to a solution of (*S*)-**2** (150 mg) in dry ether (4 mL) at 0 °C under argon. After stirring for 30 min, 1,1'-ferrocenedicarbaldehyde (100 mg, 0.41 mmol) in dry ether (10 mL) was added. After stirring for 30 min at room temperature, the mixture was cooled to –78 °C, and 1.5 equiv of a solution of *t*BuLi in pentane (1.5 M, 410 μ L) was added. After stirring for 1 h at –78 °C, trimethylsilyl chloride (270 μ L, 5 equiv) was added. After aqueous workup and flash chromatography, (*R*)-**4** was isolated in 29 % yield (37 mg). For physical data, see ref. [18].

(R,R)-5 was prepared as (*R*)-**4** but with 3 equiv of *t*BuLi in the deprotonation step. After purification, 32 mg (25 %) of (*R*)-**4** and 46 mg (29 %) of (*R,R*)-**5** were obtained. ¹H NMR (250 MHz, CDCl₃, 23 °C): δ = 9.99 (s, 2H), 5.04 (dd, *J* = 2.5, 1.3 Hz, 2H), 4.72 (t, *J* = 2.5 Hz, 2H), 4.49 (m, 2H), 0.31 (s, 18H); ¹³C NMR (63 MHz, CDCl₃, 23 °C): δ = 193.7 (CHO), 84.1, 80.3, 76.0, 75.7, 75.2, –0.1 (SiMe₃); GC-MS (IE, 70 eV) *m/z* (%): 387 [*M*+1] (31), 386 [*M*] (100), 371 (51), 191 (10); [α]_D = +419 (CHCl₃, *c* = 0.12).

(R,R)-7 was obtained by reduction of (*R,R*)-**5** with NaBH₄ in methanol (71 %). ¹H NMR (250 MHz, CDCl₃, 23 °C): δ = 94.49 (d, AB system, *J* = 12.5 Hz, 2H), 4.38 (d, AB system, *J* = 12.5 Hz, 2H), 4.36 (m, 2H), 4.26 (t,

J = 2.3 Hz, 2H), 4.06 (dd, *J* = 2.3, 1.3 Hz, 2H), 3.42 (brs, 2H), 0.23 (s, 18H); ¹³C NMR (63 MHz, CDCl₃, 23 °C): δ = 93.7, 74.2, 70.7, 70.6, 69.6, 60.6, 0.2 (SiMe₃); [α]_D = –9.57 (CH₂Cl₂, *c* = 0.53).

(R,R)-8 was prepared in 44 % yield by a modification of the procedure described by Hillman et al.^[18] ¹H NMR (250 MHz, C₆D₆, 23 °C): δ = 94.47 (dd, *J* = 2.4, 1.3 Hz, 2H), 4.29 (t, *J* = 2.4 Hz, 2H), 4.12 (dd, *J* = 2.4, 1.3 Hz, 2H), 4.02 (d, AB system, *J* = 13.0 Hz, 2H), 3.92 (d, AB system, *J* = 13.0 Hz, 2H), 0.37 (s, 18H); ¹³C NMR (63 MHz, CDCl₃, 23 °C): δ = 87.3, 76.5, 74.2, 73.0, 71.4, 64.0 (CH₂), 0.8 (SiMe₃); GC/MS (IE, 70 eV) *m/z* (%): 372 [*M*] (100); [α]_D = –27 (CH₂Cl₂, *c* = 0.7).

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- [15] [α]_D = –7.6 (*c* = 0.9, CHCl₃) for **6**. Comparison with an authentic sample of the enantiomerically pure diol (*S*)-**6** ([α]_D = +8.1; *c* = 0.9, CHCl₃) gave an *ee* of 94 %. See also ref. [19].
- [16] Crystal data for **5**: C₁₈H₂₆O₂Si₂Fe, *M_r* = 386.42; orthorhombic, space group *P*2₁2₁2₁, *a* = 6.970(1), *b* = 12.266(2), *c* = 23.068(2) Å, *V* = 1971.9(4) Å³, *Z* = 4, ρ_{calcd} = 1.302 g cm^{–3}; μ = 8.882 cm^{–1}; empirical absorption correction applied (ψ scan), MoK α radiation, *T* = 293 K, $\omega/2\theta$ scan (Enraf-Nonius CAD4 diffractometer); 2 θ_{max} = 56°; of 4445 reflections collected, 3805 were independent (*R_m* = 0.017) and 3583 were regarded as observed (*I* > 3 σ (*I*)); 210 parameters were refined; *R*/*R_w* = 0.0346/0.0400, GOF = 0.849, Δ/σ = 0.095, [$\Delta\rho$]_{min}/[$\Delta\rho$]_{max} = –0.41/0.75; Flack's parameter = 0.01(1). Crystal data for **8**: C₁₈H₂₈O₂Si₂Fe; *M_r* = 372.4; orthorhombic, space group *P*2₁2₁2₁, *a* = 7.113(1), *b* =

11.963(2), $c = 22.865(4)$ Å, $V = 1945.7(3)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.271$ g cm⁻³; $\mu = 8.942$ cm⁻¹; no absorption correction applied; MoK α radiation; $T = 293$ K; F scan (Stoe IPDS diffractometer); F range 0–250°; of 7483 reflections collected, 2983 were independent ($R_m = 0.074$) and 2037 were regarded as observed ($I > 2\sigma(I)$); 210 parameters refined; R/R_w 0.0424/0.0460, GOF = 1.104, $\Delta/\sigma = 0.041$; $[\Delta\rho]_{\text{min}}/[\Delta\rho]_{\text{max}} = -0.37/0.56$; Flack's parameter = 0.00(3). The structures of **5** and **8** were solved with the programs SIR92 and CRYSTALS. 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-100607. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

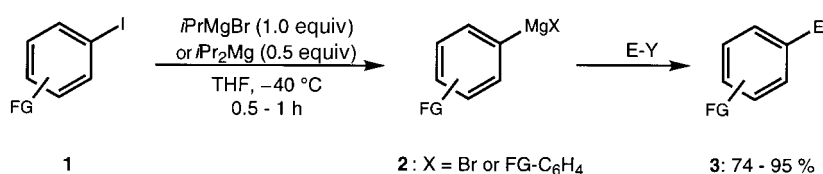
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Preparation of Highly Functionalized Grignard Reagents by an Iodine–Magnesium Exchange Reaction and its Application in Solid-Phase Synthesis

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In memoriam Henri Normant

Organomagnesium reagents are extremely important in synthetic organic chemistry. Since their discovery, there has great interest in these versatile reagents, and numerous industrial applications have been reported.^[1] Grignard reagents can be conveniently synthesized from organic halides and exhibit high reactivity and satisfactory chemoselectivity, which can be further improved by transmetalation.^[2] However, very few functionalized organomagnesium reagents have been prepared due to the low functional-group tolerance of these reagents.^[1] Here we report a general route to highly functionalized arylmagnesium halides of type **2**, which contain functional groups such as ester, amide, or cyano groups, or a



Scheme 1. Functional group (FG) = Br, CONR₂, CN, CO₂Et, CO₂tBu; E–Y = aldehyde, allyl bromide.

halogenide substituent and were synthesized from functionalized aryl iodides of type **1** by an iodine–magnesium exchange reaction.^[3] The reaction of **2** with electrophiles E–Y (aldehyde or allyl bromide) gave the expected aromatic products of type **3** in good to excellent yield (Scheme 1 and Table 1).

Preliminary experiments showed that treatment of 1-iodonaphthalene (**1a**) with *i*PrMgBr or *i*Pr₂Mg in THF at 25 °C for 1 h or 0.5 h, respectively, gave the corresponding Grignard reagent **2a** in 90% yield (GC analysis of aliquots of

Table 1. Synthesis of compounds **3** by iodine–magnesium exchange of aryl iodides **1a–i** with *i*Pr₂Mg followed by reaction with an electrophile E–Y.

Entry	Aryl iodide 1	T [°C]/ t [h] ^[a]	E–Y	Product 3	Yield [%] ^[b]
1		25/0.5	CH ₂ CHCH ₂ Br		80 (87) ^[c]
2		–40/0.5	CH ₂ CHCH ₂ Br		79 ^[d]
3		–25/0.5	PhCHO		93
4		–25/0.5	CH ₂ CHCH ₂ Br		95
5		–25/0.5	CH ₂ CHCH ₂ Br		81
6		–40/1	CH ₂ CHCH ₂ Br		75 ^[d]
7		–40/1	PhCHO		94
8		–40/1	<i>n</i> -C ₆ H ₁₃ -CHO		74
9		–40/0.5	CH ₂ CHCH ₂ Br		89
10		–40/0.5	PhCHO		89
11		–40/1	PhCHO		94 (91) ^[c]
12		–40/1	PhCHO		90 (90) ^[c]

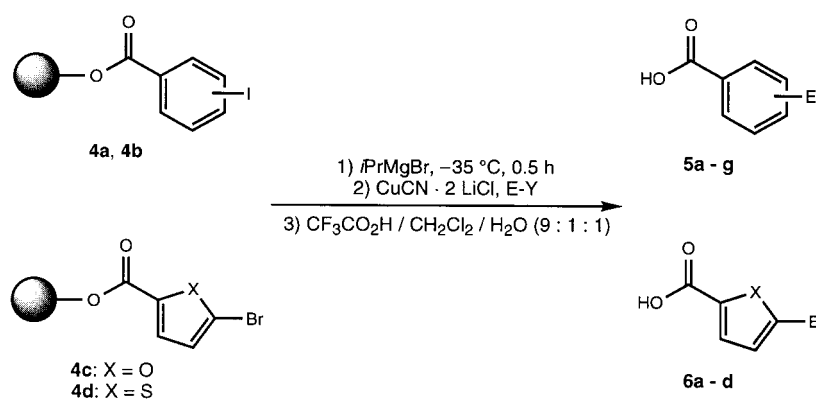
[a] Reaction conditions for iodine–magnesium exchange. [b] Yield of analytically pure product. [c] Yield obtained by performing iodine–magnesium exchange with (*cyclo*-C₃H₅)₂Mg. [d] The allylation was performed in the presence of CuCN·2LiCl (10 mol %). [e] *i*PrMgBr (1.05 equiv) was used in this case.

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the reaction mixture after quenching with water). The stability of the Grignard reagent is lowered by the presence of the isopropyl iodide formed in the iodine–magnesium exchange reaction. Elimination of hydroiodic acid presumably occurs. This can be avoided by using dicyclopentylmagnesium, since the resulting cyclopentyl iodide less readily eliminates HI. Alternatively, the arylmagnesium reagents can be stabilized by using one equivalent of *i*Pr₂Mg instead of 0.5 equivalents; the excess is presumably used for the elimination reaction. Treatment of the Grignard reagent derived from 1-iodonaphthalene (**1a**) and *i*Pr₂Mg (0.53 equiv, THF, 25 °C, 0.5 h) with allyl bromide gave 1-allylnaphthalene (**3a**) in 80 % yield. When (*cyclo*-C₅H₉)₂Mg was used for the exchange reaction (0.53 equiv, 25 °C, 3 h), **3a** was obtained in 87 % yield. Iodine–magnesium exchange can also be performed at –20 °C: the aryl iodide **1a** is converted into the magnesium compound **2a** in 4–5 h. Since Grignard reagents are unreactive towards many functional groups at low temperature, iodine–magnesium exchange opens the way for the preparation of functionalized Grignard reagents. Treatment of 4-bromoiodobenzene (**1b**) with *i*Pr₂Mg (THF, –40 °C, 0.5 h) afforded the corresponding Grignard reagent **2b** (>98 % conversion), which was quenched with allyl bromide (1.1 equiv) in the presence of CuCN·2LiCl^[4] (10 mol %) to give **3b** in 79 % yield. No bromine–magnesium exchange product could be detected. Treatment of **2b** with benzaldehyde gave the corresponding alcohol **3c** in 93 % yield (Table 1, entry 3). The conversion of 2-bromoiodobenzene (**1c**) to the corresponding Grignard compound **2c** proceeds smoothly, and treatment with allyl bromide leads to the allylated product **3d** in 95 % yield (entry 4). As expected, an amide function as in **1d** does not affect the iodine–magnesium exchange reaction (entry 5). When the exchange reaction is carried out at –40 °C, nitrile groups in the *ortho*, *meta*, and *para* positions are tolerated (entries 6–10). Even ester groups are compatible with a carbon–magnesium bond in the same molecule; quenching with benzaldehyde gave the corresponding benzylic alcohols **3k–l** in 90–94 % yield (entries 11 and 12).

After these initial successes, we envisioned that this exchange reaction could be used to generate an aryl Grignard reagent on a polymer support and therefore have applications in combinatorial chemistry.^[5] Various substituted aryl or heteroaryl iodides or bromides attached to Wang resin^[6] through an ester function (**4a–d**) were treated with *i*PrMgBr (ca. 7 equiv) at –35 °C for 15–30 min. The desired Grignard reagents were formed with >95 % conversion, as indicated by quenching experiments with electrophiles such as allylic bromides, tosyl cyanide,^[7] diphenyl disulfide, or an aldehyde (Scheme 2 and Table 2). After cleavage from the resin with trifluoroacetic acid, the expected products of type **5** or **6** were obtained in good to excellent purity. Remarkably, heteroaryl bromides such as **4c** and **4d** undergo a smooth bromine–magnesium exchange reaction under the same reaction conditions (–35 °C, 0.5 h, entries 8–11 of Table 2).



Scheme 2. For **4a**, **4b**, **5a–g**, **6a–d**, and E–Y, see Table 2.

Table 2. Synthesis of the compounds **5** and **6** obtained by solid-phase synthesis via an intermediate functionalized resin-bound Grignard reagent.

Entry	Resin-bound ester 4	E–Y	Product 5 or 6	Purity [%] ^[a]
1		CH ₂ CHCH ₂ Br		98
2	4a	CH ₂ C(CO ₂ Et)CH ₂ Br	5a : R=H 5b : R=CO ₂ Et	99
3	4a	TosCN		95
4	4a	PhSSPh		87
5	4a	PhCHO		95 ^[b,c]
6		PhSSPh		87
7	4b	TosCN		92 ^[b,d]
8		TosCN		94 ^[b]
9		TosCN		91 ^[b]
10	4d	CH ₂ CHCH ₂ Br		99
11	4d	CH ₂ C(CO ₂ Et)CH ₂ Br		94

[a] Purity determined by HPLC analysis (RP-18, MeCN/H₂O, 0.1 % CF₃CO₂H, UV detection at 254 nm). The yield in each case was >90 % as determined by weighing. [b] No CuCN·2LiCl was used in this case. [c] After treatment of the cleaved product with aqueous solutions of NaOH and HCl and filtration of the product. [d] UV detection at 215 nm.

We have shown that the iodine–magnesium or bromine–magnesium exchange with *i*Pr₂Mg or *i*PrMgBr proceeds under mild conditions, tolerates various functional groups, and is therefore a widely applicable method for preparing highly functionalized magnesium compounds. The scope and limitations of this method are currently under investigation.^[8]

Experimental Section

Typical procedure for an iodine–magnesium exchange reaction: Preparation of **31**: A solution of ethyl 4-iodobenzoate (552 mg, 2 mmol) in THF (20 mL) was cooled to -40°C , and $i\text{Pr}_2\text{Mg}$ (2.3 mL, 1.06 mmol) in *tert*-butyl methyl ether was added. After 1 h at -40°C , benzaldehyde (233 mg, 2.2 mmol) was added. After stirring for 3 h, the reaction mixture was worked up as usual to give a crude yellow oil, which was purified by flash chromatography (pentane/ether, 80/20) to give 460 mg of pure **31** (90% yield).

Typical procedure for an iodine–magnesium exchange reaction on the solid phase: Preparation of **5a**: Wang resin (100 mg) charged with 4-iodobenzoic acid (70 μmol) was dried for 2 h under vacuum (0.1 Torr) at 50°C . After cooling to room temperature under an inert atmosphere, the resin was allowed to swell for 10 min in THF (2 mL). The heterogeneous mixture was cooled to -35°C , and a solution of $i\text{PrMgBr}$ (0.70 mL, 0.51 mmol, 0.73 M) in THF was added. After stirring for 15 min, a solution of $\text{CuCN} \cdot 2\text{LiCl}$ (0.70 mL, 0.7 mmol, 1.0 M) was added, followed, after a further 15 min, by allyl bromide (0.30 mL, 50 equiv). After stirring for 40 min, the reaction mixture was filtered, and the resin was successively washed with DMF, MeOH, and CH_2Cl_2 (six cycles) and treated with $\text{CF}_3\text{CO}_2\text{H}$ (4 mL of $\text{CF}_3\text{CO}_2\text{H}/\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, 9/1/1) for 20 min. After filtration and evaporation of the volatile materials under high vacuum, **5a** (10.8 mg, 95% yield) was isolated as a white solid. The HPLC purity was 98% (RP-18, $\text{MeCN}/\text{H}_2\text{O}$, 0.1% $\text{CF}_3\text{CO}_2\text{H}$; UV detection at 254 nm).

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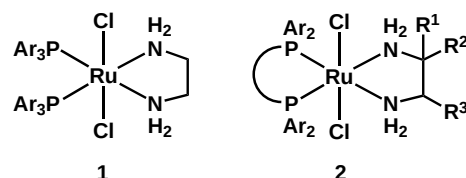
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trans-[RuCl₂(phosphane)₂(1,2-diamine)] and Chiral *trans*-[RuCl₂(diphosphane)(1,2-diamine)]: Shelf-Stable Precatalysts for the Rapid, Productive, and Stereoselective Hydrogenation of Ketones**

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We recently discovered that a system comprising [RuCl₂-(phosphane)_n], 1,2-diamine, and an inorganic base is an excellent catalyst for the hydrogenation of simple ketones in 2-propanol, at high substrate/catalyst molar ratios (S/C) under mild conditions.^[1] In addition to other features, this reaction is characterized by high diastereo-, enantio-, and C=O/C=C selectivity. However, the concentration of the catalytic species generated *in situ* remains unknown. Because the quantities of the metallic and organic components used are extremely small, it is possible that the intermolecular reactions may be incomplete. Furthermore, the catalytically active metal complexes may not be the only complexes formed. We speculated that the use of a pure, stable phosphane/diamine complex would significantly increase the catalytic efficiency. We describe here procedures for the preparation of Ru^{II} complexes with phosphane and diamine ligands from commercial or other readily available materials. As expected, these complexes proved to be exceedingly efficient hydrogenation precatalysts. The reaction rate and productivity were two orders of magnitude higher than those obtained from the complexes generated *in situ*.

Achiral Ru type **1** complexes with triarylphosphane, ethylenediamine, and chloro ligands were prepared by the addition of two equivalents of ethylenediamine to [RuCl₂(phosphane)₃]^[2] in CH₂Cl₂ at 25°C . The mixture was stirred for three hours (method A). Type **2** chiral complexes were most



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conveniently obtained by treatment of oligomeric $[\text{RuCl}_2(\text{diphosphane})(\text{dmf})_n]^{[3]}$ with 1.1 equivalents of a diamine^[4] in dmf at 25 °C for three hours (method B). In place of $[\text{RuCl}_2(\text{binap})(\text{dmf})_n]$, $[\text{NH}_2(\text{C}_2\text{H}_5)_2][\{\text{RuCl}(\text{binap})\}_2(\mu\text{-Cl})_3]^{[5]}$ and $[\text{RuCl}(\text{binap})(\eta^6\text{-arene})]\text{Cl}^{[6]}$ can also be used (abbreviations are given in Figure 1). The desired mixed-ligand com-

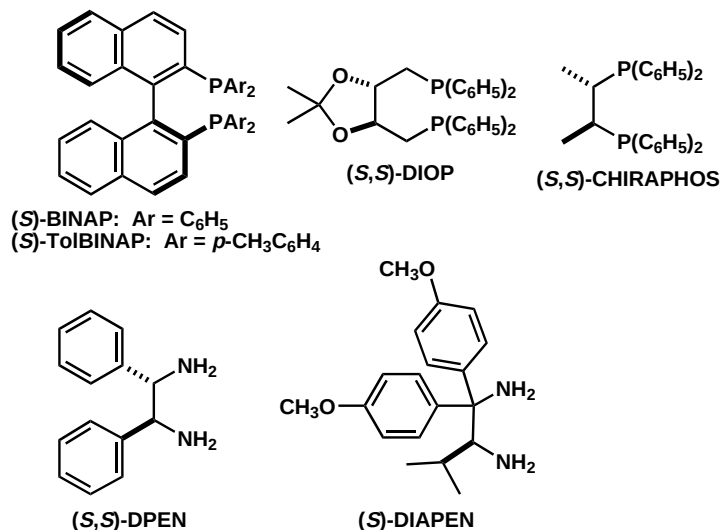


Figure 1. Chiral diphosphanes and diamines

plex can also be obtained by the reaction of $[\text{Ru}\{\eta^3\text{-CH}_2\text{C}(\text{CH}_3)\text{CH}_2\}_2(\text{diphosphane})]^{[7]}$ in acetone with two equivalents of methanolic HCl, followed by treatment of the resulting $[\text{RuCl}_2(\text{diphosphane})]_n$ with one equivalent of a diamine in DMF at 25 °C for three hours (method C). This procedure, though somewhat tedious, provides a general route to the preformed complexes. The diphosphane/diamine Ru complexes thus prepared^[8] are listed in Table 1. These complexes are soluble in many common organic solvents. The *p*-tolylphosphane and TolBINAP^[9] complexes are more soluble than the triphenylphosphane and BINAP analogues. The isolated Ru complexes are fairly air- and moisture-stable and can be stored in an ordinary vial for a long period, preferably under an argon atmosphere.

All the complexes in Table 1 have *trans*-dichloro geometries. Single-crystal X-ray analysis^[10] of (*R*),(*R*),(*R*)-**2d** indicated a distorted octahedral geometry of the Ru center that approaches C₂ symmetry, in which both the TolBINAP and DPEN chelate ligands are coordinated in a λ fashion (Figure 2a). In the diastereomer, (*R*),(*S*),(*S*)-**2e**, the TolBINAP ligand forms a λ seven-membered structure, while the DPEN ligand assumes a five-membered ring structure with a δ conformation (Figure 2b).

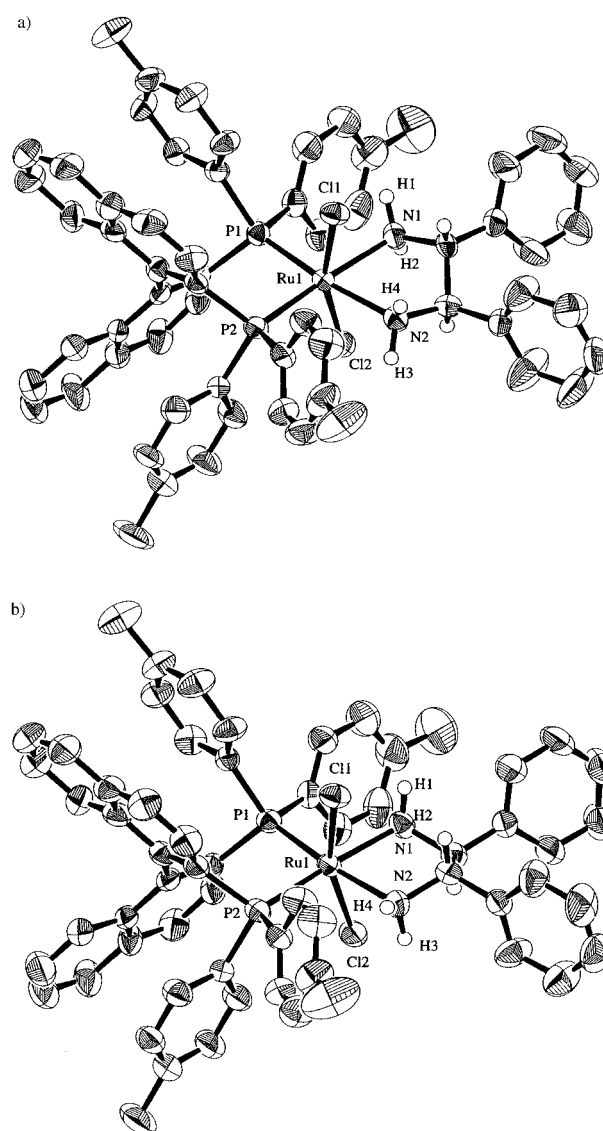


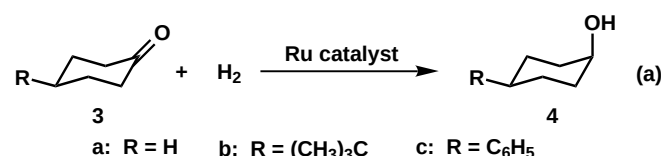
Figure 2. ORTEP diagrams of the structures of (*R*),(*R*),(*R*)-**2d** (a) and (*R*),(*S*),(*S*)-**2e** (b). All hydrogen atoms except for the amino and methine protons of DPEN have been omitted for clarity. Selected distances [Å] and bond angles [°]: (*R*),(*R*),(*R*)-**2d**: Ru–Cl1 2.421(2), Ru–Cl2 2.420(2), Ru–P1 2.282(3), Ru–P2 2.273(2), Ru–N1 2.196(7), Ru–N2 2.183(7), Cl1–(H4)N2 2.74, Cl2–(H2)N1 2.77; Cl1–Ru–Cl2 162.96(8), P1–Ru–P2 92.22(8), N1–Ru–N2 77.7(2). (*R*),(*S*),(*S*)-**2e**: Ru–Cl1 2.408(2), Ru–Cl2 2.426(2), Ru–P1 2.276(2), Ru–P2 2.296(2), Ru–N1 2.141(5), Ru–N2 2.189(6), Cl1–(H1)N1 2.70, Cl2–(H3)N2 2.70; Cl1–Ru–Cl2 163.23(6), P1–Ru–P2 91.50(7), N1–Ru–N2 78.0(2).

Table 1. Synthesis and properties of the Ru complexes **1** and **2**.

Complex	formula ^[a]	Method	Decomp [° C] ^[b]	δ (³¹ P) ^[c]
1a	$[(OC-6-13)\text{-RuCl}_2\{\text{P}(\text{C}_6\text{H}_5)_3\}_2(\text{en})]$	A	176	45.5 (s)
1b	$[(OC-6-13)\text{-RuCl}_2\{\text{P}(p\text{-CH}_3\text{C}_6\text{H}_4)_3\}_2(\text{en})]$	A	185	44.3 (s)
(<i>R</i>),(<i>R</i>),(<i>R</i>)- 2a	$[(OC-6-13)\text{-RuCl}_2\{(R)\text{-binap}\}\{(R,R)\text{-dpn}\}]$	B	235	47.4 (s)
(<i>R</i>),(<i>S</i>),(<i>S</i>)- 2b	$[(OC-6-13)\text{-RuCl}_2\{(R)\text{-binap}\}\{(S,S)\text{-dpn}\}]$	B	242	46.9 (s)
(<i>S</i>),(<i>S</i>)- 2c	$[(OC-6-13)\text{-RuCl}_2\{(S)\text{-binap}\}\{(S)\text{-daipen}\}]$	B	183	47.9 (d), 48.9 (d) ^[d]
(<i>R</i>),(<i>R</i>),(<i>R</i>)- 2d	$[(OC-6-13)\text{-RuCl}_2\{(R)\text{-tolbinap}\}\{(R,R)\text{-dpn}\}]$	B	209	46.2 (s)
(<i>R</i>),(<i>S</i>),(<i>S</i>)- 2e	$[(OC-6-13)\text{-RuCl}_2\{(R)\text{-tolbinap}\}\{(S,S)\text{-dpn}\}]$	B	234	45.5 (s)
(<i>S</i>),(<i>S</i>)- 2f	$[(OC-6-13)\text{-RuCl}_2\{(S)\text{-tolbinap}\}\{(S)\text{-daipen}\}]$	B	173	45.9 (d), 47.6 (d) ^[e]
(<i>S</i>),(<i>R</i>),(<i>R</i>)- 2g	$[(OC-6-13)\text{-RuCl}_2\{(S,S)\text{-diop}\}\{(R,R)\text{-dpn}\}]$	B	226	38.9 (s)
(<i>S</i>),(<i>S</i>),(<i>S</i>)- 2h	$[(OC-6-13)\text{-RuCl}_2\{(S,S)\text{-chiraphos}\}\{(S,S)\text{-dpn}\}]$	C	204	79.1 (s)

In these stereoisomers, the two phenyl substituents of the N,N-ligated five-membered ring are oriented in the equatorial direction, and the flexible $P(p\text{-H}_3\text{CC}_6\text{H}_4)_2$ moieties adopt similar spatial arrangements. The Cl–HN distances (2.7–2.8 Å) are rather short due to intramolecular hydrogen bonding (expected van der Waals separation, 3.0 Å). ^1H and ^{31}P NMR analysis of these compounds show that they exist as a single conformer in C_6D_6 .

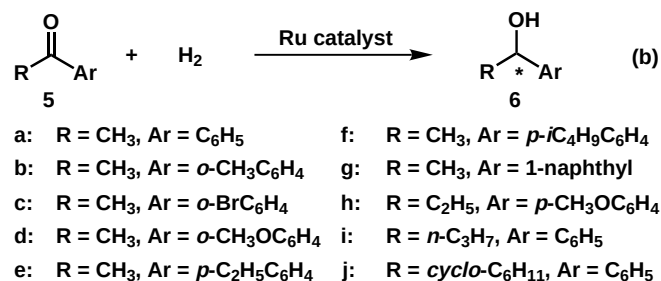
The isolated Ru complexes are among the most reactive (pre)catalysts for homogeneous hydrogenation so far reported.^[11] When cyclohexanone (**3a**) was hydrogenated in 2-propanol (2.1 M) in the presence of **1b** and $(\text{CH}_3)_3\text{COK}$ (ketone:**1b**:base = 100 000:1:450) at 10 atm H_2 and 60 °C for two hours, cyclohexanol (**4a**) was produced in 96 % yield [Eq. (a)]. The reaction was extremely rapid with an initial



turnover frequency (TOF) of 563 000 h^{-1} or 156 s^{-1} .^[11, 12] Hydrogenation of 4-*tert*-butylcyclohexanone (**3b**) in the presence of **1b** and $(\text{CH}_3)_3\text{COK}$ (50 000:1:250) at 10 atm and 60 °C, proceeded with a TOF of 178 000 h^{-1} (49 s^{-1}), and produced the *cis* alcohol **4b** with a *cis/trans* stereoselectivity of 97/3. The 4-phenyl derivative **3c** was produced with a *cis/trans* selectivity of 96/4.^[14]

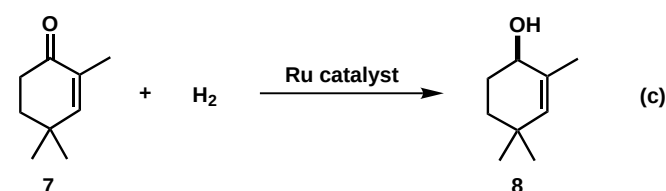
Rapid, highly productive asymmetric hydrogenation of ketones can be achieved with chiral precatalysts. When a mixture of acetophenone (**5a**) (601 g), (*S,S*)-**2d** (2.2 mg), and $(\text{CH}_3)_3\text{COK}$ (5.6 g) in 2-propanol (1.5 L) was stirred under H_2 (45 atm) at 30 °C for 48 h, (*R*)-1-phenylethanol ((*R*)-**6a**) was obtained with 80 % *ee* and in 100 % yield (94 % after distillation). The turnover number (TON) was 2400 000, while the TOF at 30 % conversion was 228 000 h^{-1} (63 s^{-1}).^[11, 12] Hydrogenation of 1'-acetonaphthone (**5g**) in 2-propanol in the presence of (*R,R*)-**2d** and $(\text{CH}_3)_3\text{COK}$ ([ketone] = 2.1 M, ketone:**2d**:base = 50 000:1:200) at 10 atm

H_2 and 80 °C proceeded with an initial TOF of 259 000 h^{-1} (72 s^{-1}), and after one hour afforded (*S*)-1-(1-naphthyl)ethanol ((*S*)-**6g**) with 91 % *ee* in 93 % yield.^[13] As exemplified in Table 2, high level enantioselectivity was obtained with various ring-substituted acetophenones, including the *o*-bromo and -methoxy derivatives **5c** and **5d**, and higher



analogues of acetophenone, with an S/C as high as 100 000 [Eq. (b)].^[14, 15] The degree of enantioselectivity and the absolute configuration of the products are the same as those obtained with the complexes generated in situ.

Asymmetric hydrogenation of 2,4,4-trimethyl-2-cyclohexenone (**7**) with (*S,S*)-**2e** acts on the carbonyl group only and gave (*R*)-2,4,4-trimethyl-2-cyclohexenol ((*R*)-**8**) with 94 % *ee* and in 100 % yield [Eq. (c)]. The chiral alcohol **8** is an intermediate in the synthesis of various carotenoid-derived bioactive terpenes and odorants.^[16]



This new hydrogenation procedure is clean, mild, and efficient, and offers a very practical method of chiral alcohol synthesis.

Table 2. Ruthenium-catalyzed asymmetric hydrogenation of ketones.^[a]

Ketone	Precatalyst	S/C ^[b]	Conditions			Alcohol product	
			H_2 [atm]	<i>t</i> [h]	Yield [%] ^[c]	<i>ee</i> [%] ^[c]	Config. ^[d]
5a	(<i>S,S</i>)- 2d	2400 000 ^[e]	45	48	100	80	<i>R</i>
5b	(<i>S,S</i>)- 2f	100 000	10	48	94	99	<i>R</i>
5c	(<i>R,R</i>)- 2f	10 000	10	6	100	98	<i>S</i>
5d	(<i>S,S</i>)- 2f	2 000	4	10	98	82	<i>R</i>
5e	(<i>R,R</i>)- 2f	10 000	10	21	100	97	<i>S</i>
5f	(<i>R,R</i>)- 2d	100 000	10	48	99	96	<i>S</i>
5f	(<i>S,S</i>)- 2d	800	1	24	98	94	<i>R</i>
5g	(<i>S,S</i>)- 2d	100 000	10	40	99.5	98	<i>R</i>
5g	(<i>R,R</i>)- 2d	50 000	10	1 ^[f]	93	91	<i>S</i>
5h	(<i>R,R</i>)- 2f	10 000	10	14	100	95	<i>S</i>
5i	(<i>S,S</i>)- 2f	100 000	10	48	87	94	<i>R</i>
5j	(<i>S,S</i>)- 2f	100 000	10	48	98	92	<i>R</i>
7	(<i>S,S</i>)- 2e	10 000	10	48	100	94	<i>R</i>

[a] Reactions were conducted at 24–30 °C with a 2.1–2.4 M solution of substrate (25 mmol) in 2-propanol in the presence of $(\text{CH}_3)_3\text{COK}$ (ketone:base = 220:1). [b] Substrate/catalyst molar ratio. [c] Determined by GC or HPLC analysis of the chiral phase. [d] Determined by sign of rotation. [e] Reaction with 601 g **5a** (ketone: $(\text{CH}_3)_3\text{COK}$ = 100:1) [f] at 80 °C.

Experimental Section

1a^[8] (method A): [RuCl₂[P(C₆H₅)₃]₃] (1.11 g, 1.16 mmol) was placed in a 50-mL Schlenk flask filled with argon. CH₂Cl₂ (10 mL) and NH₂(CH₂)₂NH₂ (0.15 mL, 2.2 mmol) were then added. The mixture was degassed and stirred under argon at 25 °C for 3 h. After removal of turbidity by filtration, the filtrate was concentrated to about 5 mL, *n*-hexane (20 mL) was added, and a light brown powder was obtained. The supernatant was removed and the resulting solid was dried under reduced pressure (1 Torr) to give analytically pure **1a** (0.55 g, 63% yield). ¹H NMR (400 MHz, C₆D₆, 25 °C, TMS): δ = 2.1 (m, 4H; CH₂), 2.8 (m, 4H; NH₂), 6.8–8.0 (m, 30H; aromatic H).

1b (method A): A light brown solid was obtained from CH₂Cl₂:ether (1:3) (79%). ¹H NMR: δ = 2.00 (s, 18H, CH₃), 2.2 (m, 4H, CH₂), 2.9 (m, 4H, NH₂), 6.86 (d, 12H, *J* = 7.5 Hz, *o*-aromatic H), 7.9 (m, 12H, *m*-aromatic H).

(*R*),(*R*),(*R*)-**2a** (method B): [RuCl₂(C₆H₆)₂] (129 mg, 0.258 mmol) and (*R*)-BINAP (341 mg, 0.55 mmol) were placed in a 50-mL Schlenk flask. After the air in the flask was replaced with argon, DMF (9 mL) was added, the mixture was degassed and stirred under argon at 100 °C for 10 min to form a reddish brown solution. After the solution was cooled to 25 °C, ^[14] (*R*),(*R*)-DPEN (117 mg, 0.55 mmol) was added and the mixture was stirred for 3 h. The solvent was removed under reduced pressure (1 Torr). The residue was dissolved in CH₂Cl₂ (10 mL) and turbidity was removed by filtration. The filtrate was concentrated to about 1 mL, then ether (10 mL) was added and a light brown powder was obtained. The supernatant was removed and the resulting solid was dried under reduced pressure to give (*R*),(*R*),(*R*)-**2a** (0.34 g, 66% yield). ¹H NMR: δ = 3.3 (m, 2H, NHH), 3.45 (m, 2H, NHH), 4.55 (m, 2H, NH₂CH), 6.3–8.8 (m, 42H, aromatic H).

(*R*),(*S*),(*S*)-**2b** (method B): A light brown solid was obtained from CH₂Cl₂:ether (1:12) (62%). ¹H NMR: δ = 3.0 (m, 2H, NHH), 4.4 (m, 2H, NHH), 4.65 (m, 2H, NH₂CH), 6.3–8.8 (m, 42H, aromatic H).

(*S*),(*S*)-**2c** (method B): A cream yellow solid was obtained from CH₂Cl₂:ether (1:10) (50%). ¹H NMR δ = −0.12 (d, 3H, *J* = 6.8 Hz, CH₃CHCH₃), 0.54 (d, 3H, *J* = 6.8 Hz, CH₃CHCH₃), 1.7 (m, 1H, (CH₃)₂CH), 2.75 (m, 1H, NHH((CH₃)₂CH)CH), 3.05 (m, 1H, NHH((CH₃)₂CH)CH), 3.12 (s, 3H, CH₃O), 3.31 (s, 3H, CH₃O), 3.8 (m, 1H, NHH(*p*-CH₃OC₆H₄)₂C), 4.40 (m, 1H, NHH(*p*-CH₃OC₆H₄)₂C), 5.05 (m, 1H, NH₂CH), 6.2–8.4 (m, 40H, aromatic H).

(*R*),(*R*),(*R*)-**2d**: A light brown solid was obtained from CH₂Cl₂:ether (1:5) (58%). ¹H NMR: δ = 1.70 (s, 6H, CH₃), 1.87 (s, 6H, CH₃), 3.3 (m, 2H, NHH), 3.5 (m, 2H, NHH), 4.55 (m, 2H, NH₂CH), 6.55–8.8 (m, 38H, aromatic H).

(*R*),(*S*),(*S*)-**2e**: A light brown solid was obtained from CH₂Cl₂:ether (1:5) (51%). ¹H NMR: δ = 1.70 (s, 6H, CH₃), 1.81 (s, 6H, CH₃), 3.05 (m, 2H, NHH), 4.4 (m, 2H, NHH), 4.7 (m, 2H, NH₂CH), 6.3–8.8 (m, 38H, aromatic H).

(*S*),(*S*)-**2f**: A cream yellow solid was obtained from CH₂Cl₂:ether (1:14) (60%). ¹H NMR: δ = −0.08 (d, 3H, *J* = 6.8 Hz, CH₃(CH₃)CH), 0.67 (d, 3H, *J* = 6.8 Hz, CH₃(CH₃)CH), 1.66 (s, 3H, *p*-CH₃C₆H₄P), 1.70 (s, 3H, *p*-CH₃C₆H₄P), 1.72 (m, 1H, (CH₃)₂CH), 1.99 (s, 3H, *p*-CH₃C₆H₄P), 2.00 (s, 3H, *p*-CH₃C₆H₄P), 2.9 (m, 1H, NHH((CH₃)₂CH)CH), 3.1 (m, 1H, NHH((CH₃)₂CH)CH), 3.18 (s, 3H, CH₃O), 3.40 (s, 3H, CH₃O), 3.8 (m, 1H, NHH(*p*-CH₃OC₆H₄)₂C), 4.4 (m, 1H, NHH(*p*-CH₃OC₆H₄)₂C), 5.15 (m, 1H, NH₂CH), 6.2–8.8 (m, 36H, aromatic H).

(*S*),(*S*),(*R*),(*R*)-**2g**: Conditions: [RuCl₂(C₆H₆)₂] (248 mg, 0.495 mmol), (*S*),(*S*)-DIOP (504 mg, 1.01 mmol), DMF (10 mL), 100 °C, 2 h, and (*R*),(*R*)-DPEN (220 mg, 1.03 mmol), 25 °C, 3 h.^[14] Isolation: removal of DMF (1 Torr, 25 °C → 50 °C), extraction with CH₂Cl₂ (20 mL), and crystallization (CH₂Cl₂:ether, 1:14, 45 mL), to give a light brown solid (530 mg, 61% yield). ¹H NMR: δ = 1.43 (s, 6H, CH₃), 3.25–3.70 (m, 6H, CH₂P and NHH), 3.95–4.15 (m, 2H, NHH), 4.55 (m, 2H, NH₂CH), 4.73 (m, 2H, CHO), 6.5–8.2 (m, 30H, aromatic H).

(*S*),(*S*),(*S*)-**2h** (method C): [Ru(*η*³-CH₂C(CH₃)CH₂)₂](*S*),(*S*)-chiraphos]^[7] (2.13 g, 3.0 mmol) was placed in a 150-mL Schlenk flask filled with argon. Acetone (50 mL) and HCl in CH₃OH (2.27 mL, 3.2 mmol) were added and the mixture was stirred at 25 °C for 2 h. The turbidity was removed by filtration, and the solvent was evaporated under reduced pressure (1 Torr). Then dmf (20 mL) and (*S*),(*S*)-dpn (632 mg, 3.0 mmol)

were added to the residue. The mixture was degassed and stirred under argon for 3 h. The solvent was evaporated under reduced pressure and the residue was dissolved in CH₂Cl₂ (10 mL). The turbidity was removed by filtration and the filtrate was concentrated to about 2 mL. Ether (10 mL) was then added and the turbidity was again removed by filtration. Ether (10 mL) was again added to the filtrate and a light brown powder precipitated. The supernatant was removed and the resulting solid was dried to give (*S*),(*S*),(*S*)-**2h** (1.90 g, 78%). ¹H NMR: δ = 0.95 (d, 6H, *J* = 4.3 Hz, CH₃), 2.77 (m, 2H, CH₂CH), 3.84 (m, 2H, NHH), 4.05 (m, 2H, NHH), 4.69 (m, 2H, NH₂CH), 6.7–8.1 (m, 30H, aromatic H).

Hydrogenation of cyclohexanone: (**3a**):^[14] Conversions were determined by gas chromatography (HP-INNOVAX (30 m), 100 °C, He (55 kPa), 9.2 min (**3a**), 12.8 min (**4a**)). Correlations between reaction time (min) and TON were as follows: (5, 12330), (10, 59280), (15, 68980), (20, 76150), (120, 96130). **4b**: *cis*/*trans* = 97/3; GC: HP-INNOVAX, 130 °C, 17.4 min (*cis*), 20.1 min (*trans*). **4c**: *cis*/*trans* = 96/4; GC: HP-INNOVAX, 190 °C, 28.6 min (*cis*), 30.4 min (*trans*).

Asymmetric hydrogenation:^[14] (*S*),(*S*),(*S*)-**2d** (22 mg) was dissolved in degassed 2-propanol (20 mL), which was used as the catalyst stock solution. Ketone **5a** (601 g), 2-propanol (1.5 L), (CH₃)₃COK (5.6 g), and an aliquot of the catalyst solution (2.0 mL, 0.002 mmol) (molar ratio ketone:Ru:base = 2400000:1:24000) were placed in a 10 L stainless steel autoclave. The mixture was degassed and hydrogen was introduced to a pressure of 45 atm. The mixture was vigorously stirred at 30 °C for 48 h. The yield was determined by GC to be 100%. GC: Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), 115 °C, He (50 kPa), 26.7 min ((*R*)-**6a**), 28.7 min ((*S*)-**6a**), 17.8 min (**5a**). After the solvent was removed under reduced pressure, the residue was passed through a silica gel column (300 g, ethyl acetate) and then distilled (99 °C, 15 Torr) to give (*R*)-**6a** (577 g, 94%, 80% *ee*).^[1a] [α]_D²⁴ = +38.1 (*c* = 1.02, CH₂Cl₂).^[1a, 17]

Hydrogenation of **5g** at 80 °C: (*S*)-**6g**, 91% *ee*; GC: Chirasil-DEX CB (25 m), 150 °C, He (50 kPa), 46.8 min ((*R*)-**6g**), 42.3 min ((*S*)-**6g**), 19.1 min (**5g**). Correlations between reaction time (min) and TON were as follows: (5, 7815), (10, 29360), (15, 37870), (60, 46350).

(*R*)-**6b**: [α]_D²⁴ = +52.8 (neat);^[1a, 18] 99% *ee*; Chirasil-DEX CB, 125 °C, 17.1 min ((*R*)-**6b**), 20.0 min ((*S*)-**6b**).

(*S*)-**6c**: [α]_D²⁴ = −60.5 (*c* = 0.57, CH₂Cl₂);^[19] 98% *ee*; Chirasil-DEX CB, 150 °C, 13.0 min ((*R*)-**6c**), 16.2 min ((*S*)-**6c**).

(*R*)-**6d**: [α]_D²⁴ = +59.1 (*c* = 1.10, toluene);^[20] 82% *ee*; Chirasil-DEX CB, 130 °C, 20.7 min ((*R*)-**6d**), 23.5 min ((*S*)-**6d**).

(*S*)-**6e**: [α]_D²⁴ = −48.2 (*c* = 1.12, CHCl₃);^[21] 97% *ee*; Chirasil-DEX CB, 110 °C, 43.3 min ((*R*)-**6e**), 47.2 min ((*S*)-**6e**).

(*S*)-**6f**: [α]_D²⁵ = −35.5 (neat);^[22] 96% *ee*; Chirasil-DEX CB, 130 °C, 30.1 min ((*R*)-**6f**), 33.4 min ((*S*)-**6f**).

(*R*)-**6g**: [α]_D²⁵ = +77.0 (*c* = 1.02, ether);^[1a, 23] 98% *ee*.

(*S*)-**6h**: [α]_D²² = −36.1 (*c* = 5.10, benzene);^[24] 95% *ee*; Chirasil-DEX CB, 140 °C, 23.7 min ((*R*)-**6h**), 22.9 min ((*S*)-**6h**).

(*R*)-**6i**: [α]_D²³ = +36.7 (*c* = 1.40, CH₃OH);^[25] 94% *ee*; HPLC: CHIRALCE-L OB (Daicel, 250 mm), 2-propanol:hexane (1:9), 30 °C, 254 nm, 0.5 mL min^{−1}, 11.2 min ((*R*)-**6i**), 9.4 min ((*S*)-**6i**).

(*R*)-**6j**: [α]_D²² = +26.8 (*c* = 3.29, benzene);^[26] 92% *ee*; Chirasil-DEX CB, 110 °C, 64.6 min ((*R*)-**6j**), 66.6 min ((*S*)-**6j**).

(*R*)-**8**: [α]_D²³ = +87.9 (*c* = 1.00, CH₃OH);^[1d, 16a] 94% *ee*; Chirasil-DEX CB, 90 °C, 49.1 min ((*R*)-**8**), 46.4 min ((*S*)-**8**).

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- [13] Reaction with the diastereomeric isomer (*R*),(*S*),(*S*)-**2e**, either pre-formed or formed in situ, gave the *S* alcohol in 15 ± 2%.
- [14] Various alkaline bases, such as KOH, (CH₃)₂CHOK, (CH₃)₂CHONa, (CH₃)₃COK, and K₂CO₃ can be used as cocatalysts. For reactions with a high S/C, acidic impurities should be carefully removed from substrates and solvents.
- [15] Reaction of [RuCl₂](*S*)-TolBINAP(dmf)_{*n*} and (*S*),(*S*)-DPEN in DMF at 50 °C (method B) gave a mixture of (*S*),(*S*),(*S*)-**2d** and its *cis* isomer (³¹P NMR, δ = 50.2 (d, *J* = 38.0 Hz), 57.0 (d, *J* = 38.0 Hz)). Hydrogenation of **5g** with the *cis* isomer showed comparable reactivity to (*S*),(*S*),(*S*)-**2d**, to give (*R*)-**6g** with 97% *ee*.
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Parallel Synthesis of Sialyl Lewis X Mimetics on a Solid Phase: Access to a Library of Fucopeptides**

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In response to injury or inflammation the damaged tissue releases cytokines, which trigger the expression of P-selectin followed by E-selectin on the endothelium. The initial recognition of the tetrasaccharide sialyl Lewis X (sLe^x) of the terminal unit of surface glycoconjugates by the selectins leads to leukocyte “rolling” followed by protein–protein interactions (integrins CD11/18, ICAM-1 ligand) and extravasation of leukocytes into the endothelium.^[1] Thus, blocking the sLe^x/selectin interactions at an early stage of the inflammatory cascade, especially the P-selectin/ligand interactions, has been considered to be an effective way of treating acute and perhaps chronic inflammatory diseases.^[2]

Although sLe^x is being clinically evaluated for the treatment of reperfusion injury, it must be administered by injection at high doses, as it binds the selectins weakly and is orally inactive and unstable in the blood. However, the structure of sLe^x has served as a useful guide for designing simpler and better low molecular weight compounds as

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selectin antagonists.^[3] On the basis of the crystal structure of E-selectin, NMR studies of the conformations of sLe^x in solution and bound to E-, P-, and L-selectin,^[5] and structure/activity studies on sLe^x derivatives and mimetics,^[6] the essential functional groups and their spatial arrangement required for binding of the sLe^x epitope to the selectins have been elucidated. By using this recognition model, numerous structurally diverse low molecular weight sLe^x mimetics have been prepared (Figure 1).^[3, 7] Some of them exhibit an affinity towards the selectins equal to or higher than that of sLe^x.

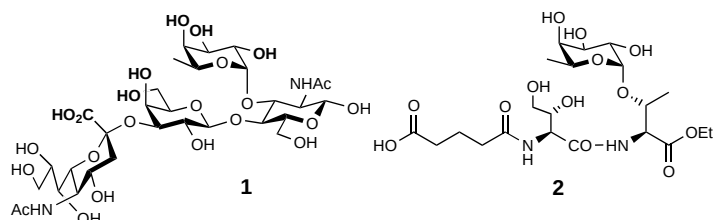
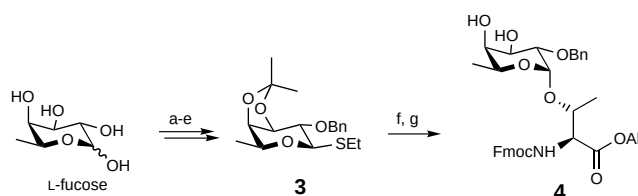


Figure 1. The tetrasaccharide sialyl Lewis X (**1**) and the fucosepeptide **2** as an oligosaccharide mimic.

Recently, interest in solid-phase syntheses has increased dramatically, since they allow combinatorial chemistry to be performed for the discovery of biologically active compounds and for optimization of lead structures.^[8] In particular, the parallel synthesis of individual compounds on solid phases is considered to be a promising approach to rapid optimization of previously identified lead structures. Here we report on our efforts to develop new strategies for the parallel and/or combinatorial synthesis of a substance library of *O*- and *C*-fucosylpeptides structurally related to **2**, which is nearly as active as sLe^x towards E-selectin.^[7a]

Fucose, which contains the three hydroxyl groups required for recognition of sLe^x by E-selectin, was retained as the only carbohydrate moiety in the mimic, while GlcNAc was replaced by L-threonine and its derivatives. Anchoring the fucose–GlcNAc surrogate through its 3,4-*cis*-diol unit^[9] enables the bidirectional elongation of the glycosylated amino acid while bound to the solid support. *N*-terminal elongation allows the elaboration of optimal substitutions for the galactose and sialic acid residues. *C*-terminal modifications^[10] can be used to install additional functionalities that interact with new groups in selectins.^[7b, 11] The use of Fmoc–peptide chemistry and the application of an orthogonal protective-group strategy ($R^1 = \text{All}$, $R^2 = \text{Fmoc}$, $R^3 = \text{Bn}$; for abbreviations, see legends to schemes), as well as the reversible immobilization of the 3,4-*cis*-diol moiety of fucose by a highly acid labile linker group, enable the rapid and bidirectional assembly of fucosylpeptides.

The synthesis of orthogonally protected α -fucoside **4** is depicted in Scheme 1. L-Fucose was converted into ethylthiofucoside

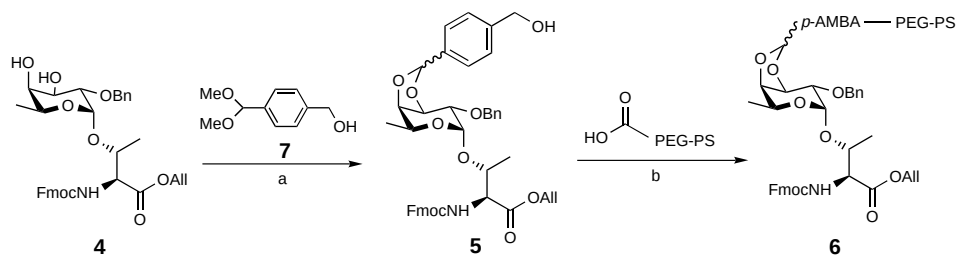


Scheme 1. a) Ac₂O, 4-DMAP, pyridine, 0 → 20 °C; b) EtSH, BF₃·Et₂O, 0 → 20 °C (60%, two steps); c) NaOMe (cat.) in MeOH, 20 °C; d) 2,2-dimethoxypropane, cat. *p*-TsOH·H₂O, CH₂Cl₂, 20 °C (94%, two steps, $\alpha/\beta = 1:7$); e) NaH, BnBr, TBAI (cat.), THF (84%, 100% β); f) Fmoc-Thr-OAll, CuBr₂/TBAI, CH₂Cl₂, DMF; g) aqueous AcOH, (80%, 1% TFA). All = allyl, Bn = benzyl, 4-dmap = 4-(dimethylamino)pyridine, Fmoc = 9-fluorenylmethyloxycarbonyl, TBAI = tetrabutylammonium iodide, TFA = trifluoroacetic acid, Thr = threonine, Ts = toluenesulfonate.

3 (five steps, 47% overall yield) by standard methods. By using CuI₂/[Bu₄N]I,^[12] Fmoc-protected L-threonine allyl ester was glycosylated with **3** to give selectively the α anomer ($\alpha/\beta \approx 9/1$). Cleavage of the acetone with 80% aqueous acetic acid containing 1% TFA followed by column chromatography gave fucoside **4** as the pure α anomer (64% yield, two steps).

Treatment of the diol **4** with the dimethyl acetal **7** and a catalytic amount of *p*-TsOH·H₂O gave a diastereomeric mixture of benzylidene acetals **5** (Scheme 2). The bifunctional linker **7** was easily derived from commercially available 4-formylbenzoic acid by formation of the dimethyl acetal and reduction of the acid group (62%, two steps). By using a moderate excess (2.1 equiv) of the alcohol **5** and DIC/4-DMAP activation, **5** was immobilized nearly quantitatively (0.24 mmol g⁻¹) on a carboxyl-functionalized poly(ethylene glycol) graft copolymer resin (PEG-PS) to give **6**.^[13] The loading was determined by photometric analysis of the cleaved Fmoc groups and gravimetrically by means of the product released from the resin with aqueous acetic acid (80% + 2% TFA). The diol **4** was liberated quantitatively without any detectable cleavage of the acid-sensitive α -fucosidic bond. Thus, the combination of the *para*-acyloxymethylbenzylidene acetal (*p*-AMBA) anchor group and PEG-PS solid support achieved maximal loading, recovery of excess reagent, appropriate swelling of the solid support, desirable stability of the acetal linkage during synthesis, and selective cleavage by a weak acid.

Starting with 0.8 mmol resin-bound **6**, we conducted a parallel synthesis of sLe^x mimetics **8** on a preparative scale (Scheme 3). At branching points of the synthesis, the material



Scheme 2. Immobilization of fucosepeptide **4** on a carboxyl-functionalized PEG-PS resin by anchor group **7**. a) **7**, *p*-TsOH (cat.), CH₂Cl₂, 20 °C; b) DIC, 4-DMAP (cat.), CH₂Cl₂, 20 °C, 18 h, 100% (0.24 mmol g⁻¹). *p*-AMBA = *p*-(acyloxymethyl)benzylidene acetal anchor group, DIC = diisopropylcarbodiimide, PEG-PS = poly(ethylene glycol) graft copolymer; for other abbreviations, see legend to Scheme 1.

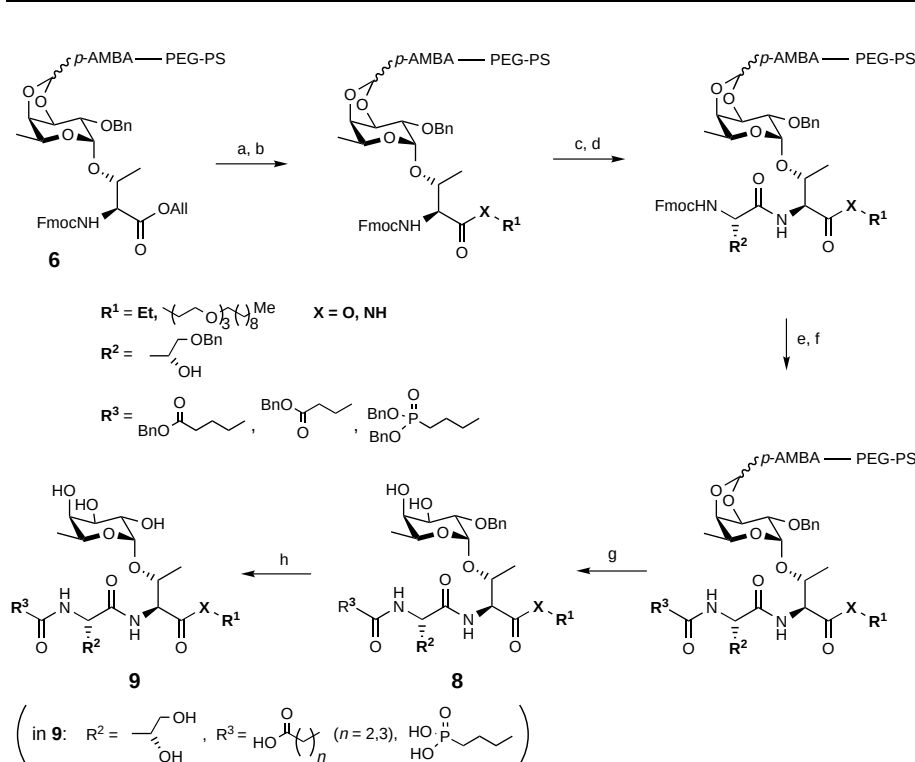


Table 1. Structures, yields, and biological activities of the sLe^x mimics **8** and **9**.

8 or 9 ^[a]	Yield of 8 ^[b]	Yield of 9 ^[c]	XR ¹	R ³ ^[d]	E-selectin IC ₅₀ [mM] ^[e]	P-selectin IC ₅₀ [mM] ^[e]
a	62	88	OE _{Et}		0.8	3.0
b	65	97	OE _{Et}		4.0	0.66
c	47	76			3.2	0.057
d	58	67			4.1	0.030
e	49	81			1.8	0.059
f	51	95			3.2	0.256
g	65	94	OE _{Et}		0.7	> 1.0
h	55	90			4.1	0.017

[a] In this series R² remains constant, and Fmoc-protected γ -benzyloxy-L-*allo*-threonine^[17] was used as amino acid building block. [b] Yields based on purified fucoseptides **8**. [c] Yields based on purified **9** after fractional precipitation of crude hydrogenation products from MeOH/Et₂O (**9a–f**), ion-exchange chromatography (**9g** and **9h**) and lyophilization from H₂O. [d] The substituents shown refer to **9**; compounds **8** contain the corresponding benzylated substituents. [e] The activities were measured according to the procedure described previously with sLe^x–polyacrylamide conjugate. The values are an average of three measurements, $\pm 10\%$; IC₅₀ for sLe^x = 0.8 mM towards E-selectin and > 3 mM towards P-selectin).^[16a]

DMF (6 $\times$, 1 mL per 100 mg dry resin), a pre-stirred (5–10 min) solution of the acids used for coupling (3 equiv for step d and 6 equiv for step f, Scheme 4), HOBT, NMM, and HBTU (1.6 equiv, 2.2 equiv and 1.05 equiv, based on the amount of acid) in dry DMF (0.2–0.25 M in acid) was added to the resin. After shaking for 4–4.5 h at room temperature, the coupling reaction was terminated by filtration, and the resin was washed with DMF and CH₂Cl₂ (6 $\times$ each).

Cleavage from the resin: A suspension of resin in aqueous AcOH (80%, 0.9 mL per 100 mg dry resin) containing 2% TFA was shaken for 18–22 h at room temperature. After filtration and washing three times with AcOH (80%), the cleavage procedure was repeated. The filtrate was concentrated in vacuo, and residual AcOH and H₂O were removed by coevaporating twice with dry toluene. The colorless to slightly yellow oil or solid was purified by column chromatography on silica gel to afford material that was homogeneous according to HR-MS, ¹H, and ¹³C NMR spectroscopy.

9b: colorless hygroscopic solid; ¹H NMR (500 MHz, D₂O): δ = 4.95 (d, J = 3.5 Hz, 1H), 4.68 (brs, 1H), 4.54 (d, J = 7.2 Hz, 1H), 4.44 (q, J $\approx$ 6.1 Hz, 1H), 4.22 (dq, J = 10.6, 7.2 Hz, 1H), 4.12 (dq, J = 10.6, 7.2 Hz, 1H), 3.97 (m, 1H), 3.74–3.69 (m, 5H), 3.60 (dd, J = 12.1, 6.4 Hz, 1H), 2.62–2.52 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H), 1.15 (br d, J $\approx$ 6.4 Hz, 6H); HR-MS: m/z calcd for C₂₀H₃₄O₁₃N₂CS: 643.1115 [M +Cs]⁺, found: 643.1139. **9d**: colorless hygroscopic solid; ¹H NMR (500 MHz, D₂O): δ = 4.94 (d, J = 3.7 Hz, 1H), 4.53 (d, J = 9.0 Hz, 1H), 4.44 (brs, 1H), 4.41 (d, J = 6.3 Hz, 1H), 3.89–3.87 (m, 1H), 3.75–3.52 (m, 16H), 3.43 (t, J = 6.7 Hz, 2H), 3.31–3.36 (m, 2H), 2.29 (t, J $\approx$ 7.1 Hz, 2H), 2.24 (t, J = 7.4 Hz, 2H), 1.81 (t, J $\approx$ 7.3 Hz, 2H), 1.55–1.50 (m, 2H), 1.28–1.21 (m, 14H), 1.18 (d, J = 6.1 Hz, 3H), 1.14 (d, J = 6.4 Hz, 3H), 0.83 (brt, J $\approx$ 6.6 Hz, 3H); HR-MS: m/z calcd for C₃₅H₆₅O₁₅N₃CS: 900.3470 [M +Cs]⁺, found: 900.3498. **9e**: colorless hygroscopic solid; ¹H NMR (500 MHz, D₂O): δ = 4.94 (d, J = 3.5 Hz, 1H), 4.70 (brs, 1H), 4.58 (d, J = 7.2 Hz, 1H), 4.42–4.35 (m, 2H), 4.18–4.16 (m, 1H), 3.97–3.96 (m, 1H), 3.74–3.55 (m, 16H), 3.42 (t, J = 6.5 Hz, 2H), 2.64–2.53 (m, 4H), 1.53 (brs, 2H), 1.30–1.23 (m, 14H), 1.17 (d, J = 6.1 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H), 0.85 (brt, J $\approx$ 6.5 Hz, 3H); HR-MS: m/z calcd for C₃₄H₆₂O₁₆N₂CS: 887.3154 [M +Cs]⁺, found: 887.3184.

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Complex Fluids Based on the Flexible One-Dimensional Mineral Polymers [K(MPS₄)]_∞ (M = Ni, Pd): Autofragmentation to Concave, Cyclic (PPh₄)₃[(NiPS₄)₃]**

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In memory of Jean Rouxel

The discovery of the lyotropic nematic phase of LiMo₃Se₃ in *N*-methylformamide,^[1] a rare example of a liquid crystal based on a mineral core, was achieved 70 years after the pioneering work of the German physicist H. Zocher.^[2] This event, soon followed by the study of the nematic behavior of V₂O₅ ribbons^[3] and smectic clays^[4] in water, has aroused acute interest in the development of solution-phase chemistry of charged, all-inorganic molecules. The motivation for such investigations is the prospect of unraveling the organic/inorganic interfacial chemistry and physics of unprecedented anisotropic fluids based on one- and two-dimensional, charged, extended mineral polymers.^[5, 6]

The solid-state chemistry of transition metal chalcogenides^[7] is abound with low-dimensional motifs, such as ¹[Mo₃Se₃][−]. Their dimensionality arises from the balance between the strong covalent character of the transition metal–chalcogen bonds within the negatively charged chains or slabs and their effective ionic screening by alkali metal cations.^[8, 9] A recent example is the series of transition metal chalcogenide phosphates KMPS₄ (M = Ni, Pd) with infinite anionic chains ¹[MPS₄][−].^[10] Here we demonstrate 1) that KMPS₄ compounds are soluble in polar organic solvents such as dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), and form complex fluids made up of flexible inorganic polymers; 2) that [(NiPS₄)₃]^{3−}—an unprecedented, concave trimetallic thiophosphate molecular trianion adopting pseudo-C_{3v} symmetry—is formed in DMF at room temperature from the autofragmentation and rearrangement of ¹[NiPS₄][−]; and 3) that it is possible to follow the dissolution and fragmentation processes with mass spectrometry, solution-state ³¹P NMR spectroscopy, and transmission electron microscopy (TEM). Thus, the contrasting behavior and stability of the Ni and Pd phases can be revealed.

In accordance with their highly anisotropic bonding, KNiPS₄ and KPdPS₄ are soluble in polar organic solvents

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such as DMF and DMSO, and rapidly form highly viscous gellike solutions at high concentrations ($[\text{KMPS}_4] > 10^{-2} \text{ mol L}^{-1}$).^[11] However, there is a striking difference in the stabilities of these solutions. The KPdPS_4 solution is stable with respect to time and temperature (up to about 323 K), whereas the solution of KNiPS_4 changes in color from dark brown to orange-brown, and progressively becomes more fluid; it approaches the solvent fluidity within a few hours at 323 K.

Differences between the KNiPS_4 and KPdPS_4 solutions can also be observed by optical microscopy under polarized light. Crystals of the solid compounds were sandwiched between a microscope slide and a cover glass, and pure DMF was added, which diffused between the two slides. For both compounds the crystals immediately swelled and rapidly dissolved when they came into contact with the solvent. The birefringence observed in the surrounding solution decreased as the distance from the crystal increased.^[12] When the crystals had totally dissolved, the birefringence slowly disappeared, and within a few minutes at room temperature the solutions appeared isotropic. If these solutions were then sheared, for example by applying pressure to the top microscope slide, a strong transient birefringence was immediately observed again (Figure 1).^[13] However, as the solution of KNiPS_4 aged



Figure 1. Transient birefringence (reminiscent of nematic threaded textures) observed by optical microscopy under polarized light (polarizers crossed) from a sheared concentrated gel of KPdPS_4 in DMF.

and became more fluid, the intensity of this transient birefringence decreased to zero. This is in stark contrast to the unlimited reproducibility of the transient birefringence of KPdPS_4 at room temperature. Such flow birefringence is commonly observed for solutions of lyotropic mesophases at concentrations lower than the isotropic/anisotropic transition concentration and is proof of transient anisotropy in the fluid.^[14] This behavior can arise from either a preferred orientation of anisotropic rigid molecules induced by flow (analogous to logs aligned with the flow of a river), or from stretching of interdigitated, folded, flexible polymers (like drawn spaghetti). Both models imply the persistence of $[\text{MPS}_4]^-$ chains in solution.

Transmission electron microscopy of KPdPS_4 obtained after evaporation of the solvent (Figure 2)^[15] confirms that the chains remain intact in solution. The separation between the

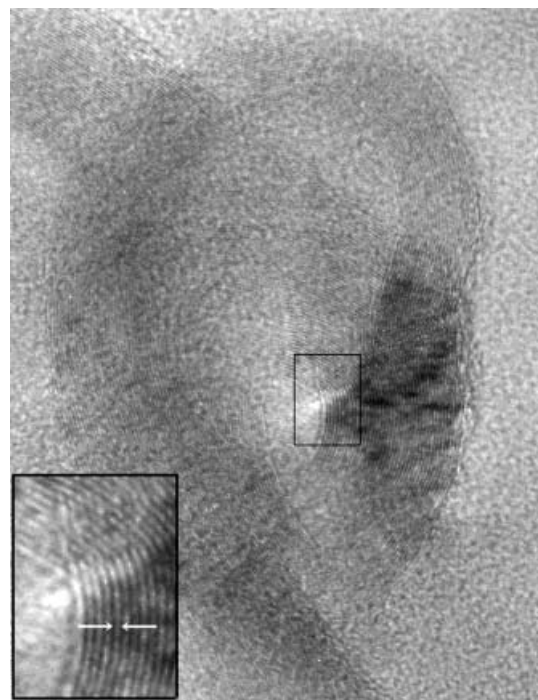


Figure 2. TEM micrograph of the chains in KPdPS_4 . The sample was prepared by directly depositing one drop of a solution in DMF ($[\text{KPdPS}_4] = 10^{-6} \text{ mol L}^{-1}$) onto a carbon grid and drying overnight. The distance between the arrows is $3.5(1) \text{ Å}$, which indicates a hexagonal stacking of the chains.

chains, indicated in Figure 2 by the arrows, is $3.5(1) \text{ Å}$, which is consistent with a hexagonal packing of chains that are 7.0 Å apart. This distance is approximately equal to the calculated van der Waals radius of a PdS_4 square-planar unit and is slightly greater than the size of a tetrahedral PS_4 group. Another striking feature of the micrograph is that the chains appear to be highly flexible. A curvature radius as low as 50 Å was measured, which supports the spaghetti-like model. X-ray experiments are in progress to determine the coherence length of the chains.

Recrystallization of the original KMPS_4 compounds was not possible from the initial solutions under various conditions; only amorphous compounds were obtained. However, again, there is a difference in the behaviors of aged and freshly prepared solutions of $\text{KNiPS}_4/\text{DMF}$: A crystalline compound can be isolated from the aged solution upon replacing K^+ by PPh_4^+ through a metathesis reaction. The structure of the corresponding phase^[16] $(\text{PPh}_4)_3[\text{Ni}_3\text{P}_3\text{S}_{12}]$ discloses the unprecedented inorganic anionic ring $[\text{Ni}_3\text{P}_3\text{S}_{12}]^{3-}$ (Figure 3). In light of these observations, the loss of transient birefringence in aged solutions of $\text{KNiPS}_4/\text{DMF}$ can be understood in terms of autofragmentation of the $[\text{NiPS}_4]^-$ chains to form $[\text{Ni}_3\text{P}_3\text{S}_{12}]^{3-}$ cycles. This would also account for the inability to recrystallize freshly prepared samples, as the solutions predominately consist of tangled chains, which cannot be induced to arrange in an ordered fashion necessary for crystallization. This is analogous to the behavior of an organic polymer.

We followed the evolution of these solutions with ^{31}P NMR spectroscopy and mass spectrometry. The mass spectrum of

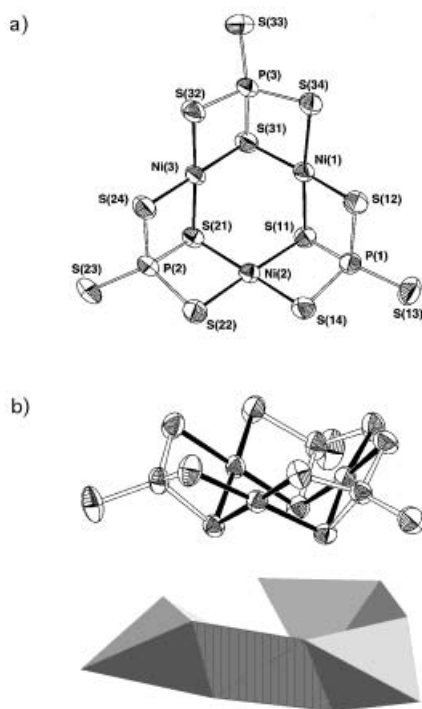


Figure 3. The concave $[(\text{NiPS}_4)_3]^{3-}$ cyclic anion: a) ORTEP representation showing the pseudo- C_{3v} symmetry adopted in the solid state; b) ORTEP (top) and polyhedra representation (bottom) exemplifying the bowl-like configuration. The Ni–S bond lengths are homogeneous (av 2.217(10) Å). There are three types of P–S bond lengths: P–(μ_3 -S) 2.112(5), P–(μ_2 -S) 2.046(8), P–(μ_1 -S) 1.949(7) Å. A Mulliken analysis based on extended-Hückel calculations indicates that the negative charge is essentially located on the μ_1 -S ligands at the periphery of the anion.

KPdPS₄/DMF consists of a broad peak with some superimposed sharp peaks. The extremely broad background is characteristic of a polydispersed distribution of chain lengths in solution. The peaks of low intensity can be attributed to a small concentration of $[\text{Pd}_3\text{P}_3\text{S}_{12}]^{3-}$ anions with different types and numbers of charge-compensating cations (H^+ or K^+) and/or solvent molecules. The solution-state ^{31}P NMR spectrum of KPdPS₄ remains unchanged even after the sample has been heated at 323 K for several months; a single peak is observed at $\delta = 146.4$, which we assign to the $[\text{PdPS}_4]^-$ chain by comparison with the solid-state ^{31}P NMR chemical shift of KPdPS₄. Since there is no evidence for the fragmentation of the Pd chains at this temperature (decomposition occurs above 368 K), we believe that the $[\text{Pd}_3\text{P}_3\text{S}_{12}]^{3-}$, $[(\text{Pd}_4\text{P}_4\text{S}_{16})\text{K}_3]^-$, and $[\text{PdPS}_4]^-$ anions observed in small concentrations in the mass spectrum are produced in situ upon vaporization of the sample. In contrast, the mass spectrum of aged KNiPS₄/DMF shows only a series of sharp peaks, of which the three of greatest intensity can be assigned to $[\text{Ni}_3\text{P}_3\text{S}_{12}]^{3-}$ with different types and numbers of cations. This formula is consistent with that of the cyclic anion described above. Other species formed in smaller quantities are tentatively assigned as larger anions of the type $[\text{NiPS}_4]_n^{n-}$ ($n = 4-6$) and as smaller anions. Again, the latter are probably produced in situ upon vaporization of the sample, as no evidence for their existence was observed by ^{31}P NMR spectroscopy. The changes at 300 K in the solution-state ^{31}P

NMR spectrum of KNiPS₄ in $[\text{D}_7]\text{DMF}$, which was previously dissolved by rigorous stirring at 263 K in order to avoid fragmentation, is shown in Figure 4. Initially, a peak at $\delta = 122$ is observed^[17] which decreases in intensity with time while

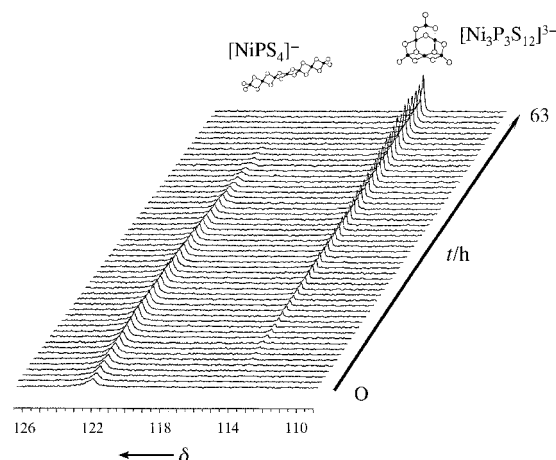


Figure 4. Changes with time t in the solution-state ^{31}P NMR spectrum of KNiPS₄ in $[\text{D}_7]\text{DMF}$ at 300 K. The chain undergoes autofragmentation and rearrangement to form the cyclic anion.

another peak appears and grows at $\delta = 114$. After 63 h the peak at higher frequency has completely disappeared, and the intensity of the other peak remains constant. Based on the solid-state ^{31}P NMR shifts of KNiPS₄ and $(\text{PPh}_4)_3[\text{Ni}_3\text{P}_3\text{S}_{12}]$ we assign the peaks at $\delta = 122$ and 114 to the $[\text{NiPS}_4]^-$ chain and the cyclic anion $[\text{Ni}_3\text{P}_3\text{S}_{12}]^{3-}$, respectively. This data confirms that $[\text{NiPS}_4]^-$ initially exists in solution, and that the infinite mineral polymer autofragments to form the cyclic structure. The rate of fragmentation of KNiPS₄ in DMF is highly dependent on temperature. Upon raising the temperature by just 20 K to 320 K, the conversion of the chain into the cyclic anion is complete after only 12 h.

Why the $[\text{Ni}_3\text{P}_3\text{S}_{12}]^{3-}$ anion is favored over any other anion is an interesting question. To our knowledge, cyclic anions of this type have never been reported to form in solid-state reactions. Finally, it appears that the remarkable dispersion/autofragmentation/rearrangement sequence disclosed here extends the concept of mere excision in solution of monomeric molecular motifs from low-dimensional inorganic solids.^[18]

Experimental Section

KNiPS₄^[10] (2 g) was dissolved in DMF (50 mL, $1.56 \times 10^{-1} \text{ mol L}^{-1}$); complete dissolution was obtained after stirring the solution for a few hours. The cation was exchanged by adding Ph_4PBr (2 g, 4.77 mmol, ca. 20 % excess) to an aged (2 d at ambient temperature) solution of KNiPS₄ in DMF. This mixture was stirred for 30 min, and then Et_2O (500 mL) was added slowly. A brown precipitate formed, which was isolated by filtration and recrystallized from a minimum of CH_3CN (yield 75 %); elemental analysis calcd (found) for $\text{C}_{24}\text{H}_{20}\text{P}_2\text{NiS}_4$: C 47.64 (47.95), H 3.33 (3.71).

The mass spectra were collected with a VG BioTech spectrometer equipped with a Quatro II triple quadrupole detector. The solutions of KNiPS₄ and KPdPS₄ in DMF were heated at 323 K for 5 d before being analyzed.

Samples were prepared for solution-state ^{31}P NMR spectroscopy by vigorous stirring of the compounds in $[\text{D}_7]\text{DMF}$ for 18 h at 263 K. Spectra

were collected on a Bruker AM200 spectrometer operating at a frequency of 81 MHz, and were recorded with a $\approx 20^\circ$ pulse length of 2 μ s and a recycle time of 3–5 s. No proton decoupling was used, and so the relative intensities of the signals are quantitative. Spectra were referenced to phosphoric acid as the standard ($\delta = 0$). The data were processed with the PC version of WINNMR (Bruker).

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- [12] The difference between the crystal and the solution can be readily determined by uncrossing the polarizers, which reveals a crystal surrounded by a particle-free phase that flows when compressed; this confirms its fluid nature.
- [13] Relaxation times are on the order of about 1 s at $10^{-2} \text{ mol L}^{-1}$ and about 15 min at 1.2 mol L^{-1} ($\text{KMPS}_4 \cdot 11 \text{ DMF}$).
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- [16] Crystal data for $(\text{PPh}_4)_3[\text{Ni}_3\text{P}_3\text{S}_{12}]$: monoclinic, space group $P2_1/c$, $a = 15.828(2)$, $b = 10.099(1)$, $c = 47.112(6)$ Å, $\beta = 91.11(1)^\circ$, 6862 independent reflections with $I \geq 3\sigma(I)$, $R_F = 0.0624$, $R_w F = 0.0848$, min./max. residual electron density: $-0.61/0.76 \text{ e Å}^{-3}$, $S = 1.88$. The data were collected on a Siemens CCD single diffractometer with an automated three-axis goniometer; $\text{MoK}_{\alpha 1,2,3}$ radiation was used. The data collected at room temperature were reduced to net intensities, and estimated standard deviations were calculated on the basis of counting statistics; Lorentz polarization corrections were applied, and equivalent reflections were averaged. The structures were solved by direct methods with SHELXTL (G. M. Sheldrick, SHELXTL version 5, Siemens Analytical X-Ray Instruments, Inc. Madison, WI) and refined with JANA98 (V. Petříček, M. Dušek, JANA98 Crystallographic Computing System, Institute of Physics, Academy of Sciences of the Czech Republic, Prague, **1998**). Final refinements were performed on F_0 with anisotropic atomic displacement parameters for Ni, P, and S atoms and isotropic parameters for C atoms. The positions of the H atoms were introduced in the structure factors calculations with the same isotropic atomic displacement as the C

atoms on which they ride. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101 227. 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).

- [17] As only one peak is observed for the chain, we assume that either there is no difference in the chemical shifts of phosphorus atoms in the middle and at the ends of a chain, or that the chains are so long that the intensities of the signals for phosphorus atoms at the ends are negligible with respect to those phosphorous atoms in the central part. The latter is more probable based on the observation from electron microscopy. No other peaks, apart from those from the chain and the cyclic structure, are observed during the in situ NMR study. If we assume that the chemical shift is different for the atoms at the ends and the middle of a chain, then the breaking of the chains must be the rate-limiting step for the cyclization, and hence the concentration of the chain fragments in solution is never high enough to be observed.
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Organometallic Triskelia: Novel Tris(vinylideneruthenium(II)), Tris(alkynylruthenium(II)), and Triruthenium–Triferrocenyl Complexes**

Mitsunari Uno* and Pierre H. Dixneuf*

*Dedicated to Professor Warren Roper
on the occasion of his 60th birthday*

Multitopic carbon-rich metal complexes, with rigid conjugated branches are potentially useful for building carbon-rich networks,^[1] supramolecular polymeric assemblies,^[2] and nanoarchitectures for material science.^[3] They have found application as the core of metal-containing dendrimers^[4,5] and polymers,^[6] and as the basis of liquid crystals.^[7] Polymetallic complexes containing multiple identical redox systems are of special interest for electron storage^[5,8] and as modified electrodes^[9] due to their ability to provide several electrons at the same potential.

We now report the novel polymetallic complexes containing reversible redox systems, and displaying a C_3 -symmetric triskelion shape,^[10] formed by activation of the tritopic polyene 1,3,5-($\text{HC}\equiv\text{CC}_6\text{H}_4\text{C}\equiv\text{C}$)₃C₆H₃ (**1**) namely the first examples of tris(vinylideneruthenium(II)) complexes (**2**),

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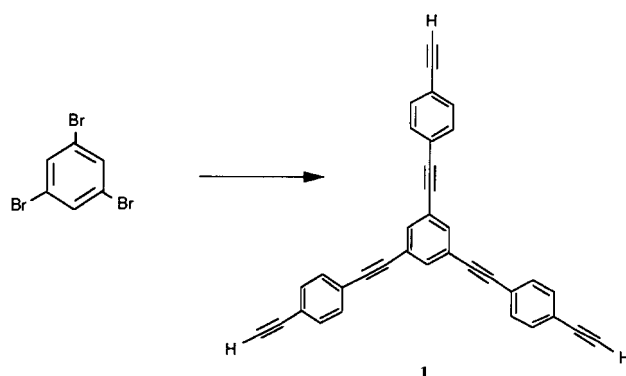
tris(alkynylruthenium) derivatives (**3** and **4**), and mixed triruthenium–triferrocenyl systems (**5**).

Tris(alkynylmetal) derivatives with identical Pt^{II} or Fe^{II} moieties and an apparently redox-passive bridge were synthesized from 1,3,5-triethynylbenzene. The bridge legs were too short to allow the incorporation of three bulky ruthenium(II) redox systems by direct activation of the terminal $\text{C}\equiv\text{CH}$ bonds. We therefore synthesized the rigid, long-legged tripodal polyne **1** from 1,3,5-tribromobenzene by successive catalytic reactions adapted from the preparation of unidimensional polyynes,^[12] as indicated in Scheme 1.

The activation of **1** containing three terminal $\text{C}\equiv\text{CH}$ functionalities was attempted with the bulky 16-electron species $[\text{RuCl}(\text{dppe})_2]\text{PF}_6$, generated in situ from $[\text{RuCl}_2(\text{dppe})_2]$ in the presence of KPF_6 at room temperature. This reaction led to the isolation of the novel tris(vinylideneruthenium(II)) complex **2** [70%; $\tilde{\nu}(\text{Ru}=\text{C}=\text{C}) = 1627\text{ cm}^{-1}$ (KBr)]. The ^{13}C NMR spectrum of complex **2** shows the three vinylidene ($\text{Ru}=\text{C}$) carbon nuclei as a multiplet at very low field ($\delta = 356.6$). The high symmetry of complex **2** is reflected by the singlets in the ^{13}C NMR spectrum for the two $\text{C}\equiv\text{C}$ ($\delta = 88.23$ and 90.70) and $\text{Ru}=\text{C}=\text{C}$ ($\delta = 109.47$) carbon nuclei, and in the ^{31}P NMR spectrum at $\delta = 37.55$ for the twelve Ph_2P phosphorus nuclei. The latter signal is consistent with a *trans* arrangement of the chloro and vinylidene ligands in the complex (Scheme 2).

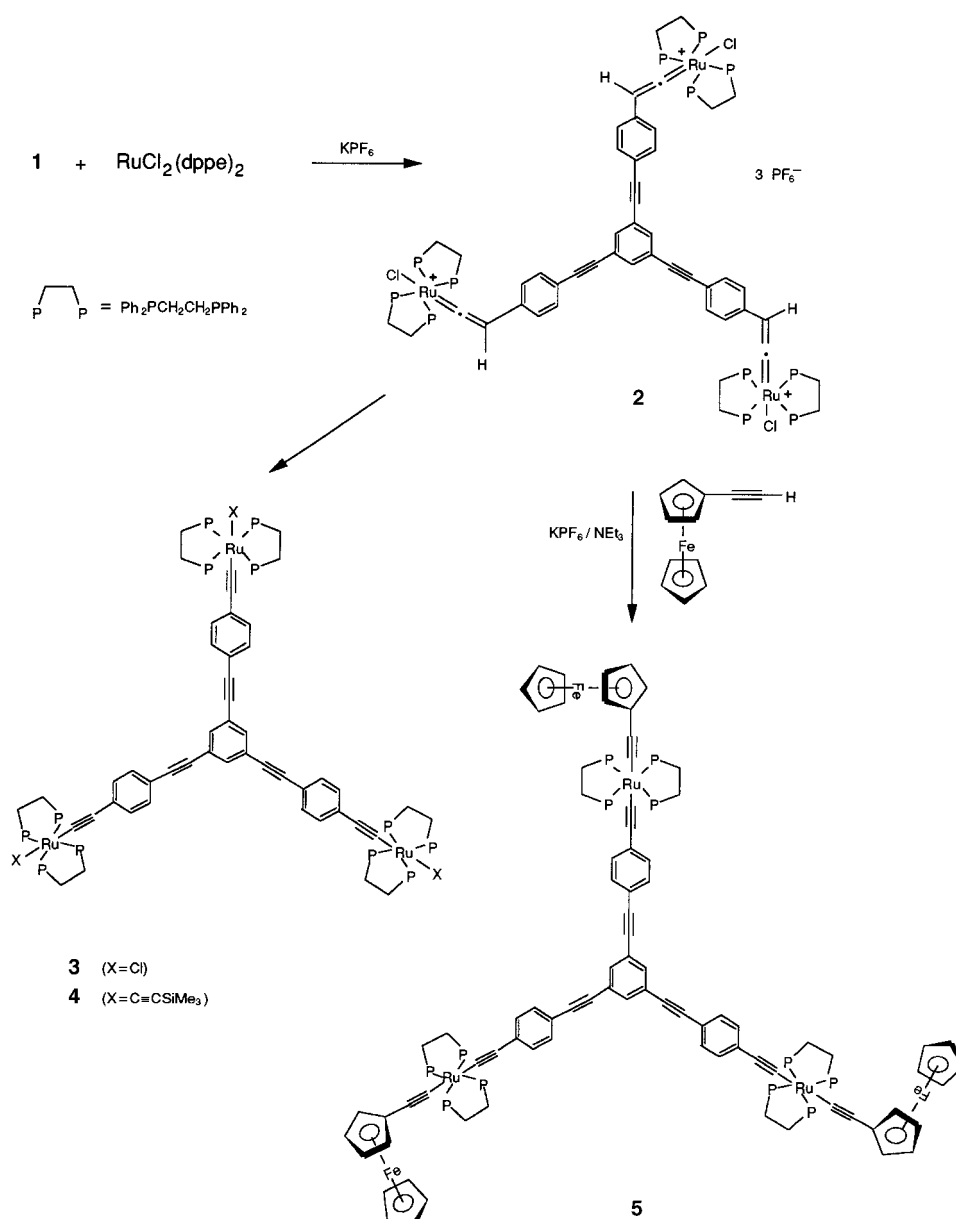
The tris(vinylidene) complex **2**, like most vinylideneruthenium(II) complexes,^[13] is acidic and easily deprotonated on treatment with NEt_3 to afford the new yellow tris(alkynylruthenium) complex **3** [93% $\tilde{\nu}(\text{C}\equiv\text{C}) = 2056\text{ cm}^{-1}$; ^{31}P NMR $\delta = 49.93$ (s, 12 PPh_2)].

The complexes **2** and **3** show different behavior in their coupling to an additional functionalized alkynyl group. The remaining three halogen atoms of complex **3** can be substituted on reaction with trimethylsilylacetylene by the cooperative action of KPF_6 and NEt_3 for $\text{Ru}-\text{Cl}$ bond dissociation and alkyne deprotonation. Complex **4** was isolated in 42% yield [$\tilde{\nu}(\text{cm}^{-1}) = 2199$ ($\text{CC}=\text{CC}$), 2059 ($\text{CC}=\text{CRu}$), 1992 ($\text{RuC}\equiv\text{CSi}$)] and displays mixed alkynyl ligands in a *trans* arrangement as indicated by the observation of



Scheme 1. Catalytic synthesis of the tripodal polyne **1**. a) $\text{HC}\equiv\text{CSiMe}_3$, NEt_3 , Pd/Cu catalyst; b) NaOH (aq); c) $\text{IC}_6\text{H}_4\text{C}\equiv\text{CSiMe}_3$, NEt_3 , Pd/Cu catalyst; d) NaOH (aq).

only one singlet in its ^{31}P NMR spectrum [$\delta = 54.28$] (Scheme 2).



Scheme 2. Synthesis of the triskelion-shaped, carbon-rich ruthenium complexes.

By contrast it was not possible to incorporate the ferrocenylacetylene unit directly into **3**, but the reaction of the tris(vinylidene) complex **2** with $\text{FcC}\equiv\text{CH}$, KPF_6 , and NEt_3 led to the slow, but selective, formation of the novel mixed hexanuclear triruthenium–triferrocenyl complex **5** (92 %) containing a linear arrangement of the alkynyl fragments [$\delta = 53.95$ (s, 12 PPh_2)] (Scheme 2).

The isolation of the tris(vinylidene) complex **2** is a keystone in the formation of **5**, as in the absence of NEt_3 , the vinylidene ligand inhibits the introduction of an additional alkynyl group in the *trans* position and thus avoids the formation of oligomers from **1**.

A cyclic voltammetric study of complexes **2–4** showed that each produces a single quasi-reversible redox wave for the three ruthenium systems, but the peak separation is larger for the cationic tris(vinylidene) derivative **2** [$E_{1/2}$ versus $\text{Cp}_2\text{Fe}^+/\text{Cp}_2\text{Fe}$: $+0.72$ V ($\Delta E_p = 135$ mV) for **2**; $+0.02$ ($\Delta E_p = 100$ mV) for **3**; $+0.03$ ($\Delta E_p = 115$ mV) for **4**].^[14] This unique oxidation wave shows that **3** and **4**, in particular, are able to provide three electrons at the same potential, and that their long-legged carbon-rich C_{3v} bridge does not allow significant communication between the three ruthenium(II) centres.

Of special interest is the behavior of **5**, which provides two reversible oxidation waves at $E_{1/2} = -0.28$ V ($\Delta E_p = 75$ mV) and at $E_{1/2} = +0.30$ V ($\Delta E_p = 75$ mV). These data show that both the sets of three ruthenium and three ferrocenyl units are able to provide three electrons at a specific potential. The redox potentials of **5** can be assigned on the basis of the redox potentials of **3** ($E_{1/2} = +0.02$ V), **4** ($E_{1/2} = +0.03$ V), ferrocenylacetylene ($E_{1/2} = +0.16$ V), and *trans*-[$\text{Ru}(\text{C}\equiv\text{CPh})_2(\text{dppe})_2$] ($E_{1/2} = +0.40$ V). Further evidence for the assignments is the observation that the linear mixed-metal derivative *trans*-[$\text{FcC}\equiv\text{CRu}(\text{dppe})_2\text{C}\equiv\text{CFc}$] (**I**)^[15] provides three reversible waves at $E_{1/2} = -0.36$, -0.16 and $+0.53$ V in its cyclic voltammogram. The wave of **5** at low potential ($E = -0.28$ V) is thus attributed to the three equivalent ferrocenyl groups and that at higher potential ($E = +0.30$ V) to the three ($\text{Ru}^{\text{II}}/\text{Ru}^{\text{III}}$) redox processes in the $\text{Ru}(\text{dppe})_2$ subunits. The linkage of the alkynyl– $\text{Ru}(\text{dppe})_2$ unit to the $\text{C}\equiv\text{CFc}$ groups, therefore, increases the ease of oxidation of the ferrocenyl groups. Surprisingly, the tripodal tris(alkynylruthenium(II)) moieties are electron-releasing toward the ferrocenyl groups. This is likely a result of the unique capability of a $\text{RuC}\equiv\text{CCFc}$ moiety to rearrange by oxidation into the stable allenylidene intermediate ($\text{Ru}^+=\text{C}=\text{C}(\text{Fc})$).

The hexametallic species **5** contrasts with the linear trimetallic $\text{FcC}\equiv\text{RuC}\equiv\text{CFc}$ derivative **I**: While **I** contains an organometallic redox-active communicating bridge between the two ferrocenyl groups, the tripodal triruthenium carbon-rich bridge in **5** behaves as an apparent redox-passive noncommunicating bridge between the ethynylferrocene units.

Experimental Section

2: Ligand **1** (0.135 g, 0.300 mmol), *cis*-[$\text{RuCl}_2(\text{dppe})_2$] (0.872 g, 0.900 mmol), KPF_6 (0.331 g, 1.80 mmol), and CH_2Cl_2 (50 mL) were stirred at room temperature for 72 h. After evaporation of the solvent, a brown solid was obtained and purified by recrystallization from mixture of CH_2Cl_2 (100 mL) and pentane (200 mL). The pure tris(rutheniumvinylidene)

complex **2** was isolated as a brown solid (0.771 g, yield 70 %). ^1H NMR (300.133 MHz, CDCl_3): $\delta = 7.51$ (s, 3 H, C_6H_3), 6.75 (AB, $J = 8.0$ Hz, 6 H, 3×2 H of C_6H_4), 5.59 (AB, $J = 8.0$ Hz, 6 H, 3×2 H of C_6H_4), 3.75 (br. s, 3 H, $3 \times \text{Ru}=\text{C}=\text{CH}$); ^{13}C NMR (75.469 MHz, CDCl_3): $\delta = 356.6$ (m, $\text{Ru}=\text{C}$), 109.48 (br, $\text{Ru}=\text{C}=\text{CH}$) 90.72, 88.23 ($\text{C}\equiv\text{C}$); ^{31}P NMR (121.496 MHz, CDCl_3): $\delta = 37.55$ (s, RuPPh_2), -143.40 (sept $J_{\text{PF}} = 713$ Hz, PF_6); IR (KBr, cm^{-1}): $\tilde{\nu} = 2199$ ($\text{C}\equiv\text{C}$), 1627 ($\text{C}=\text{C}$); elemental analysis calcd for $\text{C}_{192}\text{H}_{162}\text{Cl}_3\text{F}_{18}\text{P}_{15}\text{Ru}_3$: C 62.57, H 4.43; found: C 62.43, H 4.62.

3: Complex **2** (0.869 g, 0.236 mmol) was suspended in THF (50 mL) and then triethylamine (1 mL) added. After stirring at room temperature for 1 h, the solvent was evaporated. The yellowish brown residue was dissolved in CH_2Cl_2 (40 mL) and washed with water. A yellow-orange powder was obtained and characterized as **3** (0.713 g, yield 93 %). ^1H NMR: $\delta = 7.55$ (s, 3 H, C_6H_3), 6.56 (AB, $J = 8.5$ Hz, 6 H, 3×2 H of C_6H_4); ^{13}C NMR: $\delta = 132.95$ (quint, $J_{\text{PC}} = 15$ Hz, $\text{RuC}\equiv\text{C}$), 131.22 (C_{ipso} of C_6H_3), 130.40 (CH of C_6H_3), 114.39 ($\text{RuC}\equiv\text{C}$), 91.67, 88.39 ($\text{C}\equiv\text{C}$); ^{31}P NMR: $\delta = 49.90$ (s, RuPCH_2); IR (KBr, cm^{-1}): $\tilde{\nu} = 2199$, 2056 ($\text{C}\equiv\text{C}$); elemental analysis calcd for $\text{C}_{192}\text{H}_{159}\text{Cl}_3\text{P}_{12}\text{Ru}_3$: C 71.01, H 4.93; found: C 70.81, H 5.00.

4: To a solution of **3** (0.330 g, 0.1 mmol) and KPF_6 (0.130 g, 0.7 mmol) in CH_2Cl_2 (20 mL) was added trimethylsilylacetylene (0.2 mL 1.4 mmol) and NEt_3 (0.5 mL). After stirring for 72 h, the reaction mixture was filtered through celite and the filtrate evaporated. The yellow solid was dissolved in CH_2Cl_2 (40 mL) and washed with water. After drying in vacuo, **4** was obtained as a yellow powder and recrystallized from a mixture of CH_2Cl_2 and pentane (0.148 g, yield 42 %). ^1H NMR: $\delta = 7.61$ (s, 3 H, C_6H_3), -0.02 (s, 27 H, $3 \times \text{SiMe}_3$); ^{13}C NMR: $\delta = 153.36$ (quint, $J_{\text{CP}} = 14$ Hz, $\text{RuC}\equiv\text{C}$), 140.98 (quint, $J_{\text{CP}} = 14$ Hz, $\text{RuC}\equiv\text{C}$), 131.06 (C_{ipso} of C_6H_3), 133.23 (CH of C_6H_3), 116.15, 115.61, 91.74, 88.29 ($\text{C}\equiv\text{C}$ carbon), 1.09 (SiMe_3); ^{31}P NMR: $\delta = 54.64$ (s, RuPPh_2); IR (KBr, cm^{-1}): $\tilde{\nu} = 2199$, 2058, 1992 ($\text{C}\equiv\text{C}$); elemental analysis calcd for $\text{C}_{207}\text{H}_{186}\text{P}_{12}\text{Ru}_3\text{Si}_3$: C 72.42, H 5.46; found: C 72.18, H 5.51.

5: Complex **2** (0.120 g, 0.032 mmol), ferrocenylethyne (0.050 g, 0.23 mmol), and KPF_6 (0.055 g, 0.3 mmol) were dissolved in CH_2Cl_2 (15 mL) and then NEt_3 (0.2 mL) was added. After stirring for 5 days the reaction mixture was evaporated under reduced pressure to give a yellow solid. Recrystallization from CH_2Cl_2 and pentane gave **5** as small orange crystals (0.112 g, yield 92 %). ^1H NMR: $\delta = 7.62$ (s, 3 H, C_6H_3), 7.32 (AB, $J = 8.7$ Hz, 6 H, 3×2 H of C_6H_4), 6.59 (AB, $J = 8.7$ Hz, 6 H, 3×2 H of C_6H_4), 4.05 (m, 27 H, $3\text{C}_3\text{H}_5 + 3\text{C}_3\text{H}_4$); ^{13}C NMR $\delta = 133.66$ (CH of C_6H_3), 125.14, 116.78 ($\text{RuC}\equiv\text{C}$), 122.80, 118.21 (m, $\text{Ru}-\text{C}\equiv\text{C}$), 92.18, 88.63 ($\text{C}_6\text{H}_3=\text{CC}_6\text{H}_4$), 69.306, 69.150, 68.45, 67.27 (C_3H_5 , C_3H_4); ^{31}P NMR: $\delta = 53.95$ (br. s, PCH_2); IR (KBr, cm^{-1}): $\tilde{\nu} = 2199$, 2053 ($\text{C}\equiv\text{C}$); elemental analysis calcd for $\text{C}_{228}\text{H}_{186}\text{P}_{12}\text{Fe}_3\text{Ru}_3$: C 72.67, H 4.98; found: C 72.18, H 5.03.

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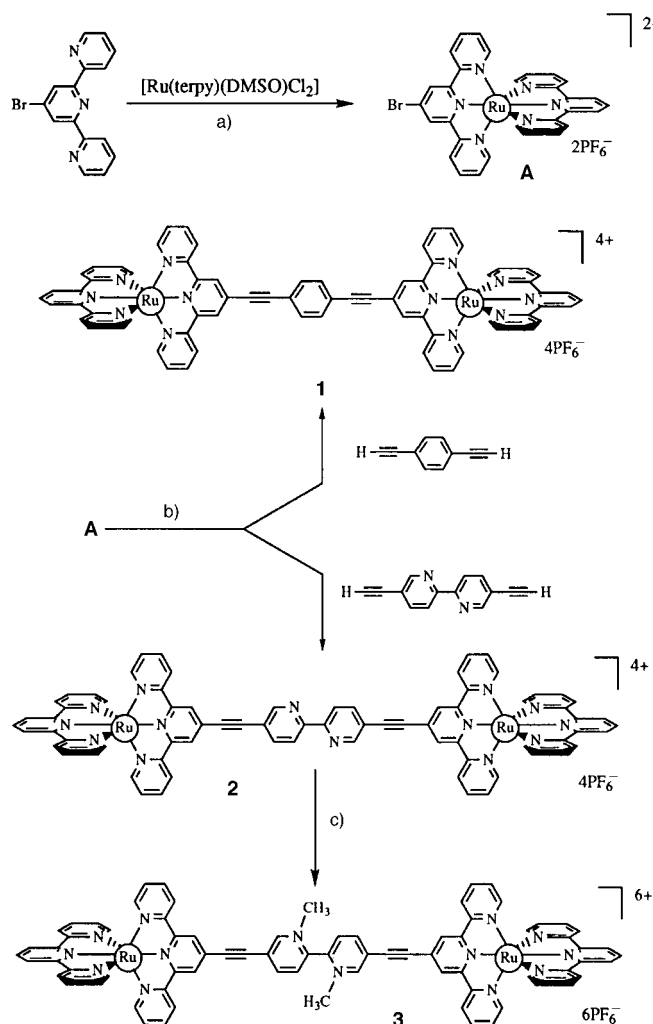
Fine-Tuning the Electronic Properties of Binuclear Bis(terpyridyl)ruthenium(II) Complexes**

Muriel Hissler, Abdelkrim El-ghayoury, Anthony Harriman,* and Raymond Ziessel*

Bis(2,2':6',2''-terpyridine)ruthenium(II) is essentially non-emissive in fluid solution, and in deoxygenated acetonitrile at 20°C the lifetime of the excited triplet state is about 550 ps.^[1] Such photophysical properties compare unfavorably with tris(2,2'-bipyridine) ruthenium(II) and have restricted the utilization of $[\text{Ru}(\text{terpy})_2]^{2+}$ as a building block for preparation of photoactive supramolecular assemblies. Recently, however, it was shown that attaching an acetylenic function at the 4'-position caused a dramatic prolongation of the triplet lifetime,^[1,2] especially in those cases where the acetylene group was the bridge for a ditopic ligand capped with "Ru(terpy)" metallo-fragments. This upgrade to the photophysical properties provides new opportunities to construct elaborate molecular assemblies around the photoactive Ru(terpy) unit.^[3] The protracted triplet lifetime can be explained within the framework of the energy-gap law in

terms of residence of the promoted electron in an extended π^* orbital that encompasses much of the bridging ligand.^[4] Enlargement of the LUMO lowers the triplet energy, and thereby curtails mixing with higher-energy, metal-centered excited states.^[5] In attempting to exploit this effect further we have found that the acetylene residue must be attached directly to the coordinated terpyridine ligand while the polyacetylenic bridge cannot comprise more than four ethynylene groups. Longer carbon chains act as a low-energy sink for photons absorbed by the terminal chromophores.^[6] We now describe an alternative strategy for extending the length of the acetylenic bridge that involves the use of a central aromatic core.

Thus, two new Ru(terpy)-based binuclear complexes were synthesized in which the butadiynylene bridge is interspersed with either a 1,4-phenylene (**1**) or a 5,5'-(2,2'-bipyridylene) (**2**) spacer. Preparation of these complexes was accomplished with an original strategy by using a metallo-synthon bearing a bromide group in conjunction with 1,4-diethynylbenzene or 5,5'-diethynyl-2,2'-bipyridine in Sonogashira-type cross-coupling reactions (Scheme 1). These coupling reactions proceed



Scheme 1. Synthetic method used to prepare the binuclear Ru^{II} terpy-based complexes **1** and **2**: a) Ag^+ dehalogenation in methanol (6 h) followed by reaction with terpy-Br in methanol at 80°C (19 h); b) $[\text{Pd}^{\text{II}}(\text{PPh}_3)_2\text{Cl}_2]$ 6 mol %, $\text{CH}_3\text{CN}/\text{C}_6\text{H}_6$, $(i\text{Pr}_2)\text{NH}$, 25°C (6 days); c) CH_3I (excess) in CH_3CN , 80°C (5 days), anion exchange.

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smoothly at ambient temperature in the presence of a catalytic quantity of Pd⁰. It is noteworthy that complex **2**, which could not be prepared by the classical method,^[7] contains a vacant coordination site that remains freely accessible to incoming cations. Indeed, the N atoms of the central 2,2'-bipyridine are easily quaternized to give the viologen-like complex **3**, and in this respect **2** differs markedly from known systems of this general type.^[8] The photophysical properties of all newly prepared complexes were recorded in deoxygenated acetonitrile at 20 °C with both steady-state and time-resolved luminescence spectroscopy.

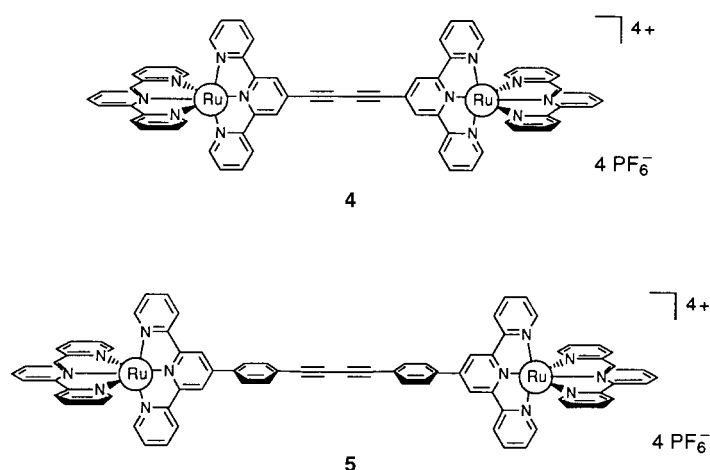
Relative to [Ru(terpy)₂]²⁺ both **1** and **2** are strongly emissive such that luminescence quantum yields (Φ_{lum}) could be estimated (Table 1). The luminescence maxima (λ_{lum}) are red-shifted with respect to that of [Ru(terpy)₂]²⁺, while the

Table 1. Photophysical and electrochemical properties of the bis-terpyridyl ruthenium(II) complexes as measured in deoxygenated acetonitrile at 20 °C.

Cmpd	λ_{lum} [nm] ^[a]	Φ_{lum} ^[b]	τ_{T} [ns] ^[c]	E_{red} ^[d]	E_{ox} ^[e]
1	685	0.0006	110	−1.06	1.37
2	678	0.0006	100	−1.06 ^[f]	1.31
3	710	< 0.0001	4.0 ^[g]	−0.70 ^[h]	1.37
4	735	0.0021	610	−0.92	1.41
5	665	< 0.0001	5.8 ^[g]	−1.08	1.39
[Ru(terpy) ₂] ²⁺	650	< 0.0001	0.56 ^[g]	−1.27	1.28

[a] Luminescence maximum, ± 5 nm. [b] Luminescence quantum yield, $\pm 25\%$: The reproducibility is better than $\pm 3\%$ while comparative emission yields are accurate to within $\pm 5\%$. [c] Triplet lifetime, $\pm 5\%$. [d] Reduction potential, V vs. SCE, ± 15 mV. [e] Oxidation potential, V vs. SCE, ± 15 mV. [f] *N,N*-Dimethylformamide. [g] Measured by transient absorption spectroscopy. [h] First reduction peak of the central viologen unit.

triplet lifetimes (τ_{T}) are prolonged almost 200-fold (Table 1). Complexes **1** and **2** exhibit comparable behavior but stabilization of their triplet states is less significant than found^[1] for the binuclear complex **4** having a butadiynylene bridge but



without an interspersed aromatic core. In the latter case, the promoted electron is delocalized over the entire ditopic ligand. The poor sensitivity towards the nature of the central aromatic unit reflects a relatively small amount of mixing

between π^* orbitals localized on the aromatic group with those on the acetylene–terpyridine residue, presumably due to a mismatching of their LUMO energies. In this respect, the aromatic group can be regarded as imposing a high-energy barrier to electron delocalization.

It is instructive to compare the photophysical properties of **1** with those of the corresponding complex **5** in which the phenyl rings are attached directly to the coordinated terpyridine ligand. Complex **5** shows photophysical properties^[1] that remain similar to those of [Ru(terpy)₂]²⁺ and that are less impressive than those of **1** (Table 1). This comparison suggests poor orbital overlap at the LUMO level between the phenyl and pyridine rings, presumably because of their mutual orientation.^[9] The symmetry of the acetylene group provides for increased orbital overlap with the pyridine ring and thereby favors extended delocalization of the promoted electron.^[10] It is important to realize that the phenyl ring, which extends the molecular axis by approximately 4 Å, can be easily functionalized so as to modulate the local energetics and to provide an anchor for secondary groups.

A further important benefit of direct attachment of the acetylene to the coordinated ligand is that the one-electron reduction potential (E_{red}) of the latter becomes less negative (Table 1). Thus, comparison of the E_{red} values of [Ru(terpy)₂]²⁺ and **1** shows that the acetylene substituent renders that ligand easier to reduce by ca. 210 mV. Inserting the phenylene group between pyridine and acetylene units loses approximately 20 mV whereas omitting the aromatic unit gains a further 140 mV. A less negative reduction potential of the ditopic ligand ensures selective charge injection into that ligand within the lowest energy, triplet excited state. Because this state is of metal-to-ligand charge-transfer (MLCT) character there is a substantial decrease in triplet energy upon raising E_{red} for the ditopic ligand since the corresponding one-electron oxidation potential (E_{ox}) is little affected by substitution. This effect serves to further decouple the MLCT triplet from higher energy excited states.^[5]

Complex **2** is the prototype of a new class of rigid binuclear complexes possessing an accessible coordination site in the bridging ligand. Binding of adventitious cations to the central 2,2'-bipyridine provides a further simple means by which to tune the electronic properties of the bridge. This effect becomes apparent upon protonation of the vacant N atoms of the 2,2'-bipyridine group following addition of trifluoroacetic acid to an acetonitrile solution of **2**. A small red shift of the emission maximum and a slight increase in luminescence yield and lifetime (Table 2) is present, although the overall changes are small.^[11] The process can be followed more conveniently in aqueous solution where the pK is 3.9 ± 0.1 . This value is somewhat lower than that of 2,2'-bipyridine ($pK = 4.5 \pm 0.2$) due to the presence of the acetylene functions and the neighboring ruthenium(II) cations. Protonation lowers the energy of the LUMO localized on the 2,2'-bipyridine unit, thereby increasing the extent of interaction with π^* orbitals resident on the acetylene–terpyridine moiety. This, in turn, increases the propensity for electron delocalization along the ditopic ligand, but the effect is disappointingly small.

Other cations coordinate to the vacant 2,2'-bipyridine ligand in a manner that facilitates subtle control of the local

Table 2. Stability constants and photophysical properties of the cation complexes of **2** as measured in deoxygenated water at 20 °C and pH 7, when the ionic strength is kept constant at 0.1 by addition of KCl.

Cation	λ_{lum} [nm] ^[a]	Φ/Φ° ^[b]	τ_{T} [ns] ^[c]	$\log K$ ^[d]
H ⁺	683	1.13	115	3.95
Li ⁺	678	1.04	105	1.58
K ⁺	678	0.98	100	0.80
Mn ²⁺	682	1.07	110	1.73
Zn ²⁺	695	2.15	210	4.42
Cd ²⁺	700	2.43	255	3.64
Ba ²⁺	690	1.80	190	2.97
Hg ²⁺ ^[d]	690	0.41	30	3.22
Ag ⁺ ^[f]	705	0.12	10	4.16

[a] Luminescence maximum recorded after complete complexation, ± 5 nm. [b] Ratio of luminescence quantum yields recorded after complete complexation (Φ) and in the absence of cation (Φ°), $\pm 9\%$. [c] Triplet lifetime recorded after complete complexation, $\pm 8\%$. [d] Stability constant, $\pm 7\%$. [e] Studied at pH 5 in the presence of 0.1 M KNO₃. [f] in 0.1 M KNO₃.

energetics (Table 2). Indeed, binding constants (K) were measured for several cations in neutral aqueous solution by monitoring the luminescence (or absorption) intensity for the terminal Ru(terpy) metallo-fragments as a function of cation concentration (Figure 1). Both the magnitude of K and the

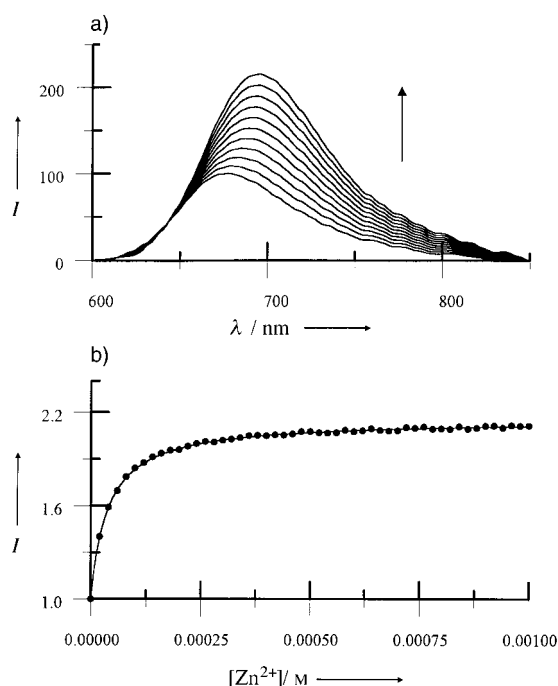


Figure 1. Luminescence titration following complexation between **2** and Zn²⁺ cations in acetonitrile at 20 °C. a) Overlay of luminescence spectra recorded during the titration showing the progressive increase in intensity and red-shift noted for the emission peak on coordination of the cation to the vacant 2,2'-bipyridine site. b) Correlation between emission quantum yield and concentration of added Zn²⁺ cations. The solid line represents a nonlinear, least-squares fit to formation of a 1:1 complex having $\log K = 4.42$ and $\Phi/\Phi_{\text{lum}} = 2.15$.

photophysical properties of the resultant 1:1 complexes depend on the nature of the added cation. Certain cations, notably Li⁺, K⁺, and Mn²⁺, bind weakly to the vacant 2,2'-bipyridine ligand and barely perturb the photophysical

properties of **2** in deoxygenated solution. Other cations, notably Ba²⁺, Cd²⁺, and Zn²⁺, bind more avidly and cause a substantial increase in luminescence intensity and lifetime without apparent change to the absorption spectral profile. In these latter cases, coordination of the cation causes a pronounced red shift to the emission maximum (Table 2). The shape of each titration curve indicates that luminescence enhancement is associated only with the bound cation and there is no additional effect from any cation remaining in solution. This modulation of the luminescence intensity can be reversed by adding a competitive complexing agent, such as neocuproine or ethylenediamine. Identical behavior, at least in qualitative terms, was found in acetonitrile solution.

Complexation of cations such as Ag⁺ and Hg²⁺, these being strong 2,2'-bipyridine binders, causes a marked decrease in luminescence from the terminal Ru(terpy)-based chromophores (Table 2). A similar effect is observed upon methylation of the vacant N atoms of the 2,2'-bipyridine. In the case of **3**, luminescence quenching is most likely due to light-induced electron transfer^[12] from a terminal metallo-chromophore to the central viologen unit. Since both Ag⁺ and Hg²⁺ cations are easily reduced^[13, 14] it seems reasonable to attribute luminescence quenching to electron transfer from the triplet state of a Ru(terpy)-based chromophore to a bound cation. In these cases, any free cation quenches the excited triplet state of the chromophore but such bimolecular processes are apparent only at very high concentration of cation.

Of the cations studied here those that amplify luminescence from the terminal chromophores are the most interesting since amplification is a measure of electron delocalization over the ditopic ligand. Binding of these cations to simple polypyridyl ligands is known to raise the one-electron reduction potential of the ligand.^[15] Presumably, the same effect takes place with **2** such that coordination of Cd²⁺ or Zn²⁺ ions at the vacant 2,2'-bipyridine site pushes E_{red} for the 2,2'-bipyridine unit closer to that of the coordinated terpyridine ligands. This ensures better blending of LUMOs localized on the individual components that comprise the ditopic ligand so that an extended π^* becomes available for the promoted electron. Cyclic voltammetry studies made with the Zn²⁺ complex of **2** support this hypothesis. Thus, reduction of **2** in *N,N*-dimethylformamide takes place progressively at the substituted terpyridine ($E_{\text{red}} = -1.06$ V vs. saturated calomel electrode (SCE), 2e process), parent terpyridine ($E_{\text{red}} = -1.42$ V vs. SCE, 2e process), and bipyridine ($E_{\text{red}} = -1.57$ V vs. SCE, 1e process) units. Upon coordination of Zn²⁺ to the central ligand, reduction of the substituted terpyridine ($E_{\text{red}} = -0.99$ V vs. SCE, 2e process) and bipyridine ($E_{\text{red}} = -1.23$ V vs. SCE, 1e process) becomes easier and takes place at more comparable potentials while reduction of the parent terpyridine ($E_{\text{red}} = -1.43$ V vs. SCE, 2e process) remains unchanged. It seems likely that by more precise matching of the relevant LUMO energies it will be possible to create a giant π^* orbital that encompasses the entire ditopic ligand. In following this strategy, however, it is essential that the central unit does not become too easily reduced such that the promoted electron becomes trapped at a low energy site, as seems to be the case with **3**.

For supermolecules of the type discussed here, extended electron delocalization at the triplet level demands that the acetylene function is attached directly to the coordinated terpyridine ligand. The molecular axis can be lengthened while retaining rigidity by including aromatic groups in the polyacetylene wire. Such groups provide a facile means by which to modify the solubility, electronic charge, molecular shape, and photoproperties of the emergent multicomponent array. The acetylene unit ensures selective charge injection into the ditopic ligand under illumination, while the nature of the central aromatic core controls the extent of electron delocalization over the ditopic ligand. These two molecular fragments are highly complementary, and they act cooperatively to direct electronic charge along the molecular axis. In the case of the prototypic system **2**, where the terminal Ru^{II} cations are separated by about 23 Å, the photophysical properties can be fine-tuned by selective coordination of additional cations. Presumably, external complexation of this type could be used to modulate the rates of light-induced energy or electron transfer through the bridge in mixed-metal analogues of **2**. Provided high binding constants prevail, this strategy could be used to stimulate electron transfer between remote reactants by injection of a low concentration of a specific cation into the system. This situation is reminiscent of biological regulatory mechanisms and is a future goal for our research.

Experimental Section

Synthesis and characterization of all new complexes will be reported elsewhere, but a typical experimental procedure is given for **2**: A Schlenk flask was charged with 5,5'-diethynyl-2,2'-bipyridine (0.010 g, 0.49 mmol), [Ru(terpy)(terpy-Br)](PF₆)₂ (0.091 g, 0.98 mmol), 10 mL degassed CH₃CN, [Pd(PPh₃)₂Cl₂] (0.004 g, 6% in mol) and CuI (0.002 g, 10% in mol). After purging with argon, (*i*Pr)₂NH (5 mL) was added. The solution was stirred at room temperature for 6 days before KPF₆ (0.018 g, 4 equiv.) in water (5 mL) was added and the solvent removed. The crude product was chromatographed on alumina with a mixture of CH₃CN and H₂O (gradient of water 0–25%). The analytically pure compound was obtained by recrystallization from CH₃CN/diethyl ether. Yield 70%. *R*_f = 0.45 (alumina, CH₃CN/H₂O/KNO₃, 80/20/0.5 as eluent). ¹H NMR (CD₃OD): δ = 9.24 (s, 3H), 9.12 (s, 1H), 9.02 (d, 4H, ³*J* = 8.3 Hz), 8.86–8.67 (m, 6 lines, 11H), 8.52 (t, 3H, ³*J* = 5.9 Hz), 8.38 (dd, 2H, ³*J* = 8.3 Hz, ⁴*J* = 1.9 Hz), 8.08–7.97 (m, 8H), 7.59–7.51 (m, 8H), 7.35–7.26 (m, 8H). FAB-MS: *m/z* = 1772.1 [*M* – PF₆ + H], 1626.0 [*M* – 2 PF₆], 1481.0 [*M* – 3 PF₆]. UV/Vis (CH₃CN): λ_{max} nm (ε M^{–1} cm^{–1}) 495 (41400), 258 (45000), 332 (56000), 308 (69400), 272 (58400). Analysis calcd for C₇₄H₄₈Ru₂N₁₄P₄F₂₄ (*M*_r = 1915.30): C 46.41, H 2.53, N 10.24; found: C 46.29, H 2.42, N 10.15.

Luminescence lifetimes were measured by a time-correlated, single-photon counting methodology following laser excitation at 440 nm (detection at the peak of the emission spectrum). Binding constants were determined by monitoring absorption and/or luminescence spectral profiles as a function of cation concentration and using global analytical iterative routines provided by the SPECFIT commercial software. Reduction potentials were measured by conventional cyclic voltammetry with Pt discs as working and counterelectrodes and an SCE reference, calibrated vs. ferrocene.

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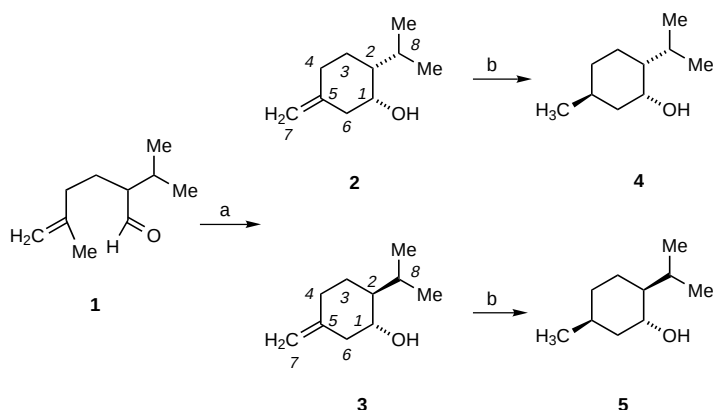
Models for the Carbonyl–ene Cyclization Reaction: Open and Closed Transition States**

D. Christopher Braddock, King Kuok (Mimi) Hii, and John M. Brown*

During a study of stereospecific syntheses of menthol-related terpenoids we prepared racemic and enantiomerically pure 5-methyl-2-(1-methylethyl)hex-5-enal (**1**).^[1] From preliminary experiments with simple Lewis acids, catalytic BCl₃, and catalytic or stoichiometric quantities of SnCl₄ gave cleanly the anticipated ene-cyclization products **2** and **3** (Scheme 1). In these two cases the ratio of **2** to **3** was 9:1, which is in accord with related results obtained by Snider and

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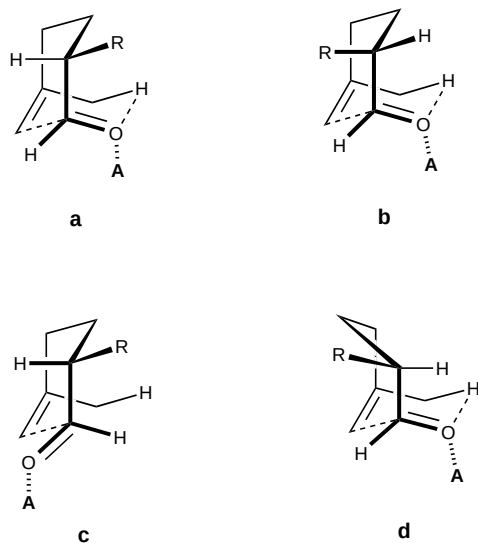
[**] We thank EPSRC for a CASE award (to D.C.B.) and support (to K.K.H.). We greatly appreciate the encouragement of Dr. Charles Sell (Quest International, Ashford). Dr. Tim Claridge helped with NMR experiments. We are grateful for an exchange of information with Professor Hisashi Yamamoto and Dr. Takashi Ooi, and thank Professor Ei-ichi Negishi for some experimental details.



Scheme 1. Carbonyl-ene cyclization of 5-methyl-2-(1-methylethyl)hex-5-enal **1** and hydrogenation of the products: a) Lewis acid catalysts, see Experimental Section; b) $[\text{Ir}(\text{COD})(\text{PCy}_3)(\text{py})]\text{PF}_6$ (cod = 1,5-cyclooctadiene, Cy = cyclohexyl, py = pyridine) H_2 , CH_2Cl_2 .

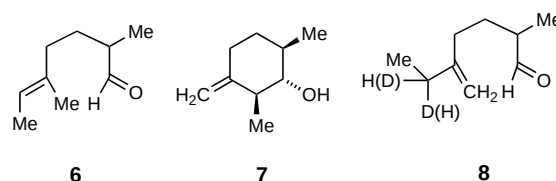
co-workers with Me_2AlCl .^[2] The bulky monocyclic^[3] methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxy) (MABR) also gives a clean reaction but with the opposite stereochemical preference, as defined by Yamamoto and co-workers.^[4] As in Yamamoto's work, the configuration of products **2** and **3** was confirmed by reduction; in our case OH-directed stereospecific addition of H_2 with Crabtree's catalyst^[5] gave **4** and **5**, respectively (Scheme 1).

Early mechanistic understanding of the stereochemical course of ene cyclization reactions stems from the work of Snider and co-workers.^[6] They proposed that the predominant *cis*-cycloadduct formed in the dimethylaluminum chloride mediated ene cyclization of 2-alkylhex-5-enal derivatives arises from a concerted path through a six-membered chair-like transition state (**a**, Scheme 2), in which the long alkyl chain also orients itself in a chairlike conformation; the alkyl substituent adopts an equatorial position. Strictly speaking, the model is based on a bicyclo[3.3.1]nonane framework



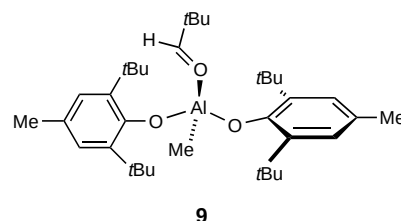
Scheme 2. Mechanistic models for ene-cyclization: a) Snider, leading to *cis*-product, b) Snider, leading to *trans*-product; c) Yamamoto's "open" model leading to *trans*-product, and d) boat precursor of *trans*-product proposed here.

(drawn in Scheme 2 so as to highlight this aspect). The *trans*-cycloadducts observed when bulky MABR reagents were used were explained by Yamamoto as arising through an open chairlike transition-state (**c**, Scheme 2). His results pertaining to *trans*-decalin products rule out the alternative closed transition state **b** (Scheme 2) where the alkyl substituent occupies an axial position.^[4c] The possibility of a closed boatlike transition state for the MABR-promoted cyclization (**d**) was not considered. Yamamoto's explanation fits the stereochemical course of MABR-promoted cyclization from compound (*E*)-**6** to **7**, although cyclization of the *Z* stereoisomer of compound **6** is anomalous in that the *trans*-cyclization product is obtained with either MABR or Me_2AlCl . An open transition state, implying a lack of concert between the H transfer and C-C bond-forming steps, is not



easily reconciled with the stereospecific H or D transfers seen by Marshall and co-workers in the cyclization of the isotopomers of compound **8** with either Me_2AlCl or MABR, however.^[7]

Models for the ene cyclization of enal **1** were made based on the transition state geometry calculated at the STO-3-21G level by Houk and co-workers for the ene-reaction between propene and formaldehyde.^[8] The location of the aluminum Lewis acid was defined by analogy with the series of X-ray structures of Lewis acid complexes of bulky alanes, specifically the aldehyde complex **9** published by Barron's group.^[9] An important feature of this and related compounds is that



the Al-O=C donor bond eclipses the aldehyde C-H bond and is thus in the nodal plane of the carbonyl group. In situations where the bulk of the aluminum substituents may be ignored, as in promotion of ene cyclization by Me_2AlCl , the Snider model shown in **a** (Scheme 2) accords very well with the theoretically derived geometry. Applying this model to the MABR-promoted cyclization reaction demonstrates exactly why reverse stereoselectivity is observed; only one face of the aldehyde is accessible for reaction, but only the boat conformation of **d** (Scheme 2) shown in Figure 1a makes the reagent and substrate sterically compatible. The chair transition state engenders a severe clash between the isopropyl group of enal **1** and an *ortho*-*tert*-butylphenoxy group on the aluminum center, indicated in Figure 1b. The required boat transition state in **d** (Scheme 2) also fits all of the other

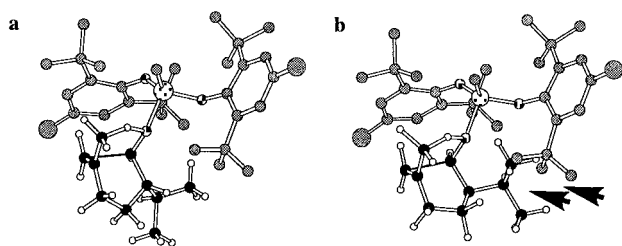
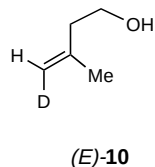


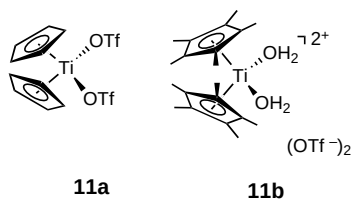
Figure 1. Models for the MABR cyclization based on the X-ray structure of the pivalaldehyde complex **9** and the *ab initio* transition state of the carbonyl–ene reaction. a) Boat conformation as in **d** (Scheme 2). b) Chair conformation as in **a** (Scheme 2). Hydrogen atoms are omitted from the ligand for clarity. The upper model is free of steric hindrance while the lower has a serious clash in the arrowed region. The diastereoisomeric form of b) is also sterically strained to a high degree. The MABR backbone is in grey, and that of **1** in black.

examples of intramolecular ene cyclizations promoted by MABR reported by Yamamoto and co-workers, with the exception of one observation involving a trisubstituted alkene.^[4c] If this result can be reconciled, the need for mechanistic diversity would be removed.



The above conflicting possibilities were resolved by cyclization of stereospecifically labeled **1**. The key step involves Negishi's Zr-catalyzed carboalumination of butynol with AlMe_3 . Workup with AcOD proceeds to give more than 98% (E)-**10**.^[10] The remainder of the synthesis follows that of the racemic compound, and the configuration of (E)-[^2H]**1** was confirmed by NOE measurements. The NMR spectra of the products of ene cyclization of **2** and **3** were fully assigned by 1D and 2D NMR experiments, and demonstrated that the axial and equatorial protons at C6, derived from the vinylic methylene protons of aldehyde **1**, were distinguishable in both diastereoisomers of the cyclohexanol derivative.^[11] For cyclization of (E)-[^2H]**1**, a single isotopomer of the major product was formed in each case. For the cyclization promoted by MABR, the product [^2H]**3** has an axial D-atom at C6, indicated by comparison between the ^1H NMR spectra of undeuterated (**A**) and deuterated products (**B**) in Figure 2. In contrast, the Me_2AlCl -promoted cyclization product [^2H]**2** has an equatorial D atom at C6, as evident from comparing the spectra of undeuterated (**C**) and deuterated (**D**) products. Given these results for a system perturbed only by an isotope, the preferred pathways for Me_2AlCl and MABR must involve the transition-state models shown in Scheme 2, **a** and **d**, respectively; the Yamamoto model of Scheme 2 **c**, would have predicted equatorial deuteration.

What then is the status of open transition-states in carbonyl ene–cyclizations? The two titanocene-derived Lewis acids



11a and **11b** at 4 mol% gave different product distributions in Lewis acid catalyzed ene cyclization of aldehyde **1**.^[12] The products of the reaction were now the isomeric cyclohexenols **12** and

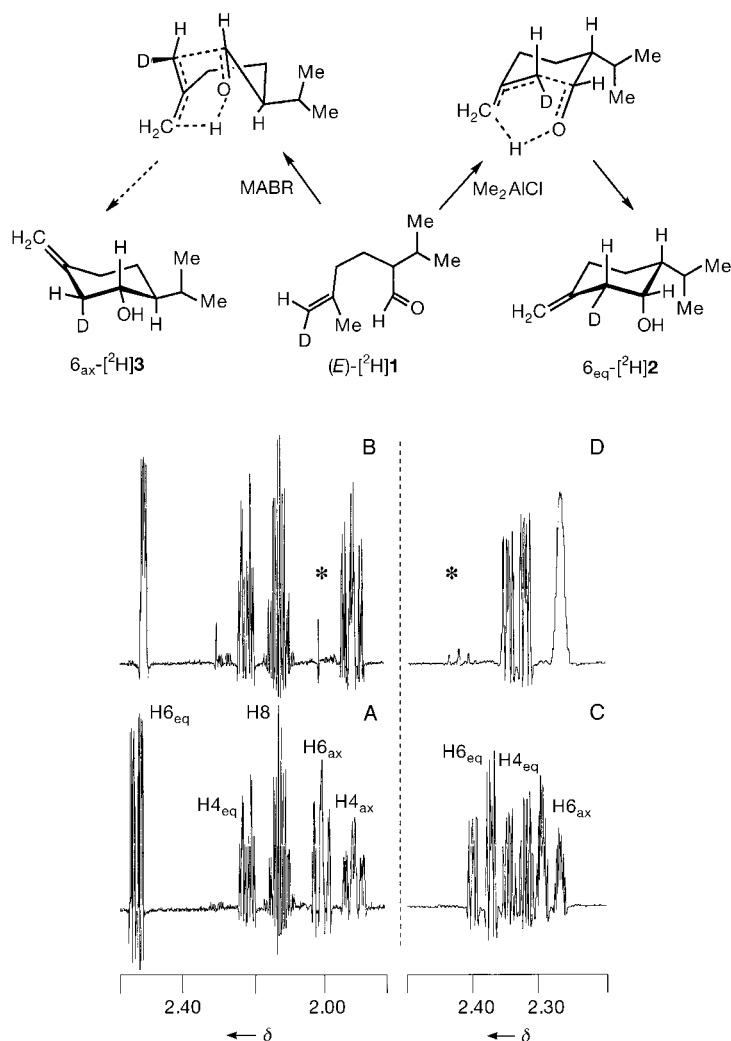
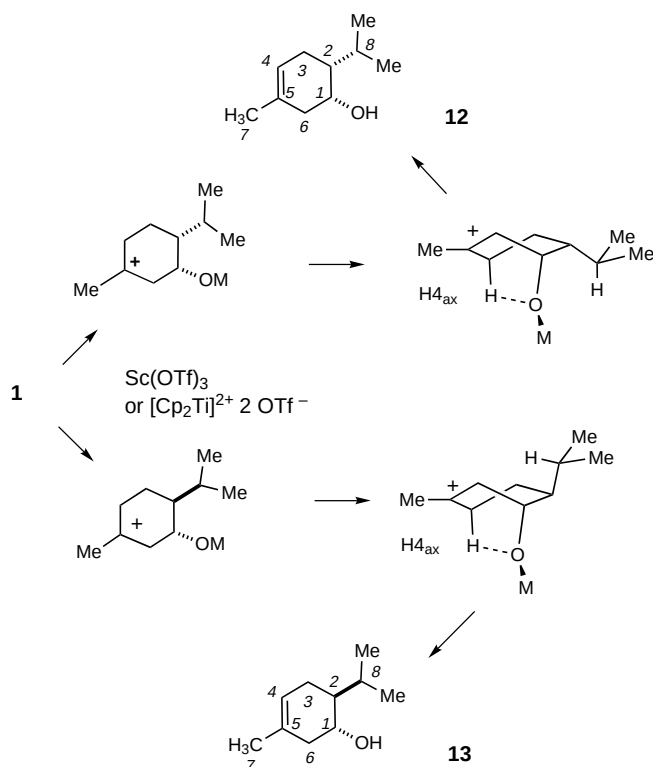


Figure 2. ^1H NMR spectra of cyclization products. A) Compound **3** from MABR reaction, in the 2.6–1.8 ppm range; B) as A, starting from (E)-[^2H]**1**; C) compound **2** from Me_2AlCl reaction in the 2.5–2.2 ppm range; D) as C, starting from (E)-[^2H]**1**.

13, formed in an approximate 3:1 ratio (Scheme 3). Their configuration was again demonstrated through directed hydrogenation with Crabtree's catalyst to the corresponding neomenthol isomers. The “expected” exocyclic alkenes **2** and **3** were shown not to isomerize under the standard reaction conditions, hence the Ti-catalyzed reaction cannot proceed by ene cyclization followed by isomerization.

Furthermore 20 mol% of $\text{Sc}(\text{OTf})_3$ was an efficient catalyst, leading to the exclusive formation of **12** and **13** in a 7:3 ratio. This is explained by an open transition-state model analogous to that shown in **c** (Scheme 2). A methylcyclohexylation is generated from 1-methylcyclohexan-1-ol in super-acid solution and exists as a rapidly equilibrating mixture of twist-boat and flattened-chair conformations whereby maximum hyperconjugation with the 2- and 6-axial C–H is maintained. The twist-boat conformation was estimated to be 2 kJ mol $^{-1}$ more stable than the corresponding chair conformer.^[13] A twist-boat intermediate is disposed to permit regiospecific intramolecular proton transfer to the Lewis acid



Scheme 3. Cyclization pathway proceeding via an open transition state with a cyclohexyl cationlike intermediate.

coordinated oxygen functionality from the pseudoaxial 4-proton, giving the experimentally observed *cis*- and *trans*-endocyclic cycloadducts.^[14] The stereoisomeric twist-boat carbocation intermediates leading to the *cis*- and *trans*-cyclohexenols **12** and **13** are shown in Scheme 3.

Finally an acid-catalyzed cyclization was effected with Amberlyst 15, or 5 mol % *p*-TsOH. This intramolecular Prins reaction^[15] was quite unselective and led to the above-mentioned endo- and exocyclic alcohols **2**, **3**, **12** and **13**, accompanied by the stereoisomers of (±)-piperitol (the Δ⁵-isomers of **12** and **13**) as well as related endocyclic dienes α-phellandrene and α-terpinene. Hence the hydride transfer step of Scheme 3 is distinct from the purely stepwise intermolecular pathway observed in proton catalysis.

Experimental Section

(*E*)-**10**^[10]: A solution of Me₃Al (2 M in hexanes, 100 cm³) was added slowly to a stirred solution of [Cp₂Zr]Cl₂ (14.6 g, 20 mmol) in ClCH₂CH₂Cl (200 cm³) at room temperature, followed by a solution of 3-butyne-1-ol (4.6 g, 66 mmol) in ClCH₂CH₂Cl (20 cm³) at 0 °C. The reaction mixture was stirred at ambient temperature for 19 h before being quenched carefully with a 1 M solution of CH₃COOD/D₂O (25 cm³) at 0 °C. Volatile compounds (< 80 °C) were removed by careful distillation with a 20 cm Vigreux column and the residue was extracted with diethyl ether (2 × 200 cm³). The combined ether extracts were washed with saturated NaHCO₃ (100 cm³) and water (100 cm³), dried (MgSO₄), and carefully evaporated (< 60 °C). The product was purified by fractional distillation to yield the required deuterated alcohol as a colorless liquid. Yield 2.6 g, 45%; > 98% deuteration by integration of residual proton signal in the NMR spectrum.

2 and **3**: Following the procedures of Yamamoto et al.^[4c] enal (±)**1** was mixed with Me₂AlCl in toluene at –78 °C; (30:1 **2**:**3**, 83% yield of purified

2) or with MABR in toluene at –78 °C to –40 °C; (1:20 **2**:**3**, 78% yield of purified **3**).

12 and **13**: (±)-**1** (208 mg, 2 mmol) was added to a solution of titanocene ditriflate **11a** (0.013 M, 6 mL, 4 mol %) prepared in situ in nitromethane.^[12] After 10 min the orange solution was passed through a pad of silica and washed through with diethyl ether. The combined organic extracts were evaporated and the yellow residue was purified by flash chromatography on silica gel (10% ethyl acetate in pentane) to give first (1*R**,2*R**)-5-methyl-2-(1-methylethyl)-4-cyclohexen-1-ol (**12**; 0.112 g, 56%)^[14a] and second (1*S**,2*R**)-5-methyl-2-(1-methylethyl)-4-cyclohexen-1-ol (**13**; 0.049 g, 25%)^[14b]

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Application of the 2-Azaallyl Anion Cycloaddition Method to an Enantioselective Total Synthesis of (+)-Cocaine**

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The montanine-type alkaloids (e.g., **1–8**, Figure 1) form a small class of Amaryllidaceae alkaloids that share the 5,11-methanomorphanthridine ring system^[1] and differ primarily

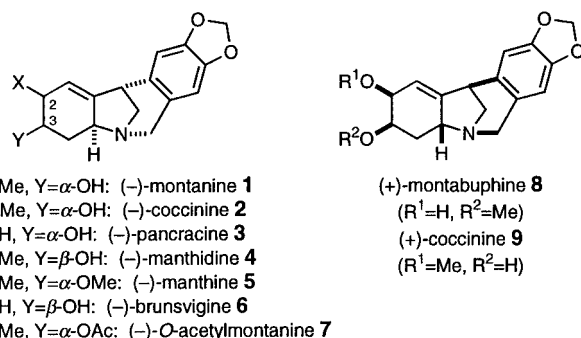


Figure 1. Montanine-type alkaloids.

in the configurations at the stereocenters and the type of oxygen substitution at C-2 and C-3. The recent isolation of (+)-montabuphine, assigned structure **8**,^[2] suggests that both enantiomers of the methanomorphanthridine ring may exist in nature. While Amaryllidaceae alkaloids have in general been the subject of much synthetic effort, the 5,11-methanomorphanthridine class alkaloids has attracted much less attention. Overman and Shim reported the total syntheses of (±)- and (–)-pancracine (**3**),^[3] and total syntheses of racemic montanine (**1**), cocaine (**2**), pancracine (**3**), brunsvigine (**6**), and O-acetylmontanine (**7**) were published by Hoshino et al.^[4] Most recently, Jin and Weinreb reported the enantioselective syntheses of (–)-cocaine (**2**) and (–)-pancracine (**3**).^[5] We now describe an enantioselective total synthesis of (+)-cocaine (**9**), the nonnatural enantiomer of (–)-cocaine (**2**), which uses our 2-azaallyl anion cycloaddition methodology^[6,7] as the key step. This represents the first assembly of the 5,11-methanomorphanthridine ring system in the uncommon enantiomers.

For the retrosynthesis (Figure 2) we envisioned the assembly of montanine-type alkaloids from the perhydroindole **10**, which should be available by the intramolecular cycloaddition of the 2-azaallyl anion **11**.^[6] Pictet–Spengler cyclization, previously applied by Overman and Shim,^[3] would be used to incorporate the methano bridge, and elimination of HX from **10** would form the requisite alkene. The precursor to the

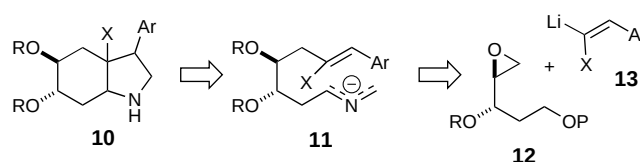
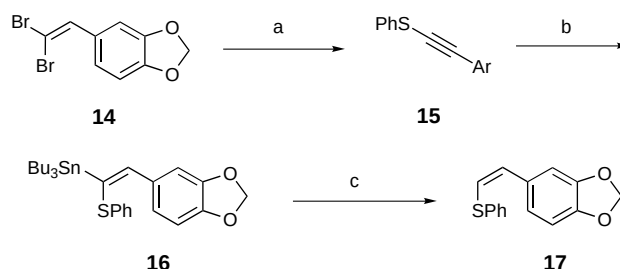


Figure 2. Synthetic strategy for montanine alkaloids.

anion **11** should be accessible from the epoxide **12** and the vinyl lithium compound **13**.^[8] The diastereoselectivity of the intramolecular 2-azaallyl anion cycloaddition is still relatively unexplored.^[9] On the basis of molecular models, we proposed that anion **11** would produce the isomer of **10** required for a synthesis of (–)-montanine (**1**). As revealed below, an alternate stereochemical outcome which ultimately allowed access to the alternative enantiomer was observed experimentally.

Our synthesis began with the assembly of the vinyl lithium precursor **17** (Scheme 1). Piperonal was converted into the



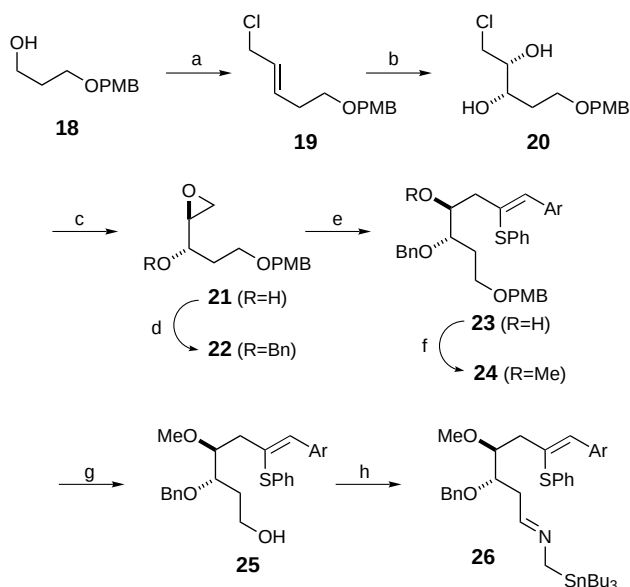
Scheme 1. Synthesis of the vinyl sulfide **17**: a) *n*BuLi (2 equiv), THF, –78 °C, 1 h, RT, 1.5 h; PhSSPh, THF, –78 °C, 0.5 h, RT, 0.5 h, 78%; b) [Pd(PPh₃)₄] (cat.), Bu₃SnH, C₆H₆, RT, 14 h; c) *n*BuLi (3 equiv), THF, –78 °C, 0.5 h, sat. aq. NH₄Cl, RT, 89% based on **15**.

known vinylidene dibromide **14**^[10] with CBr₄/PPh₃/Zn.^[11] Conversion of **14** into the alkynyllithium compound followed by quenching with diphenyl disulfide produced the alkynyl sulfide **15**. Regioselective hydrostannylation^[12] of **15** provided the vinyl stannane **16**, which was best used without purification. Tin–lithium exchange followed by protonation gave the (Z)-vinyl sulfide **17** in good overall yield.^[13]

The synthesis of the (2-azaallyl)stannane **26** required for the 2-azaallyl anion cycloaddition is shown in Scheme 2. The epoxide **22** needed for coupling with the vinyl sulfide **17** was prepared by the Sharpless asymmetric dihydroxylation method.^[14] The known *p*-methoxybenzyl-protected diol **18**^[15] was subjected to Swern oxidation, Horner–Wadsworth–Emmons olefination, reduction with diisobutylaluminum hydride, mesylation, and in situ displacement of the chloride substituent^[16] to provide the allylic chloride **19**. Asymmetric dihydroxylation of **19** gave the diol **20**,^[17] which was converted into the epoxyl alcohol **21** with sodium hydride. Mosher's ester analysis of **21** indicated an enantiomeric excess of 88% for this material. Protection of **21** as a benzyl ether provided the desired epoxide **22**. Deprotonation of the vinyl sulfide **17** with *tert*-butyllithium followed by reaction with epoxide **22** in the presence of BF₃·OEt₂^[18] afforded the alcohol **23** in good yield with complete retention of the alkene geometry.^[19] Methylation of **23** gave **24**, which was selectively deprotected to

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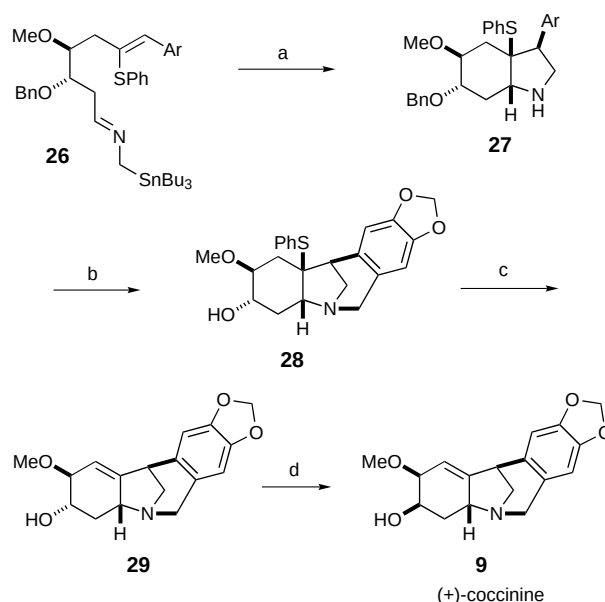
[**] This work was supported by the National Institutes of Health (GM-52491).



Scheme 2. Synthesis of (2-azaallyl)stannane **26**: a) 1. (COCl)₂, DMSO, NEt₃, CH₂Cl₂; 2. (MeO)₂P(O)CH₂CO₂Me, NaH, C₆H₆, RT, 14 h; 3. *i*Bu₂AlH, toluene/THF, 0 °C, 45 min, RT, 30 min; 4. MsCl, *i*Pr₂NEt, CH₂Cl₂, –23 °C, 45 min, dilute with DMF, add LiCl (2 equiv), RT, 5 h, 41 % based on **18**; b) AD-mix- α , THF, *t*BuOH, H₂O, MeSO₂NH₂, 0 °C, 48 h, 100%; c) NaH, THF, DMSO, RT, 12 h, 81 %; d) NaH, BnBr, THF, DMSO, 0 °C, 2 h, RT, 24 h, additional portion of NaH/BnBr, RT, 8 h, 82 %; e) **17** (2.8 equiv) + *t*BuLi (2.8 equiv), –78 °C, THF, 15 min, add **22**, add BF₃·OEt₂ (2.8 equiv), –78 °C, 45 min, 80%; f) NaH, THF, 0 °C, MeI, RT, 14 h, 100%; g) EtSH (27 equiv), CH₂Cl₂, BF₃·OEt₂, –78 °C, then –25 °C, 24 h, 92%; h) 1. (COCl)₂, DMSO, NEt₃, CH₂Cl₂, 94 %, or tetrapropylammonium perruthenate (cat.), *N*-methylmorpholine *N*-oxide, 4-Å molecular sieves, CH₂Cl₂, RT, 14 h, 78%; 2. Bu₃SnCH₂NH₂, Et₂O, 4-Å molecular sieves, RT, 16 h, 86 %. Bn = benzyl, Ms = methanesulfonyl, PMB = *p*-methoxybenzyl.

provide the alcohol **25**. Oxidation and condensation with (aminomethyl)tri-*n*-butylstannane^[6c] gave the desired (2-azaallyl)stannane **26**.

Without purification, **26** was subjected to tin–lithium exchange at low temperature with *n*-butyllithium (Scheme 3). Quenching the reaction with water provided a single stereoisomer of the perhydroindole **27** in 45 % yield. At this point, the configuration of the three new stereocenters was not known. Pictet–Spengler cyclization of **27** with concomitant removal of the benzyl protecting group gave the 5,11-methanomorphanthridine **28**. Oxidation of the HCl salt of **28** to generate the sulfoxide followed by thermolysis gave **29**, which differed from an authentic sample of (–)-montanine (**1**).^[20] The optical rotation of **28** (and all subsequent compounds) was dextrorotatory rather than levorotatory, which provides evidence that the cycloaddition had produced the enantiomeric 5,11-methanomorphanthridine skeleton. Thus, we inverted the alcohol of **29** to produce the nonnatural enantiomer of coccine. Mesylation of **29** followed by displacement with acetate and saponification provided (+)-coccine (**9**), which was identical to natural (–)-coccine (**2**)^[20] in all respects (*R*_f value in thin-layer chromatography (TLC), 500-MHz ¹H NMR and 90-MHz ¹³C NMR spectra, and mass spectrum) with the exception of optical rotation [synthetic (+)-coccine: [α]_D²⁵ = +96 (*c* = 0.05, EtOH), [α]_D²⁵ = +182.2 (*c* = 0.045,



Scheme 3. Synthesis of (+)-coccine (**9**): a) *n*BuLi (4 equiv), THF, –78 °C, 2 h, 45 %; b) 37 % aq. CH₂O, MeOH, RT, 5 min; 6 *N* HCl, 80 °C, 12 h, 53 %; c) 1. Et₂O, anhydrous HCl, 0 °C, 20 min, concentrate in vacuo; *m*-CPBA, CH₂Cl₂, 0 °C; 2. C₆H₆, K₂CO₃, 80 °C, 1.5 h, 76 % based on **28**; d) 1. Ms₂O, pyridine, CH₂Cl₂, 0 °C, 1 h; 2. CsOAc, DMF, [18]crown-6, 125 °C, 48 h; 3. K₂CO₃, MeOH, RT, 3 h, 52 % based on **29**. *m*-CPBA = *m*-chloroperbenzoic acid.

CHCl₃); natural (–)-coccine: [α]_D²⁵ = –104 (*c* = 0.07, EtOH), [α]_D²⁵ = –218.2 (*c* = 0.055, CHCl₃)].

In our initial synthetic planning, examination of molecular models suggested that two conformations, chairlike **30** and twist-boat-like **32**, had good orbital overlap between the 2-azaallyl anion and the anionophile, leading to the *cis*-fused^[21] perhydroindoles **33** and **34**, respectively (Figure 3). The

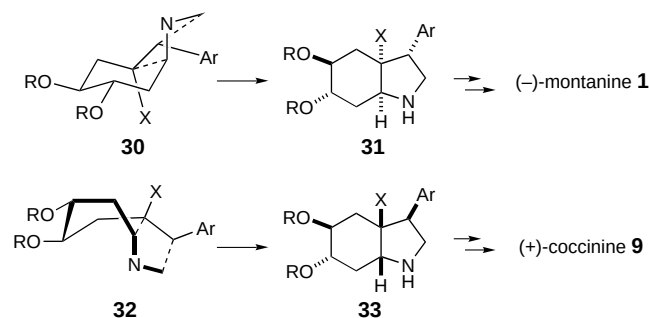


Figure 3. Possible conformations of the 2-azaallyl anion in the cycloaddition.

chairlike conformation **30** appeared to be less congested than **31**. Thus, we predicted that the perhydroindole **31** rather than **33** would result from the cycloaddition.^[21] An explanation of this surprising result is under investigation.

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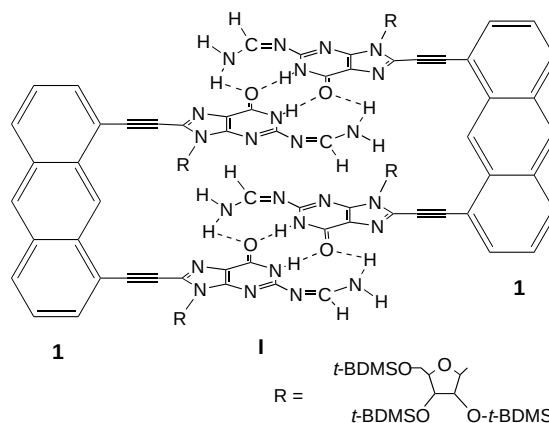
Keywords: alkaloids • cycloadditions • nitrogen heterocycles • synthetic methods • total synthesis

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- [21] Transition states leading to *trans* ring junctures are not considered based on previous experience.^[6b, 9] The alternate chairlike conformation that may lead to **33** is not shown, since it displays severe 1,3-diaxiallike interactions.

A New Base-Pairing Motif Based on Modified Guanosines**

Jonathan L. Sessler* and Ruizheng Wang

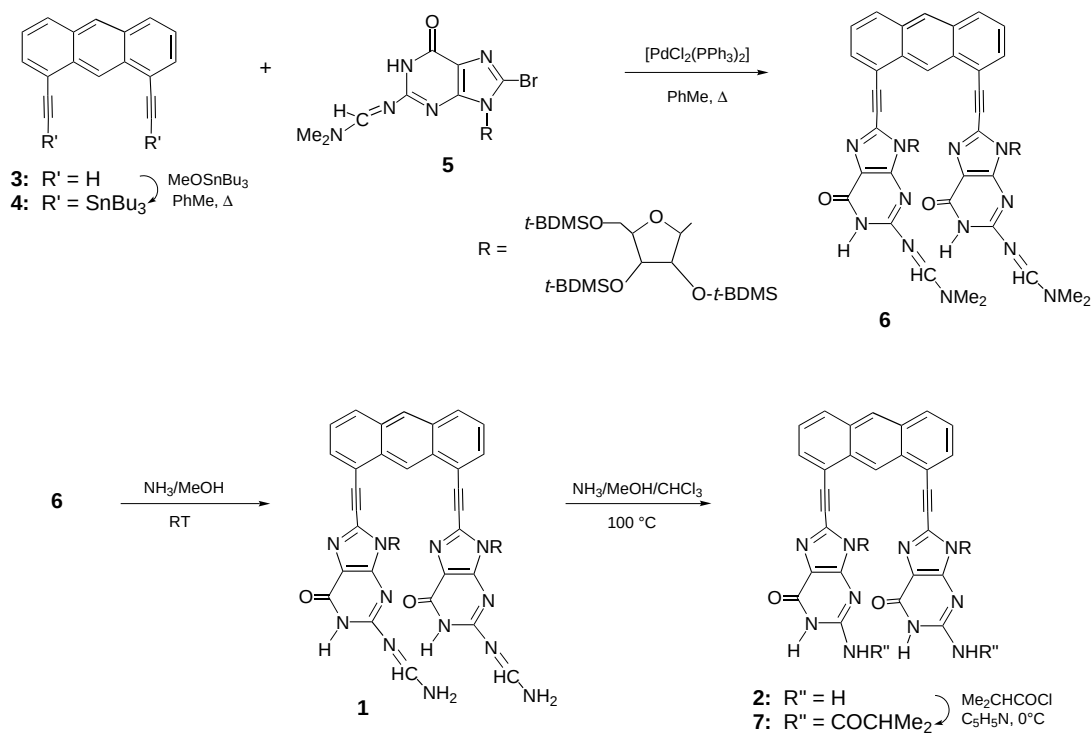
Watson–Crick base pairing involving purine and pyrimidine subunits plays a crucial role in regulating the structures and properties of, for example, duplex DNA and hairpin RNA. Studying synthetic systems with unconventional binding modes could serve to extend the genetic alphabet of DNA and RNA, and produce systems of greater structural diversity, functionality, and catalytic potential.^[1] In this context, modified systems derived from guanine are of considerable interest because of their potential antiviral activity and their possibly unique binding ability.^[2] However, the number of such systems that have been analyzed in terms of their self-association properties remains limited. One example is 7,9-dimethylguanine, a species that dimerizes in aqueous solution with the formation of three hydrogen bonds.^[3] A second example is 5'-(*tert*-butyldimethylsilyl)-2',3'-*O*-isopropylidene isoguanosine; this forms a tetramer^[4] in organic media that is more stable than the corresponding guanosine tetramer.^[5] Here we report the new guanine derivative **1**, which, when constrained within a rigid framework, self-associates in organic solution to form an unprecedented tetrameric guanine-containing array (dimer **1**). What is unique about this system is that it is held together by a pair of four-point hydrogen bonds.^[6–8]



The synthesis of **1** (Scheme 1) involves initially a Pd-catalyzed cross-coupling between *N*²-(*N,N*-dimethylformamide)-protected 8-bromoguanosine (**5**) and organostannyl derivative **4**^[9] produced in situ from 1,8-diethynylantracene (**3**). This sequence gave the bis(guanosine) derivative **6**. Treatment of **6** with methanolic ammonia at room temperature did not give the expected deprotected bis(guanine) derivative **2**, but rather **1**, in which the *NMe*₂ group of **6** is

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Scheme 1. Synthesis of **1** and **2**.

replaced by an NH₂ group. Compound **2** could then be obtained by treating **1** with methanolic ammonia in chloroform at 100 °C in a sealed tube. The amino groups in **1**, which are “extended” by two bonds with respect to those in **2**, were found to impart unique binding properties. Accordingly, compound **1** was characterized by ¹H and ¹³C NMR spectroscopy (including ¹H–¹H COSY, ¹H–¹⁵N HMQC, and ¹H–¹³C HMQC experiments), mass spectrometry, elemental analysis, and a detailed study of its general chemical properties.

Compound **1** is extremely nonpolar. It displays, for instance, an *R_f* value of 1 (thin-layer chromatography (TLC) on silica gel, hexane/ethyl acetate 3/1) under conditions where **2**, **5**, **6**, and **7** display *R_f* values close to 0. Derivative **1** is also highly soluble in nonpolar solvent such as benzene and toluene, and insoluble in pure DMSO and acetone. While puzzling at first, the low effective polarity of **1** was in due course rationalized by the self-associated formation of ensemble **I**. In this dimer the functional groups in **1** are tied up in intradimer hydrogen bonds and therefore unavailable for interaction with a polar solvent or solid support.

Initial evidence that **1** can self-associate to form a stable dimer came from fast atom bombardment mass spectrometry (FAB-MS). In addition to a peak at *m/z* = 1527, ascribable to the monomer, a second peak at *m/z* = 3054 was also seen (no peaks ascribable to higher order aggregates were observed). A high-resolution analysis of the latter signal proved consistent with the proposed existence of a dimer (calcd for C₁₅₂H₂₃₇N₂₄O₂₀Si₁₂: *M_r* = 3054.5503; found: 3054.5492). Such dimer peaks, however, were not seen in the FAB mass spectra of three control compounds, namely, **2**,^[10] **6**, and **7**.

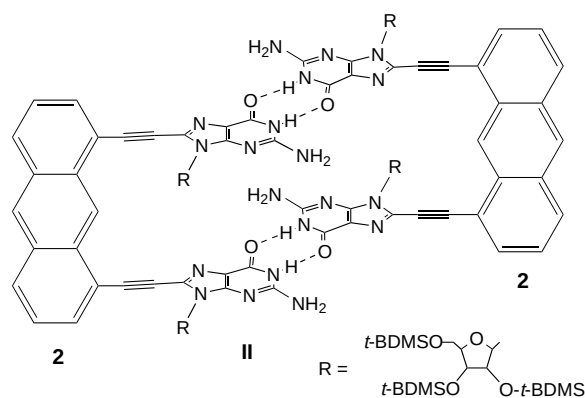
The average molecular weight of **I** was measured in solution with vapor pressure osmometry (VPO; 1,2-dichloroethane as

the solvent and diphenylacetylene as the standard). The value obtained (3125 ± 190 u; 30 °C) agrees well with that calculated for the proposed dimeric structure **I** (3054 u).

More compelling evidence for the formation of ensemble **I** came from NMR spectroscopic analyses.^[11] Simple ¹H NMR studies revealed that the chemical shifts of the imino NH resonances in CDCl₃ were at δ = 13.6, 12.6, 10.6, 11.0, and 11.7 for compounds **1**, **2**, **5**, **6**, and **7**, respectively. The large downfield shifts for the imino NH protons in **1** and **2** are consistent with the suggestion that they are involved in hydrogen bonding.^[12]

¹H–¹⁵N HMQC NMR experiments in C₆D₆ helped establish that one proton of each NH₂ group of **1** is also involved in hydrogen bonding. The ¹H resonances at δ = 11.2 and 5.2 correspond to two protons attached to the same nitrogen atom. The inequivalence of these two amino protons and the large separation between the signals (Δδ = 6) is consistent with rotation about the C–NH₂ bond being slow on the NMR time scale. Such a slow bond rotation is easily rationalized in terms of a strong hydrogen bond involving one of the two amino protons. On the basis of literature precedent,^[4] the resonance at δ = 11.2 is ascribed to the proton that is hydrogen-bonded, while that at δ = 5.2 is assigned to the “free” proton.

A similar separation of the signals for the two amino NH₂ protons is not seen for **2** in CDCl₃. Instead, a weak, very broad, upfield-shifted signal (δ ≈ 5.5) is observed. We therefore concluded that the NH₂ groups in **2** do not participate in the self-association process.^[13] Rather, **2** self-associates in CDCl₃ to form dimer **II** as a result of hydrogen-bonding interactions that involve solely the two CO/NH moieties.^[14]



Further insights into the structure of ensemble **I** were obtained from 2D ROESY experiments.^[15] Specifically, these revealed distinct correlations between H1'' of the sugar at $\delta = 6.7$ and H9 of the anthracene moiety at $\delta = 9.8$, as well as between the N=CH proton at $\delta = 9.1$ and the two protons H5'' of the sugar at $\delta = 5.3$ and 3.9 (Figure 1). These results are consistent with the glycoside bond being in the *syn* conformation.^[16]

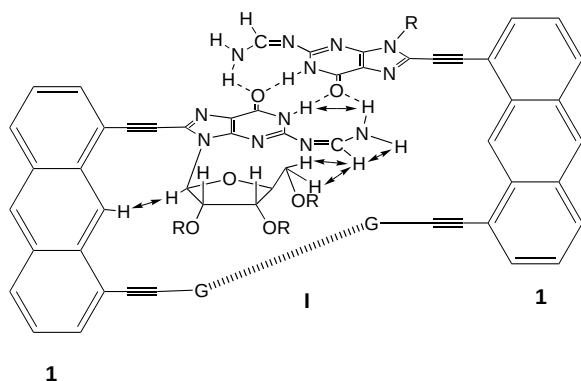


Figure 1. Schematic representation of the significant NOE interactions (indicated by arrows) deduced from the 2D ROESY spectrum of **1**. For clarity, only a part of the overall structure is shown in detail (G = guanyl substituent).

The ROESY experiments also revealed 1) a strong interaction between the imino NH protons ($\delta = 13.6$) and the hydrogen-bonded proton ($\delta = 11.2$) of the exocyclic NH₂ group, 2) a much weaker correlation between the imino NH and N=CH protons ($\delta = 9.1$), and 3) no correlation between the imino NH proton and the non-hydrogen-bonded proton of NH₂ ($\delta = 5.2$). An intense correlation for the ROESY interaction between the N=CH proton and the free proton of NH₂ as well as a much weaker correlation between the N=CH proton and the hydrogen-bonded NH₂ proton were also observed. These findings, when considered in concert, are consistent with the N=C bond existing in a *cis* configuration.

Finally, the ROESY analyses revealed an intense correlation for the interaction between the imino NH proton and the hydrogen-bonded NH₂ proton. Therefore, they must be hydrogen-bonded to the same carbonyl oxygen atom.^[7b] Certainly, the *cis* configuration of the N=C bond acts to

position the amino group much closer to the carbonyl oxygen atom than to N7; this was also shown by CPK model studies.^[17]

With respect to the stability of dimer **I**, we were quite surprised to find that it remains intact under *all* solution-phase conditions tested. Indeed, attempts to measure binding constants for the $\mathbf{1} \rightleftharpoons 1/2 \mathbf{I}$ dimerization failed due to the simple fact that we were unable to effect appreciable dissociation. For instance, dilution experiments carried out in CD₂Cl₂ did not give rise to any signals in the ¹H NMR spectrum that could be ascribed to free **1**. Indeed, the chemical shifts of both the imino NH and amino NH₂ protons were not only independent of concentration in nonpolar solvents such as CD₂Cl₂ and C₆D₆, they were also insensitive to temperature changes from 298–398 °C (solvent: [D₈]toluene). Attempts to use polar solvents such as [D₆]DMSO to break up the hydrogen-bonded ensemble^[18] also failed.^[19] While adding [D₆]DMSO to a solution of **1** in [D₈]toluene did give rise to complex splitting patterns, detailed analyses revealed that these induced changes were due to the formation of DMSO adducts rather than dissociation. By contrast, ensemble **II** completely dissociated at room temperature in [D₆]DMSO/CDCl₃ (7/3). Under these conditions, the chemical shifts of the imino NH and amino NH₂ protons appear at $\delta = 10.6$ and 6.4, respectively. These values are incidentally identical to those recorded in pure [D₆]DMSO. Thus, like a system we reported earlier with two-point hydrogen bonds,^[18] **II** constitutes a well-defined dimer that can nonetheless be cleaved to form the monomers.

NMR spectroscopic studies at various temperatures and in different polar solvent mixtures indicated that the set of individual resonances ($\delta = 13.6$ and 11.2) observed for the room-temperature ¹H NMR spectrum of **1** in [D₈]toluene appears in the form of a pair of doublets (centered at $\delta = 13.5$ and 10.6) when the same measurements are made in [D₆]DMSO/[D₈]toluene (1/1). The two doublets coalesce into singlets at 57 °C and remain as such as the temperature is further increased. An ¹H–¹⁵N HMQC NMR experiment for the same sample conducted at 100 °C in the same solvent served to identify the resonances from the imino NH proton and the two amino NH₂ protons; it was thus possible to deduce that the chemical shifts of the imino NH proton and of the hydrogen-bonded NH₂ proton are but slightly changed (both are shifted upfield by $\Delta\delta \approx 0.7$) upon passing from pure [D₈]toluene to [D₆]DMSO/[D₈]toluene (1/1). In marked contrast, the resonance of the free NH₂ proton is shifted downfield by $\Delta\delta \approx 3$ when the same change in solvent is effected. This leads us to suggest that the basic hydrogen-bonded structure of **I** is largely intact even in [D₆]DMSO/[D₈]toluene (1/1). Under these conditions the free protons of NH₂ interact with the [D₆]DMSO solvent; this causes their magnetic environment to be greatly perturbed.^[20] Such interactions do not, however, effect break up of the dimer.

Experimental Section

6: To a mixture of **3** (1.5 g, 6.6 mmol), **5** (10.0 g, 13.2 mmol), and *n*BuSnOMe (4 mL, 14 mmol) in dry toluene (100 mL) was added bis(triphenylphosphane)palladium(II) chloride (0.75 g, 8 mol %) under argon. The mixture was heated at 100 °C for 20 h. The solvent was removed under reduced pressure with a rotary evaporator, and the residue was subjected to

chromatography on a silica gel column with MeOH/ethyl acetate (5/95) as eluent to give **6** (3.4 g, 32% yield).

1: Compound **6** (3.0 g, 1.9 mmol) was treated with methanolic ammonia (50 mL) and stirred at room temperature overnight. After chromatographic purification on silica gel with hexane/ethyl acetate (4/1) as eluent, **1** was obtained as a fluorescent yellow solid (2.3 g, 80% yield). ¹H NMR (500 MHz, C₆D₆): δ = 13.63 (s, 2H, NH), 11.22 (d, *J* = 14.2 Hz, 2H, NH₂), 9.83 (s, 1H, H₉), 9.12 (dd, *J* = 5.3, 14.2 Hz, 2H, N=CH), 8.12 (s, 1H, H₁₀), 7.71 (d, *J* = 8.9 Hz, 2H, H₄, H₅), 7.53 (d, *J* = 6.89 Hz, 2H, H₂, H₇), 7.06 (dd, *J* = 8.7, 6.7 Hz, 2H, H₃, H₆), 6.67 (d, *J* = 8.15 Hz, 2H, H₁'), 5.33–5.31 (m, 4H, H₂', H₅'), 5.29 (brs, 2H, NH₂), 4.47–4.44 (m, 4H, H₃', H₄'), 3.98–3.88 (m, 2H, H₅'), 1.67–0.53 (ss, 90H, 6Si(CH₃)₂C(CH₃)₃); ¹³C NMR (125 MHz, C₆H₆): δ = 160.3 (C₆'), 160.1 (N=CH), 156.5 (C₂'), 150.7 (C₄'), 136.1, 133.1, 132.0 (aromatic C), 131.6 (C₂), 129.9 (C₄), 128.3 (C₁₀), 125.2 (C₃), 124.1 (C₉), 122.0 (C₈'), 120.1 (C₅'), 92.5 (alkynyl C), 87.9 (C₁'), 85.9 (alkynyl C), 85.7 (C₄'), 74.4 (C₃'), 71.8 (C₂'), 64.5 (C₅'), 26.6, 25.9, 25.0 (SiMe₂C(CH₃)₃), 18.6, 18.1, 17.5 (SiMe₂CMe₃), –4.4, –4.6, –4.7, –4.8, –5.3 (Si(CH₃)₂CMe₃); FAB-MS: *m/z* 1527 [*M*⁺]; high-resolution FAB-MS calcd for C₇₆H₁₁₉N₁₂O₁₀Si₆: 1527.7788 [*M*⁺ of **1**], found: 1527.7752; FAB-MS 3054; high-resolution FAB-MS calcd for C₁₅₂H₂₃₈N₂₄O₂₀Si₁₂: 3054.550 (*M*⁺ of the dimer), found: 3054.549; elemental analysis calcd for C₇₆H₁₁₉N₁₂O₁₀Si₆: C 59.73, H 7.79, N 11.01; found C 59.74, H 7.69, N 10.86.

2: Compound **1** (0.3 g, 0.2 mmol) was treated with ammonia saturated in methanol/CHCl₃ (1/1, 20 mL) at 100 °C in a sealed tube overnight. The solvents were removed under reduced pressure with a rotary evaporator, and the residue was subjected to chromatography on a silica gel column with MeOH/CHCl₃ (7/93) as eluent to give **2** (0.15 g, 52% yield). ¹H NMR (300 MHz, CDCl₃): δ = 12.65 (s, 2H), 9.33 (s, 1H), 8.57 (s, 1H), 8.14 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 6.6 Hz, 2H), 7.54 (t, *J* = 8.1 Hz, 2H), 6.13 (d, *J* = 5.1 Hz, 2H), 5.50 (br, 4H), 5.19 (m, 2H), 4.13 (d, *J* = 3.9 Hz, 2H), 3.83 (m, 6H), 0.96–0.63 (m, 90H); ¹³C NMR (75 MHz, CDCl₃): δ = 159.1, 153.4, 151.8, 133.1, 131.9, 131.5, 131.2, 130.8, 128.3, 125.4, 124.0, 119.0, 116.8, 93.4, 88.8, 86.4, 82.6, 73.3, 71.0, 62.7, 25.9, 25.6, 24.9, 18.01, 17.8, 17.7, –4.6, –4.7, –4.9, –5.9, –6.0, –6.4; CI-MS: *m/z* 1472 [*M*⁺]; high-resolution CI-MS calcd for C₇₄H₁₁₆N₁₀O₁₀Si₆: 1472.7492 [*M*⁺ of **2**], found: 1472.7477.

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- [12] Similar shifts were also observed in C₆D₆ and [D₈]toluene. Unfortunately, **2**, **6**, and **7** are insoluble in these solvents. Thus, initial comparative analyses were carried out in CDCl₃.
- [13] The broad ¹H NMR signal for the amino groups of **2** in CDCl₃ is due to fast exchange between the two free NH₂ protons. Further support for this conclusion came from the observation that sharp signals, ascribable to the amino groups in question, were seen in the ¹H NMR spectra of both **7** in CDCl₃ (where no proton is available for exchange) and **2** in [D₆]DMSO (where both NH₂ protons are hydrogen-bonded to [D₆]DMSO).
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- [15] Several features of 2D ROESY spectrum of **1** in C₆D₆ are noteworthy. First, the intense cross peaks observed between H₁' at δ = 6.7 and H₉ at δ = 9.8 as well as between N=CH at δ = 9.1 and H₅' at δ = 5.3 and 3.9 provide evidence for the *syn* conformation of the glycoside bond. Secondly, the observation of intense cross peaks between the imino NH proton at δ = 13.6 and the hydrogen-bonded proton of NH₂ at δ = 11.2, coupled with presence of a much weaker cross peak involving this imino NH proton and the N=CH proton and no cross peak with the non-hydrogen-bonded proton of NH₂ at δ = 5.2, provide evidence for the *cis* configuration of the N=CH bond. Finally, the intense cross peak observed between the signals at δ = 13.6 for the imino NH proton and at δ = 11.2 for the hydrogen-bonded NH₂ proton provides evidence of close proximity of these two protons.
- [16] a) The *syn* conformation is also believed to play a critical role during the synthesis because only it allows the 8-position to be most susceptible to nucleophilic attack by its coupling partner; b) both a *syn* conformation of the glycosidic bond and a *cis* configuration of the C=N bond are assigned to **6** on the basis of NMR spectral similarities.
- [17] The fact that the lone pairs of the two carbonyl oxygen atoms are tied up in hydrogen bonding is believed to contribute to the nonpolarity of **1**.
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- [19] The insolubility of **1** under the conditions of the experiment precluded the use of the more strongly hydrogen bonding solvent water.
- [20] The coalescence observed at higher temperature is the result of fast exchanges between different states of DMSO-derived solvation of the four amino protons. This gives rise to an average chemical shift for these protons; at lower temperature, however, the relevant exchange processes are slow enough on the NMR time scale that multiple resonances are observed.

Tethered Bis-Amidates as Supporting Ligands: A Concerted Elimination/σ–π Rearrangement Reaction Forming an Unusual Titanium Arene Complex**

John R. Hagadorn and John Arnold*

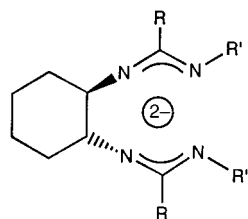
Development of ligands that play supporting roles in organotransition metal chemistry has been the subject of intense interest for many years. We are exploring amidates in this regard as they display attractive properties from a synthetic standpoint. Well characterized titanium derivatives, that utilized the *N,N'*-bis(trimethylsilyl)benzamidate li-

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- [10] A weak signal ascribable to a dimeric species was observed in the mass spectrum of **2**. However, the signal in question was not sufficiently intense to allow for a high-resolution analysis.
- [11] The assignment of the resonances in the ¹H NMR spectrum of **1** is based on information gleaned from the COSY and HMQC NMR spectroscopic analyses (¹H–¹³C and ¹H–¹⁵N).

gand^[1–3] were first reported in 1988 by Dehnicke et al.^[4] and Roesky et al.^[5] Numerous workers have since begun exploring the reaction chemistry of this class of compounds.^[6–8] We were interested in examining more robust nonsilylated amidinate ligands^[9] in which two amidinate functionalities were linked together in a constrained manner analogous to ansa-cyclopentadienyls. Additionally, we sought to introduce chirality to explore the potential of transition metal amidinates in enantioselective transformations. Our initial focus is on cyclohexane-linked amidinates. Here we describe the preparation of racemic titanium derivatives and an η^6 -toluene complex with an unusual puckered C₆ ring^[10] which labeling studies suggest is formed by an intramolecular σ - π rearrangement of a putative benzyl

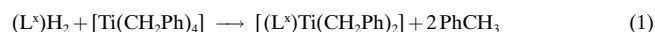


L^X , X = H : R = Ph, R' = Ph
X = Me : R = 4-MeC₆H₄,
R' = Ph

hydride complex as intermediate – a mechanism which we believe to be unprecedented in the formation of transition metal arene complexes.^[11]

Cyclohexane-linked amidinate ligands L^X were isolated in moderate yields (ca. 40%) from the reaction of the cyclohexane-linked diamides with PCl₅ and substituted aniline compounds.^[12] The reaction

of $(L^X)_2H_2$ with $[Ti(CH_2Ph)_4]$ in toluene produced the dibenzyl derivatives $[(L^X)Ti(CH_2Ph)_2]$, which were isolated in high yields as red crystals from Et₂O [Eq. (1)].



The dibenzyl complex $[(L^{Me})Ti(CH_2Ph)_2]$ reacts with H₂ (25 psig, (1.7 bar)) overnight in C₆D₆ with liberation of one equivalent of PhCH₃ to form a compound with a complex NMR spectrum that lacked the twofold axis of symmetry of the starting material. A preparative scale reaction carried out in toluene gave a solution which upon removal of the volatile materials afforded an oily solid. Crystallization from Et₂O afforded the product as dark red prisms in good yield. IR spectroscopy failed to reveal any signals that could be attributed to a ν_{Ti-H} absorption, and the compound failed to react with two equivalents of CHCl₃ in C₆D₆ solution over 2 h. X-Ray crystallography^[13] (Figure 1) revealed the product to be the η^6 -toluene complex $[(L^{Me})Ti(\eta^6-PhCH_3)]$. To accommodate the η^6 -arene, the titanium atom is forced out of the N₄ plane to form a pseudo piano-stool structure. Metrical parameters (Figure 2) suggest a significant contribution from a highly reduced cyclohexadiene dianion resonance structure resulting in the diamagnetic complex having substantial Ti^{IV} character. Accordingly, the arene ligand is puckered:^[14] the two planes defined as C4-C5-C6-C7 and C7-C2-C3-C4 intersect with a dihedral angle of 20.0°, which implies appreciable sp³ character at C4 and C7. The Ti-C bonds also reflect this trend with much shorter Ti-C4 (2.202(4) Å) and Ti-C7 (2.233(4) Å) bonds than the other four Ti-C interactions (2.35–2.42 Å). This is in contrast to the situation previously reported Ti^{II} η^6 -arene complexes (generally prepared by Friedel–Crafts reductive synthesis in the presence of an arene), which show longer, roughly equivalent Ti–C

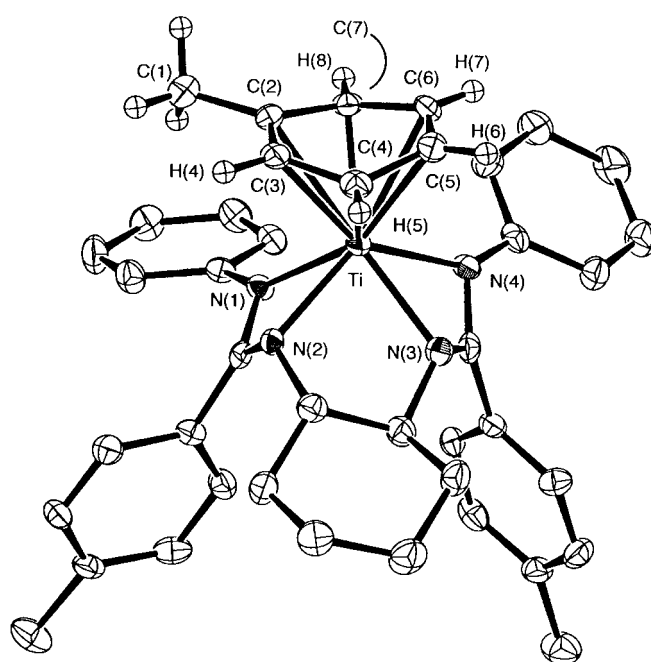


Figure 1. ORTEP view of $[(L^{Me})Ti(\eta^6-PhCH_3)]$ drawn with 50% thermal ellipsoids.

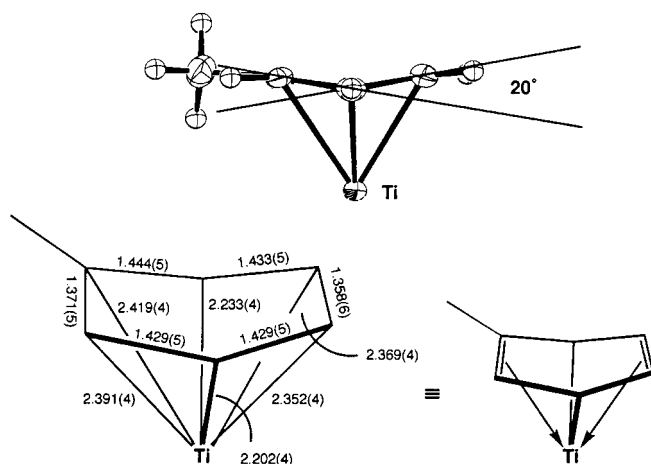
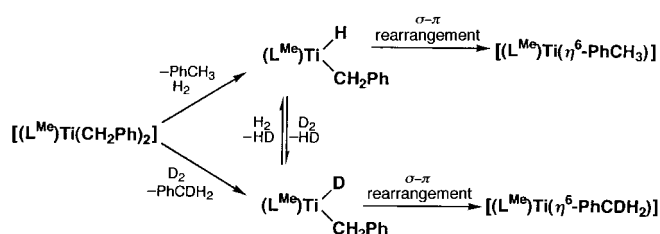


Figure 2. Metrical parameters of the η^6 -toluene ligand of $[(L^{Me})Ti(\eta^6-PhCH_3)]$. All distances are given in Å.

bonds (ca. 2.50 Å).^[15–21] Likewise, the C–C bonds in $[(L^{Me})Ti(\eta^6-PhCH_3)]$ are atypical with short C2–C3 and C5–C6 interactions of 1.371(5) and 1.358(6) Å, respectively, and longer C2–C7, C3–C4, C4–C5, and C6–C7 bonds of 1.444(5), 1.429(5), 1.429(5), and 1.433(5) Å, respectively, again suggestive of cyclohexadiene-like character.

Our data suggest that the reaction proceeds as shown in Scheme 1 via a transient Ti–H species that is too short-lived to detect directly. Evidence for this pathway includes the following: 1) Exclusive formation of $[(L^{Me})Ti(\eta^6-PhCDH_2)]$ when the dibenzyl complex was treated with D₂ (80 psig, 5.5 bar) in toluene. 2) Liberation of free PhCH₃ and PhCDH₂ in a 2.1:1 ratio and the formation of the titanium arene species $[(L^{Me})Ti(\eta^6-PhCH_3)]$ and $[(L^{Me})Ti(\eta^6-PhCDH_2)]$ in a ratio of 1.5:1. on carrying out the reaction using a 1:1 mixture of H₂ and D₂. In addition, ¹H NMR spectroscopy showed the formation of substantial quantities of HD. 3) Further evidence of the



Scheme 1. Reaction pathway of the elimination and σ - π rearrangement.

involvement of a transient hydride is the observation of rapid olefin hydrogenation when an excess of ethylene was added to a solution of the dibenzyl complex in the presence of hydrogen.

These data may be rationalized by a mechanism that involves initial formation of toluene and a reactive benzyl hydride complex that undergoes further hydrogenolysis leading to scrambling of H_2 and D_2 to HD.^[22] Elimination of the benzyl and hydride ligands (by C-H coupling) and σ - π rearrangement leads to the isolated (η^6 -arene) complex.

In summary, the use of the bis-amidinates with constrained geometry has led to some highly unusual chemistry not seen in previously reported transition metal amidinate complexes or in related metallocene systems. Further studies of these and enantiomerically pure linked-amidinates are in progress.

Experimental Section

$[(L^Me)Ti(CH_2Ph)_2] \cdot 0.5 Et_2O$: A suspension of $(L^Me)_2H_2$ (4.61 g, 9.21 mmol) in toluene (25 mL) was added to a solution (20 mL) of $[Ti(CH_2Ph)_4]$ (3.80 g, 9.21 mmol) in toluene at $-20^\circ C$. The mixture was allowed to warm to room temperature. After 5 h the volatiles were removed under reduced pressure to give a red oil. The compound was crystallized from toluene/ Et_2O (5.15 g, 73 %); m.p. $169-170^\circ C$; ^1H NMR (C_6D_6): δ = 7.41 (d, J = 7.5 Hz, 4H), 7.15 (m, 12H), 7.02 (d, J = 8.0 Hz, 4H), 6.87 (m, 8H), 3.70 (d, J = 8.6 Hz, 2H), 3.57 (d, J = 8.6 Hz, 2H), 3.24 (q, J = 7 Hz, 2H), 3.12 (m, 2H), 1.94 (s, 6H), 1.40 (m, 2H), 1.09 (t, J = 7 Hz, 3H), 1.08 (m, 4H), 0.75 (m, 2H); $^{13}C\{^1H\}$ NMR (C_6D_6): δ = 171.3, 147.6, 146.7, 139.9, 130.6, 129.6, 129.1, 128.6, 123.4, 122.9, 122.1, 91.1, 68.9, 65.9, 33.9, 24.8, 21.3, 15.6; IR (mineral oil): ν = 1594 (m), 1530 (m), 1462 (vs, br), 1340 (m), 1312 (m), 1267 (m), 1236 (w), 1207 (w), 1181 (w), 1141 (w), 1080 (w), 1020 (w), 960 (m), 828 (m), 765 (w), 741 (m), 693 (m), 510 (w), 483 (w) cm^{-1} ; elemental analysis calcd for $[LTi(CH_2Ph)_2] \cdot (C_{46}H_{44}N_4Ti)$: C 78.84; H 6.33; N 7.99; found: C 78.59; H 6.05; N 7.87.

$[(L^Me)Ti(\eta^6-toluene)] \cdot 0.5 Et_2O$: Toluene (20 mL) was added to $(L^Me)_2Ti(CH_2Ph)_2 \cdot 0.5(Et_2O)$ (2.00 g, 2.61 mmol) in a Fischer-Porter bottle, and the bottle was pressurized with H_2 (80 psig, 5.5 bar). After stirring overnight the volatiles were removed under reduced pressure affording a dark red oil. The compound was crystallized from Et_2O at $-30^\circ C$ (1.27 g, 72 %). M.p.: $170^\circ C$ (decomp); ^1H NMR (C_6D_6): δ = 8.01 (br, 2H), 7.59 (br, 1H), 7.36 (br, 1H), 7.05-6.91 (m, 8H), 6.82 (br, 1H), 6.77-6.64 (m, 5H), 4.68 (t, J = 7.6 Hz, 1H), 4.50 (m, 2H), 4.32 (d, J = 6.4 Hz, 1H), 4.23 (d, J = 6.5 Hz, 1H), 3.91 (m, 1H), 3.72 (m, 1H), 3.26 (q, J = 7.0 Hz, 2H), 2.30 (m, 1H), 2.01 (s, 3H), 1.90 (m, 1H), 1.86 (s, 3H), 1.60 (m, 1H), 1.48 (m, 1H), 1.39 (m, 1H), 1.11 (t, J = 7.0 Hz, 3H), 1.06 (m, 1H), 0.99 (s, 3H), 0.87 (m, 2H); $^{13}C\{^1H\}$ NMR (C_6D_6): δ = 168.0, 159.5, 150.3, 149.3, 140.0, 139.0, 133.7, 131.9, 131.5, 131.2, 129.7, 128.5, 124.0, 122.8, 121.7, 121.7, 120.1, 110.4, 109.4, 108.7, 108.2, 75.3, 71.6, 65.9, 37.6, 35.0, 27.1, 25.5, 21.4, 21.3, 21.1, 15.5; IR (mineral oil): ν = 1594 (m), 1568 (w), 1496 (m), 1463 (vs, br), 1265 (m), 1211 (w), 1181 (w), 1150 (w), 1110 (w), 1081 (w), 1059 (w), 1020 (w), 954 (w), 830 (m), 742 (m), 723 (w), 692 (m), 631 (w), 525 (w), 508 (w), 473 (w) cm^{-1} ; elemental analysis calcd for $C_{43}H_{47}N_4O_{0.5}Ti$: C 76.12; H 7.00; N 8.45; found: C 75.85; H 7.05; N 8.26.

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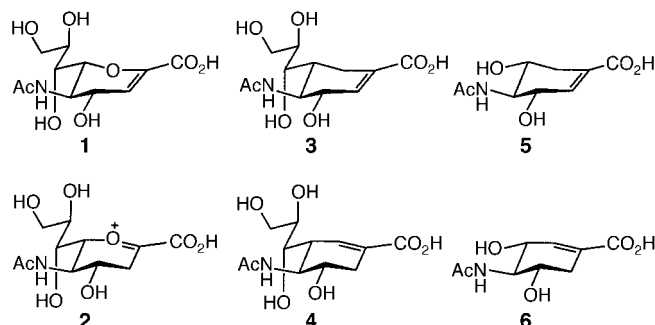
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- [13] $[(L^Me)Ti(\eta^6-PhCH_3)] \cdot 0.5 Et_2O$: crystal dimensions $0.17 \times 0.12 \times 0.07$ mm, monoclinic, $C2/c$, $a = 27.4848(6)$, $b = 11.8724(3)$, $c = 22.9332(3)$ Å, $\beta = 105.504(1)^\circ$, $V = 7211.0(4)$ Å³, $Z = 8$, $\rho_{calcd} = 1.245$ g cm⁻³, $T = -130^\circ C$, $\mu = 0.275$ mm⁻¹, $T_{min} = 0.876$, $T_{max} = 0.996$, no. of reflections = 14725 (5380 unique), no. of observations = 3167, no. of parameters = 470, $R = 0.0381$, $R_w = 0.0436$, $GOF = 1.346$. Data were collected on a Siemens SMART CCD area detector (MoK α radiation, $0 < 2\theta < 46.5^\circ$, $0.3^\circ \omega$ scans) and integrated with SAINT (4.024 ed, Siemens Industrial Automation, Inc.). The data were corrected for Lorentz and polarization effects, and a semiempirical absorption correction was applied with SADABS (Siemens). The structure was solved and refined (against $|F^2|$) with the TEXSAN (Molecular Structure Corporation, 1992) software package using direct methods. All non-H atoms were refined anisotropically. The hydrogens of the η^6 -toluene ligand were located in a difference Fourier map and were refined isotropically. Remaining hydrogens were assigned idealized positions and were not refined. Residual electron-density extremes were 0.315 and -0.296 e Å⁻³. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100894. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Carbocyclic Analogues of *N*-Acetyl-2,3-didehydro-2-deoxy-D-neuraminic Acid (Neu5Ac2en, DANA): Synthesis and Inhibition of Viral and Bacterial Neuraminidases**

Steffen Vorwerk and Andrea Vasella*

The influenza virus neuraminidase is essential for viral replication and infectivity;^[1] inhibition of this enzyme forms the basis of a chemotherapy for influenza.^[2] In contrast, little is known about the relevance of bacterial neuraminidases to the pathogenicity of many bacteria.^[3] *N*-Acetyl-2,3-didehydro-2-deoxy-D-neuraminic acid (Neu5Ac2en, DANA, **1**)^[4] is the prototypical inhibitor of neuraminidases. It inhibits viral and a number of bacterial neuraminidases.^[5a] However, it hardly binds to *Salmonella typhimurium* LT2 neuraminidase.^[5b] This is surprising, considering that X-ray analyses have shown a large degree of similarity between the active sites of the neuraminidases from *Vibrio cholerae*, *Salmonella typhimurium*, and several strains of *Influenza virus*.^[6] DANA (**1**) is considered a transition state analogous inhibitor.^[7]

One expects the carbocyclic compound **4** to be a stronger inhibitor than DANA as it more closely resembles the proposed reactive intermediate **2**^[8] of the enzymatic glycoside cleavage. For the same reasons, **4** should be a more potent inhibitor than its isomer **3**. This is in keeping with the finding that the cyclohexene **6** is a stronger inhibitor of *Influenza A* neuraminidase (N2) than its isomer **5**.^[9] The significance of

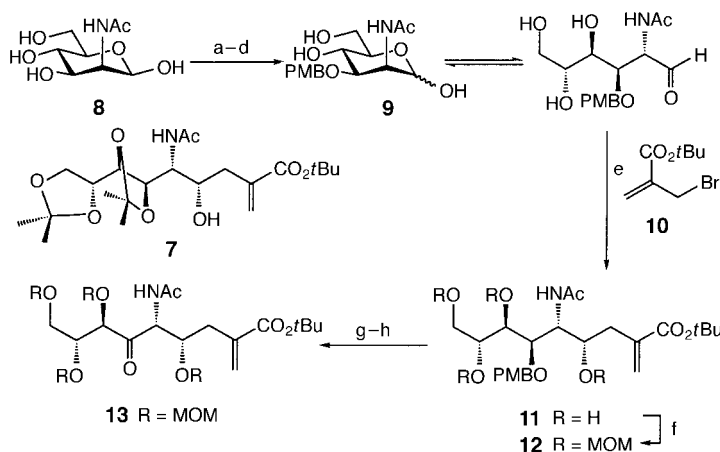


this result is not quite clear since both compounds lack the glycerol side chain. We have now synthesized the carbocyclic analogues **3** and **4** of DANA (**1**) to investigate more closely the influence of the position of the double bond on the inhibition of viral and *Salmonella typhimurium* neuraminidases.

6a-Carba-*N*-acetyl-D-neuraminic acid^[10] is the only known carbanneuraminic acid possessing an intact side chain. Carbo-

cyclic analogues lacking the side chain,^[9] or possessing a truncated^[11] or modified^[9] side chain, have been prepared either from quinic acid or by total synthesis based on a Diels–Alder cycloaddition. We planned to synthesize **3** and **4** by a ketyl–olefin cyclization.

The ester **7** (Scheme 1) is an intermediate in one of our syntheses of *N*-acetyl-D-neuraminic acid.^[12] It contains the carbon atoms required for the preparation of a carbanneuraminic acid and is readily available. However, for the regioselective generation of a radical, the OH groups must



Scheme 1. a) Allylic alcohol, $\text{BF}_3 \cdot \text{OEt}_2$, 95 °C, 80%; b) (4-methoxyphenyl)acetaldehyde dimethyl acetal, cat. $p\text{TsOH}$, MeCN, 0 °C, 70%; c) 4-methoxybenzyl 2,2,2-trichloroacetimidate, cat. trifluoromethanesulfonic acid, THF/ Et_2O , 0 °C, 88%; d) 1. cat. $[\text{Pd}(\text{PPh}_3)_4]$, HCO_2H , Et_3N , dioxane, 65–95 °C, 2. acetic acid (AcOH), room temperature (RT), 92%; e) In, MeCN/0.1M HCl 20/1, TBAI (0.1 equiv), 40 °C, 60–70% (d.e. > 90%); f) MOMCl, $i\text{Pr}_2\text{NEt}$, 1,2-dichloroethane, cat. TBAI, cat. 4-PP, 0–25 °C, 91%; g) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, RT, 92%; h) Dess–Martin periodinane, CH_2Cl_2 , RT, 98%. PMB = 4-methoxybenzyl; MOM = methoxymethyl.

be differentiated at an earlier stage of the synthesis. Therefore, *N*-acetyl- β -D-mannosamine (**8**) was transformed into the partially protected aldose **9** (five steps, 45% overall yield). To perform the chain elongation^[12] with *tert*-butyl bromomethacrylate (**10**) in aqueous solution, we replaced zinc by indium^[13] and obtained the homoallylic alcohol **11**.^[14] The diastereoselectivity of this reaction strongly depends upon the MeCN/ H_2O ratio and on the amount of tetra-*n*-butylammonium iodide (TBAI).

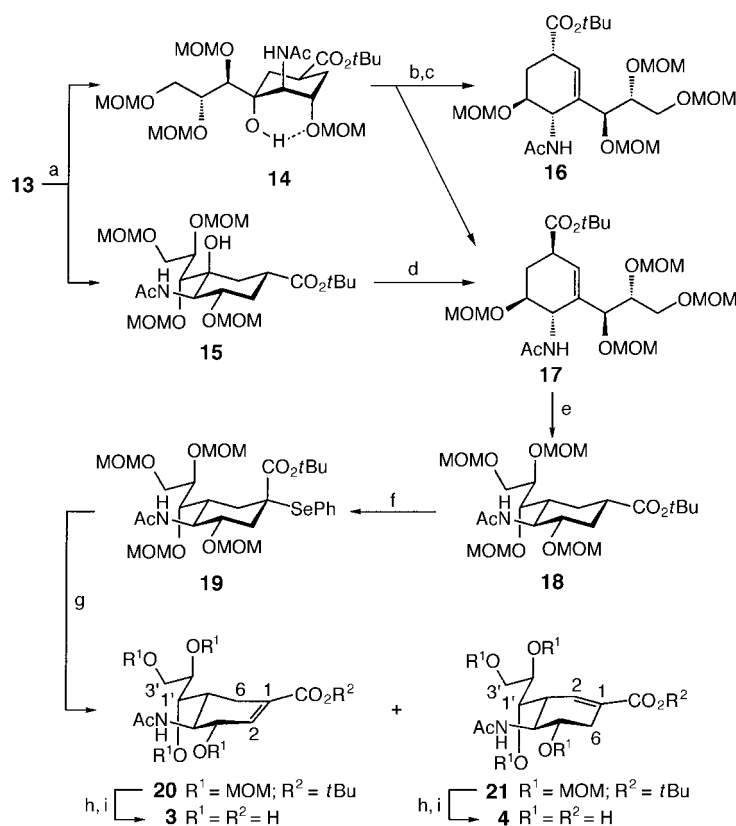
Attempts to protect the OH groups of **11** by methoxymethylation under standard conditions^[15] gave inseparable mixtures of the desired compound **12**, incompletely O-alkylated, and O- and N-alkylated products. The methoxymethylation was, however, successful with methoxymethyl chloride (MOMCl), ethyl(diisopropyl)amine and a catalytic amount of 4-pyrrolidinylpyridine (4-PP)^[16] in the presence of TBAI. Selective removal of the 4-methoxybenzyl (PMB) group^[17] and oxidation of the intermediate alcohol^[18] with periodinane^[19] gave the ketone **13** in 70% overall yield without epimerization of adjacent chiral centers.

Treatment of **13** with samarium(II) iodide in THF/hexamethyl phosphoric acid triamide (HMPT) and *tert*-butyl alcohol as the proton source^[20] led to a mixture of the

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carbocyclic esters **14**^[14] and **15**, which were separated by chromatography (Scheme 2). Regioselective dehydration to form an alkene was only successful with Martin's sulfurane.^[21] This reagent transformed the tertiary alcohol **15** at 0 °C^[22] into the desired β,γ -unsaturated ester **17**. The analogous treatment



of **14** followed by hydrolysis with dilute acetic acid^[23] yielded the unsaturated esters **16** and **17**. Attempts to isomerize the olefins **16** and **17** to the conjugated α,β -unsaturated esters failed. We, therefore, hydrogenated **17** to **18**, deprotonated **18** with lithium cyclohexyl(isopropyl)amide (LICA),^[24] and treated the ensuing enolate with Ph_2Se_2 .^[25] The resulting equatorial phenylselenide **19**^[14] (64%) proved unstable in solution and was therefore directly treated with H_2O_2 and pyridine at 0–27 °C. The resulting regioisomeric α,β -unsaturated esters **20**^[14] and **21** were isolated by preparative HPLC, and transformed into the title compounds **3** and **4** (Table 1).

The cyclohexene **3** ("CarbaDANA") proved to be a weak inhibitor^[26] of Influenza A neuraminidase (N2; IC_{50} = 0.85 mM). In contrast, isomer **4** ("Iso-CarbaDANA") showed an approximately 40-fold stronger inhibition of Influenza A neuraminidase (N2; IC_{50} = 20 μM) and is thus twice as potent as DANA.^[27] The differences between **3** and **4** must result from their different half-chair conformations, since the conformations of the side chains of **1**, **3**, and **4** are very

Table 1. Analytical data for **3** and **4**.^[a]

3 : Colorless lyophilisate; R_f : 0.35 (<i>n</i> PrOH/ H_2O 7/1); HPLC: R_t : 8.6 min; $[\alpha]_D^{25} = 42.5^\circ$ ($c = 0.08$, H_2O); ^1H NMR: $\delta = 6.41$ (brt, $J = 1.9$ Hz, 1H; H-2), 4.29 (ddt, $J = 9.1$, 3.7, 1.8 Hz, 1H; H-3), 3.79 (dd, $J = 11.6$, 2.0 Hz, 1H; H-3'), 3.76 (dd, $J = 11.9$, 9.1 Hz, 1H; H-4), 3.60 (AB system with virtual coupling, 2H; H-2', H-1'), 3.54 (dd with virtual coupling $J = 11.6$, 6.0 Hz, 1H; H-3'), 2.37 (br dd, $J = 17.5$, 5.3 Hz, 1H; H _c -6), 2.25 (ddt, $J = 17.4$, 11.2, 3.2 Hz, 1H; H _a -6), 2.08 (tdd, $J = 11.4$, 5.4, 1.6 Hz, 1H; H-5), 2.02 (s, 3H, AcN); ^{13}C NMR: $\delta = 177.87$ (s, CO ₂ H), 177.66 (s, AcN), 138.50 (s, C-1), 135.96 (d, C-2), 73.91 (d, C-2'), 73.27 (d, C-1'), 70.96 (d, C-3), 66.25 (t, C-3'), 55.77 (d, C-4), 40.26 (d, C-5), 26.35 (t, C-6), 24.73 (q, AcN); HR-MS (NESI) calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_7$: 288.1083, found: 288.1083.
4 : Colorless lyophilisate; R_f : 0.27 (<i>n</i> PrOH/ H_2O 7/1); HPLC: R_t : 10.8 min; ^1H NMR: $\delta = 6.48$ (brt, $J = 2.4$ Hz, 1H; H-2), 3.90 (t, $J = 10.1$ Hz, 1H; H-4), 3.80 (dd, $J = 12.2$, 2.8 Hz, 1H; H'-3'), 3.76 (td, $J = 10.3$, 5.0 Hz, 1H; H-5), 3.73 (ddd, $J = 9.5$, 6.5, 2.9 Hz, 1H; H-2'), 3.54 (dd, $J = 11.9$, 6.4 Hz, 1H; H-3'), 3.50 (dd, $J = 9.6$, 1.7 Hz, 1H; H-1'), 2.73 (ddd, $J = 16.7$, 5.2, 1.6 Hz, 1H; H _c -6), 2.69 (ddt, $J = 9.7$, 3.9, 2.0 Hz, 1H; H-3), 2.18 (dddd, $J = 16.8$, 10.0, 4.0, 2.9 Hz, 1H; H _a -6), 2.00 (s, 3H; AcN); ^{13}C NMR: $\delta = 177.65$ (2s, CO ₂ H, AcN), 137.61 (s, C-1), 133.52 (d, C-2), 73.68 (d, C-2'), 72.09 (d, C-1'), 72.02 (d, C-5), 66.14 (t, C-3'), 55.09 (d, C-4), 45.89 (d, C-3), 35.88 (t, C-6), 24.91 (q, AcN); HR-MS (NESI) calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_7$: 288.1083, found: 288.1078.

[a] HPLC: Hibar (Merck), RP-18 (7 μm), column: 250 $\times$ 25 mm, eluent: H_2O , flow rate: 10 mL min^{-1} . ^1H NMR: 500 MHz, D_2O ; ^{13}C NMR: 125 MHz, D_2O .

similar. Iso-CarbaDANA (**4**) inhibits *S. typhimurium* neuraminidase (IC_{50} = 39 μM), while **1** and isomer **3** did not show any inhibition at concentrations up to 350 μM .

The reasons for this decisive influence of the position of the double bond for the inhibition of the *S. typhimurium* neuraminidase are largely obscure. Conceivably, the active site of this enzyme is less flexible than that of other neuraminidases and consequently more demanding on the precise structure of an inhibitor.^[28] The mechanistic details of action of the *S. typhimurium* neuraminidase are largely unknown and partially controversial.^[29]

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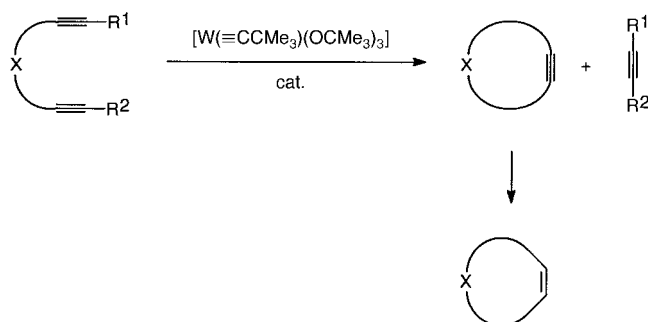
Ring-Closing Metathesis of Functionalized Acetylene Derivatives: A New Entry into Cycloalkynes

Alois Fürstner* and Günter Seidel

Olefin metathesis is rapidly evolving into a prosperous field of research, and as a result of the development of a new generation of performance catalysts with a high tolerance towards functional groups has recently found many applications in organic synthesis.^[1,2] In particular, ring-closing metathesis (RCM) of dienes to cycloalkenes provides good access to carbo- and heterocycles and has been proved to be effective in numerous syntheses of natural products.^[2] Medium-sized and macrocyclic rings can also be forged by RCM.^[3,4] The latter, however, are usually obtained as mixtures of *E* and *Z* isomers, the ratio of which can, at present, be neither predicted nor properly controlled. This is a major drawback in target-oriented syntheses as exemplified, for example, by several approaches to epothilone: Although various research teams succeeded in forming the 16-membered ring of this promising chemotherapeutic agent by RCM, separation of the resulting stereoisomeric mixtures were inevitable because only epoxidation of the *Z*-configured cycloalkene leads to the desired target molecule.^[5]

In striking contrast to olefin metathesis, the metathesis of alkynes presently plays only a minor role in organic chemistry.^[6] Even though the close mechanistic ties between both types of transformations were noticed early on,^[7] and various well-defined alkyne metathesis catalysts are available,^[8] the applications of alkyne metathesis have until now been confined to the preparation of some special polymers^[9] and to the dimerization or cross-metathesis of simple acetylene derivatives.^[10]

We now describe the first efficient syntheses of functionalized macrocycles by ring-closing metathesis of diyne substrates (Scheme 1). Partial reduction of the cycloalkyne molecules thus obtained by one of the conventional methods (e.g. Lindlar hydrogenation or hydroboration/protonation) also constitutes a stereoselective route to *Z*-configured cycloalkenes^[11] which cannot yet be directly prepared in pure form by RCM.



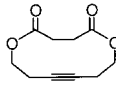
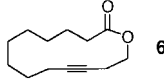
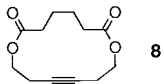
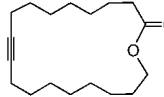
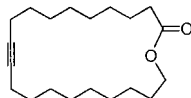
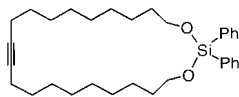
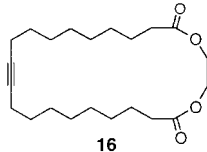
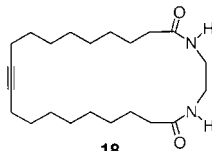
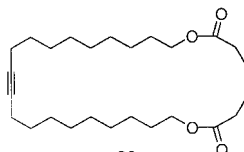
Scheme 1. Ring-closing metathesis of diyne with **1**.

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We use the tungsten alkylidyne complex $[\text{W}(\equiv\text{CCMe}_3)(\text{OCMe}_3)_3]$ (**1**) developed by Schrock as an alkyne metathesis (pre)catalyst,^[12] which is readily obtained from the reaction of $[(\text{Me}_3\text{CO})_3\text{W}=\text{W}(\text{OCMe}_3)_3]$ (**2**)^[13] with neoheptyne. This complex turned out to be a highly active catalyst for the cyclization of diynes to cycloalkynes (Table 1). Because various functional groups are tolerated in the substrates, it is possible to obtain lactones, lactams, and cyclic silyl ethers of ring sizes 12 or greater in good yields, provided that the reactions are carried out under high dilution conditions ($\leq 0.02\text{ M}$) in trichlorobenzene (in vacuo, see below), chlorobenzene, toluene, or THF as the solvent, respectively. The formation of minor amounts of cyclodimeric products has been detected in some cases (Table 1, entries 7 and 8).^[14] It is

necessary to use diyne derivatives with $\text{R}^1, \text{R}^2 \neq \text{H}$ as the starting materials because of the known incompatibility of catalyst **1** with terminal alkynes.^[8] However, we did not notice any significant difference between substrates with $\text{R}^1, \text{R}^2 = \text{Me}$ (entries 1–6, 8–12) and those with $\text{R}^1, \text{R}^2 = \text{Et}$ (entry 7). With 1,2,4-trichlorobenzene as the solvent (b.p. = 214°C), it is possible to remove the alkyne by-products $\text{R}^1\text{C}\equiv\text{CR}^2$ (e.g. 2-butyne, 3-hexyne) from the mixture by performing the reactions under reduced pressure (ca. 20 mbar); this seems to have a positive effect on the conversion (entries 4, 7, 10). Whereas the preparation of cycloalkynes by some conventional methods leads to the formation of allenic by-products,^[15] this undesirable side reaction does not occur with ring-closing diyne metathesis. The scope of this new method is currently being explored.

Table 1. Synthesis of cycloalkynes by ring-closing metathesis of diynes.^[a]

Entry	Substrate	Solvent	Product	Yield [%]
1	$[\text{MeC}\equiv\text{C}(\text{CH}_2)_2\text{OOC}(\text{CH}_2)_2]_2$ 3	$\text{C}_6\text{H}_5\text{Cl}$	 4	73 ^[c]
2	$\text{MeC}\equiv\text{C}(\text{CH}_2)_8\text{COO}(\text{CH}_2)_2\text{C}\equiv\text{CMe}$ 5	$\text{C}_6\text{H}_5\text{Cl}$	 6	52
3	$[\text{MeC}\equiv\text{C}(\text{CH}_2)_2\text{OOC}(\text{CH}_2)_2]_2$ 7	$\text{C}_6\text{H}_5\text{Cl}$	 8	73 ^[c]
4	7	$\text{C}_6\text{H}_3\text{Cl}_3$ ^[b]		79
5	7	Toluol		69
6	7	THF		64
7	$\text{EtC}\equiv\text{C}(\text{CH}_2)_7\text{COO}(\text{CH}_2)_8\text{C}\equiv\text{CEt}$ 9	$\text{C}_6\text{H}_3\text{Cl}_3$ ^[b]	 10	69 ^[d]
8	$\text{MeC}\equiv\text{C}(\text{CH}_2)_8\text{COO}(\text{CH}_2)_9\text{C}\equiv\text{CMe}$ 11	$\text{C}_6\text{H}_5\text{Cl}$	 12	52 ^[e]
9	$[\text{MeC}\equiv\text{C}(\text{CH}_2)_9\text{O}]_2\text{SiPh}_2$ 13	$\text{C}_6\text{H}_5\text{Cl}$	 14	55
10	$[\text{MeC}\equiv\text{C}(\text{CH}_2)_8\text{COOCH}_2]_2$ 15	$\text{C}_6\text{H}_3\text{Cl}_3$ ^[b]	 16	97
11	$[\text{MeC}\equiv\text{C}(\text{CH}_2)_8\text{CONHCH}_2]_2$ 17	$\text{C}_6\text{H}_5\text{Cl}$	 18	90
12	$[\text{MeC}\equiv\text{C}(\text{CH}_2)_9\text{OOC}(\text{CH}_2)_2]_2$ 19	$\text{C}_6\text{H}_5\text{Cl}$	 20	52

[a] With $[\text{W}(\equiv\text{CCMe}_3)(\text{OCMe}_3)_3]$ (**1**, 4–6 mol %) as the catalyst at 80°C under argon and 1 atm, unless stated otherwise; reaction time 2–19 h. [b] In 1,2,4-trichlorobenzene under reduced pressure (20 mbar). [c] Ca. 10 % of the substrate is recovered. [d] 8 % of the cyclic dimer is obtained. [e] 6 % of the cyclic dimer is obtained.

Experimental Section

8: A solution of diyne **7** (121 mg, 0.43 mmol) and $[W(\equiv CMe_3)(OCMe_3)_3]$ (12 mg, 6 mol %) in chlorobenzene (20 mL) was stirred under Ar at 80 °C for 2 h. The solvent was removed in vacuo, and the residue purified by flash chromatography (Merck silica gel, hexane/ethyl acetate 4/1). This led to the recovery of some unchanged starting material **7** (12 mg, 10 %) and afforded the desired cycloalkyne **8** as colorless crystals (70 mg, 73 %). M.p. = 106–107 °C; ^1H NMR: δ = 4.14 (t, 4H, J = 5.5 Hz), 2.53 (t, 4H, J = 5.6 Hz), 2.40 (m, 4H), 1.76 (m, 4H); ^{13}C NMR: δ = 173.0, 77.8, 62.4, 34.8, 24.9, 19.0. MS: m/z (rel intensity): 224 (<1, $[M^+]$), 179 (<1), 166 (1), 152 (1), 137 (1), 129 (3), 111 (7), 101 (4), 78 (100), 66 (21), 55 (10), 41 (8); elemental analysis calcd for $C_{12}H_{16}O_4$ (224.3): C 64.24, H 7.18; found: C 64.14, H 7.15.

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Methoxide Coordination at the Pocket of $[Cu^{II}Tp^{Cum}Me]$ and a Simple Model for the Cu Center of Galactose Oxidase**

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Functionalized hydrotris(pyrazolyl)borate ligands (Tp^R) have been used to create protected transition metal coordination sites. Pyrazol nitrogen atoms resemble histidine donor groups, and the Tp^R complexes of Fe, Cu, and Zn have

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provided both structural and functional models for bioinorganic metal ions.^[1] Basic ancillary ligands located in the protected pocket may be displaced by protonation to create a vacancy at the metal center. Hydroxide ions have been used, but alkoxide ions offer advantages as they are stronger bases that lead to superior leaving groups. In this communication we describe the results of a study on methoxide coordination at the pocket formed by the cumenyl-functionalized Tp ligand in $\{\text{Cu}^{\text{II}}\text{Tp}^{\text{Cum,Me}}\}$, and the formation of a simple analogue for the copper center of galactose oxidase.

The addition of a methanolic solution of $\text{Cu}(\text{ClO}_4)_2$ to $\{\text{KTp}^{\text{Cum,Me}}\}$ dissolved in dichloromethane led to the formation of $[\text{Cu}\{\text{Tp}^{\text{Cum,Me}}\}\text{Cu}(\mu\text{-OMe})_2]$ (**1**). Structural characterization shows that the complex consists of a linear arrangement of three Cu^{2+} ions.^[2] At the center of the molecule, a planar $[\text{Cu}(\text{OMe})_4]^{2-}$ anion is bridged to outer square-pyramidal $[\text{CuTp}^{\text{Cum,Me}}]^+$ cations (Figure 1). Basal methoxide oxygen

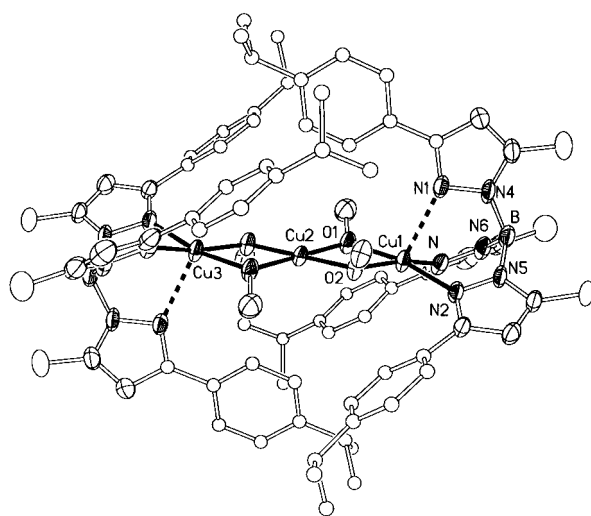
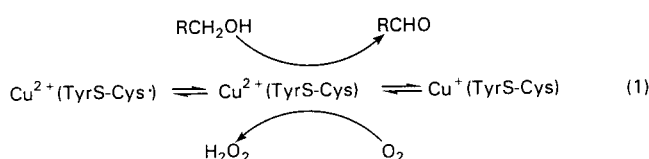


Figure 1. Solid state structure of **1**. Selected bond lengths [Å] and angles (°): Cu1–O1 1.948(3), Cu1–O2 1.947(3), Cu2–O1 1.922(3), Cu2–O2 1.917(3), Cu1–N2 2.030(3), Cu1–N3 2.038(3), Cu1–N1 2.486(4), O1–Cu1–N2 165.2(1), O2–Cu1–N3 168.8(1).

atoms provide a mechanism for strong antiferromagnetic exchange between the metal centers, resulting in a temperature-invariant $S = \frac{1}{2}$ magnetic moment of $1.82 \mu_B$ for the complex. The molecule is EPR-silent at room temperature in the solid state and in toluene solution. In a toluene glass at temperatures below 100 K a weak, featureless signal appears at $g = 2.26$. The strong basicity of the methoxide ligands of (**1**) has been used to form the sulfanyl derivative $[\text{Cu}(\text{Tp}^{\text{Cum,Me}})\{\text{O}(\text{MeS})\text{C}_6\text{H}_4\}]$ (**2**) on reaction with 2-(methylsulfanyl)phenol.

Fungal galactose oxidase (GOase) catalyzes dioxygen oxidation of primary alcohols to aldehydes.^[3] It is among an interesting class of metalloenzymes that catalyze a two-electron oxidation process with a single redox active metal ion (copper in this case) at the active site. Crystallographic and EXAFS characterization have revealed that in the partially oxidized inactive ($\text{GOase}^{\text{SEMI}}$) and fully oxidized active (GOase^{OX}) forms of the enzyme the Cu^{II} ion has a square-pyramidal geometry.^[4] An unusual cysteinyl-tyrosine ligand

(Tyr272, Cys228) that is coordinated to the Cu center through the tyrosine oxygen atom at a basal site provides additional redox activity at the metal ion.^[5] Two other basal sites are occupied by histidine nitrogen atoms, and the apical site contains the oxygen atom of a normal tyrosine molecule (Tyr495). The remaining basal site adjacent to the Tyr272 oxygen atom is the site of substrate coordination.^[6] Oxidation of $\text{GOase}^{\text{SEMI}}$ to form active GOase^{OX} occurs at the cysteinyl-tyrosine unit. Sykes has determined that the oxidation potential of this tyrosine molecule is unusually negative, 0.40 V (versus normal hydrogen electrode (NHE), pH 7.5),^[5] where tyrosine and phenolate ligands typically undergo oxidation at potentials closer to 1.0 V.^[9] Substrate oxidation occurs with dioxygen reduction [Eq. (1)].^[10]



Metal coordination and the cysteinyl substituent both contribute to the negative shift in the oxidation potential of Tyr272, placing it at a value that enables reoxidation by dioxygen or superoxide in the activation step.

Structural characterization of the sulfanyl derivative (**2**) has shown that the Cu center has a square-pyramidal geometry in which the phenolate oxygen atom and two pyrazolyl nitrogen atoms occupy basal coordination positions (Figure 2).^[11] The sulfur atom of the 2-(methylsulfanyl)phenolate ligand

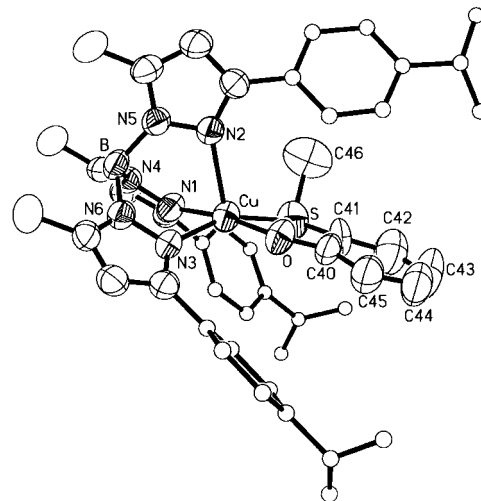
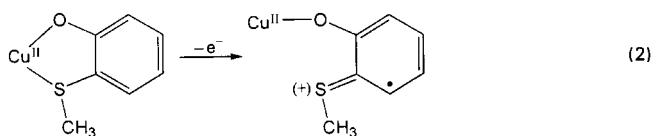


Figure 2. Crystal structure of **2**. Selected bond lengths [Å] and angles (°): Cu–O 1.900(4), Cu–S 2.394(2), Cu–N1 2.023(5), Cu–N3 2.026(5), Cu–N2 2.319(4), C40–O 1.334(8), C41–S 1.719(6), S–C46 1.795(8), C40–C41 1.315(9), C41–C42 1.456(9), C42–C43 1.385(11), C43–C44 1.318(11), C44–C45 1.367(10), C40–C45 1.447(9), O–Cu–N1 170.9(2)°, S–Cu–N3 157.7(1).

occupies the fourth basal site with a Cu–S bond length of 2.394(2) Å, a relatively short value for a thioether.^[12] In this respect **2** differs from the enzymatic Cu center, but structural features and properties of the complex may provide insights on $\text{GOase}^{\text{SEMI}}$ and GOase^{OX} .

Electrochemical characterization of **2** shows irreversible oxidation of the phenolate ligand at a potential of +0.61 V (CH_2Cl_2 , vs. ferrocene/ferrocenium (Fc/Fc^+)). This value is more positive than the reduction potentials of pendant phenoxyl ligands that contain electron releasing alkyl substituents.^[7, 13–15] Also, it is roughly 0.6 V more positive than the reduction potential of the enzymatic GOase^{OX} tyrosyl group,^[5] despite the structural similarity. A feature of the enzymatic site that may contribute to the more negative Tyr272 reduction potential is charge-transfer pairing with the indole ring of tryptophane-290.^[6] The cumenyl substituent of the apical pyrazole ring of **2** could potentially form a similar interaction with the phenolate ring.^[16] However, as the structure shows, the pairing interaction is blocked by the methyl group bonded to the sulfur atom, and the other isomeric form of the molecule, with the methyl substituent on the opposite face of the plane, is disfavored by interactions with other cumenyl substituents. Model studies indicate that the thiomethyl substituent may shift the coordinated phenolate oxidation potential by roughly –0.2 V.^[15] The strong negative shift in the enzymatic reduction potential points to a profoundly important contribution from the tryptophane interaction.

Irreversibility in the oxidation of **2** may result from dissociation of the thioether sulfur atom from the Cu center in the oxidized form of the complex [Eq. (2)]. Oxidation to



the radical would then place increased positive charge on the sulfur atom. The solid state structure of the (methylsulfanyl)-phenolate unit of **2** shows that even in the reduced form there is considerable double bond character in the $\text{C}_{\text{ring}}-\text{S}$ bond. The distance between S and the ring carbon C41 is 1.719(6) Å, considerably shorter than the distance of 1.795(8) Å to the methyl carbon atom, and the C40–O length of 1.334(8) Å is not significantly different from the values of chelated catecholate ligands. Further, the phenolate ring shows a subtle, but significant, pattern of short and long C–C lengths. The C40–C41 bond and the opposite C43–C44 bond (1.315(9) and 1.318(11) Å, respectively) are nearly the length of localized double bonds. Adjacent C40–C45 and C41–C42 lengths are longer (1.456(9) and 1.447(9) Å, respectively) and the remaining two lengths in the ring are of intermediate values (1.367(10) and 1.385(11) Å).

A feature of **2** that sets it apart from the enzymatic center is the coordination of a sulfur atom at the site that would otherwise serve for enzymatic substrate binding. In fact, **2** is formed by displacement of methanol from this coordination site, and samples of the complex obtained from methanol show that the sulfur atom is not displaced from the metal atom by the alcohol. The plane of the Tyr272 phenyl ring of GOase^{SEMI} is oriented perpendicular to the tetragonal plane of the Cu center.^[6] Rotation of the Cys-228 sulfur atom into the substrate binding site would probably deactivate the

enzyme. Instead, it is held away by the cysteine link to the protein, and also by the pairing interaction with Trp290.

The principal focus of interest in galactose oxidase has been the copper–(cysteiny-tyrosine) interaction, but tryptophane-290 is essential for active site function. Molecular modeling has shown that it contributes to substrate selectivity through a hydrogen-bonding interaction with the ring oxygen of D-galactose.^[8] Tryptophane-290 restricts rotation of the unique cysteiny-tyrosine ligand and preventing irreversible sulfur coordination at the active site, and the charge transfer interaction with the ring of Tyr272 places the reduction potential at a value that is appropriate for its oxidation by superoxide.

Experimental Section

1. $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (429 mg, 15 mmol) dissolved in methanol (20 mL) was added to $[\text{KTP}^{\text{Cum,Me}}]$ (500 mg, 0.77 mmol)^[17] dissolved in dichloromethane (15 mL). The mixture was stirred and the green precipitate that formed was separated by filtration. Compound **1** was obtained as a pale green microcrystalline solid in 78 % (460 mg) yield. Crystals suitable for crystallographic characterization were grown by slow evaporation of a saturated dichloromethane/methanol solution and obtained as the unstable dichloromethane solvate, $[\text{Cu}\{\text{TP}^{\text{Cum,Me}}\text{Cu}(\mu\text{-OMe})_2\}] \cdot 2\text{CH}_2\text{Cl}_2$.

2. Compound **1** (100 mg, 0.065 mmol) was combined with two equivalents of 2-(methylsulfanyl)phenol in a dichloromethane/methanol solution. The green-brown mixture was filtered to remove polymeric $\text{Cu}(\text{OMe})_2$, and the filtrate was slowly evaporated to give dark blue-green crystals of **2** in 50 % (53 mg) yield. Elemental analysis calcd: C 68.0, H 6.5, N 10.3; found: C 67.8, H 6.9, N 10.2. UV/Vis (toluene): λ_{max} (ϵ) = 485 (1530), 756 nm (510); magnetic moment (292 K) 1.81 μ_B .

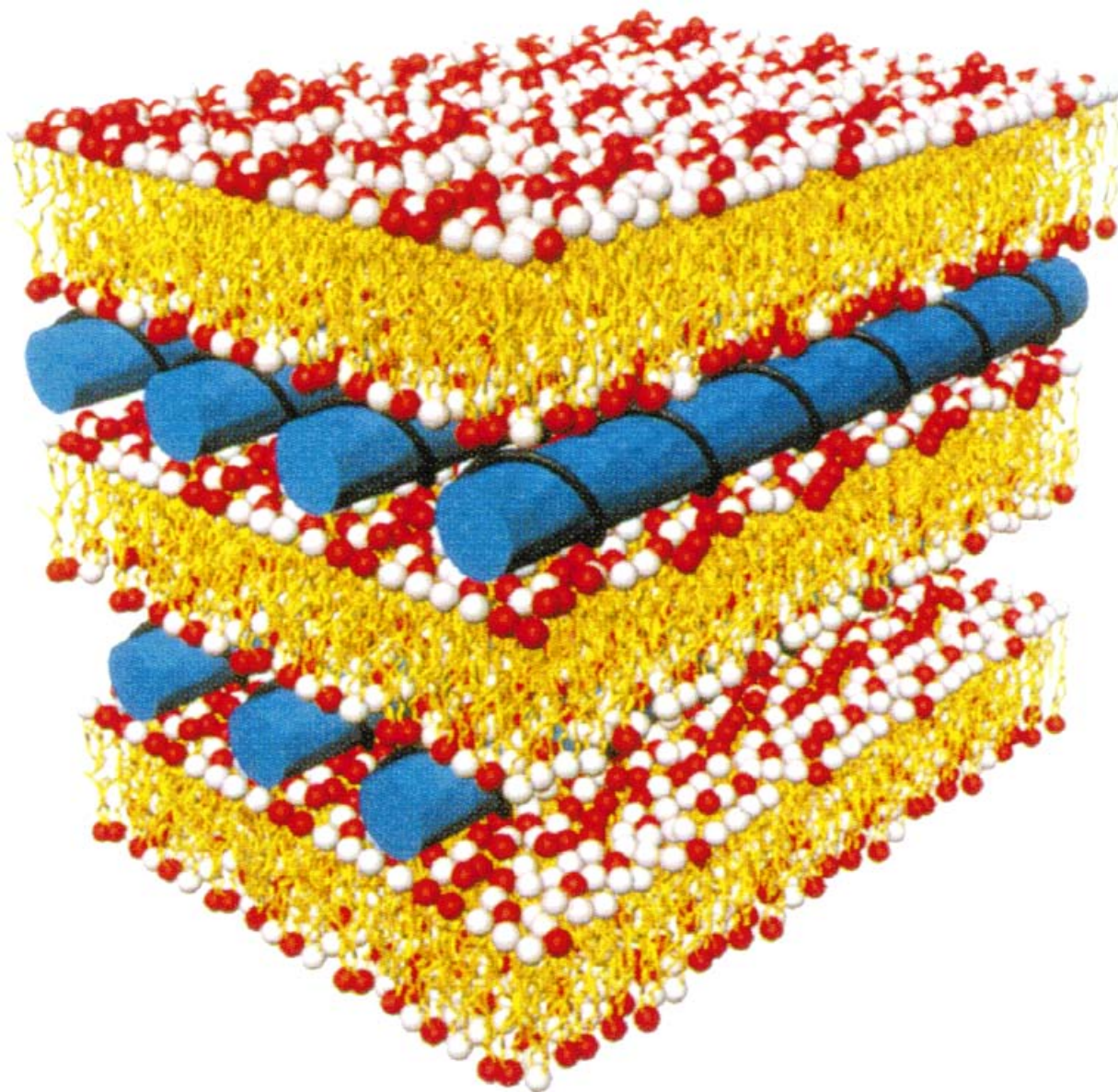
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- [12] Whittaker has described $[\text{Cu}(\text{pmdt})\{(\text{methylthio})\text{cresol}\}]^+$ (pmdt-pentamethyldiethylenetriamine) as a potential model for the Cu site of GOase^{SEMI}. The coordination geometry is trigonal bipyramidal with a relatively long Cu–S bond length of 2.55 Å. See M. M. Whittaker, Y.-Y. Chuang, J. W. Whittaker, *J. Am. Chem. Soc.* **1993**, *115*, 10029.
- [13] a) J. A. Halfen, V. G. Young, W. B. Tolman, *Angew. Chem.* **1996**, *108*, 1832; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1687; 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.
- [14] M. M. Whittaker, W. R. Duncan, J. W. Whitaker, *Inorg. Chem.* **1996**, *35*, 382.
- [15] S. Itoh, S. Takayama, R. Arakawa, A. Furuta, M. Komatsu, A. Ishida, S. Takamuku, S. Fukuzumi, *Inorg. Chem.* **1997**, *36*, 1407.
- [16] See for example the structure of $[\text{Cu}(\text{Tp}^{\text{ph}})(\text{pterin})]$: J. Perkinson, S. Brodie, K. Yoon, K. Mosny, P. J. Carroll, T. V. Morgan, S. J. Nieter Burgmayer, *Inorg. Chem.* **1991**, *30*, 719.
- [17] M. Ruf, H. Vahrenkamp, *Inorg. Chem.* **1996**, *35*, 6571.

A model for the local arrangement of cationic liposome/DNA complexes—such complexes may be of great importance in the future for gene therapy.



The DNA molecules are represented as blue rods. The head groups of anionic/zwitterionic lipids are shown as white spheres, and those of cytofectins as red spheres (reproduced with permission from J. O. Rädler, I. Koltover, T. Salditt, and C. R. Safinya, *Science* **1997**, 275, 810–814).

Cationic Liposomes for Gene Therapy**

Andrew D. Miller*

Cationic liposomes are now recognized as a potent means to assist the delivery of genes and other nucleic acids to cells. This holds out the tantalizing possibility that cationic liposomes could play a major role in the future as a core technology in the emerging field of gene therapy. In this area, cationic liposomes could function as vectors (i.e., gene-delivery vehicles) to deliver therapeutic genes and/or other nucleic acids into diseased cells and organs of patients in order to cure or treat disease. How realistic is this? Certainly, cationic liposome mediated

delivery of nucleic acids for gene therapy is still fraught with problems. However, there have been some recent spectacular successes. In view of these successes and the relative youth of the field, there does not appear to be any reason why cationic liposomes cannot be refined both now and in the future for general use in gene therapy. What makes the process of cationic liposome refinement and development so exhilarating is the opportunities for partnership between chemistry and medicine. This is a field that requires a multidisciplinary approach with organic,

physical-organic, and physical chemists in the vanguard of designing, synthesizing, formulating, and testing ever more potent cationic liposomes. This review illustrates this nascent partnership between chemistry and medicine by describing the chemical origins of cationic liposomes, their physical properties in complexes with nucleic acids, their biological efficacy, and their current limitations.

Keywords: gene therapy • lipids • liposomes • nucleic acids • vesicles

1. Introduction

With the rapid conclusion of the human genome sequencing project, more will be known about the genetic basis of human life than at any other time in history. In addition, the genetic codes of microorganisms, such as the bacterium *Methanococcus jannaschii* and yeast, have now been completely determined, and the genetic codes of further organisms will also shortly be elucidated.^[1] All this new genetic information should offer the medical research community an unparalleled opportunity to understand the genetic basis of disease, a very possible consequence of which would be the realization of gene therapy as an integral part of strategies to cure diseases in the future.^[2] Gene therapy is not yet a clinical reality, although proof of principle has now been established.^[2] Nevertheless, this is a young science, and its proponents, including myself, are quite convinced that gene therapy could change the face of medicine in the next century, with substantial consequences

for the way in which the pharmaceutical industry, in particular, conducts itself.

The principle of gene therapy is simple. If a patient is suffering from a disease caused by a known genetic defect, then the delivery of a correct copy of the defective gene to the diseased cells or body organ, by means of a specially designed vector, would be expected to correct directly for the genetic defect and hence cure the disease. Alternatively, if a patient is suffering from a disease for which there is no clear genetic cause but whose pathophysiology is well understood, then the vector might be used to deliver corrective gene(s) or some other nucleic acid agent (such as antisense oligonucleotides or mRNA) to the diseased cells and so disrupt the known disease pathophysiology in some other way. Hence, generally speaking, gene therapy may be defined either as “the use of genes as medicines to treat disease” or “the delivery of nucleic acid (with a vector) to patients for some therapeutic purpose.”

It is important to make clear that gene therapy should not be seen as a technology designed to rid future generations of genetic and other more complex diseases by permanent manipulation of the human genome. Instead, genes or other nucleic acid agents should be seen as alternatives to small-molecule drugs which, once delivered to patients, offer the real possibility of curing the disease rather than just treating the symptoms, as is currently the case with all but bacterial infections. If genes or other nucleic acid agents are “drugs”,

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[**] A list of frequently used abbreviations is provided in the Appendix.

then the principle technological hurdle which faces the budding gene therapist is the now familiar challenge of drug delivery. In other words, how do we intend to transport or deliver our therapeutic gene or nucleic acid to the site of disease so that only the diseased cells are entered by the therapeutic agent? The answer will lie ultimately in the appropriate choice of the vector for nucleic acid delivery.

2. Vectors for Nucleic Acid Delivery

At this stage, vectors fall into two broad categories, namely viral or nonviral. Neither category may lay claim to being the universal panacea of choice for nucleic acid delivery since both categories have problems which will need to be solved before clinical gene therapy will become possible. That is, no one vector for nucleic acid delivery to date fulfills the criterion of a perfect vector (i.e., offer precise nucleic acid delivery characteristics with no toxic side effects following use). However, of the current range of nonviral vectors, cationic liposomes (which are the subject of this review) show particular promise and potential as clinically useful vector systems for the delivery of therapeutic nucleic acids to patients.^[3, 4] This is a particularly exciting proposition for the organic, physical-organic, or physical chemist who is looking for a role to play at the interface between chemistry and medicine. The preparation and use of cationic liposomes is very much a “problem for chemists” at its heart, as I shall attempt to illustrate here.

2.1. Cationic Liposomes

Cationic liposomes are formed from either a single cationic amphiphile (known as a cytofectin; *cyto-* for cell and *-fectin* for transfection, that is, gene delivery and expression) or more commonly from a combination of a cytofectin and a neutral lipid. The way in which they mediate nucleic acid delivery is simple: Positively charged cationic liposomes interact electrostatically with negatively charged nucleic acid sequences to form complexes which are capable of entering a cell. Once there, nucleic acid sequences are slowly released either to be

expressed in the cell nucleus or to control gene expression. This review will emphasize that this seductively simple principle is attended with many difficult problems which as yet have no clear solution. The consequence of these problems is that most of the current cationic liposome formulations are unlikely to have any ultimate clinical use in the future. However, that is not to say that the critical problems of nucleic acid delivery mediated by a cationic liposome cannot be solved. In fact, it is my belief that they will be, with the result that cationic liposome assisted gene therapy should be a clinical reality within the foreseeable future.

2.2. Other Vectors

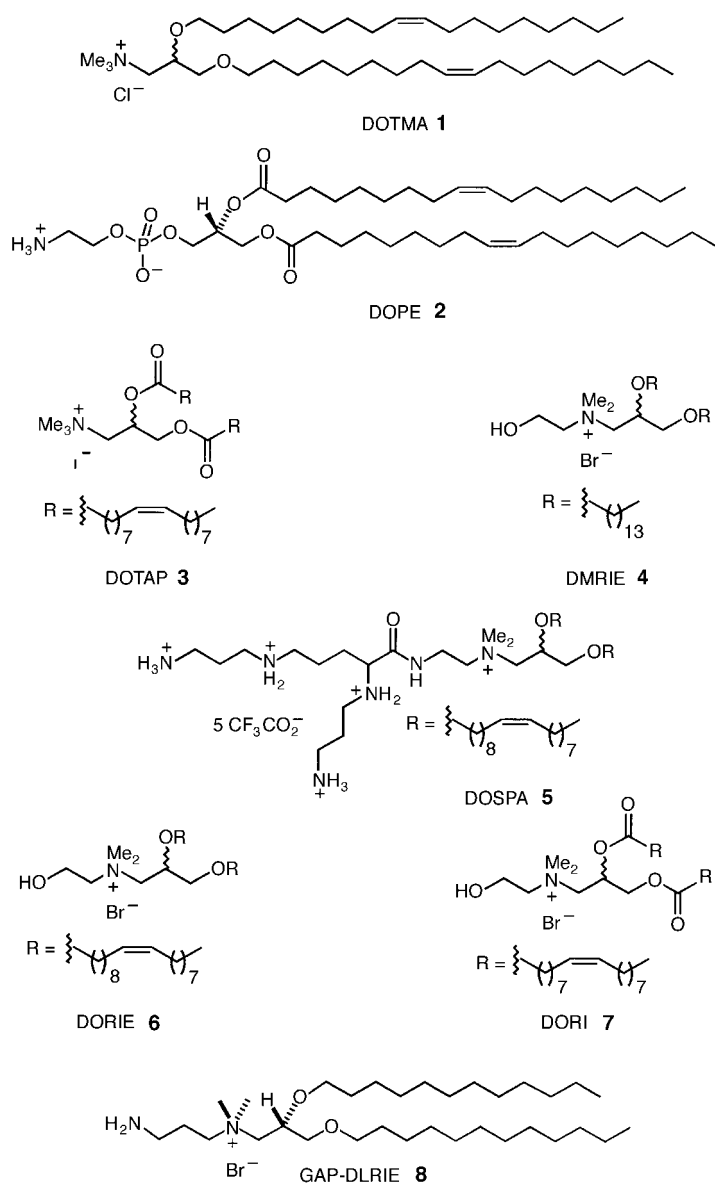
A discussion of alternative nonviral vector systems to cationic liposomes, and of course viral vectors themselves, is beyond the scope of this review. Briefly, alternative chemical vectors to cationic liposomes include calcium phosphate precipitation, (diethylamino)ethyl-dextran, and polybrene (a copolymer from *N,N,N',N'*-tetramethyl-1,6-hexanediamine and 1,3-dibromopropane; more sophisticated chemical vectors will be touched upon later in this review with respect to the development of cationic liposome systems). Physical methods such as microinjection, electroporation, and biobalistics are effective, although perhaps of doubtful clinical use with the exception of the last. Finally, of the viral vectors, adeno-viruses (AV), adeno-associated virus (AAV), and retro-viruses have seen considerable use in the context of gene delivery. For more details on all these methods, the interested chemist is referred to general reviews on the use of these vector systems.^[5–15]

3. Current Cationic Liposome Formulations

The use of cationic liposomes in nucleic acid delivery was originally pioneered by Felgner and co-workers, who developed the cationic liposome now available commercially as Lipofectin (GIBCO/BRL).^[16] Lipofectin is made up of a 1:1 ratio of the cytofectin DOTMA (**1**) and the naturally available, neutral lipid DOPE (**2**). Since this key invention,



Andrew David Miller, born in 1963, began his chemistry education at the University of Bristol (UK), where he graduated in 1984 with a BSc degree. He finished his PhD thesis at the University of Cambridge (UK) in the research group of Professor Alan Battersby, following which he was tempted to stay a further year as a postdoctoral researcher before joining the group of Professor Jeremy Knowles at Harvard University (USA). Since 1990 he has been a lecturer in the Chemistry Department at Imperial College in London (UK), where he has been particularly developing active research interests in the chemistry of stress proteins and in the design of vectors for the delivery of nucleic acids to cells for gene therapy. He has received several awards and fellowships including the Thomas Malkin and Robert Garner prizes for chemistry (Bristol University), an Emmanuel College research scholarship (Emmanuel College, Cambridge), a Lindemann Trust Fellowship, and most recently a Leverhulme Trust Fellowship. This year he was appointed a founding director of the Imperial College Genetic Therapies Centre.



upwards of twenty new cationic liposome formulations have been reported to bring about nucleic acid delivery; a number of these have been commercialized (Table 1). These new formulations usually involve the combination of a novel, synthetic cytofectin with **2** or another neutral lipid. The choice of cytofectin and the manner of formulation are both critical to the success of any given cationic liposome formulation. Therefore, the structures and syntheses of several cytofectins will be described here together with the procedures used to formulate these amphiphiles into cationic liposomes.

3.1. Structures of Cytofectins

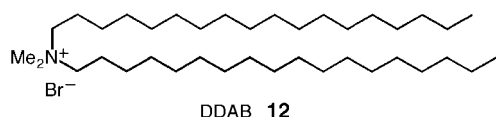
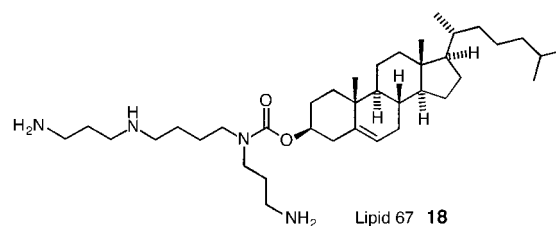
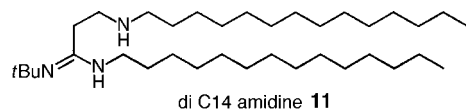
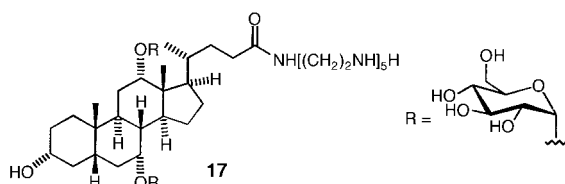
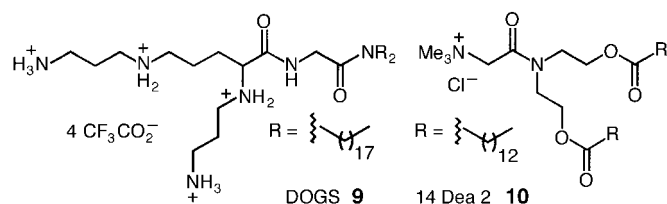
Cytofectins are made up of a cationic head group attached by a linker to a hydrophobic moiety. All cytofectins are therefore positively charged amphiphiles. This is the essential, unifying structural principle of what otherwise may be seen as a diverse family of structures. In this review, the cytofectins are classified into various subgroups: DOTMA analogues, complex alkylamine/alkylamides, cholesterol derivatives, and synthetic derivatives of dipalmitoyl L- α -phosphatidylethanolamine, glutamate, imidazole, and phosphonate.

DOTMA analogues have achieved the most widespread use in cationic liposome formulations. The main analogues are DOTAP (**3**),^[17] DMRIE (**4**),^[18] and DOSPA (**5**). Other DOTMA analogue structures reported include DORIE (**6**)^[18] and the corresponding ester analogue DORI (**7**).^[18–20] Homologues of DMRIE, DORIE, and DORI are also known.^[18, 20] The most recent and most effective addition to this subgroup of compounds has been GAP-DLRIE (**8**).^[21] The main members of the complex alkylamine/alkylamide subgroup are DOGS (**9**),^[22] 14 Dea 2 (**10**),^[23, 24] di C 14 amidine (**11**),^[25, 26] and DDAB (**12**).^[27] Homologues of both 14 Dea 2 and di C 14 amidine have been reported.^[23–26] Most recently, GS 2888 (**13**) was added to this subgroup.^[28] Of these, only **9** and **12** have experienced widespread utility thus far.

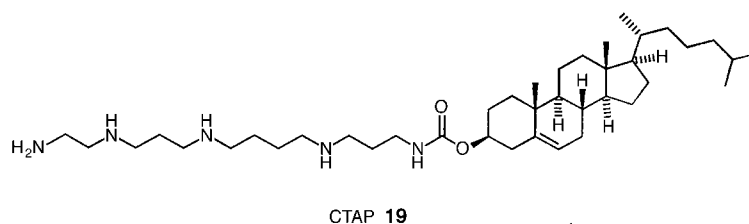
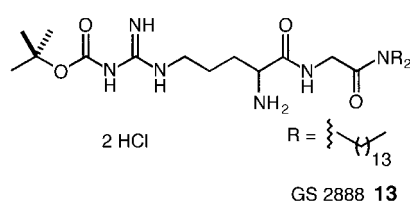
Table 1. The main cationic liposome formulations to date.^[a]

Commercialized		Not commercialized	
Cytofectin	Formulation (trade name/manufacture)	Cytofectin	Formulation
DOTMA 1 ^[16]	DOTMA/DOPE 1:1 ^[b] (Lipofectin/GIBCO BRL)	DMRIE 4 ^[18]	DMRIE/DOPE 1:1
DOTAP 3 ^[17]	DOTAP (DOTAP/Boehringer Mannheim)	DORIE 6 ^[18]	DORIE/DOPE 1:1
DOSPA 5	DOSPA/DOPE 3:1 ^[b] (LipofectAMINE/GIBCO BRL)	DORI 7 ^[18, 20]	DORI/DOPE 1:1
DOGS 9 ^[22]	DOGS (Transfectam/Promega)	14 Dea 2 10 ^[23, 24]	14 Dea 2
di C 14 amidine 11 ^[25, 26]	di C 14 amidine/DOPE 1:1 (Clonfectin/Clontech)	GS 2888 13 ^[28]	G 2888/DOPE 1:1
DDAB 12 ^[27]	DDAB/DOPE 1:2.5 ^[b] (LipofectAce/GIBCO BRL)	DC-Chol 14 ^[29]	DC-Chol/DOPE 6:4
cholesteryl spermidine 20 ^[35]	cholesteryl spermidine (Transfectall/Apollon Inc.)	cholic acid hexamine 17 ^[31]	17 /DOPE 1:1 ^[b]
		lipid 67 18 ^[32]	lipid 67/DOPE 1:2
		CTAP 19 ^[33]	CTAP/DOPE 1:2
		BGTC 21 ^[36]	BGTC/DOPE 3:2
		DPPES 22 ^[22]	DPPES
		Lys-Pam ₂ -GroPEtn 23 ^[37]	Lys-Pam ₂ -GroPEtn/Chol/egg PC 1.5:3.0:5.5 ^[b]
		L-PE 23a ^[38]	L-PE/CE/BA 39 6:4
		2C ₁₂ -L-Glu-ph-C ₂ -N ⁺ Br [−] 24 ^[39]	2C ₁₂ -L-Glu-ph-C ₂ -N ⁺
		2C ₁₄ -L-Glu-C ₂ -N ⁺ Cl [−] 25 ^[39]	2C ₁₄ -L-Glu-C ₂ -N ⁺
		DOTIM 26 ^[40]	DOTIM/Chol 1:1 or DOTIM/DOPE 1:1

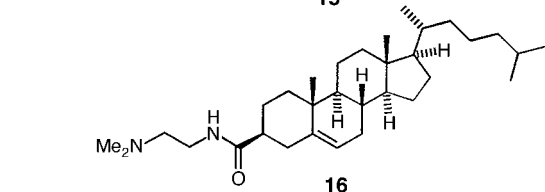
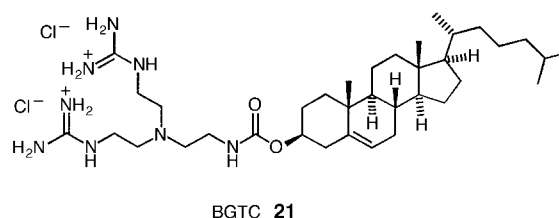
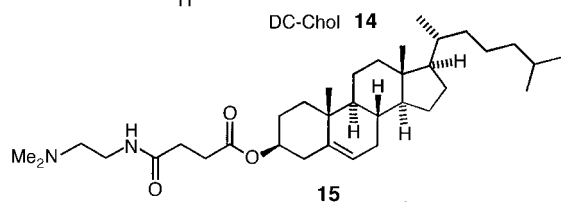
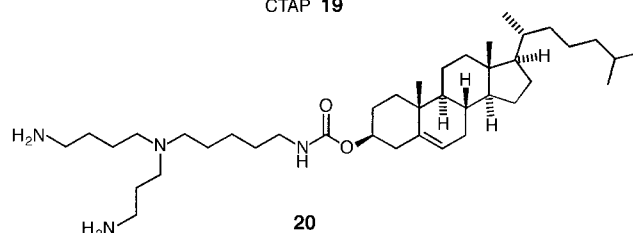
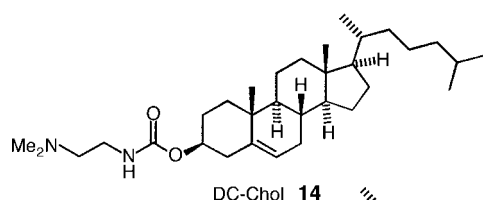
[a] Abbreviations used: Chol: cholesterol (**38**), egg PC: egg phosphatidyl ethanolamine. Ratios given are molar ratios, unless indicated otherwise. [b] Weight ratio.



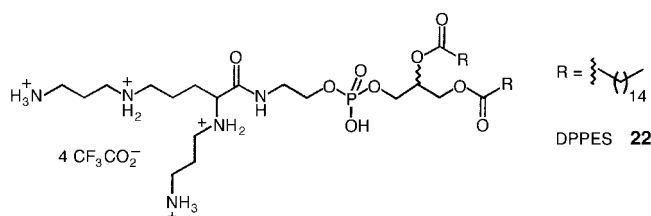
been described,^[34–36] including cholesteryl spermidine (**20**),^[35] and BGTC (**21**).^[36]



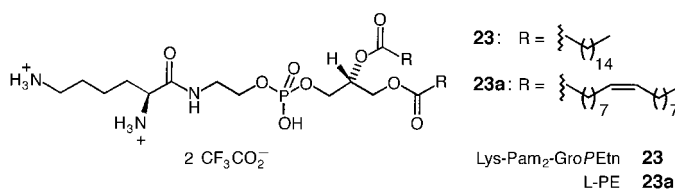
The first reported cholesterol derivative was DC-Chol (**14**),^[29] and it is still widely used. Other derivatives were described soon after, including cholesteryl-3 β -oxysuccin-amidoethylenedimethylamine (**15**) and cholesteryl-3 β -carboxyamidoethylenedimethylamine (**16**)^[30] as well as ester analogues of both.^[17] Recently, three unusual classes of polyamine cholesterol cationic “face” amphi-



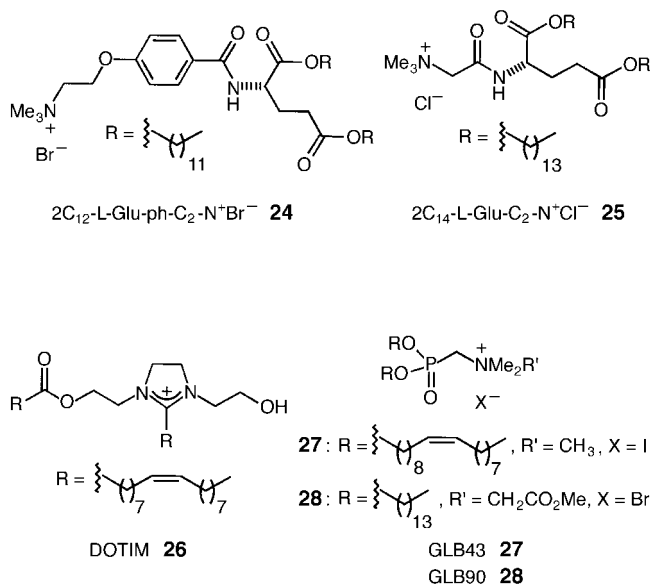
Of the remaining subgroups, there are two main dipalmitoyl L- α -phosphatidylethanolamine derivatives which have been reported, namely, DPPES (**22**)^[22] and Lys-Pam₂-GroPEtn



philes have been reported that are based on the three naturally occurring cholesterol-derived bile acids.^[31] These are typified by the bisglycosylated cholic acid hexamine **17**. Two of the most efficacious cytofectins reported to date are cholesterol derivatives; these are polyamine lipid 67 (**18**)^[32] and CTAP (**19**).^[33] Other polyamine derivatives have also



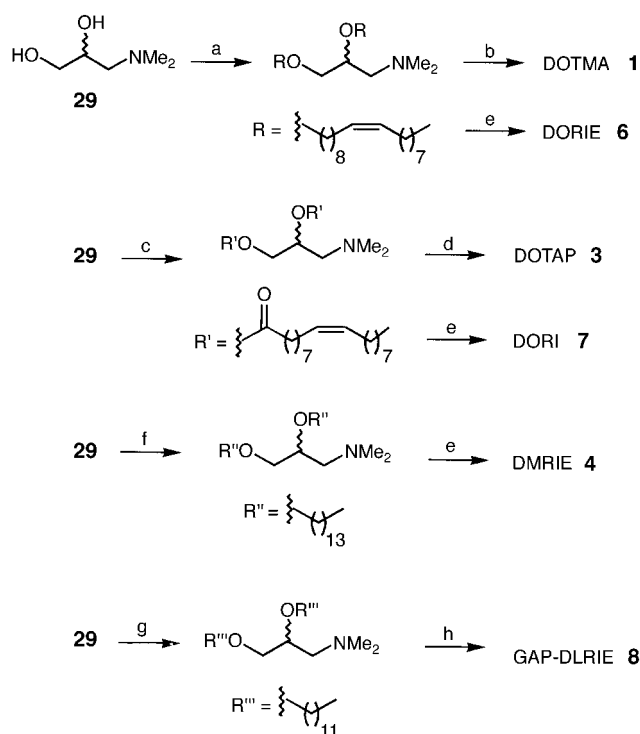
(**23**).^[37] A third derivative, L-PE (**23a**), is known, but is apparently little more than an “oleoyl version” of **23**.^[3, 38] 2C₁₂-L-Glu-ph-C₂-N⁺Br[−] (**24**) and 2C₁₄-L-Glu-C₂-N⁺Cl[−] (**25**) are reported to be the best glutamate-derived cytofectins.^[24, 39] Finally, imidazole derivatives, typified by DOTIM (**26**), have recently been announced^[40] as well as two phosphonate diester derivatives, GLB43 (**27**) and GLB90 (**28**).^[41]



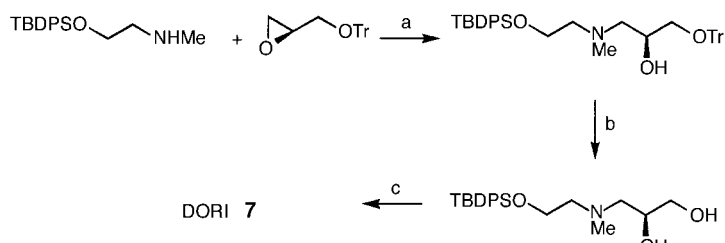
3.2. Syntheses of Cytofectins

The organic syntheses of the main cytofectins are in general short and high-yielding, a fact which has certainly aided their utility. The synthesis of DOTMA (**1**) is shown in Scheme 1 together with the syntheses of DOTMA analogues DOTAP (**3**), DMRIE (**4**), DORIE (**6**), and DORI (**7**). DOTMA is prepared in a two-step procedure from 3-(dimethylamino)-1,2-propanediol (**29**).^[16] Both **3** and **7** are made in a similar way by oleoylation of propanediol **29** followed by alkylation of the resulting tertiary amine with methyl iodide or 2-bromoethanol, respectively.^[17, 18] Alternatively, alkylation of **29** with myristyl or oleyl mesylate, followed by N-alkylation with 2-bromoethanol, gives **4** and **6**, respectively.^[18] GAP-DLRIE (**8**) is synthesized in an analogous manner to **4** and **6**.^[21] More complex syntheses of DOTMA analogues have also been reported, including an elegant synthesis of **7** (Scheme 2),^[19] which proved flexible enough to allow the synthesis of a range of fatty acid analogues of **7**.^[20] The synthesis of the polyamine DOSPA (**5**) appears not to have been reported.

The complex alkylamine/alkylamide subgroup of cytofectins have been prepared in a variety of different ways consistent with their more diverse structures. DOGS (**9**) is synthesized by a multistep, convergent procedure culminating in the coupling of L-5-carboxytetrabutoxycarbonylspermine (**30**) with glycyldioctadecylamide (**31**, Scheme 3),^[22] cytofectin 14 Dea 2 (**10**) and its homologues by N-acylation and amine substitution (Scheme 4),^[24] and di C 14 amidine (**11**) and its



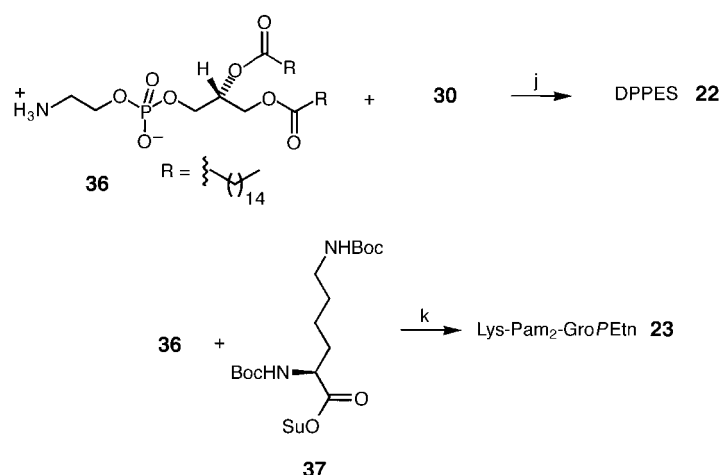
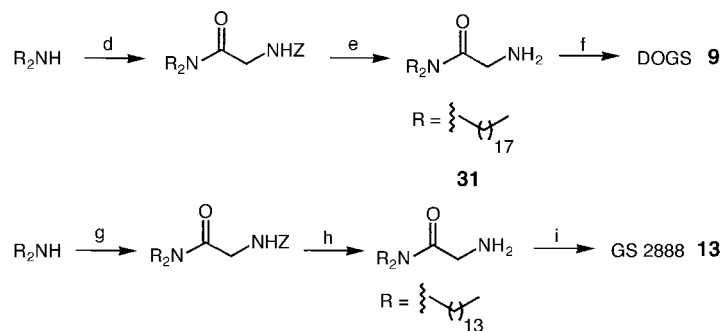
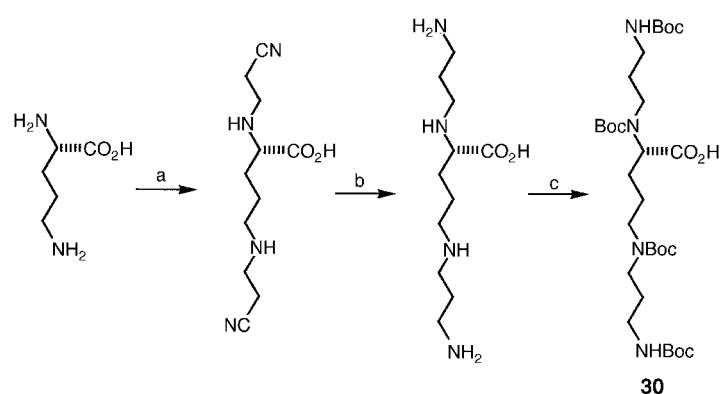
Scheme 1. Reagents and conditions: a) xylene, *t*BuOK (3 equiv), oleyl toluenesulfonate (3 equiv) or oleyl mesylate (3 equiv), 140 °C, 3 h; b) MeCl, 70 °C, 48 h; c) Et₂O, pyridine, oleyl chloride, 40 h, 78 %; d) CHCl₃/DMSO (1/1), MeI, 63 %; e) Br(CH₂)₂OH; f) xylene, *t*BuOK (3 equiv), myristyl mesylate (3 equiv), 70 °C; g) 1. THF (anhydrous), NaH, reflux, 24 h; 2. THF (anhydrous), dodecyl mesylate (3 equiv), reflux, 72 h, 65 %; h) 1. DMF (anhydrous), *N*-(3-bromopropyl)phthalimide (2 equiv), 105 °C, 72 h, 61 %; 2. EtOH, hydrazine (30 equiv), room temperature (RT), 18 h, 75 %.



Scheme 2. Reagents and conditions: a) EtOH, LiClO₄ (2 equiv), 65 °C, 72 %; b) Et₂O, 85 % HCO₂H, 71–75 %; c) 1. CH₂Cl₂, oleyl chloride (2.2 equiv), Et₃N, DMAP (cat.), 0 °C, 92 %; 2. THF, TBAF (3 equiv), 0 °C, 88–91 %; 3. MeI. TBDSO = *tert*-butyldiphenylsilyl, Tr = triphenylmethyl, DMAP = 4-dimethylaminopyridine, TBAF = tetrabutylammonium fluoride.

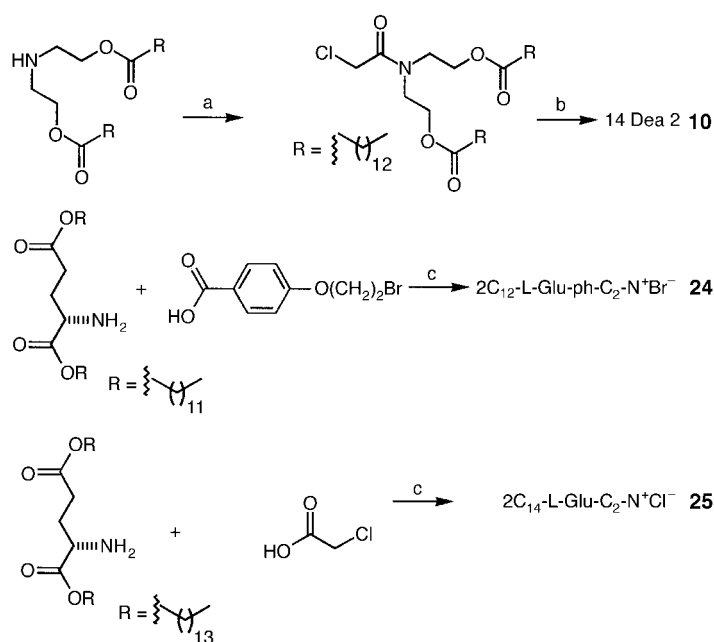
homologues by aminolysis of ethyl *N*-*tert*-butylacrylimide (**32**, Scheme 5).^[26] DDAB (**12**) is prepared by dialkylation of dimethylamine.^[27] The recently reported GS 2888 (**13**) was prepared (Scheme 3) in a very similar way to **9**.^[28]

A single aminolysis reaction is sufficient to prepare DC-Chol (**14**) from cholesterol chloroformate (**33**),^[29] and to prepare **15** and **16** from cholesterol hemisuccinate (**34**) and cholesteryl-3 β -carboxylic acid (**35**), respectively (Scheme 6).^[30] Aminolysis of **33** followed by guanidinylation of the product was sufficient to synthesize BGTC (**21**) as well (Scheme 6).^[36] Rather surprisingly, workers in the field have often used a similar one-step aminolysis procedure to prepare

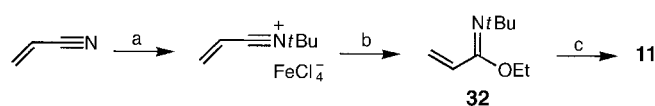


Scheme 3. Reagents and conditions: a) DMF, CH_2CHCN ; b) EtOH, Raney Ni, H_2 ; c) THF, Boc-ON; d) CH_2Cl_2 , ZGlypNP, Et_3N (1.1 equiv), 5 h; e) $\text{CH}_2\text{Cl}_2/\text{EtOH}$, 10% Pd/C, H_2 , 1 h, 87%; f) 1. CH_2Cl_2 , **30**, DCC (1.1 equiv), 12 h, 90%; 2. TFA, 10 min; g) 1. THF, Z-glycine, NHSu (1 equiv), DCC (1.1 equiv), RT, 16 h; 2. CH_2Cl_2 , Et_3N (1.4 equiv), RT, 5 h, 18%; h) $\text{CH}_2\text{Cl}_2/\text{EtOH}$, 10% Pd/C, H_2 , 8 h, 94%; i) 1. CH_2Cl_2 , L-Boc-Arg(Boc)₂-OH, DIC (1.1 equiv), RT, 16 h, 37.5%; 2. dioxane, 4 M HCl, RT, 2.5 h; j) 1. $\text{CH}_2\text{Cl}_2/\text{THF}$, NHSu (1.1 equiv), DCC (1.1 equiv), 12 h; 2. $\text{CHCl}_3/\text{EtOH}$, Et_3N , 40 °C, 12 h, 55%; 3. CH_2Cl_2 , TFA; k) 1. $\text{CHCl}_3/\text{EtOH}$ (1/1), Et_3N (0.1 mol %), 50 °C, 12 h; 2. CHCl_3 , TFA, 3 h. Boc = *tert*-butoxycarbonyl, Boc-ON = 2-(*tert*-butoxycarbonyloximino)-2-phenylacetoneitrile, Z = benzyloxycarbonyl, pNP = *para*-nitrophenyl, DCC = dicyclohexylcarbodiimide, TFA = trifluoroacetic acid, NHSu = *N*-hydroxysuccinimide, DIC = diisopropylcarbodiimide.

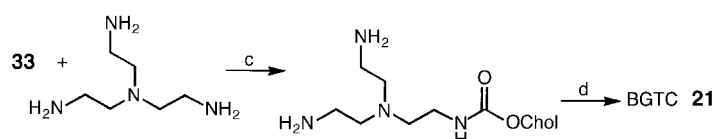
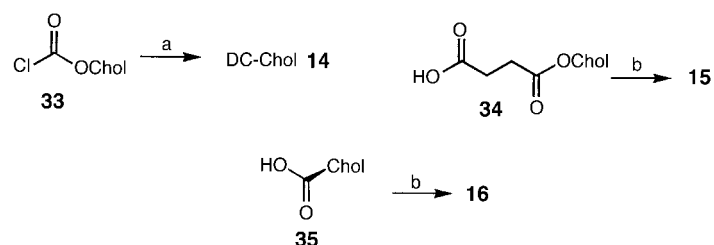
cholesterol polyamine derivatives leading to mixtures of polyamine regioisomers rather than pure compounds.^[34] For instance, cholic acid hexamine **17** has been prepared in several steps from cholic acid, but the addition of the hexamine was also accomplished by an uncontrolled aminolysis step that left



Scheme 4. Reagents and conditions: a) CHCl_3 , DCC (1.1 equiv), $\text{ClCH}_2\text{CO}_2\text{H}$; b) Me_3N ; c) 1. CH_2Cl_2 , DCC (1.1 equiv); 2. Me_3N .

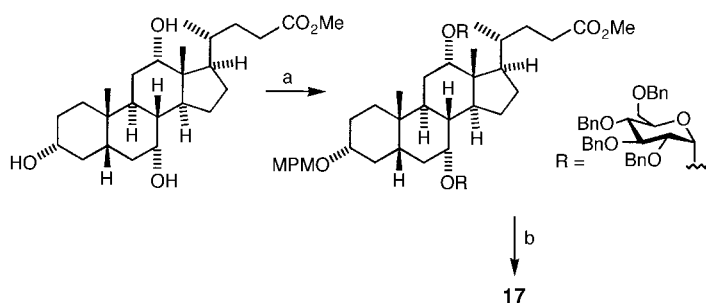


Scheme 5. Reagents and conditions: a) CH_2Cl_2 , FeCl_4^- , 0 °C, 15 min, then *t*BuCl, 30 min; b) EtOH; c) $\text{CH}_3(\text{CH}_2)_{13}\text{NH}_2$ (2 equiv).



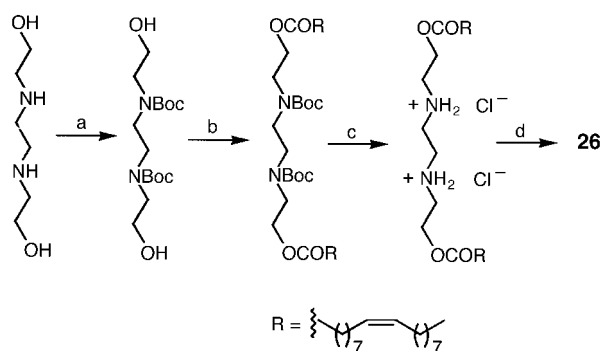
Scheme 6. Reagents and conditions: a) CHCl_3 , $\text{Me}_2\text{N}(\text{CH}_2)_2\text{NH}_2$ (3.6 equiv), 0 °C, 22%; b) CH_2Cl_2 , $\text{Me}_2\text{N}(\text{CH}_2)_2\text{NH}_2$, CDI; c) CH_2Cl_2 , TREN; d) THF/MeOH, 1*H*-pyrazole-1-carboxamidine (2 equiv), *i*Pr₂NH (2 equiv), RT, 18 h, 60%. CDI = carbonyldiimidazole, Chol = 3-cholester-yl, TREN = tris(2-aminoethyl)amine.

17 as a mixture of polyamine regioisomers (Scheme 7).^[31] By contrast, polyamine CTAP (**19**) has recently been synthesized in a high-yielding, multistep procedure designed to avoid regioisomer formation.^[33] The synthetic route devised proved to be flexible enough to allow the syntheses of a host of triamine, tetraamine, and pentamine variants of cholesterol-derived cytofectins. The synthetic routes to lipid **67** (**18**) and cholesteryl spermidine (**20**) have not thus far been reported.



Scheme 7. Reagents and conditions: a) 1. THF, NaH, MPMCl; 2. PhMe, Ti_2O (4 equiv), 2,6-di-*tert*-butyl-4-methylpyridine, -78°C , then RS(O)Ph (4 equiv), 30 min, $\rightarrow\text{RT}$; b) 1. NaOH/EtOH/THF, 2–48 h, reflux; 2. CH_2Cl_2 , NHSu , DCC, 3 h; 3. $\text{H}_2\text{O}/\text{Et}_3\text{N}$, hexamine, 48 h; 4. EtOH, $\text{Pd}(\text{OH})_2/\text{C}$, H_2 . MPM = *p*-methoxybenzyl, Ti_2O = trifluoromethylsulfonic anhydride.

Of the remaining subgroups of cytofectins, the two main dipalmitoyl-phosphatidylethanolamine derivatives, DPPES (**22**) and Lys-Pam₂-GroPEtn (**23**), were synthesized analogously by *N*-acylation of the parent lipid **36** with *N*-hydroxy-succinimide-activated **30** or Boc-Lys(Boc)-OSu (**37**), respectively (Scheme 3).^[22, 37] *N*-Acylation followed by amine substitution sufficed for the syntheses of both main glutamate diester derivatives 2C₁₂-L-Glu-ph-C₂-N⁺Br[−] (**24**) and 2C₁₄-L-Glu-C₂-N⁺Cl[−] (**25**) from glutamate esters (Scheme 4).^[24] Finally, imidazole derivative DOTIM (**26**) and its homologues have been prepared by a four-step procedure culminating in a novel cyclization to form the imidazolium ring (Scheme 8).^[40]



Scheme 8. Reagents and conditions: a) CHCl_3 , Boc_2O (2.1 equiv), NaHCO_3 , 5 h, 80%; b) CH_2Cl_2 , oleoyl chloride (2.1 equiv), Et_3N (2.4 equiv), 45 min, 94%; c) dioxane, HCl , 2 h, 95%; d) ethylene glycol, 110°C , 10 min, 75%.

3.3. Methods for Cationic Liposome Formulation

The formulation of cytofectins into cationic liposomes, with or without a neutral colipid, has involved a number of different possible procedures. Broadly speaking these are sonication and/or vortex-mixing of an aqueous solution, reverse-phase evaporation, or aqueous dilution of an ethanolic stock solution. The method of formulation is undoubtedly important, but the extent to which this affects the efficiency of nucleic acid transfer has yet to be properly evaluated.

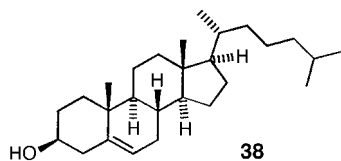
DOTMA (**1**) and its main analogues (**4**–**8**) are usually formulated into cationic liposomes with the neutral colipid DOPE (**2**). Liposomes are prepared by vortex-mixing of equimolar amounts of cytofectin and **2** at room temperature to produce large multilamellar vesicles (MLVs), which are then sonicated at 10°C to produce small unilamellar vesicles (SUVs) suitable for gene transfection.^[18, 20, 21] Cationic liposomes with DOSPA (**5**) are available commercially as LipofectAMINE (GIBCO/BRL) and contain **5** and **2** in a 3:1 ratio. Cationic liposomes containing DOTAP (**3**) are also available (Boehringer Mannheim) without neutral colipid; however, prior to commercialization, DOTAP cationic liposomes were also customarily formulated with **2**. In that instance, DOPE/DOTAP liposomes were prepared either by sonication^[17] or by reverse-phase evaporation.^[17, 42]

Cationic liposomes of the complex alkylamine/alkylamide cationic amphiphile DOGS (**9**) may be obtained commercially as Transfectam (Promega). Such liposomes are formulated simply by tenfold dilution of an aqueous ethanol stock solution of **9** into an aqueous buffer.^[22] By contrast, cationic liposomes containing DDAB (**12**) are usually formulated with DOPE (**2**). Indeed, the commercial product LipofectAce (GIBCO/BRL) is a formulation of **12** with **2** in a 1:2.5 ratio. Di C 14 amidine (**11**) liposomes are now available commercially as Clonfectin (Clontech). These are mainly formulated by dilution of an ethanolic stock solution into neutral buffer,^[25] a method analogous to the formulation of DOGS liposomes;^[22] a second method has also been used in which **11** was combined with **2**, in 1:1 molar ratio, and liposomes formed by vortex-mixing and sonication.^[25] This second method has also been used to form liposomes from GS 2888 (**13**), although the best formulation involved vortex mixing followed by freeze-thawing of a mixture of **13** and **2** in a 2:1 molar ratio.^[28] Finally, sonication of a 10 mM suspension in water of cytofectin 14 Dea 2 (**10**) or its homologues is apparently sufficient to form active liposomes.^[23]

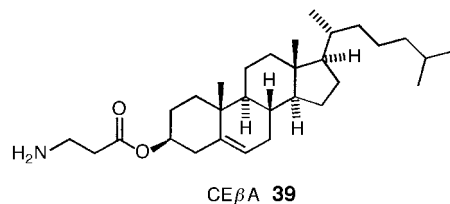
Cholesterol derivatives are usually formulated into liposomes with DOPE (**2**), but in a number of different ways. For instance, DC-Chol (**14**) is usually combined with **2** in a 6:4 molar ratio, and liposomes are generated either by sonication alone,^[29] vortex-mixing followed by sonication,^[43] or reverse-phase evaporation followed by sonication.^[44] Liposomes containing cytofectins **15** and **16** have also been formulated with **2** in a 1:1 molar ratio by sonication or by vortex-mixing followed by sonication.^[29, 43] The cholic acid hexamine **17** and related amphiphiles are combined with **2** in a 1:1 ratio, and liposomes formed by sonication.^[31] Polyamines lipid 67 (**18**) and CTAP (**19**) have so far been transformed into liposomes, in combination with **2** in a 1:2 molar ratio, by vortex-mixing alone.^[33] Out of the remaining cholesterol polyamine cytofectins, BGTC (**21**) has been reported to form liposomes, in a 3:2 molar ratio with **2**, by vortex-mixing and then sonication,^[36] whilst cholesteryl spermidine (**20**), now marketed as Transfectall (Apollon Inc), appears to be formulated without colipid.^[35]

The remaining subgroups of cytofectins are frequently formulated either without colipid or with neutral colipids other than DOPE (**2**). For instance, liposomes of DPPES (**22**) are prepared without colipid, in the same way as DOGS (**9**).^[22]

whilst those of Lys-Pam₂-GroPEtn (**23**) are formed by sonication of mixture of **23** with cholesterol **38** and egg



phosphatidylcholine in a ratio of 1.5:3.0:5.5.^[37] L-PE (**23a**) is formulated into liposomes in combination (6:4 molar ratio) with a second cationic amphiphile, namely the cholesterol ester of β -alanine (CE β A, **39**).^[38] In contrast, liposomes of



DOTIM (**26**) and its homologues are prepared by sonication of a mixture of the cytofectin with a 1:1 molar ratio of either cholesterol **38** or **2**.^[40] Finally, the two main glutamate diester derivatives, 2C₁₂-L-Glu-ph-C₂-N⁺Br⁻ (**24**) and 2C₁₄-L-Glu-C₂-N⁺Cl⁻ (**25**), are formulated on their own by simple sonication of a suspension in neutral buffer.^[39]

4. Mechanism of Nucleic Acid Delivery

The mechanism of cationic liposome mediated nucleic acid delivery is complicated. Therefore, to characterize the present state of knowledge, this process will be discussed in three separate stages. Firstly, the structures of complexes between cationic liposomes and nucleic acids will be described. Heterogeneous complexes are formed rapidly following the combination of nucleic acids with a suspension of cationic liposomes. It is these complexes which enter the cells. Nucleic acid delivery appears to be most efficient when complexes are formed under conditions where the ratio of liposome positive charges to nucleic acid negative charges lies around 1 and above. For gene delivery *in vitro*, the optimal charge ratio is frequently greater than 1 (i.e., complexes are cationic),^[22] whilst the optimal ratio tends to be nearer to 1 for efficient *in vivo* gene delivery.^[45] Therefore, the main focus of our attention in the next section will be on the special character of cationic liposome/nucleic acid complexes formulated with charge ratios of around 1 and above.

Second, the mechanism(s) involved in the entry of cationic liposome/nucleic acid complexes into cells will be discussed. The predominant mechanism now appears to be endocytosis, irrespective of the type of cationic liposome involved. Therefore, the best evidence for this will be presented together with some other possible mechanisms for cell entry. Finally, the fate of the nucleic acids will be described with special emphasis on the trafficking of nucleic acids to the nucleus, where their therapeutic site of action would be in most instances.

4.1. Structures of Cationic Liposome/DNA Complexes

The original, stylized depiction of Felgner and Ringold shows cationic liposomes binding to DNA electrostatically without changing their size and shape.^[46] Experimental evidence now shows that cationic liposome/DNA complexes are in fact very heterogeneous and dynamic, varying in size and shape depending upon the molar ratio of cationic liposomes to DNA. The most dramatic changes in structure appear to occur when the positive/negative charge ratio is around 1.

The first key experiments were carried out by Gershon et al.^[47] Using ethidium bromide as a fluorescent probe for exposed DNA base pairs, they titrated fixed concentrations of DNA with DOTMA or DOPE/DOTMA liposomes (1:1 molar ratio) and observed the effects. They observed that DNA was generally accessible until the positive/negative charge ratio approached 1, at which point extensive DNA masking was diagnosed by a rapid decline in fluorescence intensity (Figure 1a). Sharp changes in behavior at the 1:1

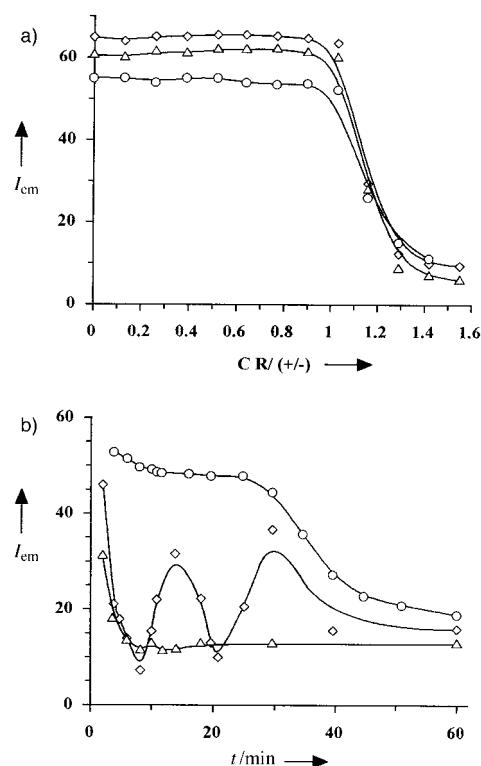


Figure 1. Effects of DNA length and liposome-to-DNA ratio (in terms of the positive/negative charge ratio) on the fluorescence intensity of ethidium bromide. a) A fixed concentration of DNA (nucleotide concentration) was titrated with DOPE/DOTMA liposomes (1:1 molar ratio) in the presence of ethidium bromide. Increasing liposome concentrations are reflected by the increasing liposome-to-DNA [positive/negative charge ratio: CR/(+/-)]. The intensity of fluorescence emission (I_{em}) for ethidium bromide is given in arbitrary units. Lengths of DNA segments were 100–300 ($\circ$), 500–8000 ($\triangle$), and 23000 base pairs ($\diamond$). b) Three different concentrations of DOPE/DOTMA liposomes (1:1 molar ratio) were combined with DNA in the presence of ethidium bromide, and the change in fluorescence intensity was measured over time t . The liposome-to-DNA charge ratios (+/-) were 1.0 ($\circ$), 1.1 ($\diamond$), and 1.2 ($\triangle$). Throughout, DNA concentration was normalized at 25 μ M (nucleotide concentration); ethidium bromide (1:50 molar ratio of fluorescence probe to nucleotides) was added immediately prior to measurement. This figure was adapted with permission from Gershon et al.^[47]

charge ratio were also observed in lipid-mixing experiments with the resonance energy transfer (RET) method of Struck et al.^[48] In this method, liposomes containing two complementary fluorescent-labeled lipids are combined with unlabeled liposomes. In the event of lipid mixing/fusion, the labeled lipids become diluted into the previously unlabeled liposomes, with the result that fluorescence quenching effects between complementary labeled lipids are reduced and fluorescence intensity is enhanced.

The studies with the RET method showed that whilst lipid mixing/fusion was generally promoted by DNA, in common with other multivalent anions,^[49–52] a noticeable change in behavior occurred around the 1:1 charge ratio (Figure 2a). In interpreting these sharp changes in behavior, Gershon et al. proposed that the cationic liposomes were probably sufficiently neutralizing the negative charge of DNA to induce a

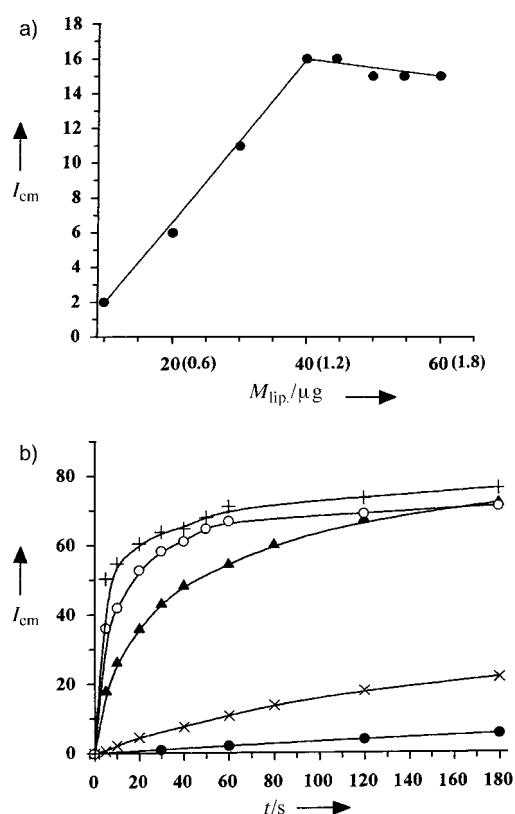


Figure 2. Lipid mixing of labeled and unlabeled liposomes induced by DNA. a) DOPE/DOTMA liposomes (1:1 molar ratio) were combined with fluorescent-labeled DOPE/DOTMA liposomes in the presence of DNA (25 μM , nucleotide concentration), and the increase in fluorescence intensity (I_{cm} in arbitrary units) due to lipid mixing was measured with increasing lipid concentration (expressed as mass of liposome M_{lip} , added to DNA). The DNA-induced increase in fluorescence was obtained by subtracting the fluorescence of labeled liposomes alone from that obtained in the presence of DNA. Estimated ratios of positive to negative charges are shown in parentheses. This figure was adapted with permission from Gershon et al.^[47] b) Liposomes containing 16 μM and 4 μM DOTAP (3) were combined with fluorescently labeled DOTAP liposomes, and the change in fluorescence intensity due to lipid mixing was measured over time t in the presence of different concentrations of DNA (nucleotide concentration). Different DNA concentrations are reflected by the negative-to-positive charge ratio. DNA-to-liposome charge ratios ($-/+$) in the mixtures after the addition of oligonucleotides were 0 (i.e., no DNA present; ●), 0.03 (×), 0.2 (▲), 0.8 (○), and 1.2 (+). This figure was adapted with permission from Jääskeläinen et al.^[52]

cooperative collapse in the DNA structure,^[47] in analogy to previous observations.^[53, 54] They further proposed that collapsed DNA, whose exposed surface area is then much smaller, could then be efficiently encapsulated by lipid. This proposal was corroborated by Kleinschmidt metal-shadowing electron microscopy experiments in which liposomes appeared as localized DNA-bound spherical clusters, at low liposome-to-DNA ratios, and as much larger (ca. 700 nm) rod-shaped structures above the critical charge ratio (Figure 3). The latter were proposed to arise from the encapsulation of several condensed DNA molecules together.

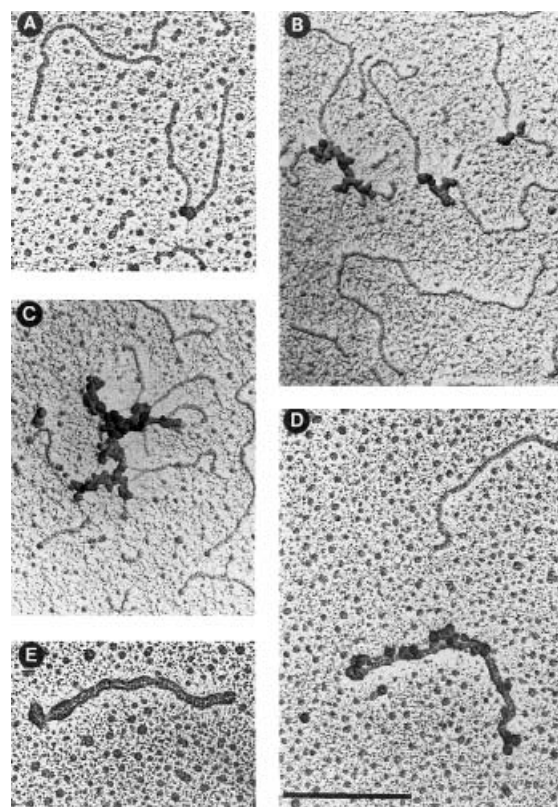


Figure 3. Kleinschmidt metal-shadowing electron microscopy of liposome/DNA complexes. The complexes were prepared with gradually increasing amounts of DOPE/DOTMA liposomes and a constant amount of DNA (3.5 $\mu g mL^{-1}$). The liposome-to-DNA ($+/-$ charge) ratios were 0.2 (A), 0.4 (B), 0.6 (C), 1.0 (D), and 1.5 (E). The scale bar represents 0.5 μm . This figure was reproduced with permission from Gershon et al.^[47]

These observations and the two main proposals have since been supported by the results of other research groups. In particular, Gustafsson et al. have obtained cryo-transmission electron microscope images of DNA complexed with DOTAP and DOPE/DDAB liposomes which revealed the presence of “free” or loosely bound DNA, when the positive/negative charge ratio was less than 1, and large (> 100 nm) lipid/DNA structures at liposome-to-DNA molar ratios in excess of the neutral charge ratio.^[55] They proposed that these large structures were characteristic of multilamellar lipid structures within which DNA was totally encapsulated.

Encapsulation of DNA has also been supported by observations that cationic liposomes are able to protect DNA from degradation by nucleases, shearing by aerosoliza-

tion, and ultrasonic damage during sonication.^[56, 57] The exact nature of this encapsulation has been very recently revealed through some spectacular X-ray diffraction data obtained by Rädler and co-workers in studying DOPE/DOTAP liposomes (1:1) complexed with λ -phage DNA.^[58] They observed that DNA was encapsulated in highly ordered multilamellar structures and sandwiched between cationic bilayers. The DNA itself is arranged in highly ordered one-dimensional monolayer arrays forming a regular lattice (Figure 4). The

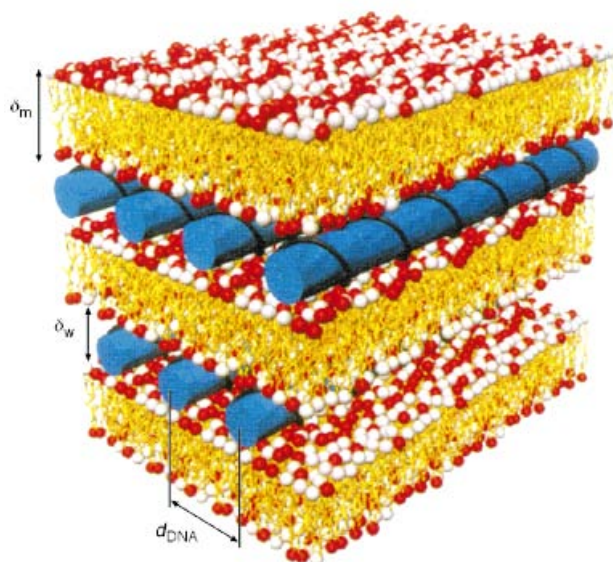


Figure 4. Schematic diagram of the proposed local arrangement of cationic liposome/DNA complexes. The DNA molecules are represented as blue rods. The head groups of anionic/zwitterionic lipids are shown as white spheres, and those of cytofectins as red spheres. Cytofectins are present in a higher concentration near the DNA. δ_m refers to the thickness of the bilayer, δ_w to the separation between the bilayers, and d_{DNA} to the interaxial spacing of the DNA. The magnitude of d_{DNA} increases from about 25 to 60 Å as the ratio of cationic liposome to DNA (positive/negative charge ratio) increased from less than 1 to more than 1. This figure was reproduced with permission from Rädler et al.^[58]

formation of these ordered arrays was suggested to arise from initial condensation of DNA on the surface of the cationic liposomes. This results in screening of the electrostatic repulsion between lipid bilayers, thereby allowing multilayer formation driven by the release of DNA-associated counterions.

However, this is probably not the whole story. Behr originally showed how DNA may coat or wrap around the surface of cationic liposomes.^[59] This observation has since been supported by Eastman et al., whose new data suggest that DNA binding to the surface of cationic liposomes may also conveniently mediate the formation of the large cationic liposome/DNA complexes described above.^[60] Therefore, it seems most probable and conceivable that the interaction between cationic liposomes and DNA involves a combination of both total encapsulation and surface association.

The variation of the size of the cationic liposome/DNA complex by changing the molar ratio of cationic liposome to DNA has been investigated by a number of groups. For

instance, quasielastic light scattering measurements of DOTAP or DOPE/DDAB liposomes in association with DNA have shown that at low liposome-to-DNA ratios, only small particles (ca. 40 nm) form.^[52] The average size then appeared to increase dramatically (ca. 3000 nm) as a positive/negative charge ratio of 1 is approached, but then gradually declined again as the liposome-to-DNA molar ratio was increased further (Figure 5). The same phenomenon has been observed

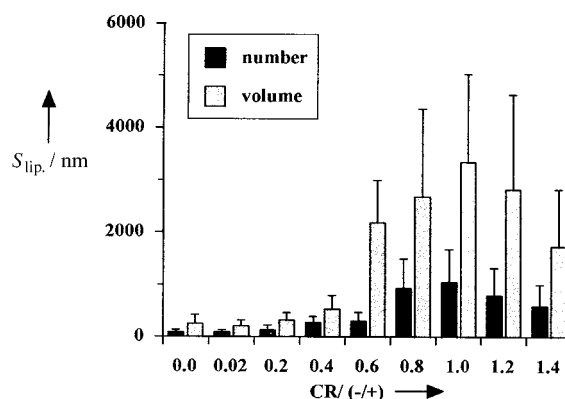


Figure 5. Quasi-elastic light scattering measurements of the particle size of liposome/DNA complexes. The complexes were prepared by incubating increasing amounts of a 15-mer S-oligonucleotide with cationic liposomes containing 10 μ M DOTAP (3); the average particle size was then measured. The increase in DNA concentration is reflected by the increasing ratio of DNA to liposome [CR/(-/+)]. Size distributions $S_{lip.}$ were determined as the mean $\pm$ standard deviation of the diameter on the basis of vesicle number and volume. This figure was adapted with permission from Jääskeläinen et al.^[52]

by Rädler and co-workers with a combination of dynamic light scattering measurements and differential interference microscope imaging.^[58] Whilst large (> 100 nm) multilamellar particles with encapsulated DNA are almost certainly formed readily around and above the neutral charge ratio, these particles are probably in dynamic equilibrium with many other smaller complex species and even free DNA. Zabner et al. have provided evidence for this in studies with DOPE/DMRIE liposomes complexed to DNA.^[61] Their electronphotomicrographs (Figure 6) showed not only typical large, dense lipid/DNA structures (> 100 nm) with looped DNA extensions, but also smaller clusters and free DNA. They also observed what appeared to be DNA strands coated with a thin layer of lipid, analogous to some “spaghettilike” structures which had been previously described in freeze-fracture electron microscope images of DNA complexed to DOPE/DC-Chol liposomes.^[62]

The kinetics of liposome/nucleic acid complex formation have been analyzed at two levels. Using ethidium bromide as a fluorescent probe for exposed DNA base pairs, Gershon et al. observed that DNA encapsulation by DOPE/DOTMA liposomes was almost instantaneous when liposome and DNA were combined at concentrations where the positive/negative charge ratio significantly exceeded unity (> 1.2).^[47] However, between a charge ratio of 1.0 to 1.1, more complex behavior was observed, and equilibration times of at least 60 min were required (Figure 1b). The observed oscillatory behavior is certainly indicative of a highly dynamic system, although it is

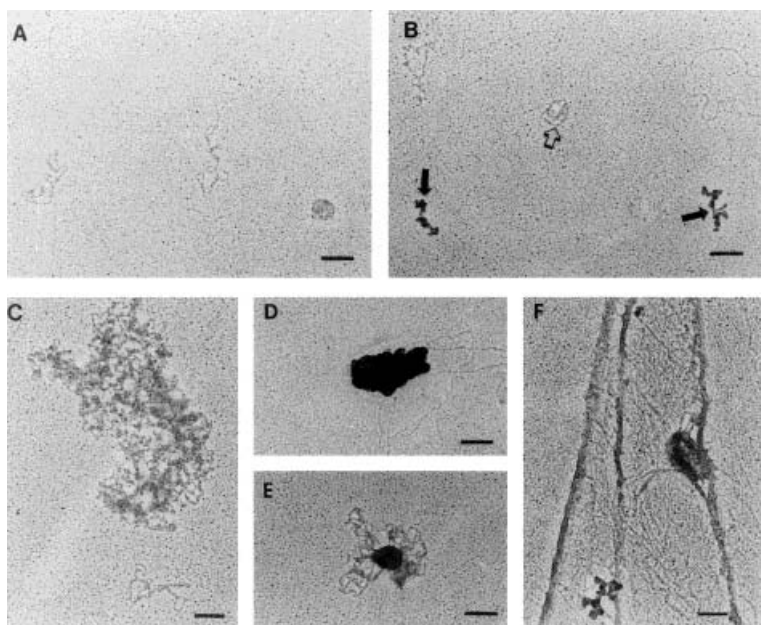


Figure 6. Transmission electron photomicrographs of liposome/DNA complexes. The complexes were prepared at a liposome-to-DNA ratio of 5:1 with DOPE/DMRIE liposomes (1:1 molar ratio). A) DNA without lipid, B)–F) examples of various types of complex. In (B) the open arrow shows uncomplexed plasmid, and the solid arrow plasmid complexed to lipid. The bar corresponds to 100 nm. This figure was reproduced with permission from Zabner et al.^[61]

somewhat difficult to account for. At a ratio of 1.2, equilibration was achieved in 10 min (Figure 1b). A more detailed kinetic analysis using resonance energy transfer (RET) lipid-mixing experiments^[48] revealed that DNA was able to induce aggregation and subsequent fusion of DOTAP and DOPE/DDAB liposomes at rates consistent with equilibration after a few minutes (<5 min, Figure 2b); however, no results were reported when the positive/negative charge ratio is between 1.0 and 1.1, as above.^[52]

It is interesting to note how the results described above do begin to interlock to form a coherent picture of how cationic liposomes and DNA interact, inspite of the fact that these studies were performed by different research groups with a wide range of DNA lengths, lipids, liposome formulations, buffers, etc. Clearly the stylized depiction of Felgner and Ringold^[46] is untenable. Cationic liposome/DNA complexes appear to be highly heterogeneous and encompass every manner of structure—from naked DNA—to ordered multilamellar arrays of encapsulated DNA—which are almost certainly at equilibrium 30–60 min after the initial mixing of the cationic liposome and DNA. Given the fact that cationic liposome mediated nucleic acid delivery frequently appears to be most efficient when the molar ratio of cationic liposome to DNA is such that the positive/negative charge ratio is around or above 1, it is tempting to suggest that the large multilamellar particles containing ordered, encapsulated DNA are the principle structures responsible for nucleic acid delivery. However, since cationic liposome/DNA complexes are also highly dynamic and in equilibrium with smaller structures, this may not necessarily be true.

4.2. Entry of Complexes into Cells

The entry of complexes into cells is the first step of cationic liposome mediated nucleic acid delivery. Formerly, it was thought that membrane fusion between liposome and cell membrane was the primary means of cell entry^[11, 16] on the premise that cationic and anionic liposomes readily fuse.^[51, 63] However, cationic liposome/DNA complexes fuse much less readily with negatively charged membranes, indicating that cell entry by membrane fusion may not apply in this case.^[17] Instead, evidence now suggests that slow endocytosis of intact complexes is the primary method,^[64–66] and it is mediated by proteoglycan interactions.^[67, 68] This process was first suggested by Behr et al.^[22, 69] and has since been beautifully observed by Zabner et al., who used electron microscopy to follow the cell entry (into COS and HeLa cells) of gold-labeled DNA complexed to DOPE/DMRIE liposomes (positive/negative charge ratio = 1.2).^[61] After initial association to the cell surface, complexes enter by endocytosis and remain localized within a vesicle or endosome (Figure 7). With confocal microscopy, the subsequent intracellular fate of the endosome-trapped complex was then monitored. Upwards of

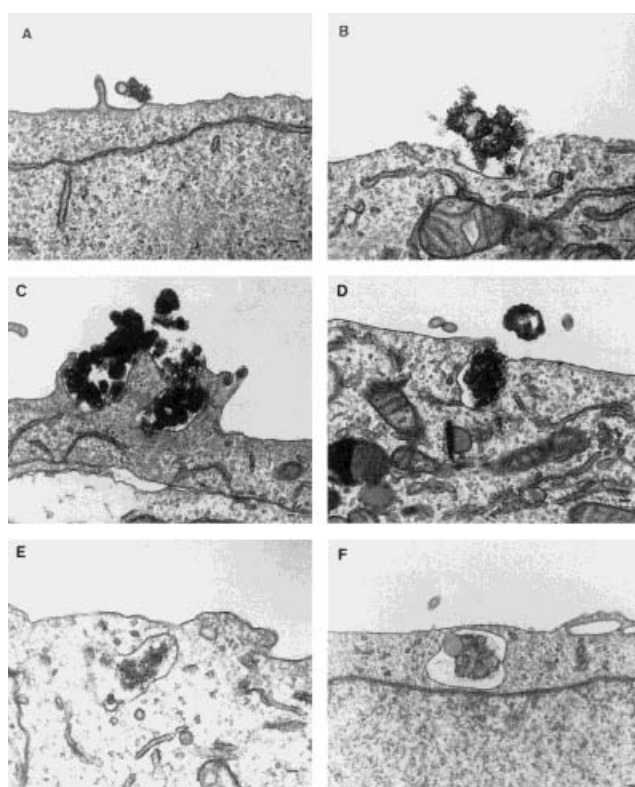


Figure 7. Transmission electron photomicrographs of COS cells transfected with gold-labeled DNA complexed with liposomes. Cells were exposed to complexes of DOPE/DMRIE with gold-labeled DNA, which were prepared with a liposome-to-DNA ratio of 5:1; cells were removed for electron microscopy at the indicated times: A) 5 min, B) 30 min, C) 1 h, D) 6 h, E) 24 h; F) cells transfected with unlabeled DNA. The bar corresponds to 100 nm, gold particles were 10 nm. This figure was reproduced with permission from Zabner et al.^[61]

24 h after internalization, complexes were found to accumulate in the perinuclear region. This was interpreted to be the result of endosome migration toward the cell nucleus followed by endosome fusion, thereby allowing the enclosed complexes to coalesce and form macromolecular lipid/DNA structures. These macromolecular lipid/DNA structures are highly ordered and comprise an array of regularly packed tubules in which DNA is surrounded by bilayers or tubular monolayers of lipid. There was no evidence of lysosome fusion with endosomes, although this has been reported elsewhere.^[66]

Zabner et al. were also able to examine the kinetics and efficiency of cell entry by liposome/DNA complexes by using fluorescence-activated cell sorting (FACS) to follow the uptake into COS cells of fluorescent-labeled DNA complexed with DOPE/DMRIE liposomes.^[61] Only 5% of cells had internalized complexes after 30 min, but the process appeared to be 70% complete after 6 h, which is consistent with other data on cellular uptake.^[12]

Whilst the recent evidence for endocytosis and endosome localization is strong, cell entry may still involve some elements of membrane fusion. For instance, Felgner and co-workers have observed that cationic liposome/DNA complexes containing fluorescent labeled DOPE (**2**) appear to stain the cell membrane.^[16] However, it is unlikely that fusion processes dominate. Very recently, evidence has been advanced to suggest that phagocytosis may also play a role in complex entry alongside endocytosis.^[70]

4.3. Trafficking of Nucleic Acids to the Nucleus

Cell entry of liposome/nucleic acid complexes appears to be a surprisingly efficient if slow process.^[61, 64] However, not all the nucleic acid which enters the cell will be functional. This point has been illustrated by Zabner et al. They followed cationic liposome mediated gene delivery into COS or HeLa cells and observed that gene expression occurred in less than 50% of the cells, even though endocytosis was determined to have an efficiency of at least 80%.^[61] In other cell lines, the divergence between gene expression levels and endocytosis efficiency was much worse.^[61] Unfortunately, the largest proportion of delivered nucleic acid is usually unable to escape from the endosomal compartments into the cell cytoplasm after entry. As a result, cationic liposome mediated delivery actually appears to be a very wasteful and inefficient way to deliver nucleic acids into cells, depriving them of most of the potential therapeutic benefit of the nucleic acids—whether this be from gene expression, antisense oligonucleotide inhibition, and so on.

Zabner et al. have clearly shown how inefficient the escape of nucleic acids from the endosome is by attempting to use electron and confocal microscopy to detect DNA in the cytoplasm of COS cells after cell entry mediated by DOPE/DMRIE liposome.^[61] They were unable to detect any significant quantities, although enough DNA was apparently escaping for significant cytoplasmic gene transcription to be driven by a recombinant vaccinia virus expressing T7 polymerase. Nevertheless, the vast majority of delivered DNA accumulated in perinuclear endosomes in the form of

the macromolecular lipid/DNA structures described in the previous section. Similar observations have also been made by Gao and Huang.^[71]

When nucleic acids do succeed in escaping from endosomes, the most recent evidence indicates that they do so at an early stage after endocytosis has taken place, that is, when the cationic liposome/nucleic acid complexes are in an “early” endosome compartment.^[65, 66] The mechanism of early endosome escape is not well understood, but when DOPE (**2**) forms part of the cationic liposome, escape may be aided by the tendency of **2** to promote significant polymorphic changes in the lipid phase under physiologically relevant conditions.^[72–74] In particular, **2** readily promotes the formation of an inverted hexagonal phase (at room temperature and neutral pH) from the lamellar liquid crystal phase characteristic of most biological membranes.^[72] This hexagonal phase is frequently observed when membranes fuse.^[3] Therefore, **2** could provide the means for endosome disruption by promoting membrane fusion. When **2** is not part of the cationic liposome [e.g., liposomes of DOTAP (**3**) or DOGS (**9**)], local cationic lipid detergent effects may be the cause of endosome escape.^[18] Very recently, Xu and Szoka proposed a model for early endosome breakout in which cationic liposome/DNA complexes destabilize the endosome membrane to allow the DNA to escape.^[75] Electrostatic interaction between cationic liposome and endosome membrane induces the flip-flop of anionic lipids from the monolayer of the endosome membrane that faces the cytoplasm; these lipids laterally diffuse into the complex where they form charge neutral ion pairs with cytofectins. Ionic interaction between DNA and cytofectins is thereby disrupted allowing DNA to diffuse freely into the cytoplasm (Figure 8).

Once in the cytoplasm, nucleic acids may face a further difficulty in entering the nucleus to perform their therapeutic task. This is not always necessary, for instance, if mRNA is delivered then it does not need to enter the nucleus to function. However, where nuclear entry is required, this can be as serious a problem facing the net efficiency of cationic liposome mediated nucleic acid delivery as escape from the endosome. The difficulty of nucleic acid trafficking to the nucleus has been clearly demonstrated by Capecchi. Using a mouse cell line, he showed that nuclear-injected DNA led to protein expression in over 50% of the cells, whilst cytoplasm-injected DNA led to expression in less than 0.01% of the cells.^[76]

Zabner et al. obtained similar results in comparable experiments with a *Xenopus* oocyte system.^[61] The size of the nucleic acids appears to be the most important factor in determining whether they will reach the nucleus or not. Small oligonucleotides (between approximately 20 and 30 base pairs in length) readily accumulate in the nucleus whether delivered by cationic liposomes^[65, 77] or cytoplasmic injection.^[78] However, larger DNA is probably excluded from the nucleus because the pore sizes of the nuclear membrane have a diffusion cutoff of about 40 kDa.^[79] That is not to say that larger DNA may not enter the nucleus at all, otherwise the expression of delivered genes would be impossible. However, the pore-size limitations of the nuclear membrane do require that assistance is given for larger DNA to enter the nucleus.

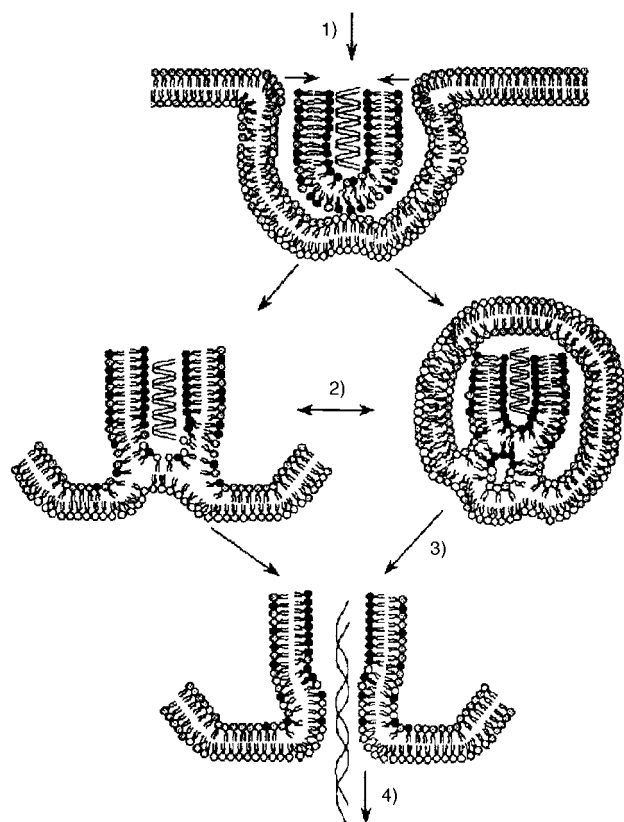


Figure 8. Proposed mechanism for the entry of cationic liposome/DNA complexes into cells and subsequent release of DNA from endosomes. Step 1: electrostatic interaction of cationic liposome/DNA complex with cell membrane followed by endocytosis. Step 2: membrane destabilization in the early endosome results in anionic/zwitterionic lipid flip-flop. Step 3: anionic lipids diffuse into the complex and form a charge neutral ion pair with cytofectins. Step 4: DNA dissociates from the complex and diffuses into the cytoplasm. The head groups of anionic/zwitterionic lipids are shown as open or shaded circles, those of cytofectins are shown as black circles. This figure was reproduced with permission from Xu and Szoka.^[75]

Quite clearly, viruses are very efficient at this process. It remains to be seen whether cationic liposomes can be adapted to give all sizes of nucleic acid oligomers similar levels of assistance to enter the nucleus.

5. General Applicability of Cationic Liposome Formulations

Owing to the relative simplicity of use and reasonable efficiency, cationic liposome mediated gene delivery has been used widely to introduce foreign genes into a variety of primary and cultured cells *in vitro*. Perhaps unsurprisingly, commercially available cationic liposome formulations have tended to be used extensively, in part because they have proven, widespread efficacy. However, other formulations have also been used. Some recent examples include the use of Lipofectin (Table 1) to transfect rat oligodendrocytes^[80] and rabbit endothelial cells;^[81] LipofectAMINE to transfect murine myoblasts,^[82] human hepatoma,^[83] prostatic epithelial,^[84] and ovarian cells;^[85] DOTAP (3) to transfect murine cell lines^[86] and human cervical carcinoma (CaSki) cells;^[87]

and finally DDAB liposomes to transfect CaSki cells^[87] and human breast adenocarcinoma cells.^[88] Liposomes containing DOPE (2) and DC-Chol (14) have also achieved fairly widespread use *in vitro*, for example in the transfection of human ovarian,^[85] epidermoid carcinoma,^[89, 90] epithelial,^[91] and neuronal cells.^[44]

There appear to be few structural principles to define which series of cytofectin and corresponding liposome formulations will be efficacious as *in vitro* vectors for nucleic acid delivery and which not. Often, where structural restrictions have been noted with one series of cationic amphiphiles, other series appear to flout those restrictions. For instance, quaternized derivatives of cholesterol-derived cationic amphiphiles are much less efficient at *in vitro* delivery than their tertiary amine counterparts.^[43] However, DOTMA (1) and its analogues are all quaternary amines. As a result, structure–activity comparisons, within a given series of cytofectins and liposomes, have often been the only way to optimize nucleic acid delivery rationally. For example, both Felgner *et al.*^[18] and Balasubramaniam *et al.*^[20] carried out extensive, carefully controlled studies to assess the relative merits of liposomes containing DOTMA analogues. In a similar way, Lee *et al.*,^[32] Cooper *et al.*,^[33] and Walker *et al.*^[31] recently optimized the transfection abilities of a series of polyamine cholesterol derived cytofectins. Other more limited comparisons have been made between homologues of other cytofectins.^[23, 43]

In searching for a general link between cytofectin structure and efficiency of gene delivery, Akao *et al.* have suggested that the primary requirement for successful transfection is that the phase-transition temperature T_c of the cationic liposome formulation should be less than 37 °C.^[23] However, a recent analysis of liposomes containing DOTMA analogues does not support this suggestion.^[20] Instead, cell toxicity may well be the most important criterion. In this respect, DOPE/DC-Chol liposomes are very useful in that they have low toxicity.^[92] Nevertheless, this is probably not the only factor. Recently, it has been suggested that gene delivery efficiency may be determined in part by the zeta potential of the cationic liposome, which is itself a partial function of cytofectin structure.^[93] By comparing the efficiency of gene delivery for a series of cationic liposomes—formulated with cholesterol-derived cytofectins such as DC-Chol (14), 15, and 16—there appeared to be a direct proportional relationship between delivery efficiency and the zeta potential, as measured by laser Doppler spectroscopy.

The very simplicity of cationic liposome mediated nucleic acid delivery *in vitro* has resulted in a rapid increase in the application of cationic liposomes to gene delivery *in vivo* as well.^[3, 94] The same liposomes whose *in vitro* efficacy has been described above have also proved to have some *in vivo* efficacy as well. However, *in vitro* efficacy frequently appears to be a poor guide to the absolute efficacy of a given cationic liposome *in vivo*.^[32, 33] A number of recently reported examples of uses *in vivo* are presented in the following.

Liposomes containing DOPE (2) and DDAB (12) have been found to transfect murine lung, spleen, and kidney cells with cytokine genes after intraperitoneal injection of liposome/DNA complexes.^[95] In addition, cholesterol/DDAB liposomes produced high-level systemic transfection with a

chloramphenicol acetyltransferase (CAT) marker gene in mice following intravenous injection.^[96] Lipofectin has been shown to transfect porcine arterial wall cells in vivo with foreign histocompatibility genes.^[97] Better results were obtained with DOPE/GAP-DLRIE cationic liposomes.^[98] Murine tumors have also been transfected in vivo with a tumor necrosis factor α gene following direct subcutaneous injection of the tumor with Lipofectin/DNA complexes.^[99] Correspondingly, DOPE/DMRIE liposomes have been used to transfect cerebral murine tumors in vivo with the thymidine kinase gene by means of a continuous injection method.^[100] A remarkable recent discovery was that liposomes containing DOGS (**9**) were able to transfect the embryos of pregnant mice with a CAT marker gene following intravenous injection of liposome/DNA complexes. The transgene was expressed in both the fetuses and progeny.^[101] There are as yet no further reports to corroborate this finding, and so this fascinating discovery should be viewed with some care until that has been done.

Some of the most successful in vivo applications of cationic liposome mediated gene delivery can be found in recent work concerned with the transfection of airway passages. Following a demonstration that DOPE/DOTMA liposomes could deliver a CAT marker gene to murine lung by aerosol administration of the complex,^[102] Alton et al.^[103] and Hyde et al.^[104] reported that DOPE/DC-Chol and Lipofectin liposomes could be used in a similar way to deliver the cystic fibrosis transmembrane conductance regulator (CFTR) gene to the lungs of cystic fibrosis transgenic mice; this resulted in correction of lung defects associated with cystic fibrosis. This demonstration of physical benefit has led to the application of DOPE/DC-Chol liposomes in clinical trials directed at the human gene therapy of cystic fibrosis.^[105] Since then Cooper et al.^[33] and Lee et al.^[32] have reported that DOPE/CTAP and DOPE/lipid 67 cationic liposomes respectively are at least 100-fold more efficient than DOPE/DC-Chol liposomes at delivering a CAT marker gene to murine lung. As a result, lipid 67 (**18**) is now the subject of new cystic fibrosis gene therapy trials. In the future, many more cationic liposome formulations are likely to be tested for their ability to act as gene delivery agents for therapeutic genes in human gene therapy trials.

6. Summary and Outlook

The use of cationic liposomes for the transfer of nucleic acids into primary or cultured cells in vitro is now a well-established technique. There is also a rapidly increasing use of cationic liposomes for the gene delivery in vivo of both marker and potentially therapeutic genes. What are the prospects for cationic liposome mediated gene therapy? I believe the prospects are good. Cationic liposomes have already been involved in human gene therapy clinical trials.^[92, 105] Whilst the results indicated that the cationic liposomes used in these trials were not efficient enough to bring about significant clinical benefit, there is every reason to believe that two of the most recently reported cationic

liposome formulations, involving lipid 67 (**18**)^[32] and CTAP (**19**)^[33] are efficient enough for them to be clinically useful in gene therapy approaches to lung disorders.

However, ever improved cationic liposome formulations will be required with ever more improved cytofectins if cationic liposomes are to see widespread use in the human gene therapy of the future. Most notably, cationic liposome/nucleic acid complexes are not very cell-type selective, which may not be a problem for the gene therapy of some lung disorders, but will almost certainly be one for other diseases. Even if the complexes were selective, in general they still bind nucleic acids with relatively low efficiency, so that the amount of liposome required to deliver therapeutically useful levels is too large to be clinically useful. Moreover, the entry of cationic liposome/nucleic acid complexes into cells is really much too slow. Finally, once internalized, too much of the nucleic acids remain trapped in endosome compartments unable either to function in the cytoplasm or traffick to the nucleus to perform a therapeutic function. It is conceivable and possible that some or all of these problems may be solved by the design of new cytofectins. However, to overcome this substantive list of problems, cationic liposomes will probably have to be equipped not only with lipid components, but also with batteries of appropriate ligands designed to deal with cell recognition, accelerating cell entry, endosomolysis, nuclear targeting, etc. In effect, chemists will need to construct artificial viruses.

Some progress has already been made to suggest that cationic liposomes could be developed and improved in the way just described. For instance, a Transfectam/DNA complex has been used to target hepatoma cells using a triantennary galactose ligand attached to the liposome.^[106] Recently, mannosylated poly(L-lysine) has been found to promote receptor-mediated gene transfer into macrophages expressing a cell-surface mannose receptor.^[107, 108] Other glycosylated poly(L-lysines) also promote receptor-mediated gene transfer into lung epithelial cells^[109] and monocyte-derived macrophages.^[110] Therefore, the covalent attachment of a variety of monosaccharides, and even oligosaccharides, to cationic liposomes could represent a fruitful area for the development of cell-targeting cationic liposomes. Proteins are also credible cell-targeting ligands, including lectins^[111] and/or antibodies.^[112] The latter approach has recently been demonstrated with an antithrombomodulin antibody coupled to poly(L-lysine), which was used in combination with DOPE/DC-Chol liposomes to bring about successful targeted transfection of mouse lung endothelial cells.^[113] Clean and selective ways of coupling proteins to cationic liposomes will almost certainly have to be developed in the future. The potential use of peptide ligands has been recently demonstrated by Hart et al., who constructed a peptide with an N-terminal integrin-binding amino acid sequence motif [arginine-glycine-aspartic acid (RGD)] and a C-terminal hexadeca(L-lysine) which was able to promote gene delivery by an integrin receptor mediated uptake mechanism.^[114] When combined with cationic liposome/DNA complexes, a variant of this peptide enhanced cationic liposome mediated DNA delivery.^[127] Barry et al. have also described the selection of cell-binding peptides, derived from random peptide-presenting phage

libraries, which could easily be attached to cationic liposomes in the future.^[115]

One useful by-product of this receptor-mediated approach to cell targeting is that the entry of cationic liposome/nucleic acid complexes into cells is generally accelerated. However, the other problems of low nucleic acid binding efficiency, inadequate endosome escape, and inefficient trafficking of nucleic acids to the nucleus still remain. The first problem should easily be solved through the inclusion of polycations with cationic liposomes. For example, polycationic histone proteins have recently been used to enhance lipofectin-mediated gene delivery.^[116] In other cases, polycations such as lipopoly(L-lysine) (LPLL),^[117] and poly(L-lysine) have proved efficacious.^[118] Polyamine dendrimers may also prove useful in this regard.^[118, 119] The remaining problems can almost certainly be overcome, and potential solutions appear to be emerging. For example, Lyons et al. reported some time ago the existence of a pentapeptide nuclear localization signal in adenovirus protein E1a,^[120] whilst Gottschalk et al. recently reported an amphipathic peptide capable of disrupting endosomal membranes.^[121] Either or both peptides could prove to be useful tools to enhance cationic liposome mediated nucleic acid transfer inside cells.

In addition to all the problems and potential solutions outlined above, there will undoubtedly be additional problems to face depending upon the desired site of action of cationic liposome/nucleic acid complexes in vivo. For instance, administration of complexes to the lung by aerosol, mentioned in connection with cystic fibrosis gene therapy above, involves a completely different set of problems to systemic administration. In the latter case, the need to prolong systemic circulation time and avoid interactions with either plasma components^[122] or the Complement system^[123] may require that cationic liposomes adopt “stealth” technology,^[124, 125] where moieties such as poly(ethylene glycol)^[126] or ganglioside G_{M1} oligosaccharide^[112] are covalently linked to cationic liposomes.

There are clearly many different possibilities to improve cationic liposome mediated nucleic acid delivery, and a good deal of research into the use of general modifications to confer improvement will be necessary. However, this potential variety lends hope that cationic liposomes will fulfill their promise as key vector technology for human gene therapy, irrespective of disease type or site of action. Therefore, the design, synthesis, and testing of ever more efficient cytofectins and cationic liposomes offers superb opportunities both now and in the future for the chemists interested in working at the interface between chemistry and medicine.

Appendix: List of Abbreviations

BGTC	bis(guanidinium)-TREN-cholesterol (21)
CAT	chloramphenicol acetyl transferase
CE β A	cholesterol ester of β -alanine (39)
CTAP	N ¹⁵ -cholesteryloxycarbonyl-3,7,12-triazapentadecane-1,15-diamine (19)

DC-Chol	3 β -[N-(N',N'-dimethylaminoethyl)carbamoyl]cholesterol (14)
DDAB	dimethyldioctadecylammonium bromide (12)
di C 14 amidine	N-tert-butyl-N'-tetradecyl-3-tetradecylaminopropionamidine (11)
DMRIE	1,2-dimyristyloxypentyl-3-dimethylhydroxyethylammonium bromide (4)
DOGS	dioctadecylamidoglycylspermine · 4 trifluoroacetic acid (9)
DOPE	dioleoyl-L- α -phosphatidylethanolamine (2)
DORI	1,2-dioleoyloxypentyl-3-dimethylhydroxyethylammonium bromide (7)
DORIE	1,2-dioleoyloxypentyl-3-dimethylhydroxyethylammonium bromide (6)
DOSPA	2,3-dioleoyloxy-N-[2-(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate (5)
DOTAP	1,2-dioleoyloxy-3-(trimethylammonio)propane (3)
DOTIM	1-[2-(oleoyloxy)ethyl]-2-oleyl-3-(2-hydroxyethyl)imidazolinium chloride (26)
DOTMA	N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (1)
DPPES	dipalmitoylphosphatidylethanolamidospermine · 4 trifluoroacetic acid (22)
GAP-DLRIE	($\pm$)-N-(3-aminopropyl)-N,N-dimethyl-2,3-bis(dodecyloxy)-1-propanammonium bromide (8)
L-PE	lysinyll phosphatidylethanolamine (23a)
Lys-Pam ₂ -GroPEtn	lysinyll-dipalmitoyl-(L)- α -phosphatidylethanolamine · 2 trifluoroacetic acid (23)
RET	resonance energy transfer
14 Dea 2	tetradecanoyl-N-(trimethylammonioacetyl)diethanolamine chloride (10)
2C ₁₂ -L-Glu-ph-C ₂ -N ⁺	O,O'-didodecyl-N-[p-(2-trimethylammonioethoxy)benzoyl]-(L)-glutamate (24)
2C ₁₄ -L-Glu-C ₂ -N ⁺	O,O'-ditetradecyl-N-(2-trimethylammonioethanoyl)-(L)-glutamate (25)

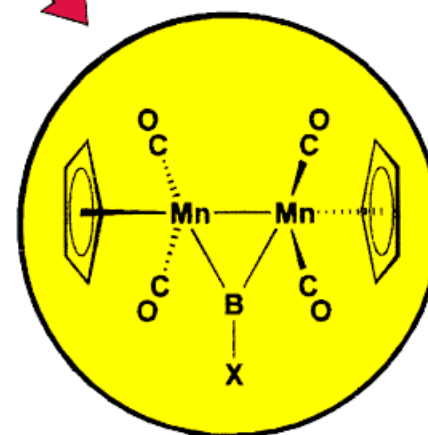
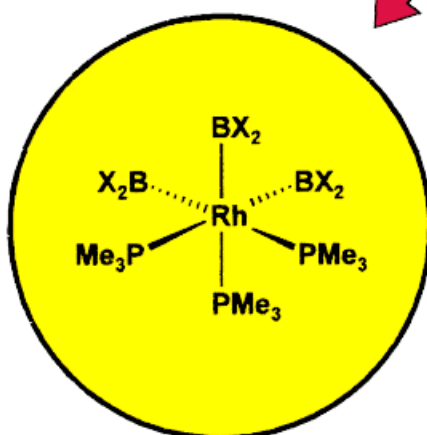
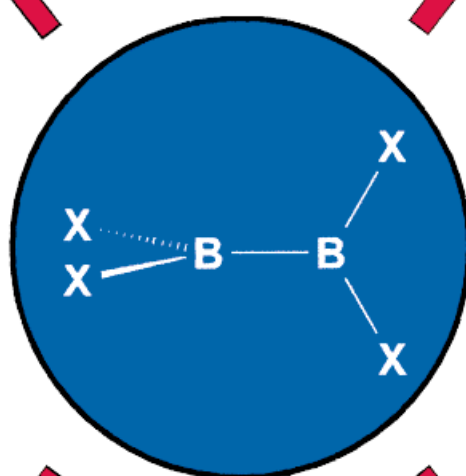
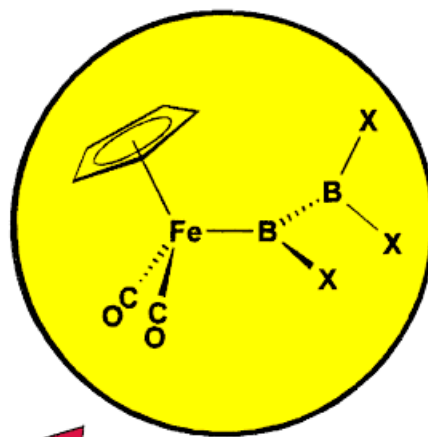
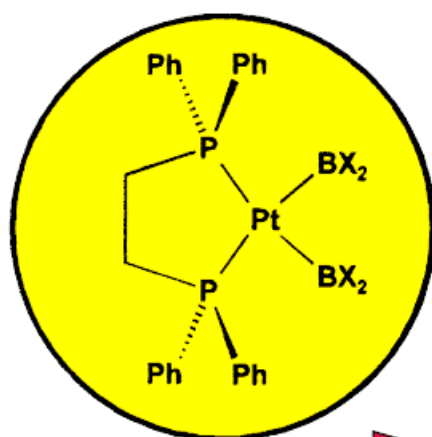
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Diborane(4) derivatives as starting materials for various transition metal complexes of boron: bis- and trisboryl complexes (left, top and bottom), complexes with diboran(4)-1-yl and bridging borylene ligands (right, top and bottom).

Transition Metal Complexes of Boron

Holger Braunschweig*

Borane, boryl, and borylene complexes exhibit two-center, two-electron bonds between the metal and the boron atoms. This differentiates them from other transition metal compounds of boron such as borides or metallaboranes. Although transition metal complexes of boron were first reported between 1963 and 1970, their existence was only proved about thirty years later. This demonstrates the degree of difficulty associated with the synthesis and characterization of these products. This area of research has developed

rapidly in the past six years, however, which can be attributed to the interesting application potential of the boryl complexes. Particularly noteworthy are the functionalization of organic compounds by C–H activation and the transition metal catalyzed hydroboration. This review describes synthetic methods which have proven themselves in the preparation of boryl and borylene complexes, and what influence the choice of substituents on boron can have. It is now possible to conduct a more detailed discussion

on the nature of the metal–boron bond based on numerous confirmed spectroscopic findings. Preliminary theoretical studies in this field have contributed considerably to the understanding of bonding in boryl complexes as well as to the clarification of the mechanism for the transition metal catalyzed hydroboration.

Keywords: B ligands • boron • hydroboration • transition metal complexes

1. Introduction

Boron, the only nonmetal in Group 13 of the periodic table, forms a number of different compounds with transition metals which display remarkable structural variety. If we restrict ourselves to those compounds in which boron is directly bonded to one or more metal centers, up until 1990 there was confirmed knowledge on borides, metallaboranes, and metal-laheteroboranes as well as transition metal complexes with π -bonded ligands containing boron.

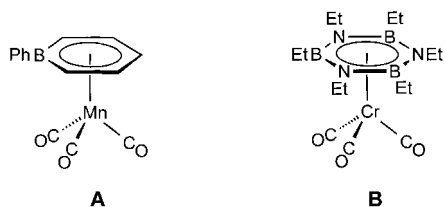
The group that has been known the longest is the class of the transition metal borides, for which over 130 structural types and several hundred binary and ternary compounds have been described to date.^[1–3] The compositions of the borides range from boron-deficient phases such as $\text{Y}_2\text{Co}_{14}\text{B}$ ^[4] with isolated boron atoms to boron-rich compounds such as YB_{66} ,^[5] which form three-dimensional networks of linked boron clusters. The transition metal borides often demonstrate more interesting physical properties (electrical conductivity or magnetism) than the pure elements. As expected, the bonding in borides cannot be described by a single type of bonding. Instead, the total bonding situation made up of ionic,

covalent, and metallic bonding contributions has to be considered; the individual components are dependent on the respective metal and the composition of the boride.

In addition to the transition metal borides, metallaboranes^[6–8] and metallacarboranes^[9–11] form a further class of boron–transition metal compounds, of which several hundred have been characterized since the middle of the 1960s. As in the case of boranes, these metallaboranes and metallacarboranes are electron-deficient. The central atomic frameworks are stabilized by three-center, two-electron ($3c-2e$) bonds, and, in most cases, the compounds can also be described as *closo*-, *nido*-, *arachno*-, *hypho*-, *commo*-, or *conjuncto*-boranes in accordance with Wade's rules.^[12, 13]

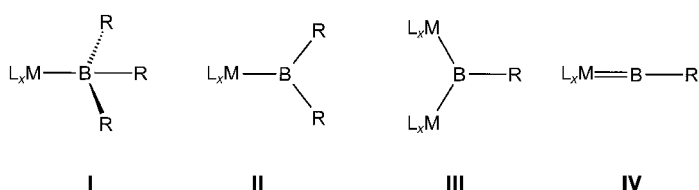
Transition metal complexes with π -bonded ligands containing boron are less numerous than the representatives of the above-mentioned classes of compounds, but have also been known for several decades. These are mainly heterocycles, which contain nitrogen or sulfur in addition to boron and carbon as ring atoms.^[14] Among these are borole,^[15, 16] diborolene,^[17] borabenzene,^[18, 19] and borazine.^[20, 21] The structures of these compounds show many similarities to those of the corresponding complexes with η^5 - or η^6 -coordinated carbocyclic ligands; the observed differences are due to the nature of the heteroatoms involved. For example, in the borabenzene complex **A** the π -bonded ligand is displaced to one side such that the ring carbon atom farthest from the boron atom (C4) has the shortest Mn–C distance.^[22] In

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contrast to the isoelectronic benzene complex, the π -bonded six-membered ring in the η^6 -borazine complex **B** is slightly puckered, which is attributed to the different covalent radii of boron and nitrogen.^[21]

In the 1990s the work of several groups led to the establishment of a new class of boron–transition metal compounds: transition metal complexes in which boron is coordinated to the metal through 2c–2e bonds. Such compounds can be systematically classified as borane, boryl, and bridging and terminal borylene complexes. Borane–transition metal complexes **I** can be described as Lewis acid–base



adducts between basic metal centers and acidic boranes BR_3 ; in these compounds boron is four-coordinate. In contrast, boryl transition metal complexes **II** contain a terminal σ -bonded boryl group BR_2 , and the coordination number of the boron atom is reduced to three. There are two possible coordination modes for the borylene ligands BR : either bridging between two metal centers (**III**) with three-coordinate boron, or terminal with formation of a metal–boron double bond (**IV**) and boron with the coordination number two.

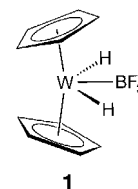
Transition metal complexes with 2c–2e bonds between the metal and a main group element of Groups 14 to 17 have been known for a long time. Silicon, for example, forms numerous silyl^[23, 24] and silylene complexes;^[25, 26] owing to the diagonal relationship in the periodic table, silicon shows some parallels

to boron in its chemical behavior. Until 1990, however, there was no definite knowledge of corresponding boron compounds, although this area of research had been extensively studied between 1963 and 1970. Although numerous compounds—mainly boryl complexes of Mo, W, Mn, Re, Fe, and Co—were described in the course of these early investigations, none could be structurally characterized.^[27] Some of the findings from this period have now been disproved by more recent studies.

Today, about thirty years later, these complexes are again being focused on. This is primarily due to the importance of boryl complexes in the functionalization of organic compounds. They appear, for example, as intermediates in the transition metal catalyzed hydroboration, whose application and mechanism has recently been the subject of numerous studies. In addition, use of a special substituent bonded to boron—namely, the phenylene-1,2-dioxy or catechol group—has permitted the synthesis of numerous stable and crystalline boryl complexes of various transition metals within a short time.

2. Borane Complexes

The chemistry of boron-containing compounds is characterized by the fact that boron has only three valence electrons, but four valence orbitals available for bonding. This results in a tendency for many boranes to form multicenter bonds and Lewis acid–base adducts. Thus, the reaction of a suitable borane with a basic transition metal complex could lead to the formation of a corresponding adduct with a metal–boron bond. Reactions of bis(cyclopentadienyl) hydride complexes such as $[(C_5H_5)_2MoH_2]$, $[(C_5H_5)_2WH_2]$, and $[(C_5H_5)_2ReH]$, which all have a basic metal center that can be protonated, with various boranes was studied as early as the 1960s.^[28, 29] Based on IR spectra, the presence of the borane–tungsten complex **1** was postulated,^[29] which then found its way into textbooks in this form.

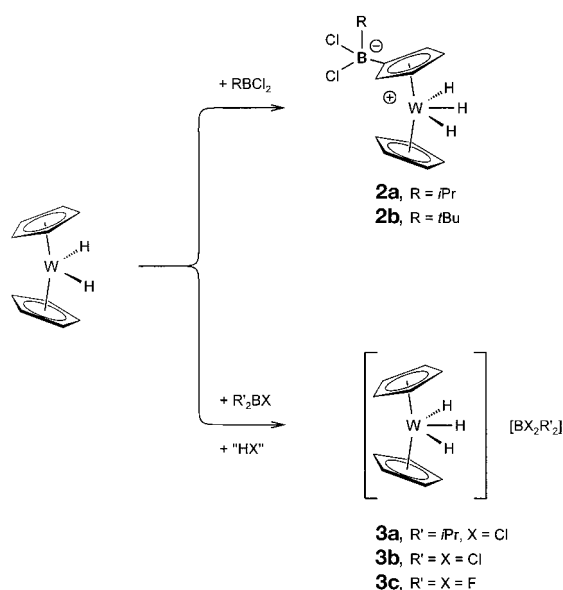


Recent studies have shown, however, that no compounds containing tungsten–boron bonds are formed in the reaction of $[(C_5H_5)_2WH_2]$ with boranes. Instead, alkylchloroboranes such as $tBuBCl_2$ or $iPrBCl_2$ react with $[(C_5H_5)_2WH_2]$ under



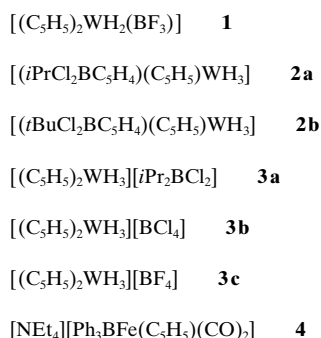
Holger Braunschweig was born in Aachen (Germany) in 1961. After studying chemistry at the Technische Hochschule Aachen from 1983 to 1988, he completed his Ph.D. in 1990 with Professor Peter Paetzold on reactions of iminoboranes with tantalum–carbene complexes. During a one-year research stay with Professor Mike F. Lappert, FRS, at the University of Sussex in Brighton, he studied the synthesis and characterization of heteroleptic germylenes and stannylenes. Since 1992 he has worked as a Scientific Assistant at the Technische Hochschule Aachen. His research interests are in the field of organometallic chemistry, and the main emphasis is on the synthesis and study of the reactivity of transition metal complexes of boron. In addition, he has reported on the use of (borylorganyl)phosphanes as complex ligands and on boron-bridged ferrocenophanes.

substitution of a hydrogen atom bonded to cyclopentadienyl by the neutral borane and addition of a proton to the tungsten center to give the zwitterionic complexes **2a, b** (Scheme 1).^[30]



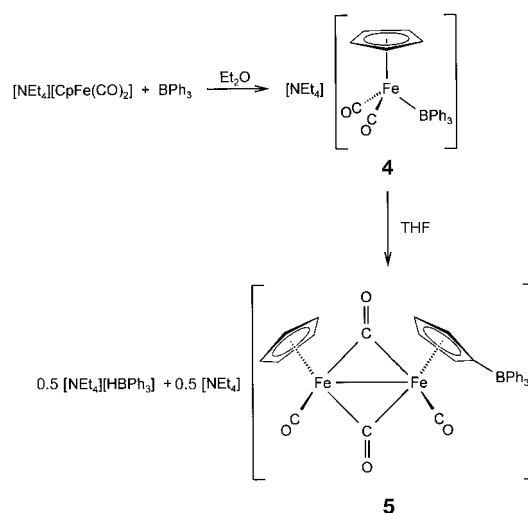
Scheme 1. Reaction of $[(C_5H_5)_2WH_2]$ with boranes.

In contrast, reactions of $[(C_5H_5)_2WH_2]$ with trihaloboranes, such as BCl_3 or BF_3 , or iPr_2BCl lead to the saltlike compounds **3a–c**.^[31]



In the case of the second reaction, one equivalent of HCl or HF is required per formal conversion for the synthesis of the products. The only possible halide sources are the boranes. Reactions in deuterated solvents^[31] and with $[(C_5Me_5)_2WH_2]$ ^[32] show that the required protons are provided by the WH_2 unit. Complexes **2** and **3** were unequivocally identified by spectroscopy in solution and by X-ray structure analysis in the solid state. The original description of the products as borane–tungsten complexes was thus disproved.

In addition to the uncharged basic transition metal compounds, corresponding anionic complexes should also, in principle, be capable of forming adducts with boranes. One example is **4**^[33] (Scheme 2), which is isolated as an amorphous solid when synthesized in diethyl ether. However, when dissolved in tetrahydrofuran, **4** spontaneously reacts, with migration of the BPh_3 group to the cyclopentadienyl ligand, to form $[NEt_4][HBPh_3]$ and **5**, whose structure was subsequently characterized by X-ray crystallography.^[34] The composition



Scheme 2. Synthesis of **4** and its further reaction to **5**.

of **4** in solution was determined from the high-field ^{11}B NMR signal at $\delta = -28.8$, which is typical of compounds with four-coordinate boron, and from the positions of the CO bands in the IR spectrum, which correspond to those of the analogous, structurally characterized alane complex.

Since 1963 several other borane–transition metal complexes such as $Na[H_3BRe(CO)_4]$, $Na[H_3BMn(CO)_3PPh_3]$, $Na[H_3BCo(CO)_4]$,^[35] $[X_3BRh(PPh_3)_2(CO)X]$ ($X = Cl, Br$),^[36] and $[(Me_2PC_2Me_2BMe_2)_2Rh(CO)Cl]$ ^[37] have been reported. However, because of incomplete spectroscopic studies and the absence of structural characterization the presence of metal–boron bonds in these products cannot be regarded as being certain.

3. Boryl Complexes

3.1. Phenylene-1,2-dioxyboryl Complexes

The use of the phenylene-1,2-dioxy or catechol group (Cat = 1,2- $O_2C_6H_4$) as a substituent on boron has allowed pivotal advances in the study of boryl–transition metal complexes. Of the approximately 30 fully characterized compounds of this type, 20 are phenylene-1,2-dioxyboryl complexes of metals of Groups 5–10 (Table 1).^[38] As far as the early transition metals are concerned, only metallocene hydride derivatives of niobium, tantalum, and tungsten—for example, **6a**,^[39] **7a, b**,^[40] **8**,^[39, 41] and **9**^[41, 42]—are known. In the case of the tantalum compound **7**, the *endo* isomer **7a** and the *exo* isomer **7b** are initially formed. The latter is kinetically favored and dominates slightly, but converts on warming into the thermodynamically more stable *endo* form. Although this

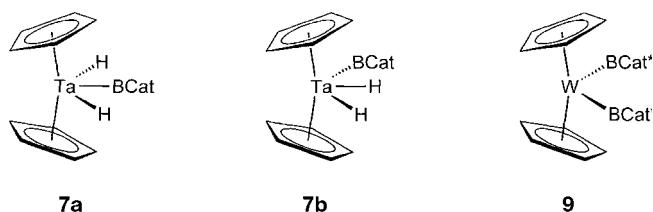
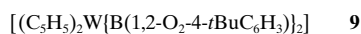
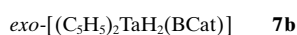
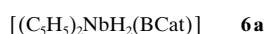


Table 1. Syntheses, M–B bond lengths, and $\delta(^{11}\text{B})$ values of boryl complexes.

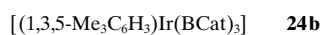
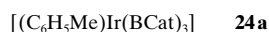
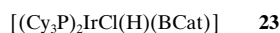
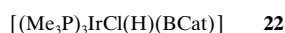
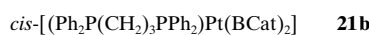
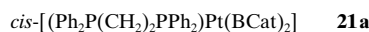
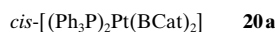
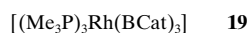
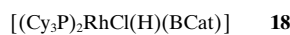
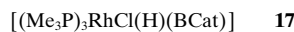
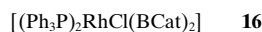
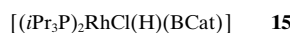
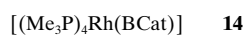
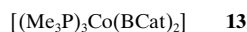
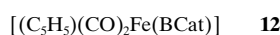
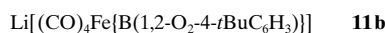
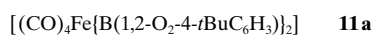
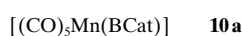
Compound	Synthesis ^[a]	<i>d</i> (M–B) [pm]	$\delta(^{11}\text{B})$	Ref.
$[(\text{C}_5\text{H}_5)_2\text{NbH}_2(\text{BCat})]$ 6a	B	229.2(5)	59.0	[39]
<i>endo</i> - $[(\text{C}_5\text{H}_5)_2\text{TaH}_2(\text{BCat})]$ 7a	A	226.3(6)	70.0	[40]
<i>exo</i> - $[(\text{C}_5\text{H}_5)_2\text{TaH}_2(\text{BCat})]$ 7b	A	229.6(11)	64.7	[40]
$[(\text{C}_5\text{H}_5)_2\text{WH}(\text{BCat})]$ 8	A	219.0(7)	57.2	[39, 41]
$[(\text{C}_5\text{H}_5)_2\text{W}\{\text{B}(1,2\text{-O}_2\text{-4-}t\text{BuC}_6\text{H}_3)\}_2]$ 9	C	219(1), 223(1)	59.3	[41, 42]
$[(\text{CO})_3\text{Mn}(\text{BCat})]$ 10a	A	210.8(6)	49.0	[44]
$[(\text{CO})_3\text{Re}(\text{BCat})]$ 10b	A	— ^[b]	44.0	[44]
$[(\text{CO})_4\text{Fe}\{\text{B}(1,2\text{-O}_2\text{-4-}t\text{BuC}_6\text{H}_3)\}_2]$ 11a	A, C	202.8(7)	45.0	[45]
$[(\text{C}_5\text{H}_5)(\text{CO})_2\text{Fe}(\text{BCat})]$ 12	A	195.9(6)	51.8	[46]
$[(\text{Me}_3\text{P})_3\text{Co}(\text{BCat})_2]$ 13	C	194.5(11), 197.0(11)	— ^[c]	[47]
$[(\text{Me}_3\text{P})_4\text{Rh}(\text{BCat})]$ 14	C	204.7(2)	49.0	[48]
$[(i\text{Pr}_3\text{P})_2\text{RhCl}(\text{H})(\text{BCat})]$ 15	B	196.1(1)	37.7	[49]
$[(\text{Ph}_3\text{P})_2\text{RhCl}(\text{BCat})_2]$ 16	B	195.6(8), 200.8(7)	35.9	[50]
$[(\text{Me}_3\text{P})_3\text{RhCl}(\text{H})(\text{BCat})]$ 17	B	196.7(9)	42.5	[51]
$[(\text{Cy}_3\text{P})_2\text{RhCl}(\text{H})(\text{BCat})]$ 18	B	196.5(5)	37.0	[51]
$[(\text{Me}_3\text{P})_3\text{Rh}(\text{BCat})_3]$ 19	C	205.3(4), 205.5(4), 206.1(4)	46.8	[48]
<i>cis</i> - $[(\text{Ph}_3\text{P})_2\text{Pt}(\text{BCat})_2]$ 20a	C	204.9(6)	47.0	[52, 53]
<i>cis</i> - $[(\text{Ph}_3\text{P})_2\text{Pt}(\text{BPin})_2]$ 20b	C	207.6(6), 207.8(7)	46.3	[53, 59, 60]
<i>cis</i> - $[(\text{Ph}_2\text{P}(\text{CH}_2)_2\text{PPh}_2)\text{Pt}(\text{BCat})_2]$ 21a	C	204.8(8), 205.8(8)	48.9	[53]
$[(\text{Me}_3\text{P})_3\text{IrCl}(\text{H})(\text{BCat})]$ 22	B	202.3(10)	32.8	[54]
$[(\text{Cy}_3\text{P})_2\text{IrCl}(\text{H})(\text{BCat})]$ 23	B	200.0(7)	— ^[d]	[51]
$[(\text{C}_6\text{H}_5\text{Me})\text{Ir}(\text{BCat})_3]$ 24a	B	201.8(5), 202.4(5), 203.6(4)	37.7	[55]
$[(1,3,5\text{-C}_6\text{H}_3\text{Me}_3)\text{Ir}(\text{BCat})_3]$ 24b	B	201.6(3)	37.8	[55]
$[\text{HB}(1,2\text{-N}_2\text{-3,5-Me}_2\text{C}_3\text{H}_3)(\text{CO})_2\text{W}\{\text{BEt}(\text{CH}_2\text{-4-MeC}_6\text{H}_4)\}]$ 25	D	207(1)	78	[57]
$[(\text{C}_5\text{H}_5)(\text{CO})_2\text{Fe}(\text{BPh}_2)]$ 26	A	203.4(3)	121.0	[46]
<i>fac</i> - $[(\text{Me}_3\text{P})_3\text{IrH}_2(\text{BC}_8\text{H}_{14})]$ 27	A	209.3(7)	106.2	[58]
$[(\text{Me}_2\text{PCH}_2\text{CH}_2\text{PMe}_2\text{Pd}(\text{SnMe}_3)\{\text{B}(\text{MeNCH}_2\text{CH}_2\text{NMe})\})]$ 28	D	207.7(6)	46.9	[61]
$[(\text{C}_5\text{H}_5)(\text{CO})_2\text{Fe}\{\text{B}(\text{NMe}_2)_2\text{BCl}(\text{NMe}_2)\}]$ 29a	A	209.0(3)	69.5	[62]
$[(\text{C}_5\text{H}_5)(\text{CO})_3\text{W}\{\text{B}(\text{NMe}_2)_2\text{BCl}(\text{NMe}_2)\}]$ 29b	A	237.0(8)	62.7	[62]
$[(\text{C}_5\text{Me}_5)(\text{CO})_2\text{Fe}\{\text{Cl}_2\text{B}_3\text{N}_3\text{H}_3\}]$ 30a	A	— ^[b]	59.0	[63]
$[(\text{C}_5\text{H}_4\text{Me})(\text{CO})_2\text{Fe}\{\text{Cl}_2\text{B}_3\text{N}_3\text{H}_3\}]$ 30b	A	204.5(1)	53.1	[63]
$[(\text{C}_5\text{H}_5)(\text{CO})_2\text{Fe}\{\text{B}_3\text{N}_3\text{H}_3\}]$ 30c	A	— ^[b]	49.7	[63]
$[(\text{CO})_4\text{Co}\{\text{BH}_2(\text{OC}_4\text{H}_8)\}]$ 31	D	— ^[b]	7.9	[64]
$[(\eta^1\text{-Ph}_2\text{PCH}_2\text{PPh}_2)(\text{CO})_2\text{Co}(\mu\text{-Ph}_2\text{PCH}_2\text{PPh}_2)(\text{BH}_2)]$ 32	D	222.7(6)	– 25.9	[65]

[a] A = salt elimination, B = oxidative addition of B–H, C = oxidative addition of B–B, D = other method. [b] No details of the structure in the crystal are available. [c] Paramagnetic. [d] No details for $\delta(^{11}\text{B})$.

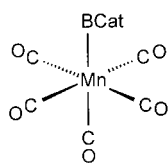
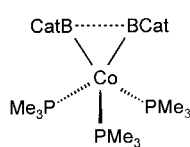
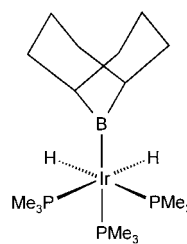
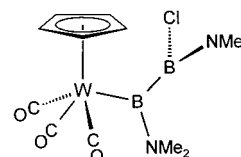
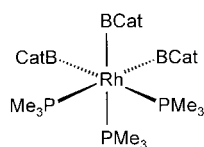
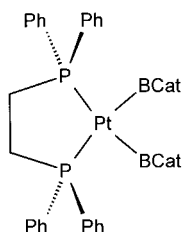
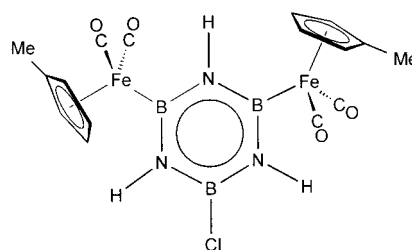
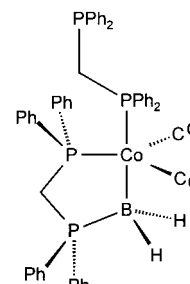
type of regioisomerism has been long known for corresponding metallocene derivatives of niobium and tantalum,^[43] this was the first time that the isomers could be separated and structurally characterized in the crystal.



The elements of Groups 7 and 8 form phenylene-1,2-dioxyboryl complexes both with and without carbonyl ligands. The first group is made up of the manganese compound **10a**,^[44] its rhenium analogue **10b**, whose crystal structure is not known, however,^[44] and the iron complexes **11a**^[45] and **12**.^[46] Transition metals of Groups 9 and 10 form phosphane



complexes such as the paramagnetic cobalt compound **13**,^[47] whose crystal structure shows a short B–B distance; the rhodium complexes **14**,^[48] **15**,^[49] **16**,^[50] **17**,^[51] **18** (Cy = cyclo-

**10a****13****27****29b****19****21a****30b****32**

hexyl),^[51] and **19**,^[48] and the platinum compounds **20a**,^[52, 53] and **21a, b**.^[53] Compounds **15**, **16**, **18**, and **19** were the first electron-deficient boryl complexes with 16 valence electrons to be characterized. In the case of iridium, the two arene complexes **24a, b**^[55] are known in addition to the phosphane complexes **22**^[54] and **23**.^[51]

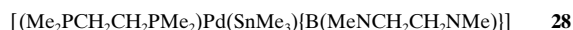
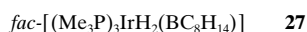
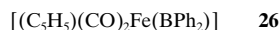
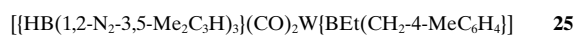
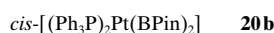
The catecholboryl complexes mentioned are crystalline and sensitive to both air and moisture; their thermal stability can differ widely and depends on the nature of the metal fragment. The tungsten complex **8**, for example, is stable in boiling toluene for days, whereas the iron compound **11a** decomposes at room temperature even in the solid state.

3.2. Boryl Complexes with Other Substituents on Boron

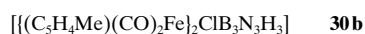
In contrast to the catecholboryl complexes, corresponding compounds with other substituents on boron are rather rare. Unambiguous knowledge of these compounds on the basis of complete spectroscopic characterization is limited to a few complexes of tungsten, iron, rhodium, palladium, and platinum. Although there is no suitable data available to make a comparison of the effect that the substituents on boron have on the strength of the metal–boron bonds, it can be assumed that the phenylene-1,2-dioxy group stabilizes the corresponding products in a special manner. To date there is no other ligand known with a comparably wide range of application. The other boryl complexes are therefore often unique cases.

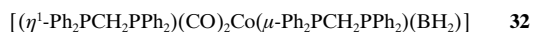
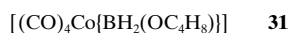
The crystal structures of just three boryl complexes with alkyl or aryl groups on boron have been described:^[56] the tungsten complex **25**,^[57] which shows an agostic interaction of a C–H unit of the methylene group on boron, the iron complex **26**,^[46] and the iridium complex **27**.^[58] The first X-ray structure analysis of a boryl–transition metal complex was

performed on **27**. Although the tetramethylethylene-1,2-dioxy or pinacol group (Pin = OCMe₂CMe₂O) resembles the catechol group, only one corresponding boryl–platinum complex is known (**20b**).^[53, 59, 60] The palladium complex **28** is the only structurally confirmed example of a compound with a comparable nitrogen-containing substituent on boron.^[61]



Recently it proved possible to synthesize boryl complexes containing ligands with more than one boron atom. Examples include **29a, b**, in which none of the previously mentioned boryl ligands but rather a diboran(4)-1-yl ligand is bonded to the metal atom.^[62] A new coordination mode was found for the borazine ligand, which has been known for a long time in organometallic chemistry, in complexes **30a–c**.^[63] In contrast to the above-mentioned compounds **B**,^[20, 21] **30a–c** contain η^1 -coordinated borazine ligands with σ bonds between the metal and boron atoms.

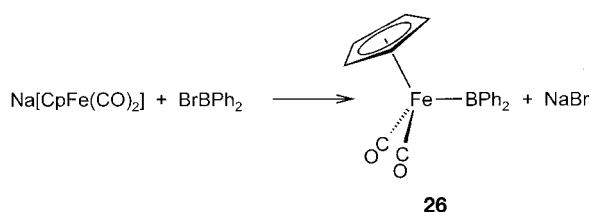




In 1990 cobalt compounds **31**^[64] and **32**^[65] were characterized spectroscopically; the latter was also structurally characterized in the crystal. These compounds containing four-coordinate boron are the only known base adducts of boryl complexes.^[66]

3.3. Synthesis of Boryl Complexes

Essentially two methods have proven to be successful for the preparation of the boryl complexes mentioned in Sections 3.1 and 3.2. Starting from an anionic transition metal complex and a haloborane, the metal–boron bond can be formed by nucleophilic substitution of the halide and salt elimination. This reaction was first successfully employed in the synthesis of the boryl–iron complexes **12**^[46] and **26**^[46] (Scheme 3).

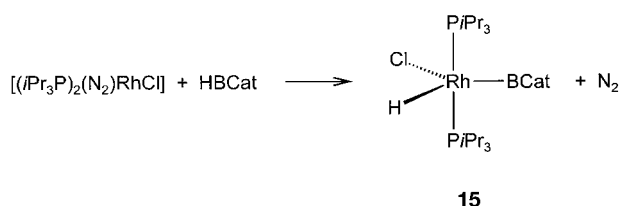


Scheme 3. Synthesis of **26**.

A large number of anionic complexes of the metals of Groups 5–7 are also available as starting materials. These can be prepared from metallocene or carbonyl derivatives and then converted into the corresponding boryl complexes (Table 1). The preparation of the bisboryl complex **11a**^[45] from $\text{Na}_2[\text{Fe}(\text{CO})_4]$ and $\text{ClB}(1,2\text{-O}_2\text{-4-}t\text{BuC}_6\text{H}_3)$ demonstrates that this method is not limited to monoanionic complexes.

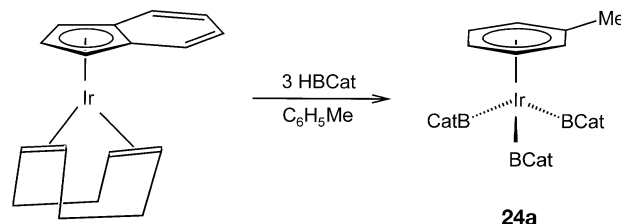
It has been known for over forty years that B–H and B–B bonds in boranes and diboranes(4) oxidatively add to unsaturated compounds such as alkenes.^[67–69] A comparable addition of boryl groups to transition metals was also used to prepare numerous boryl complexes.

The synthesis of corresponding complexes of late transition metals with boranes usually occurs with elimination of neutral ligands such as N_2 or phosphanes, as in the formation of **15** (Scheme 4),^[49] **16**,^[50] and **27**.^[58] In the case of the iridium compounds **22**^[54] and **24a, b**,^[55] however, alkenes are eliminated from the complexes. Depending on the stoichiometry, one or more boryl groups can be added, as in the reactions of $[(\text{Ph}_3\text{P})_3\text{RhCl}]$ with HBCat.^[70, 71]



Scheme 4. Synthesis of **15**.

The synthesis of the trisboryl complexes **24a, b** from $[(\text{C}_9\text{H}_7)\text{Ir}(\text{C}_8\text{H}_{12})]$ (C_9H_7 = indenyl, C_8H_{12} = cyclooctadiene) and excess HBCat in aromatic solvents such as toluene or mesitylene is particularly interesting (Scheme 5). Here, both

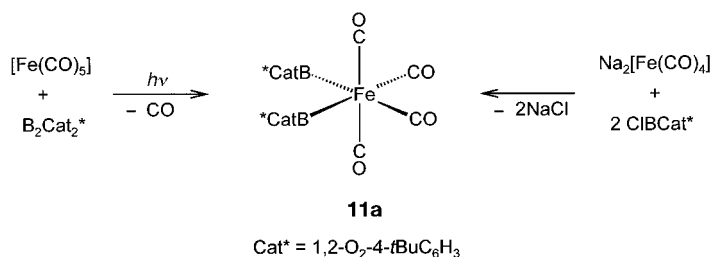


Scheme 5. Synthesis of **24a**.

the ligands on the metal are eliminated, the iridium atom is oxidized, and a solvent molecule becomes coordinated in a η^6 fashion.

The rhodium and iridium complexes **18** and **23** can be synthesized by reaction of the highly reactive electron-deficient complexes $[(\text{Cy}_3\text{P})_2\text{MCl}]$ ($\text{M} = \text{Rh}, \text{Ir}$; Cy = cyclohexyl) with HBCat; the elimination of phosphane ligands is not observed.^[51] The formation of the niobium complex **6a**^[39] from $[(\text{C}_5\text{H}_5)_2\text{NbH}_3]$ and HBCat does not occur with forced removal of neutral ligands, but rather elimination of H_2 . Theoretical studies on the reaction of $[(\text{C}_5\text{H}_5)_2\text{NbH}_3]$ with BH_3 show that initial formation of an adduct with a Nb–H–B bridge is likely. This adduct would then react further with elimination of H_2 and subsequent oxidative addition of the B–H bond to the metal center. In the case of BH_3 , addition to a central proton is energetically more favorable than to a lateral proton.^[72]

The oxidative additions of diboranes(4) to metals proceed more uniformly, because bisboryl complexes are generally formed. For the synthesis of the tungsten complex **9**,^[41, 42] the intermediate $[(\text{C}_5\text{H}_5)_2\text{W}]$ generated by irradiation of $[(\text{C}_5\text{H}_5)_2\text{WH}_2]$ may be used. In addition to the salt elimination mentioned above, an alternative photochemical method for preparing **11a** from $[\text{Fe}(\text{CO})_5]$ is known (Scheme 6).^[45] In



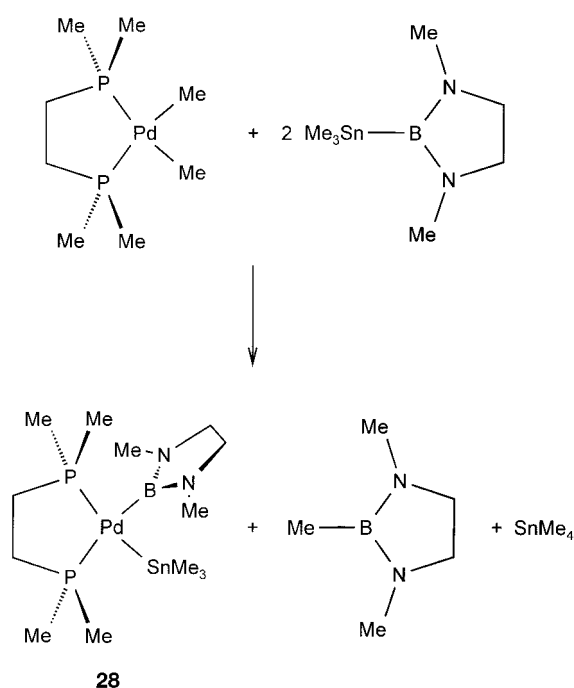
Scheme 6. Alternative syntheses of **11a**.

contrast, the bisboryl complexes of cobalt and platinum are accessible by thermal elimination of PMe_3 or alkenes and alkynes.

The only reaction that does not lead to the formation of a bisboryl complex is that of $[(\text{Me}_3\text{P})_4\text{RhMe}]$ with B_2Cat_2 . When one equivalent of B_2Cat_2 is used, the boryl complex **14** is initially formed with elimination of MeBCat . The complex

then reacts further by oxidative addition of a further B_2Cat_2 molecule to give the trisboryl complex **19**.^[48]

The synthesis of the palladium complex **28** (Scheme 7) is of particular relevance,^[61] because this was the first time that a boryl complex was obtained by addition of another compound



Scheme 7. Synthesis of **28**.

with a different boron–element bond. As the other reaction products $SnMe_4$ and $MeB(MeNCH_2CH_2NMe)$ show, the formation of **28** does not occur by oxidative addition, but rather by σ bond metathesis.

Both salt elimination and oxidative addition are synthetic methods with a wide range of application. In contrast, the reactions leading to the tungsten **25**^[57] and cobalt complexes **32**^[65] are not yet understood and are limited to the examples mentioned.^[56]

3.4. Structures of Boryl Complexes

Owing to the sp^2 hybridization, boron atoms in boryl complexes have a trigonal-planar coordination. To compensate for the electronic deficiency, the formation of a π backbond from the metal to the boron atom is possible as long as occupied d orbitals of suitable symmetry on the metal are able to interact with the empty p_z orbital on boron. A similar situation is known for isoelectronic cationic carbene complexes.^[73, 74]

Earlier work in this field^[27] had to rely solely on IR and NMR spectroscopic data to describe the bonding in boryl complexes, as none of the products had been characterized by X-ray structure analysis. For example, ^{11}B NMR shifts between $\delta = -23$ and 45 were reported for diphenylboryl complexes of various metals, which are shifted strongly upfield in comparison to the value of $\delta \approx 60$ for BPh_3 .^[75]

These results, together with IR spectroscopic data, served as proof for pronounced metal–boron backbonding. It is remarkable, however, that these findings do not concur with the spectroscopic properties of structurally characterized compounds. For example, a ^{11}B NMR shift of $\delta = 37$ for the iron compound **12**^[76, 77] first reported in 1963 conflicts with the actual value of $\delta = 121$ reported for the fully characterized compound thirty years later.^[46] The numerous structural and spectroscopic findings recently made together with ab initio studies in this field now allow a more detailed description of the bonding in boryl complexes. The evaluation of this data does not, however, result in a uniform picture which would fit all compounds. Hence, a detailed discussion of the individual types of compounds is necessary.

For the tantalum complexes **7a, b**^[40] and the tungsten complexes **8**^[39, 41] and **9**^[41, 42] in the crystalline state the catechol ligands are arranged such that the oxygen atoms on boron point towards the cyclopentadienyl rings. Although this geometry is sterically unfavorable, it permits the formation of a π backbond from the metal to boron. Complexes of the type $[Cp_2ML_n]$ have an a_1 -symmetrical metallike HOMO. If the boryl ligand is suitably arranged, this nonbonding orbital can interact with the free p orbital that is perpendicular to the bonding plane around the boron atom (**C**, Figure 1).^[78]

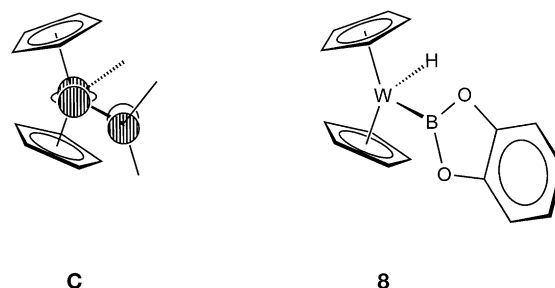
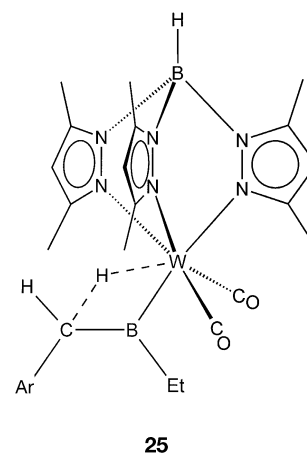


Figure 1. Arrangement of the orbitals in complexes of the type $[(C_5H_5)_2MX_2]$ with π backbonding (**C**); schematic representation of the structure of $[(C_5H_5)_2WH(BCat)]$ (**8**) in the crystal.

A corresponding geometry was also found for the tantalum–alkylidene complexes isoelectronic to **8** and **9**.^[79, 80] In the case of the tungsten complexes **8** and **9**, this arrangement is achieved with a slight shortening of the W–B bond lengths (Table 1) with respect to the sum of their covalent radii. Hindered rotation around the W–B bond was not observed for any of the above-mentioned boryl complexes by NMR spectroscopy in solution down to $-80^\circ C$. This indicates that the π backbonds must be weak in nature.

The tungsten–boryl complex **25** ($Ar = CH_2-4-MeC_6H_4$) shows a stronger W–B backbond.^[57] This



compound has the shortest of all observed W–B bonds; with 207(1) pm this bond is about 5 % shorter than the sum of the covalent radii of tungsten and boron. Furthermore, the ^{11}B NMR signal at $\delta = 77$ for the boron atom bound to tungsten is shifted strongly upfield in comparison to the resonances for other diaryl- and dialkylboryl complexes that have been characterized by X-ray structure analyses.

There are just two examples of complexes containing only carbonyl ligands in addition to the boryl ligand that have been structurally characterized: **10a**^[44] and **11a**.^[45] Although in both cases the metal–boron bond is longer than in complexes with mixed substituents, such as the iron complex **12**,^[46] there are nevertheless indications of π -bonding contributions. The metal–carbon double bond is much shorter for carbonyl groups that are arranged *trans* to pure σ donors such as hydride or alkyl ligands than for two carbonyl ligands that are arranged *trans* to one another; this can be attributed to the higher electron density on the metal atom.^[81, 82] This bond shortening does not occur in **10a** and **11a** because of the π -acceptor properties of the boryl group. IR spectroscopy of both boryl complexes also indicates metal–boron multiple bonding: The CO bands are shifted to significantly higher wave numbers compared to those for compounds such as $[(\text{CO})_5\text{MnMe}]$ ^[83] or *cis*- $[(\text{CO})_4\text{Fe}[\text{GaR}[(\text{CH}_2)_3\text{NMe}_2]_2]]$ ($\text{R} = t\text{Bu}, \text{Ph}$)^[84] for which π backbonding from the metal to the carbon or gallium atom can be ruled out.^[85]

Boryl complexes of the type $[(\text{C}_5\text{H}_5)(\text{CO})_2\text{Fe}(\text{BRR}')]]$ are of particular interest, because they allow a comparison of the structural and spectroscopic properties of a catecholboryl complex with those of corresponding compounds with other substituents on boron. Complex **12**^[46] has certain characteristics that were discussed above in some detail: 1) In the crystal the bonding plane around boron is almost coplanar with the symmetry plane of the $[(\text{C}_5\text{H}_5)(\text{CO})_2\text{Fe}]$ fragment, which is defined by the atoms B and Fe and the center of the cyclopentadienyl ligand (dihedral angle 7.9°). The formation of a π backbond from the iron atom to the boron atom for this arrangement of the boryl ligand is made possible by the interaction of the metallike a'' -symmetrical HOMO with the free p orbital on boron (**D**, Figure 2).^[86] 2) In solution the IR bands for the carbonyl groups are shifted to higher wave numbers in comparison to those for $[(\text{C}_5\text{H}_5)(\text{CO})_2\text{FeMe}]$.^[87] In contrast to this, in the crystal the iron complexes **26**,^[46] **29a**, and **30b**^[63]—which show corresponding dihedral angles of between 75 and 90° —have a geometry which does not allow the formation of π backbonds (**E**, Figure 2). This is reflected in the considerably longer Fe–B distances of these compounds in comparison to those in **12**. The position of the CO bands at lower wavenumbers also indicates Fe–B bonds with predominantly σ character.

The structurally characterized bisborylplatinum complexes *cis*- $[(\text{Ph}_3\text{P})_2\text{Pt}(\text{BCat})_2]$ (**20a**)^[52, 53] *cis*- $[(\text{Ph}_3\text{P})_2\text{Pt}(\text{BPin})_2]$ (**20b**)^[53, 59, 60] and *cis*- $[(\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2)\text{Pt}(\text{BCat})_2]$ (**21a** $n=2$; **21b**, $n=3$)^[53] have Pt–B bond lengths that, under consideration of the difference in the covalent radii between sp^2 -hybridized boron and carbon, are considerably shorter than the Pt–C distances of corresponding aryl complexes.^[88] Furthermore, with values between 1500 and 1600 Hz the coupling constants $|^1J_{\text{Pt,P}}|$ observed in solution for the

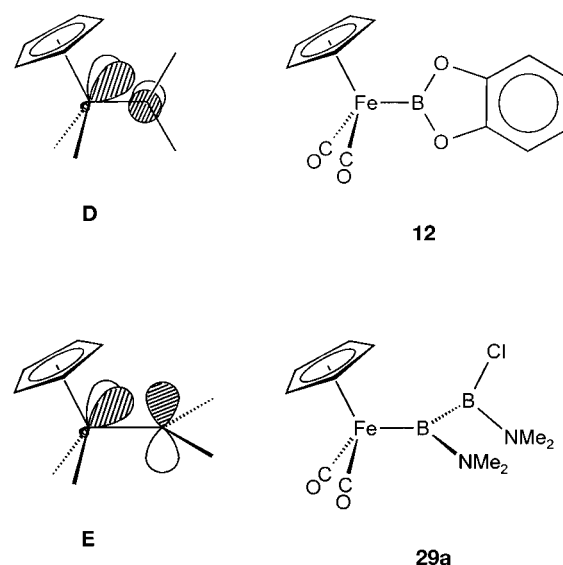
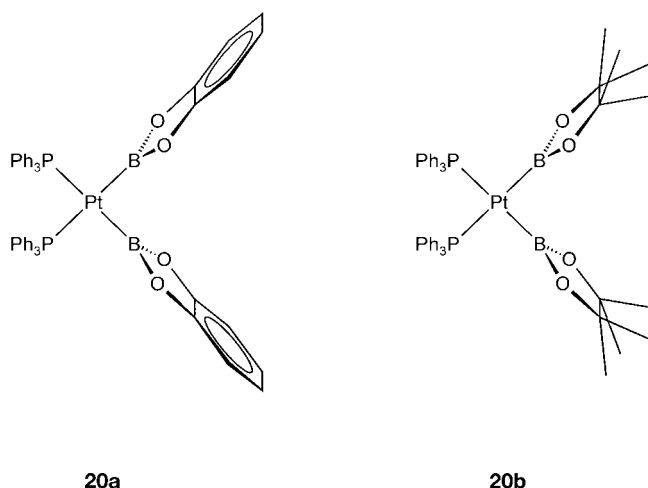


Figure 2. Arrangement of the orbitals in complexes of the type $[(\text{C}_5\text{H}_5)\text{M}(\text{CO})_2\text{X}]$ with (**D**) and without π backbonding (**E**); schematic representation of the structure of $[(\text{C}_5\text{H}_5)(\text{CO})_2\text{Fe}(\text{BCat})]$ (**12**) and $[(\text{C}_5\text{H}_5)(\text{CO})_2\text{Fe}[\text{B}(\text{NMe}_2)_2\text{Cl}(\text{NMe}_2)]]$ (**29a**) in the crystal.

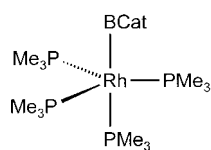
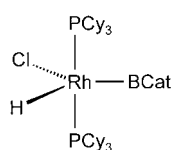
platinum–boryl complexes are about 200 Hz less than those of the platinum–aryl complexes. This can be attributed to a larger *trans* effect of the boryl ligands.^[89] Both findings indicate π backbonding from platinum to boron.



A comparison of the influence of substituents in catecholboryl and pinacolboryl complexes **20a** and **20b** does not demonstrate the same uniformity of the above-mentioned iron compounds of the type $[(\text{C}_5\text{H}_5)(\text{CO})_2\text{Fe}(\text{BRR}')]]$. Although **20a** and **21a,b** have shorter Pt–B bonds than **20b**, which could indicate a unique stabilization through the phenylene-1,2-dioxy substituents, the situation is reversed in solution. Here **20b** shows the smallest coupling constant $|^1J_{\text{Pt,P}}| = 1504$ Hz and thus the largest *trans* effect of these compounds.

In contrast to the phenylene-1,2-dioxyboryl complexes already mentioned, the corresponding iridium and rhodium compounds, barring two exceptions, show no indication of significant metal–boron backbonding, neither in solution nor in the crystalline state. The Ir–B bond lengths in **22**^[54] and

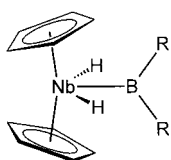
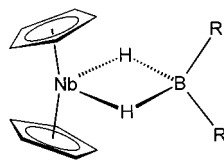
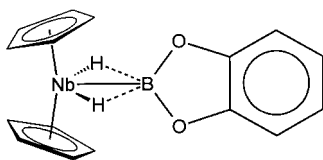
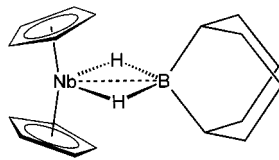
24a, b^[55] are comparable with that in *cis, trans*-[(Me₃P)₂(CO)IrBr₂(σ -2-B₅H₈)], which has predominantly σ character,^[90] and are not shortened with respect to the sum of the covalent radii of the elements. Corresponding observations have also been made for metal–boron bonds in the rhodium complexes **14**, **15**,^[49] **16**,^[50] and **19**.^[48]

**14****18**

In the case of **14** in the crystalline state, the boryl ligand occupies an axial position; in such trigonal-bipyramidal rhodium complexes this site is usually preferred by ligands with strong σ -donor and only weak π -acceptor properties. To enable the formation of backbonding from rhodium to boron, the boryl ligand must be in an equatorial position.^[91] In solution at room temperature **14** shows fluxional behavior; however, at -80°C the ³¹P NMR spectra confirm the axial arrangement of the boryl ligand.

In contrast, the boryl ligands in the rhodium and iridium complexes **18** and **23** take up equatorial positions in the crystal, and the metal–boron bond lengths are shortened with respect to the sum of the covalent radii.^[51] In **18** the Rh–B distance is about 8 pm smaller than in **14**. This indicates the presence of π backbonding in both cases.

Two complexes deserve special treatment here owing to their interesting structural characteristics. For compounds of the type [(C₅H₅)₂NbH₂(BRR')], variation of the substituents on boron leads to a transition between two structural extremes: the boryl–niobium complex **F** and the dihydridoborate–niobium complex **G**.

**F****G****6a****6b**

The phenylene-1,2-dioxyboryl complex **6a**^[39] has B–H distances of 169(4) and 162(5) pm and an H–Nb–H angle of $92(2)^\circ$; therefore, **6a** lies in an intermediate region between **F** and **G**. However, owing to the large B–H distances, the large bond angle on niobium, and the small Nb–B bond length of 229.2(5) pm, **6a** can be better described as a boryl complex.

The metallocene hydride derivatives **7a, b**^[40] and **8**^[39, 41] related to **6a** do not demonstrate any recognizable interaction between the boron atom and the hydrogen atoms bonded to the metal. If [(C₅H₅)₂NbH₃] is allowed to react with HBC₈H₁₄ instead of HBCat, [(C₅H₅)₂Nb(H₂BC₈H₁₄)] (**6b**) is obtained in an analogous manner.^[39] In the crystal **6b** has a large Nb–B distance of 240(1) pm, a H–Nb–H angle of $70(3)^\circ$, and small B–H distances of 138(7) and 139(6) pm. Because of the good agreement of these values with those of other compounds of the type [(C₅H₅)₂M(BH₄)],^[92–94] **6b** can also be described as a dihydridoborate complex. The structural data of **6b** mentioned essentially correspond with the results of the ab initio studies on [(C₅H₅)₂Nb(BH₄)].^[72]

The discussion of ¹¹B NMR spectroscopic data has for the most part been avoided until now, because they are not particularly suitable for describing the precise structure of boryl complexes in solution. The chemical shifts observed for these products cover a wide range from about $\delta = 35$ to 121 (Table 1), and are shifted downfield with respect to the values for the borane and diborane(4) derivatives used. This would indicate only low or no π electron density on boron. The spectroscopic and structural results discussed above show, however, that the bonding situation cannot be meaningfully described solely on the basis of ¹¹B NMR spectroscopy.

An initial estimation of the strength of the Ir–B bond in [(Ph₃P)₂(CO)Ir(Cl)(H)(BCat)] was provided by the measurement of the reaction enthalpy for the reaction of *trans*-[(Ph₃P)₂(CO)IrCl] with CatBH. Under consideration of the B–X bond dissociation energies for CatBX (X = H, Me) calculated by ab initio methods, an Ir–B bond strength of 66 kcal mol^{−1} was determined. This lies well above the values for Ir–H and Ir–C bonds in comparable complexes.^[95] In addition to the numerous experimental findings, preliminary theoretical studies of the bonding in boryl complexes were also considered. Ab initio calculations on complexes of the type *cis*-[(H₃P)₂M(BX₂)₂] (M = Pd, Pt; X = H, OH) provided metal–boron bond strengths of 51.0 (M = Pd; X = OH), 64.8 (M = Pt; X = H), and 62.9 kcal mol^{−1} (M = Pt; X = OH).^[96] These values are also up to 25 kcal mol^{−1} greater than the corresponding bond energies of M–C bonds. This can be explained by the additional stabilization of the M–B bonds by π interactions. This is also indicated by the good agreement between the calculated Pt–B bond lengths of 206.9 (X = H) and 205.6 pm (X = OH) and those determined for structurally characterized platinum–boryl complexes; for these π bonding may also be assumed on the basis of other spectroscopic data.

This more detailed discussion of experimental and theoretical findings shows that the question regarding the nature of the metal–boron bond in boryl–transition metal complexes cannot be answered uniformly. A tendency towards the formation of π backbonds is clearly dependent both on the substituents bonded to boron and on the metal itself. It is noticeable that, in contrast to other substituents on boron, the phenylene-1,2-dioxyboryl group in complexes of the type [(C₅H₅)(CO)₂Fe(BRR')] enables backbonding from iron to boron. This additional stabilization may be responsible for the broad applicability of catecholborane derivatives in the synthesis of boryl complexes.

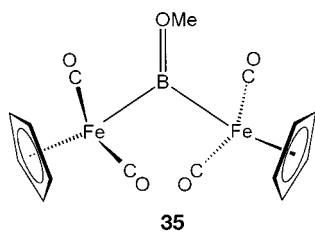
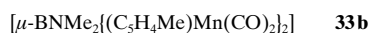
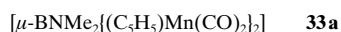
4. Borylene Complexes

Although there are numerous boryl complexes of metals of Groups 5–8, there are only a few structurally characterized examples of borylene complexes. These binuclear manganese and iron complexes each contain one bridging borylene ligand.

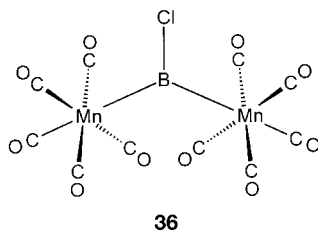
The reaction of $K[(C_5H_4R)Mn(CO)_2(SiMePh_2)]$ with the diboranes(4) $B_2X_2Cl_2$ surprisingly leads to the diboranes(6) $(XBH_2)_2$ and the borylene complexes **33a–c** (ca. 35% yield, Scheme 8); the stoichiometry of the reaction, the origin of the proton bonded to boron in **33a**, and the fate of the silyl group are still unclear.^[97] With the use of $K[(C_5H_4R)Mn(CO)_2H]$ in place of the silyl complex, the borylene complexes can be obtained as products of stoichiometric reactions in considerably higher yields (ca. 65%, Scheme 8).^[98] Further studies have shown that the unexpected formation of **33a–c** is dependent on the use of the diboranes(4), as no products with Mn–B bonds are formed when aminodichloroboranes are used.^[98]

A more direct access to bridged borylene complexes is provided by the reaction of $Cl_2B[N(SiMe_3)_2]$ with $Na[(C_5H_4Me)Fe(CO)_2]$ to form the iron compound **34** (Scheme 9).^[99] As was the case with the salt eliminations discussed in Section 3.3, the Fe–B bonds are formed by nucleophilic substitution of the chloride ligands; in addition, a carbonyl group is eliminated.

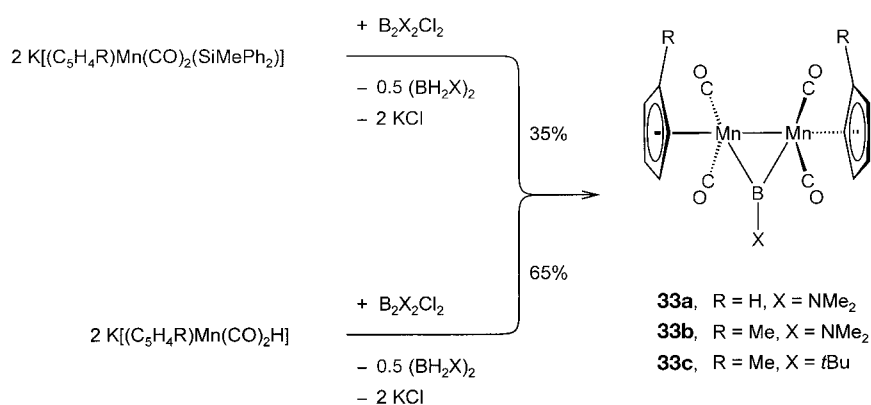
Recent results show that this synthetic method has wider applicability. Starting from $Na[(C_5H_4Me)Fe(CO)_2]$ and $Na[Mn(CO)_5]$, **35** and **36** with bridging borylene ligands were obtained.^[100] The iron complex **35** is formed without elimination of a carbonyl ligand; therefore, in contrast to the related **34**, it has four terminal carbonyl ligands.



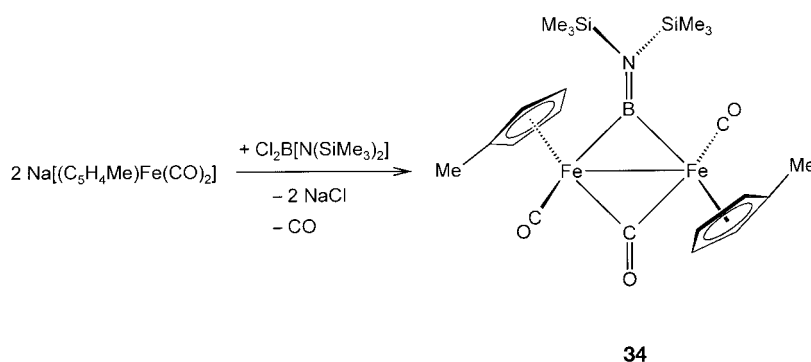
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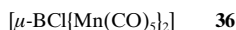
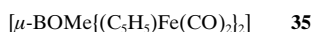
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Scheme 8. Synthesis of borylene–manganese complexes.



Scheme 9. Synthesis of **34**.



The structures of the borylene complexes **33** and **34** in solution and in the crystal are closely related with those of the isoelectronic dimanganese–^[101] and diiron–vinylidene compounds.^[102] The position of the CO bands in the IR spectra and the metal–boron bond lengths (Table 2) speak for σ -bonded borylene ligands. The metal–boron distances in **35** and **36** also give no indication of π bonding. On comparison of the ¹¹B NMR data of the borylene complexes (Table 2) with those of the boryl complexes, it is apparent that the formation of a second metal–boron bond leads to a considerable downfield shift of the signals. Whereas, for example, the resonances for alkyl-substituted boryl complexes lie in the region around $\delta = 107$, a value of $\delta = 170.0$ is found for **33c**.

Although **33a–c** and **34** show a very similar structure, they have very different chemical properties. Compounds **33c** and **34** are comparable with the above-mentioned boryl complexes, but the aminoborylene complexes **33a,b** are characterized by their remarkable inertness with respect to air and water.^[103]

Table 2. Syntheses, M–B bond lengths, and $\delta(^{11}\text{B})$ values of borylene complexes.

Compound	Synthesis ^[a]	<i>d</i> (M–B) [pm]	$\delta(^{11}\text{B})$	Ref.
$[\mu\text{-BNMe}_2\{(\text{C}_5\text{H}_5)\text{Mn}(\text{CO})_2\}_2]$ 33a	C	203(1)	103.0	[97, 98]
$[\mu\text{-BtBu}\{(\text{C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ 33c	C	— ^[b]	170.0	[97, 98]
$[\mu\text{-BCl}\{(\text{C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ 33d	B	— ^[b]	133.5	[102]
$[\mu\text{-B}(\text{NHtBu})\{(\text{C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ 33e	B	— ^[b]	102.4	[102]
$[\mu\text{-B}(\text{NHPh})\{(\text{C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ 33f	B	— ^[b]	107.6	[102]
$[\mu\text{-BOMe}\{(\text{C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ 33g	B	— ^[b]	98.9	[102]
$[\mu\text{-BOEt}\{(\text{C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ 33h	B	198.8(2), 202.1(2)	97.6	[102]
$[\mu\text{-BOH}(\text{C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ 33i	B	— ^[b]	101.6	[102]
$[\mu\text{-B}\{N(\text{SiMe}_3)_2\}(\mu\text{-CO})\{(\text{C}_5\text{H}_4\text{Me})\text{Fe}(\text{CO})_2\}_2]$ 34	A	200.7(3), 200.2(3)	119.1	[99]
$[\mu\text{-BOMe}\{(\text{C}_5\text{H}_5)\text{Fe}(\text{CO})_2\}_2]$ 35	A	206.8(9), 208.9(9)	96.7	[100]
$[\mu\text{-BCl}\{\text{Mn}(\text{CO})_5\}_2]$ 36	A	216.9(3), 217.0(3)	163.0	[100]

[a] A = salt elimination, B = substitution on boron, C = other method. [b] No details of the structure in the crystal are available.

5. Reactions

5.1. The Transition Metal Catalyzed Hydroboration and Related Reactions

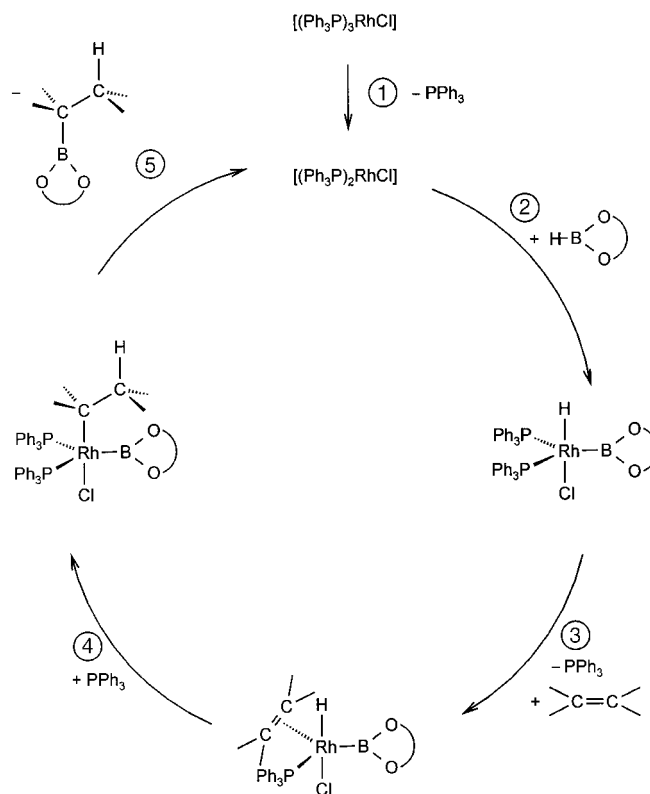
Since its discovery about 40 years ago,^[67] the hydroboration of unsaturated hydrocarbons has developed into one of the most useful methods for the functionalization of organic compounds.^[104–106] In the last few years, in addition to the transition metal catalyzed hydrosilylation,^[107–109] the influence of suitable complex compounds on the hydroboration reaction has been studied.^[110] A large proportion of these results has already been reviewed.^[111]

The current interest in boryl complexes is above all due to the fact that these compounds play a decisive role in the catalyzed hydroboration. Numerous investigations have been concerned with clarifying the mechanism of the reaction; boryl complexes synthesized since 1990 frequently serve as model substances. The longest known and beststudied is the catalytic efficacy of rhodium compounds such as the Wilkinson's catalyst $[(\text{Ph}_3\text{P})_3\text{RhCl}]$. In 1985^[110] a mechanism was suggested that is analogous to the Rh-catalyzed hydroboration of acrylic esters with carbaboranes.^[112] Starting from $[(\text{Ph}_3\text{P})_3\text{RhCl}]$, the mechanism involves the following steps (Scheme 10): 1) elimination of PPh_3 , 2) oxidative addition with cleavage of the B–H bond, 3) elimination of PPh_3 and side-on coordination of the alkene, 4) addition of PPh_3 and insertion of the alkene into the Rh–H bond, and 5) reductive elimination of the alkylborane. This mechanism is in agreement with a current theoretical^[113] and numerous experimental studies.^[54, 111, 114] As discussed in Section 3.3, the reaction of $[(\text{Ph}_3\text{P})_3\text{RhCl}]$ with CatBH does not proceed so uniformly. Side reactions such as the isomerization of the alkene or the catalytic decomposition of the catecholborane to BH_3 can occur.^[70, 71, 115] Moreover, a corresponding insertion into the Rh–B bond has been suggested as an alternative to the insertion of the alkene into the Rh–H bond.^[50, 70, 116]

The use of suitable transition metal complexes provides several advantages over the noncatalyzed hydroboration.^[70, 110, 111, 117–120] For example, less reactive or thermally sensitive boranes can be induced to react under mild conditions. Furthermore, in many cases the chemo-, regio-, and stereoselectivity may be reversed, which greatly increases the applicability of this reaction. It is thus possible to carry out

the hydroboration of C–C double bonds even in the presence of keto functional groups, or to functionalize cyclohexenone derivatives in the 3-position; in the case of the latter, noncatalyzed reactions lead to the attack of boron at the 2-position. The use of chiral complexes makes it possible to carry out stereoselective reactions even with achiral boranes, and the use of optically active material can be limited to the relatively small amount of catalyst required.

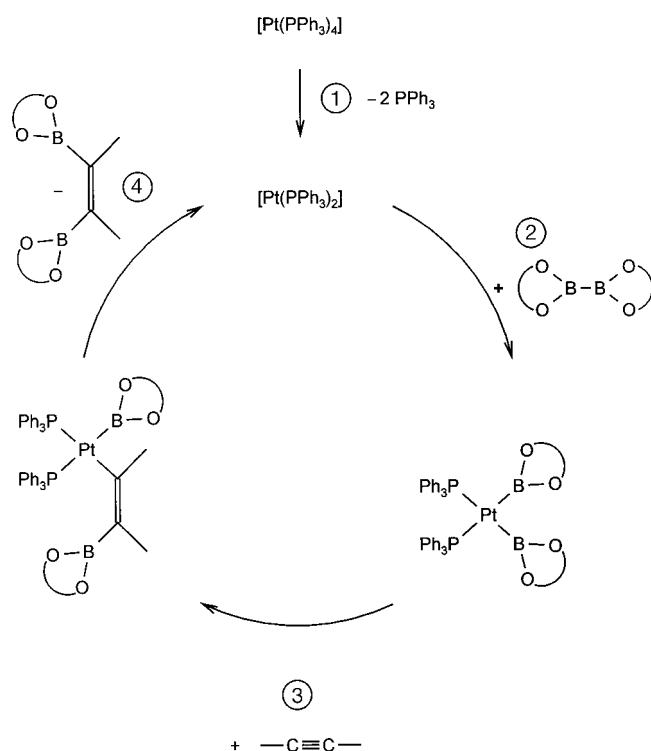
In addition to rhodium compounds, complexes of other transition metals have also been studied with regard to their catalytic activity, albeit to a lesser extent. For reactions with complexes of iridium,^[54] palladium,^[121] and nickel^[122] in low oxidation states, a mechanism similar to that postulated for the rhodium-catalyzed reaction has been suggested. However, it has only been possible to fully characterize the intermediately formed boryl complex in the case of iridium.



Scheme 10. Mechanism of the rhodium-catalyzed hydroboration of alkenes.

Unlike the reactions mentioned, the transition metal catalyzed hydroboration can also take place by a different route without formation of metal–boron bonds. Lanthanum,^[123] titanium,^[124–126] and zirconium^[127, 128] complexes have proven to be suitable catalysts. In contrast to the above-mentioned mechanism, the initial reaction in this case is that of an alkene or alkyne with the catalyst. Then, in a second step, the borane attacks this ligand now coordinated to the metal. Both mechanisms are discussed for the hydroboration of imines in the presence of copper, silver, or gold complexes, but the actual mechanism has still not been clarified.^[129]

Closely related to the transition metal catalyzed hydroboration are corresponding additions of compounds with B–B, B–Si, B–Sn, and B–S bonds to unsaturated hydrocarbons. On the basis of numerous experimental findings, a similar mechanism can be assumed for the platinum-catalyzed boroboration of alkenes^[130] and alkynes^[53, 59] with B_2Cat_2 and B_2Pin_2 (Scheme 11). As described in Section 3.3, the addition



Scheme 11. Mechanism of the platinum-catalyzed boroboration of alkynes.

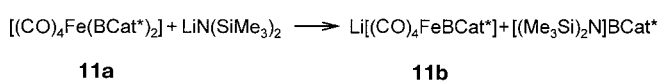
of the diborane(4) to platinum takes place with formation of a bisboryl complex (step 2), which undergoes insertion of the C–C unit into a metal–boron bond (step 3) and subsequent reductive elimination of the doubly borylated product (step 4). A corresponding mechanism has been suggested for the boroboration of vinyl arenes with B_2Cat_2 in the presence of rhodium or gold complexes. The most effective catalyst system for the preparation of the difunctionalized products proved to be $[(Et_3P)AuCl]$ in the presence of two equivalents of $(C_6H_{11})_2PCH_2CH_2P(C_6H_{11})_2$. The use of various rhodium complexes invariably involves a β -H elimination as a competing reaction, which leads to monoborated alkanes

or alkenes.^[131] Whereas noncatalyzed boroboration reactions for the synthesis of difunctionalized organic molecules are limited to the use of highly reactive tetrahalodiboranes(4),^[67, 68] the catalysts mentioned make possible the use of less reactive and thus easy-to-handle tetraalkoxydiboranes(4) and tetraaryloxydiboranes(4). A similar activation of the boron–element bond in silyl-,^[132] stannyl-,^[133] and sulfonylboranes^[134] with regard to the oxidative addition to alkynes can be achieved with palladium and platinum complexes.

5.2. Further Reactions of Boryl Complexes

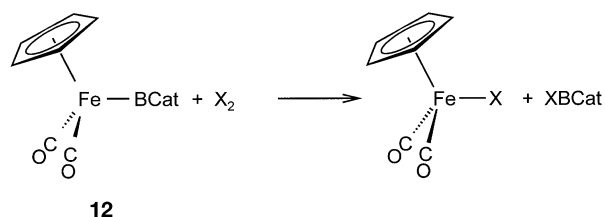
As discussed in Section 3.4, certain metal–boron bonds are stronger than corresponding metal–carbon bonds.^[95, 96] However, the catalyzed hydroboration and related reactions are based on the facile cleavage of the metal–boron bond; this is an indication of the kinetic lability of boryl complexes.^[45] Whereas reactions with unsaturated compounds have been the subject of extensive studies, comparatively little is known about the further reactivity of these complexes. For instance, the reaction of the tungsten complex **8** with $HNEt_2$ to give $[(C_5H_5)_2WH_2]$ and $Et_2NBCat^{[41]}$ takes place with cleavage of metal–boron bonds under the influence of protic compounds such as alcohols or amines to form the corresponding metal hydride complexes.^[41, 42, 45, 46]

An interesting synthesis is that of the anionic boryl complex **11b** from **11a** and $LiN(SiMe_3)_2$, in which an amino(phenylene-1,2-dioxy)borane is also formed (Scheme 12).^[45] Metal–



Scheme 12. Synthesis of **11b**.

boron bonds can also be cleaved by unpolar reagents, as is demonstrated by the reactions of the iron–boryl complex **12** with Br_2 or H_2 (Scheme 13).^[46] The corresponding addition of



Scheme 13. Reaction of **12** with X_2 ($X = H, Br$).

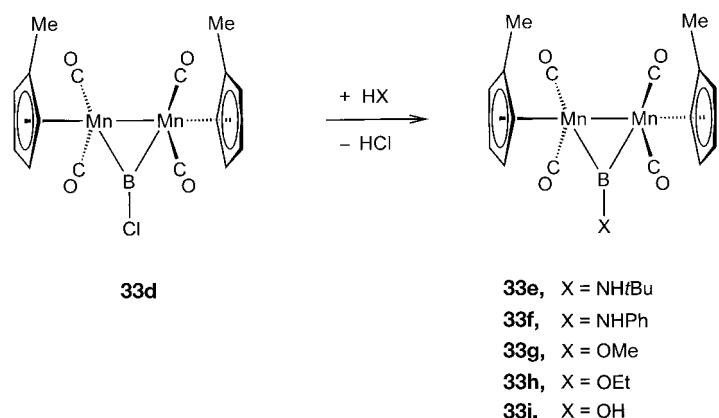
the B–B bond of a diborane(4) derivative to a metal–boron bond leads to an exchange of boryl ligands by σ -bond metathesis, as observed in the case of the rhodium complex **16**^[134] and the platinum compound **20a**.^[53]

An interesting possibility for the functionalization of organic compounds is provided by the photolysis of boryl complexes such as **10a**, **b** or **12** in the presence of arenes or alkenes.^[44] Activation of C–H bonds leads to the formation of aryl- and vinylboranes in high yields. At present, only a few complex compounds are known that can simultaneously activate and functionalize unreactive hydrocarbons.^[135, 136] The recently introduced functionalization of alkanes deserves

special attention. Alkyl esters of boronic acids are formed by selective addition of the catecholboryl group to terminal carbon atoms upon photolysis of phenylene-1,2-dioxyboryl complexes in aliphatic solvents. The functionalized alkanes thus formed can be isolated in yields of up to 85 %.^[137]

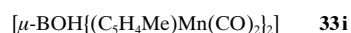
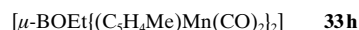
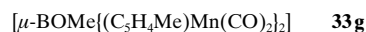
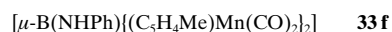
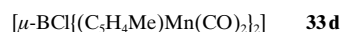
5.3. Reactions With Retention of the Metal–Boron Bond

All of the reactions of boryl complexes mentioned so far take place with cleavage of the metal–boron bonds. In contrast, substitution reactions of boryl ligands coordinated to metals are unknown. The aminoborylene complex **33a** displays a fundamentally different chemical behavior.^[103] The reaction with HCl leads, for instance, to the substitution of the amino group with formation of the chloroborylene complex **33d**; cleavage of the Mn–B bond is not observed. In agreement with the known properties of amino- and chloroboranes, **33d** is significantly more reactive than the amino derivative **33a**, which is stable to both air and moisture, and serves as the starting material for further substitution reactions on boron. With protic compounds such as primary amines, alcohols, or water, it is possible to obtain the corresponding substituted borylene complexes **33e–i** in good yield with elimination of HCl (Scheme 14). The spectroscopic



Scheme 14. Reaction of **33d** with protic compounds.

and structural properties of these derivatives (Table 2) show no great differences to those of **33a–c**.^[97]



6. Summary and Outlook

The results presented here demonstrate that the fundamental difficulties involved with the synthesis of crystalline

transition metal complexes of boron can be overcome. The salt elimination and the oxidative addition of compounds with boron–element bonds are two methods for preparing boryl complexes, and the use of phenylene-1,2-dioxyborane derivatives has proved to be extremely useful. Knowledge of the stability of the complexes as a function of the substituents on boron would greatly assist in the search for other boranes with a similar wide range of use.

Whereas the boryl complexes have been extensively studied, in particular because of their interesting application possibilities in the functionalization of organic compounds, there is only little confirmed information on borane and borylene complexes. In the case of the borane complexes only one compound could be spectroscopically characterized in solution. Access to complexes with bridging borylene ligands was initially limited to one very special and unexpected reaction; most recent results show, however, the salt elimination could find a wider scope of applicability here. Complexes containing terminal borylene ligands with a metal–boron double bond are not known as yet, and the synthesis of such compounds is certainly one of the greatest challenges in this field.

The transition metal catalyzed hydroboration has long proven to be a valuable method in the functionalization of organic compounds. Recently further interesting application possibilities for boryl complexes in organic synthesis have presented themselves. Examples include the preparation of difunctionalized hydrocarbons starting from silylboranes, stannylboranes, sulfanylboranes, and diboranes(4), and, most importantly, the selective synthesis of terminal alkyl esters of boronic acids by the photochemically induced C–H activation of alkanes.

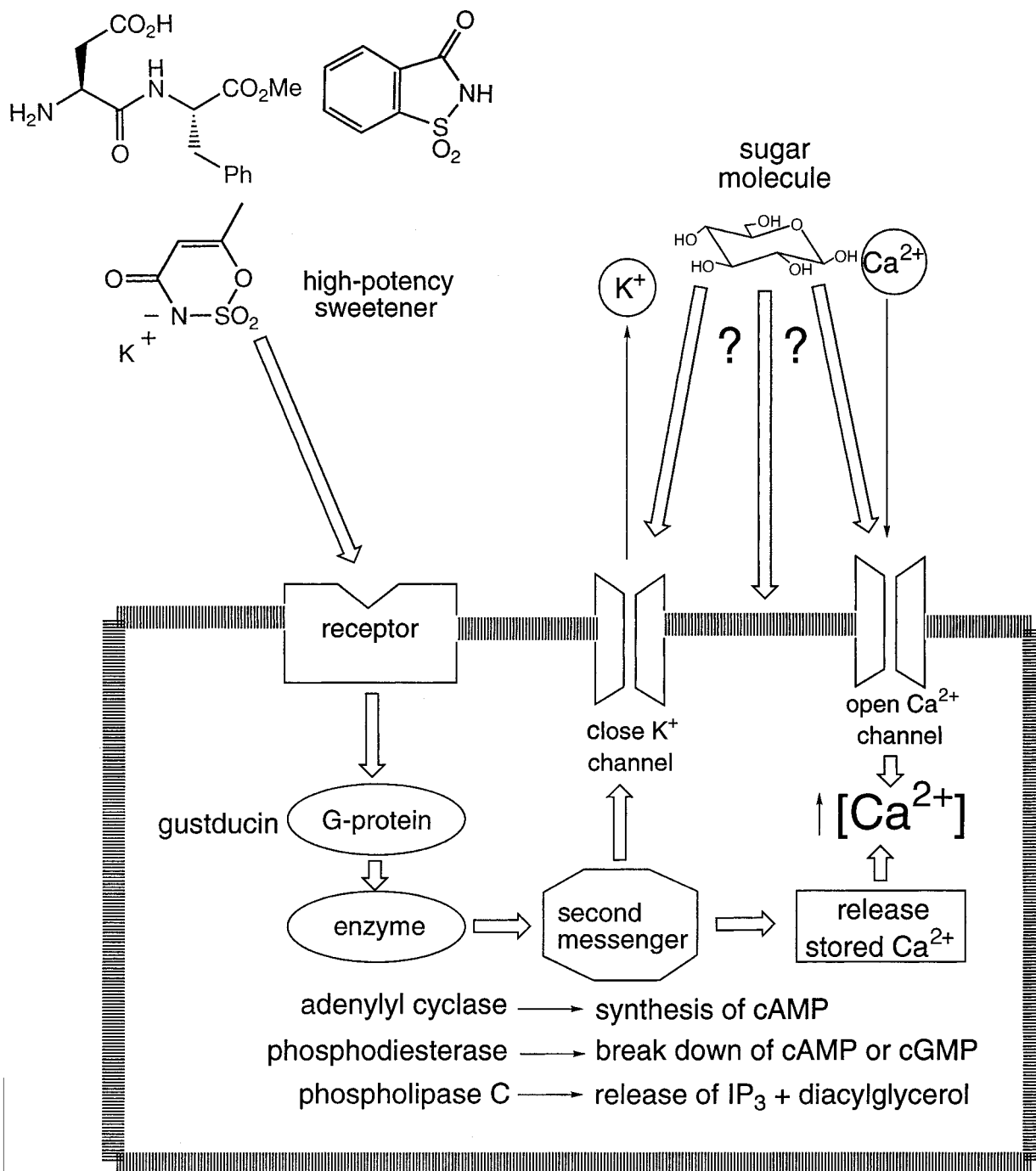
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The “sweet” taste can be obtained not only from sugar (top right) but also from synthetic sweeteners (top left).



The uses and the syntheses of such sweeteners are discussed in the review by D. Ager et al. in the following pages.

Commercial, Synthetic Nonnutritive Sweeteners

David J. Ager,* David P. Pantaleone, Scott A. Henderson, Alan R. Katritzky, Indra Prakash, and D. Eric Walters

Nonnutritive sweeteners represent a large commercial market, and both in terms of volume and value of sales they fall between the majority of pharmaceutical compounds and bulk chemicals. The synthesis of these sweeteners can offer some unique challenges. The current large-scale methods used for

the preparation of sweeteners that are currently allowed for usage in North America and Europe have been highlighted. The elegance of some of these syntheses is the simplicity of the methodology and is a reflection the amount of resources that have been expended to discover the approach and then

reduce it to practical scale. Alternative approaches to some of the sweeteners, in particular biochemical methods, have been included as these could supercede total chemical synthesis.

Keywords: enzyme catalysis • sweeteners • synthetic methods

1. Introduction

Nonnutritive sweeteners have established a significant market. This large-scale usage has presented some unique problems with regard to their chemistry and biological properties.^[1] We will only cover synthetic commercial sweeteners and all of them have been subjected to large amounts of biological testing.^[2] Thus, their entry on to the market is somewhat reminiscent of an over-the-counter drug. Despite the large number of compounds that are known to be sweet, relatively little is known about their mode of action. Although we have defined these sweeteners as nonnutritive, many, such as aspartame, are caloric. However, the amount of the sweetening agent used in a specific food application is usually so low that it makes no significant caloric contribution.

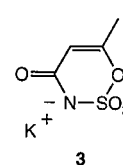
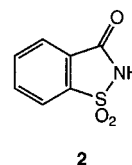
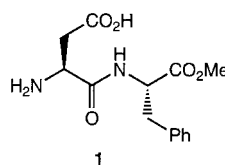
In addition to being sweet, a compound has to have a number of physical attributes associated with it before it can be considered a good sweetening agent, fit for human consumption: Obviously, the sweet character should have no

off-tastes; the compound must be safe and stable under use conditions; and as economical issues are also of importance, the compound should be sweeter than sugar in order to offset synthesis costs. We will concentrate on the commercial-scale syntheses of synthetic, nonnutritive sweeteners that have been approved for use in North America or Europe. The amounts of sweeteners produced, especially aspartame, means that these compounds are on the borderline of fine and bulk chemicals. The practice of large-scale synthesis in this arena has led to some elegant approaches and both chemical and biochemical methods are covered in this review.

1.1. Mode of Action

Taste receptor proteins have not yet been isolated or unequivocally identified. There are two major reasons why this is so:

1. Traditional receptor isolation methods have usually involved the use of a high-affinity ligand (half-maximal binding at nanomolar concentrations or less) which can be used to monitor the progress of purification. Sugars trigger sweetness only at concentrations of ~0.1 molar; aspartame (**1**), saccharin (**2**), and acesulfame-K (**3**) elicit sweetness at concentrations of a few millimoles per liter. At these concentrations, it is nearly impossible to distinguish receptor-specific binding from nonspecific binding to other



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components of the tissue from which the receptors might be extracted.

2. The difficulty in isolating taste-active cells. These are specialized epithelial cells which are embedded in taste buds among a large number of nontaste-active cells. When these cells are separated from their nerve cells, they rapidly

de-differentiate back into ordinary epithelial cells. Thus, it has not been possible to grow taste-active cells in cell cultures.

Despite these difficulties there is now a large body of evidence indicating that sweetness is mediated in many cases by G-protein-coupled receptors (GPCR). GPCR are respon-

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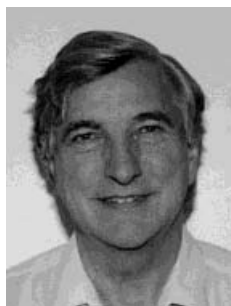
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Indra Prakash was born in Muzaffaranagar, India in 1956. Receiving an M.Sc. degree from the University of Roorkee, India, in 1977, he was awarded the Gold Medal for academic distinction. In 1982, he received a Ph.D. degree from Kurukshetra University, India, under the direction of Professor S. P. Singh. He also worked at Union Carbide at Bhopal, India. After coming to the USA, he worked for Professor Kagan, Professor Moriarty, and Professor Sosnovsky. In 1987 he joined Aldrich Chemical Company as a Senior Chemist and then became a Principal Investigator for a National Cancer Institute contract with Aldrich. Currently, Dr Prakash is a project leader developing processes for new sweetener candidates for The NutraSweet Kelco Company, a sector of Monsanto.

D. Eric Walters earned a B.Sc. in Pharmacy from the University of Wisconsin, followed by a Ph.D. in Medicinal Chemistry from the University of Kansas. He spent 12 years carrying out research in the pharmaceutical industry and food industry, particularly in the field of sweetener research while working for the NutraSweet Company. In 1991 he joined the Biological Chemistry faculty at the Chicago Medical School. He coedited a book on sweeteners.^[11a] His current research includes the search for new anti-HIV and anti-parasitic drugs as well as development of new methods for computer-aided drug discovery.

sible for detection of many neurotransmitters, hormones, odorants, and even photons. The GPCR are proteins having seven α -helical segments embedded in the cell membrane. When extracellular ligands bind to the receptor (Figure 1),

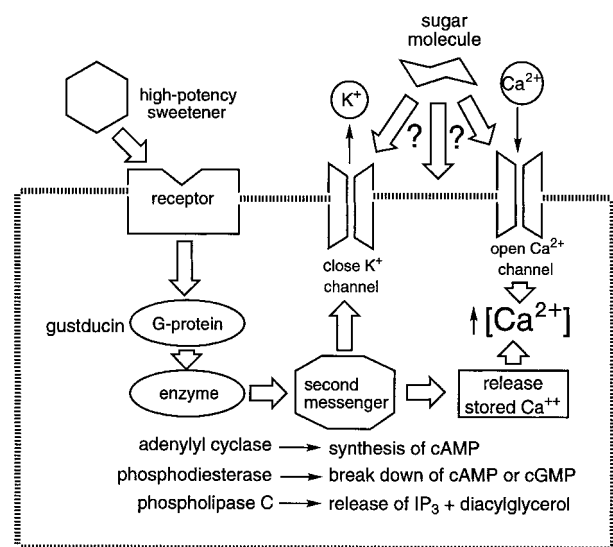


Figure 1. Schematic representation of a taste cell, indicating likely components of the taste transduction system. The initial stimulus may be either a high potency sweetener or a sugar; the final step is cell depolarization, which may involve loss of potassium ions and a sharp increase in the concentration of free intracellular calcium ions.

they induce a conformational change in the protein causing the intracellular portion to interact with one or more GTP-binding proteins (the G proteins). The G proteins may, in turn, modify the activity of an enzyme, which increases or decreases the amount of a “second messenger” molecule: Adenylyl cyclase may be induced to make higher levels of cyclic AMP (cAMP), or a phosphodiesterase may degrade cyclic nucleotides, or a phospholipase may convert phosphatidylinositol lipids to diacylglycerol and inositol trisphosphate (IP₃). These second messengers may alter calcium ion concentrations or modify ion channel activities leading to cell depolarization which, in turn, sends a nerve signal to the brain.

Margolskee et al. characterized a taste cell-specific G protein which they named gustducin because of its similarity to the retinal G protein, transducin.^[3] Gustducin is able to activate a phosphodiesterase.^[4] These workers found that mice in which the gustducin gene is inactivated have diminished responses to both sweet and bitter tastes.^[5]

The second messenger cAMP increases in rat taste-cell membrane preparations upon treatment with sucrose or saccharin.^[6] In these experiments aspartame had no effect upon cAMP levels, consistent with the observation that rats are not able to taste aspartame.

The transduction of sweetness may also involve the second messengers IP₃ and calcium. Very recently, both sucrose and high-potency sweeteners were shown to lead to high intracellular levels of calcium ions.^[7] The high-potency sweeteners do so through the second messenger IP₃, which releases *intracellularly* stored calcium ions. Sucrose in contrast opens

ion channels on the cell surface that let *extracellular* calcium enter the cell. Results from Kinnamon's research group indicate that sucrose, high-potency sweeteners, and cyclic nucleotides close a potassium channel, and cause cell depolarization.^[8] Closing potassium leak channels should lead to an increase in the cell's membrane potential; it is not yet clear whether this causes cell depolarization directly, or if the increased positive potential triggers voltage-gated calcium channels.

Another issue which is not yet resolved concerns sugars. Do they act directly on a receptor protein or ion channel? There are reasons to suspect that sugars do not bind to a specific receptor site. First, sugars taste sweet only at high concentration (about 0.1M). This is in sharp contrast to the concentrations required for hormones, neurotransmitters, etc. to trigger their receptors (typically nanomolar or picomolar concentrations). Furthermore, it is well known that D- and L-sugars have comparable sweetness potencies; for example, the taste of L-glucose is comparable to that of D-glucose. These observations suggest that sugars might act *indirectly* on receptors or ion channels, through effects on the properties of the surrounding membrane lipids.

Are there multiple receptors for sweet taste? A review of the evidence indicates that there must be more than one receptor type.^[9] First, the chemist is immediately struck by the diversity of chemical structures (including sugars, sulfamates, heterocycles, ureas, arylguanidines, peptides, proteins, oximes, and terpenes) which can evoke sweet taste. It is unlikely that a single receptor binding site could accommodate all of the known sweet-tasting compounds. Second, we know that it is easy for humans to distinguish different taste qualities for different high-potency sweeteners. Most consumers can readily tell the difference between sugar and high-potency sweeteners and trained panelists can detect taste differences among different high-potency sweeteners. Third, blends of structurally different sweeteners (aspartame plus acesulfame, for example) produce synergy, a higher-than-predicted sweetness intensity based on potencies of the two individual sweeteners.^[10] On the other hand, structurally similar sweeteners, such as saccharin and acesulfame, do not show synergy; they are simply additive. Many more studies of this type would be required to get an estimate of the number of different types of sweetness receptor which might be involved.

In summary, the available evidence indicates that high-potency sweeteners utilize a different mechanism than sugars to trigger the response of taste cells. In addition, it appears that the receptors which mediate the sweetness of aspartame are different from those which respond to saccharin and acesulfame.

1.2. Measurement of Sweetness Potency

Quantitation of sweetness must be carried out by human panelists. Experimental animals cannot be used because it is impossible to evaluate the quality of taste which an animal detects. Also, there are substantial differences between species with respect to their response to high-potency sweeteners. Typically, taste panelists use a 15 cm line scale to rate

the sweetness of solutions of sweeteners.^[11] Panelists have been trained to rate a 5 % sucrose solution at the 5 cm mark, a 10 % sucrose solution at the 10 cm mark, and so forth. With practice, such data can be quite reproducible (usually ± 1 unit). Panelists then evaluate test solutions to determine what concentration of a high-potency sweetener matches a given concentration of sucrose.

Sweetness potency is usually expressed relative to a standard concentration of sucrose, on a weight basis. For example, 0.025 % aspartame is equivalent in sweetness to 5 % sucrose, so the *potency* is $5/0.025 = 200$ times higher than sucrose. High-potency sweeteners do not show a linear response relative to sugars. At the sweetness level of a 2 % solution of sucrose (about the taste recognition threshold), aspartame has a potency of 625 while at 10 % sucrose (about the level used in carbonated soft drinks), its potency is 110. Acesulfame has potencies of 204, 140, and 34, relative to 2 %, 5 %, and 10 % sucrose, respectively. Potencies reported in the literature are often measured near the threshold value. This is probably due to the tendency to want one's new sweetener to have the highest potency possible. The nonlinear response means that, at some point, increasing the concentration no longer produces increasing sweetness; the response asymptotically approaches a maximal value. Mathematical analysis of concentration–response curves indicates that aspartame, acesulfame, and saccharin have a maximal sweetness level of 16.0, 11.6 %, and 9.0 % sucrose, respectively.

2. Aspartame

Aspartame (L-aspartyl-L-phenylalanine methyl ester, APM; **1**) is currently the most widely used nutritive sweetener worldwide. Although this compound was known in the literature, its sweetness was discovered by James Schlatter, a chemist at G. D. Searle (now part of Monsanto), who in 1965 while working on an antiulcer compound licked his finger.^[12] Several analogues, especially more stable esters,^[13] were made and evaluated for sweetness potencies, taste profile, and toxicities. In the end, however, it was the first compound that was chosen for commercial development.

Aspartame is 160–180 times sweeter than sucrose. It has a good, clean sweet taste but its time–intensity profile differs from sucrose. It has a slower onset and a lingering sweet taste. Aspartame has also been reported to enhance the flavor of the foods. Therefore, when converting a sugar-based food to aspartame, the amount of aspartame needed is not necessarily 1/160–1/180 of the weight of sugar. Aspartame is caloric and yields about 4 kcal g^{−1}; however, because of its sweetness intensity, only a minute quantity is consumed resulting in a negligible calorie contribution. It is slightly soluble in water (about 3 g per 100 mL, pH 3, room temperature). The solubility increases with higher or lower pH as well as with increased temperatures, but degradation also occurs under these conditions; at high pH it cyclizes to the diketopiperazine. In aqueous solution, the relationship between pH and stability of aspartame is a bell-shaped curve with the maximum stability at pH 4.3.^[14] At higher or lower pH, the half-life of aspartame in aqueous solution diminishes quickly.

Currently, most soft drinks are formulated at pH 2–3. The ester group of the aspartame is very susceptible to hydrolysis and hence avoidance of excessive heat is desirable as degradation with concomitant loss of sweetness can be rapid. Aspartame was approved by the FDA (Food and Drug Administration) in 1981 for use in dry goods. Two years later it gained additional approval for use in carbonated beverages, and in 1993 was approved for use in baked goods, candies, and still beverages. It can be used in almost all food categories, but the major consumption is in beverages.

2.1. Chemical Synthesis

Aspartame (**1**) is a dipeptide composed of the two amino acids L-aspartic acid and L-phenylalanine. Many chemical syntheses have been reported; most involving the coupling of the two amino acid units having appropriate functional group protection with conventional peptide synthetic reagents.^[15] Research directed towards the development of synthetic processes has been concerned largely with the problems of increasing the yield and purity of the desired product while suppressing the formation of the by-products, especially those arising from the β -coupling of the aspartyl unit. A significant amount of effort has been expended to maximize the desired α -coupling through changes in reaction conditions and protection on the aspartyl nitrogen atom.^[16] It is fortuitous that the desired product crystallizes from the reaction mixture as the hydrochloride salt, leaving all of the undesired isomers in solution.^[17]

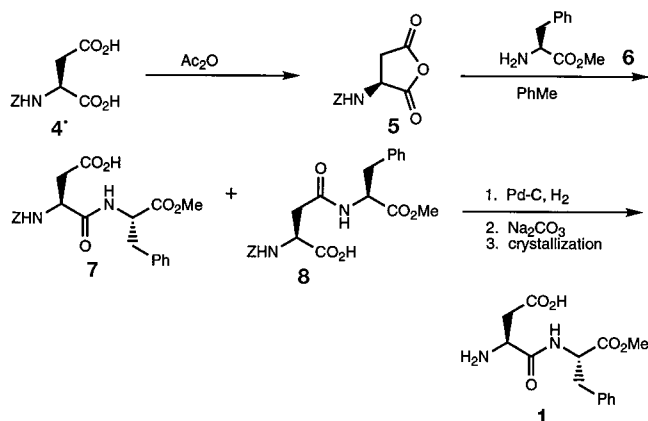
The chemical methods of industrial significance involve the dehydration of aspartic acid to form an acid anhydride, which is then coupled with the phenylalanine or its methyl ester to give the desired product. The two major processes are known as the Z- and F-processes, named after the protecting group used on the aspartyl moiety. Both of these processes produce some β -coupled products together with the desired α -aspartame (**1**), but the selective crystallization removes the undesired isomers. However, since the amino acid raw materials are expensive, they must be recovered from the by-products and waste streams for recycling.

2.1.1. The Z-Process

This process involves the dehydration of the benzyloxycarbonyl-L-aspartic acid (**4**) with acetic anhydride.^[18] The anhydride **5** is then coupled with the methyl ester of L-phenylalanine **6** in toluene to give a mixture of benzyloxycarbonyl α - and β -aspartames **7** and **8** (Scheme 1). The protecting group is removed by hydrogenolysis with Pd on carbon as the catalyst. Addition of sodium carbonate to adjust the pH of the resultant mixture of aspartame isomers to about pH 5 gives APM **1** upon crystallization.

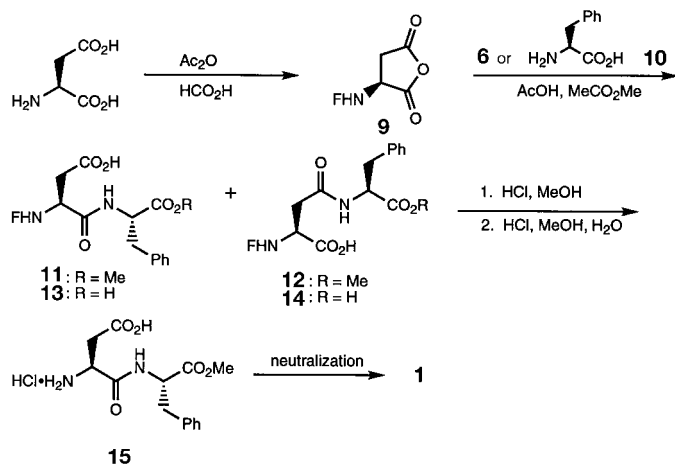
2.1.2. The F-Process

This process involves the protection of the amino group of aspartic acid with a formyl group (by treating aspartic acid



Scheme 1. Synthesis of aspartame (**1**) by the Z-process (Z = benzyloxy-carbonyl).

with acetic anhydride in the presence of formic acid) and concomitant dehydration to form the anhydride **9** (Scheme 2). The anhydride is then coupled either with L-phenylalanine (**10**)^[19] or its methyl ester **6**^[20] and the formyl group removed by acid hydrolysis. This reaction is accompanied by a number



Scheme 2. Synthesis of aspartame (**1**) by the F-process (F = formyl).

of other reactions that includes the hydrolysis of the esters **11** and **12**, and esterification of the acids **13** and **14**. The resultant mixture of α - and β -products is subjected to the esterification conditions of aqueous methanol in the presence of hydrochloric acid. α -APM hydrochloride **15** preferentially crystallizes out from this mixture and is then neutralized to yield APM **1**. This coupling procedure can be performed as a “one-pot” reaction.^[21] L-Aspartic anhydride, without amino group protection, has also been used in the synthesis of α -APM but the reaction produces a large amount of oligopeptides.^[22]

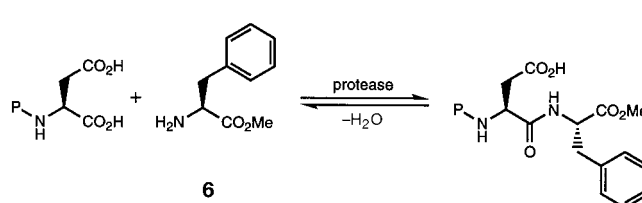
2.2. Enzymatic Synthesis

The application of biotechnology and biocatalysis toward the synthesis of the synthetic sweetener aspartame (**1**) has been extensively explored. Because of the presence of two carboxylic acid groups in the aspartic acid unit the chemical

process forms both α - and β -products, the use of enzymes that are both regio- and stereoselective is very desirable. As a result of its dipeptide structure, many variations of reverse proteolysis, that employ both kinetically and thermodynamically controlled approaches, have been investigated with different enzymes and under various reaction conditions. In addition, there have been many other approaches that utilize biocatalytic methods directed toward APM synthesis. These include enzymatic deprotection of an APM precursor, amination of methyl fumarylphenylalaninate, enzymatic esterification of α -L-aspartyl-L-phenylalanine, and the use of a synthetic polypeptide, poly(aspartate-phenylalanine). A number of these biocatalytic approaches to APM synthesis will be discussed below, but as this field is quite large, the reader is referred to the following review articles.^[23–25]

2.2.1. Peptide Coupling

The use of proteases to catalyze the synthesis of a peptide bond has been known for many years and is the major biocatalytic route to prepare precursors of APM. This thermodynamic approach is illustrated in Scheme 3. An *N*-



Scheme 3. Protease-catalyzed synthesis of an aspartame precursor (P = protecting group).

protected L-aspartic acid is reacted with methyl L-phenylalaninate (**6**) in the presence of a protease, usually a metalloprotease, to form an *N*-protected-APM derivative. This product is very often insoluble and thus shifts the equilibrium to favor synthesis of the peptide. The protecting group can then be removed either chemically or biologically to yield APM **1**.

In another type of peptide coupling reaction serine or cysteine proteases, which form acyl–enzyme intermediates when they hydrolyze peptide bonds, are used. The serine protease from yeast, carboxypeptidase Y, has been investigated extensively for this purpose.^[26] For APM, a blocked aspartic acid, usually the α -methyl ester, reacts to acylate the enzyme. This acyl–enzyme intermediate will form APM, in the presence of a competing nucleophile to water, such as methyl L-phenylalaninate (PM). Although conversions are generally low using this type of peptide coupling method, this approach has been investigated for APM synthesis using the endopeptidase from *Staphylococcus aureus* strain V8.^[27]

Over the past 20 years, there have been many variations of this reaction described in the literature and numerous review articles on reverse proteolysis utilizing both kinetic and thermodynamic approaches.^[28] The most common variations for the thermodynamic approach have been with the protecting group, P, the enzyme and the reaction conditions. Some of the more common protecting groups that have been used to enzymatically synthesize APM are shown in Table 1. Of these

Table 1. Protecting groups (P) used to synthesize APM-precursors by reverse proteolysis.

Protecting group	Abbreviation	Reference
acetoacetyl	AcAc	[25]
acetyl	Ac	[29]
benzoyl	bz	[30]
benzyloxycarbonyl	Z	[23, 24, 31, 32]
<i>tert</i> -butoxycarbonyl	Boc	[33]
formyl	F	[34]
isovaleryl	Iv	[25]
(<i>p</i> -methoxybenzyl)oxycarbonyl	Moz	[33, 35]
phenylacetyl	PhAc	[36, 37]

protecting groups, the one that has been most commonly used is the Z group. When the stoichiometry of the reaction is such that two equivalents of methyl phenylalaninate are used with one equivalent of Z-asp, the Z-APM·PM product precipitates out and shifts the equilibrium to greater than 95 % conversion.^[35] This is the basis of the commercial TOSOH process with thermolysin operated by Holland Sweetener (see below).^[24] One significant variation has been the use of racemic PM instead of only the L-isomer. Since the enzyme will only recognize the L-PM isomer to form the peptide bond, the unreacted D-PM isomer forms a salt and then, after acidification, the D-PM can be chemically racemized and recycled. A further improvement of this process employs a water-immiscible solvent, such as toluene or 4-methylpentan-2-one, which is added once the Z-APM·D-PM salt begins to precipitate. This results in lower enzyme inactivation and allows the process to be run in a continuous mode.^[38]

The most commonly used enzyme for this biosynthetic reaction is the metalloprotease thermolysin (EC 3.4.24.27) isolated from *Bacillus thermoproteolyticus*. The commercial source of the enzyme is called thermoase and is available from Daiwa Kasei Co. (Osaka, Japan).^[23] As the name implies, the enzyme is tolerant of high temperatures for extended periods of time as well as withstanding a variety of organic solvents. These features make it an excellent choice for industrial applications. In addition, immobilized enzyme^[32, 39–41] and membrane processes^[42, 43] have been developed using thermolysin. A stabilized form of the enzyme called a CLEC (cross-linked enzyme crystal) has also been shown to have utility to couple Z-asp and PM.^[44]

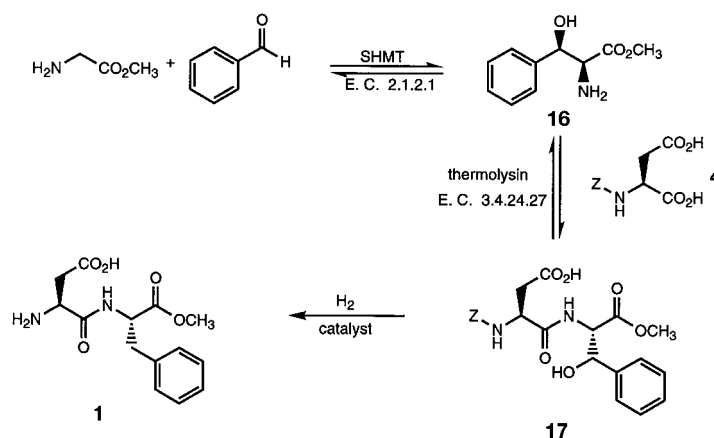
P-APM precursors have been synthesized by other enzymes such as papain^[33], pepsin,^[43, 45] *Pseudomonas aeruginosa* elastase,^[46] and aminopeptidase A.^[47] Most recently, site-directed mutagenesis of the gene encoding a neutral protease from *Bacillus proteolyticus* has been used to improve the coupling of Z-asp and PM relative to thermolysin.^[48]

Many solvent systems, both miscible and immiscible with water, have been explored in order to shift the equilibrium of this reaction.^[49] One method described by Homandberg and co-workers utilized organic cosolvents such as glycerol and other glycols to reduce the water content to favor synthesis.^[50] Other solvents such as acetonitrile,^[51] ethyl acetate,^[32, 52] *tert*-

amyl alcohol,^[40] and triethyl phosphate^[53] have been explored.^[54] A mixed solvent system of ethyl acetate and *tert*-amyl alcohol has also been shown to be quite effective with yields of 99 %.^[41]

2.2.2. Non-phenylalanine Route^[55]

Early in the development of APM processes, the high cost and lack of availability of L-phenylalanine was a key focus of chemists and biochemists alike. One approach was to prepare L-phenylalanine as a starting material and then couple it to form the sweetener **1**. An alternative approach was to build the L-phenylalanine side chain from inexpensive starting materials. Workers at W. R. Grace and Company explored a non-phenylalanine route to APM that utilized the enzyme serine hydroxymethyltransferase (SHMT) to prepare methyl L-erythro-phenylserinate (**16**) from methyl glycinate and benzaldehyde (Scheme 4). Although the enzyme is highly



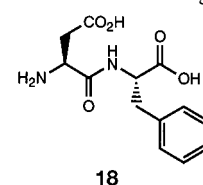
Scheme 4. Reaction sequence of a non-phenylalanine requiring route to aspartame (**1**) using two enzymatic steps followed by chemical hydrogenation.

stereospecific for the α -carbon, forming the *S*-isomer, the stereospecificity of the β -carbon is not as strict and as a result L-*threo*-phenylserine forms. However, under kinetically controlled conditions the formation of L-*erythro*-phenylserine is favored. Next, the methyl ester was coupled enzymatically with Z-aspartic acid (**4**) to form the adduct **17**. Catalytic hydrogenation was then used to remove the Z-protecting group as well as the hydroxy group to yield APM **1**.^[56]

2.2.3. Other Biocatalytic Reactions

Enzymatic Esterification

The enzymatic esterification of the dipeptide aspartyl-phenylalanine (AP, **18**) and *N*-blocked derivatives was described by Davino who used the enzyme subtilisin Carlsberg in the presence of high concentrations (60 %) of methanol for long periods of time.^[57] Due to the low concentration of AP used, the throughput for this type of reaction would be very low and not likely to



be practical. Another esterification procedure was described by Choi and co-workers.^[58] A number of proteases were tested and the best results (~40% yields) were obtained with α -chymotrypsin in 25% methanol.

Enzymatic Deprotection

As described in Table 1, many different protecting groups have been utilized to synthesize APM enzymatically. Some of these same protection methods have also been employed in chemical approaches to **1**. The Z group is removed by catalytic hydrogenation, a process that is very efficient and does not cause degradation of the resultant dipeptide. Other protecting groups are not as easy to remove due to the harsh conditions required, and the stability of the product under the reaction conditions can be of major concern. The use of enzymes or microorganisms to effect deprotection can, therefore, offer some significant advantages for deprotection over chemical methodologies.

The use of the enzyme penicillin acylase (EC 3.5.1.11) to deprotect *N*-phenylacetyl-blocked peptides has been well documented.^[59] The enzymatic removal of this protecting group from an APM precursor, PhAc-APM, has been described by Fuganti and Grasselli.^[36] More recently, *p*-substituted phenylacetyl APM derivatives were deprotected with this acylase as described by Stoineva and co-workers.^[37] Another protecting group, the phthalyl group, has been shown by Zmijewski and co-workers at Lilly to be removed from phthalimido-APM by an enzyme isolated from *Xanthobacter agilis*.^[60]

Poly(aspartyl-phenylalanine)

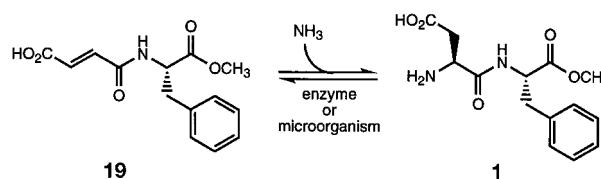
With the advent of recombinant DNA technology, several literature reports have cited the use of synthetic genes expressed in bacterial systems to form a polymer of aspartic acid and phenylalanine. This polymer can then be cleaved enzymatically to form the dipeptide α -L-aspartyl-L-phenylalanine (**18**) which can then be enzymatically esterified to form APM. The first report was by Searle Research in High Wycombe which described clones containing genes that coded for about 150 repeats of aspartylphenylalanine.^[61]

Cleavage of a polymer composed of aspartylphenylalanyllysine was achieved with trypsin producing the tripeptide Asp-Phe-Lys. Subsequent treatment with carboxypeptidase B yields the dipeptide **18**.^[58] APM was formed by enzymatic esterification as described above. A gene encoding 167 amino acids from the *N*-terminus of prochymosin followed by (Asp-Phe)₆₁ has been described.^[62] It was inserted into a plasmid and expression in *E. coli* yielded inclusion bodies of the fused poly(Asp-Phe) which was calculated as 11.2% of the total cellular protein. Although this is a clever approach, the practicality is limited due to the low expression efficiency and the need for enzymatic cleavage and esterification steps.

Amination of Methyl Fumarylphenylalaninate

With the relative ease of chemically synthesizing methyl fumarylphenylalaninate (**19**) from maleic anhydride and phenylalanine, the notion of amination with an ammonia

lyase-type enzyme to yield APM **1** has been contemplated for some time (Scheme 5). Because the substrate specificity for



Scheme 5. Amination of **19** to aspartame (**1**).

the known ammonia lyases is very strict, the enzyme activity was discovered through screening.^[63] This process, however, has not been practiced commercially, as the yields are extremely low.

Direct Coupling

The ideal enzymatic coupling scheme would utilize L-aspartic acid and methyl phenylalaninate in the presence of an enzyme. This would alleviate the need for expensive protecting groups as well as a prior chemical step to synthesize the APM precursor and a latter step to remove them. However, this would mean that the enzyme preparation must be free of esterase activity, since one substrate contains a methyl ester. Paul and co-workers at BioEurope (Toulouse, France) identified an enzyme from *Micrococcus caseolyticus* that was capable of carrying out this coupling reaction.^[64] Starting with 0.2M L-aspartic acid and 0.5M methyl phenylalaninate, the maximum APM yield was 35 mM. More recently, the BioEurope group with other colleagues have purified and characterized the aminopeptidase A (EC 3.4.11.7) from that strain, now called *Staphylococcus chromogenes*.^[47] The initial rate of APM synthesis with purified enzyme was 0.23 mM h⁻¹. Before this enzyme could be used in a process to prepare APM in quantity, the rate will undoubtedly need to be substantially increased.

Fermentation

Two Japanese companies have reported on fermentation routes to produce APM directly by incubating microorganisms with L-asp and PM. In the case of the Ajinomoto Company, a solution of L-asp and PM was incubated with a selected bacterial strain and allowed to react, usually between 16 and 24 h. Yields of these reactions ranged from 73–576 mg dL⁻¹.^[65] Toya Soda Manufacturing Company, Ltd. was issued a patent for a fermentation route that claimed a number of bacterial and yeast strains which were capable of synthesizing APM.^[66] In a typical example, 1.0M L-asp plus 1.0M PM in phosphate buffer was incubated with mycelium from a 500 mL culture of a specific strain for 16 h at 37°C with shaking. The yield of APM was reported to be 100 mg (1.4%).

The work described here on fermentation approaches for the synthesis of APM **1** is interesting and scientifically intriguing, but practically speaking the yields are just too low to be of commercial significance. Much additional work, therefore, would be needed to substantially increase the reaction yield before a commercial process could be realized.

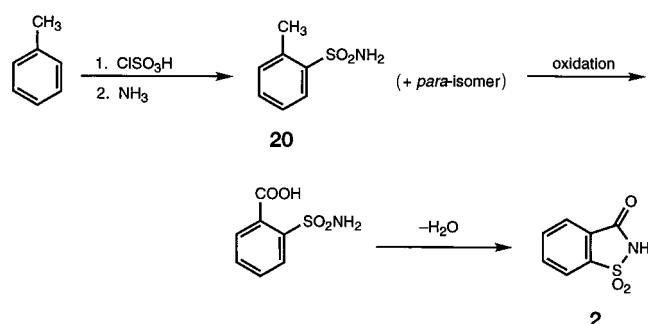
2.3. Summary

As evidenced here, a very large amount of research has been, and continues to be, directed toward the biochemical production of APM. The Holland Sweetener Company does use a process that utilizes this technology. As further advances in biotechnology are made, additional “green” processes to **1** are likely to be developed.

3. Saccharin

Saccharin (1,2-benzisothiazol-3(2*H*)-on-1,1-dioxide, **2**) is currently the most widely used nonnutritive sweetener in the world.^[67] This compound was accidentally discovered by Remson and Fahlberg in 1878 at the Johns Hopkins University, Baltimore, and has been sold since 1885.^[68] It is about 300 times sweeter than sucrose which, on a cost per sweetness basis, makes it cheaper than sugar. Thus, saccharin has a high usage in third world countries. It also had considerable usage during the World Wars when sugar was in short supply.^[67] The chemical stability of this sweetener and low cost make it suitable for use in a wide variety of applications such as toothpaste, mouthwash, and pharmaceuticals, as well as in food and beverages. Saccharin, however, does not provide a “clean” sweet taste, and some users can detect a bitter or metallic off-taste. As the parent compound **2** is only sparingly soluble in water, the sweetener is usually used as the sodium or calcium salt. The safety of saccharin has been questioned due to the report of problems associated with bladder cancer in rats. However, the interpretation of these results is still being debated.^[67] It is excreted unchanged from man with little absorption.^[69]

There are two major approaches to the chemical synthesis of saccharin (**2**), namely the oxidation of the *o*-toluenesulfonamide **20** or the replacement of the amino group of anthranilic acid by a sulfur moiety.^[70] Treatment of toluene with chlorosulfonic acid gives *o*- and *p*-toluenesulfonyl chlorides, which are then converted to the sulfonamides by reaction with ammonia; the *ortho*-isomer predominates (Scheme 6). Separation of the isomers can be accomplished

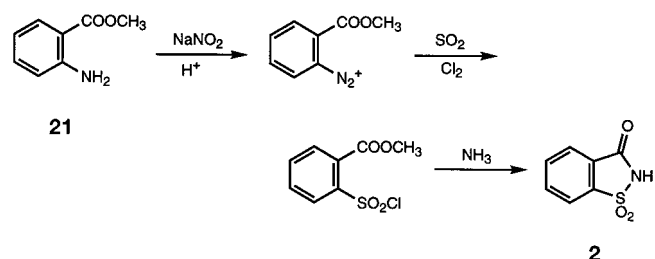


Scheme 6. Synthesis of saccharin (**2**) from toluene.

at this or a later stage.^[71, 72] The *o*-toluenesulfonamide can be oxidized to the corresponding carboxylic acid with a variety of agents including potassium permanganate,^[71] potassium chro-

mate,^[73] chromic acid,^[74] electrochemically,^[75] air,^[76] or oxygen.^[77] The *ortho* isomer is dehydrated to give the sweetener **2**.^[73, 78]

The alternative sequence (Scheme 7), a variation on the Maumee process, starts from anthranilic acid. The process involves diazotization of methyl anthranilate (**21**) and then

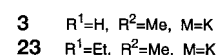
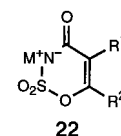


Scheme 7. Synthesis of saccharin (**2**) from methyl anthranilate **21**.

treatment of the diazonium salt with sulfur dioxide and chlorine gas to give the sulfonyl chloride which is then treated with ammonia to give **2**.^[79] Variations have been advocated to improve yields and impurity profiles.^[78] The original Maumee process involved reaction of the intermediate diazonium salt with sodium disulfide and subsequent reaction with chlorine.^[67, 80]

4. Acesulfame-K

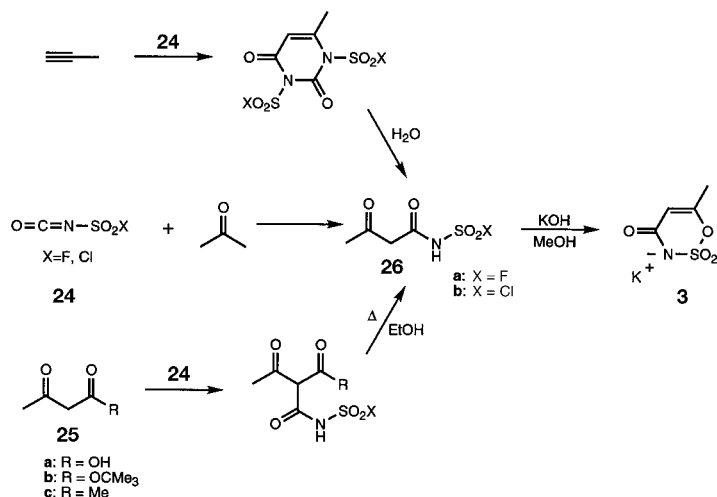
Acesulfame-K (Ace-K, **3**) has been developed as a sweetener by Hoechst^[81] as a result of the discovery of oxathiazinone dioxides **22** by Claus and Jensen in 1970.^[82] Oxathiazinone dioxides **22** that have hydrogen or lower alkyl groups as the R¹ and R² substituents taste sweet. Although the derivative **23** (R¹ = Et, R² = Me) is the sweetest oxathiazinone dioxide yet discovered, Ace-K **3** was chosen for development as the most suitable sugar substitute because it has a more pure sweet taste than the other oxathiazinone dioxides. It is approximately 120 times sweeter than sucrose and has a high water solubility, whereas most synthetic sweeteners have unsatisfactory water solubility.^[83] For practical purposes, when formulated in food products, it is stable to hydrolysis, even in highly acidic beverages, and is nontoxic.^[84, 85] Metabolism involves ring cleavage to give acetoacetamide-*N*-sulfonic acid, which is further degraded to give physiologically benign substances.^[86]



4.1. Chemical Approaches

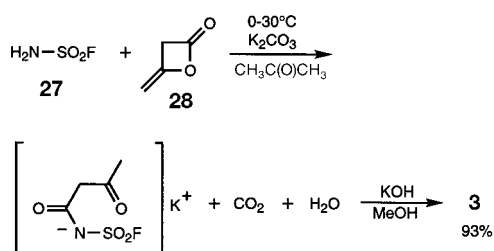
Early methods for Ace-K synthesis used chlorosulfonyl or fluorosulfonyl isocyanate (**24**) as the starting material. Although these methods allow the formation of a wide range of oxathiazinone dioxide derivatives, only Ace-K **3** formation will be discussed here. A detailed review of oxathiazinone

dioxides synthesis was published by Clauss and Jensen in 1973.^[84] Reactions of chloro- or fluorosulfonyl isocyanate (**24**) with propyne,^[82] acetone,^[81, 87, 88] acetoacetic acid (**25a**),^[89] *t*-butyl acetoacetate (**25b**),^[90] or acetylacetone (**25c**)^[87] give *N*-chloro or *N*-(fluorosulfonyl)acetoacetamide (**26**), which is then cyclized by methanolic potassium hydroxide to give Ace-K **3** (Scheme 8).



Scheme 8. Synthesis of Ace-K **3** from halosulfonyl isocyanates **24** through sulfonyl acetoacetamide **26**.

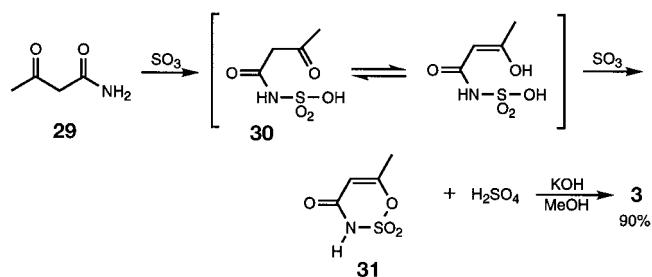
Salts of *N*-(fluorosulfonyl)acetoacetamide (**26**) can also be formed by treating diketene **28** with amidosulfonyl fluoride **27** (the product of partial hydrolysis of fluorosulfonyl isocyanate) in the presence of organic nitrogen bases^[91] or inorganic bases (Scheme 9).^[92] The use of potassium carbonate, under hetero-



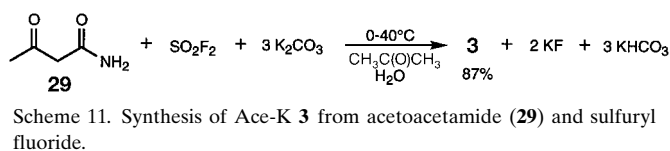
Scheme 9. Synthesis of Ace-K **3** from amidosulfonyl fluoride **27**.

geneous reaction conditions, is preferred because the *N*-(fluorosulfonyl)acetoacetamide salt formed is a crystalline solid.^[92, 93] Although high yields of Ace-K **3** can be obtained by the above methods, the difficulty in the preparation and handling of chloro- or fluorosulfonyl isocyanate limits their industrial utility.

An alternative method involves the treatment of acetoacetamide (**29**) with at least two equivalents of sulfur trioxide (Scheme 10).^[94] The initial addition of sulfur trioxide to acetoacetamide (**29**) presumably forms *N*-sulfoacetoacetamide (**30**), which is then dehydrated by sulfur trioxide to form oxathiazinone dioxide (**31**). Neutralization with potassium hydroxide gives Ace-K **3**.^[96] Reaction of acetoacetamide (**29**) with sulfonyl fluoride and potassium carbonate gives Ace-K **3** in high yield (Scheme 11).^[96] Some other fluorosulfonyl



Scheme 10. Synthesis of Ace-K **3** from acetoacetamide (**29**) and sulfur trioxide.



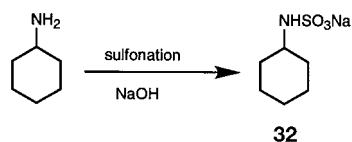
Scheme 11. Synthesis of Ace-K **3** from acetoacetamide (**29**) and sulfonyl fluoride.

compounds (i.e. chlorosulfonyl fluoride, pyrosulfonyl fluoride, and chloropyrosulfonyl fluoride) can also be used, but sulfonyl fluoride gives the highest yield of Ace-K. Yields are even higher when aqueous acetone (1–12 % w/w in water) is used as solvent.

5. Cyclamates

Cyclamates are salts of cyclohexylaminosulfonic acid (cyclamic acid). Sodium cyclamate (**32**, often also called cyclamate) is used as a nonnutritive sweetener and the analogous calcium salt is used especially in low sodium diets. This product is available only in some parts of the world, such as Canada. It was accidentally discovered by a graduate student, Michael Sveda, in 1937 at the University of Illinois.^[73, 97] The patent was issued to Du Pont in 1942, but later it became the property of Abbott Laboratories, Illinois when Abbott submitted an NDA (New Drug Application) in 1950. In 1958, the FDA classified sodium cyclamate as a GRAS (Generally Regarded As Safe) sweetener. Later in 1966, it was reported that sodium cyclamate could be metabolized in the intestine to cyclohexylamine, which had been shown to cause chromosomal damage in animals and, when administered with saccharin (10:1), tumors in rats.^[98] In 1970, the FDA banned the use of cyclamate. Abbott Laboratories did additional safety studies and submitted a petition twice but it was denied by the FDA. Cyclamate use is not permitted in the USA.

Cyclamate is 30 times sweeter than sucrose. It has a bitter off-taste, but has good sweetness synergy with saccharin. It is soluble in water, and its solubility can be increased by preparing the sodium or calcium salt. It is stable over a wide range of pH and temperatures. Many chemical syntheses have been reported of this simple compound **32**; all of them use the sulfonation of cyclohexylamine approach (Scheme 12). Sulfonation can be achieved with sulfamic acid, a salt of sulfamic acid, or sulfur trioxide.^[99] With the current regulatory ban in the USA, and the simple nature of the molecule, little work is being done on this sweetener.



Scheme 12. Synthesis of sodium cyclamate.

6. Sucralose

Sucralose (TGS) **33**, 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose, is a trichloro disaccharide nonnutritive sweetener that is currently used in Canada and Australia and recently approved in the USA. This compound was discovered through a systematic study where sucrose derivatives were prepared. It was found that substitution of certain hydroxy groups by a halogen atom increased the sweetness potency dramatically.^[100] Sucralose was chosen as the development candidate by Tate and Lyle.^[101, 102] It is licensed to McNeil Speciality (a Johnson & Johnson subsidiary) in the USA.

Sucralose is 450–650 times sweeter than sucrose. It has a pleasant sweet taste and its taste quality and time intensity profile is very close to that of sucrose. It has a moderate synergy with other nutritive^[103] and nonnutritive sweeteners.^[104] It is very soluble in water and is stable over a wide range of pH and temperatures. There is some discolorization and it does liberate HCl when stored at high temperatures.^[105]

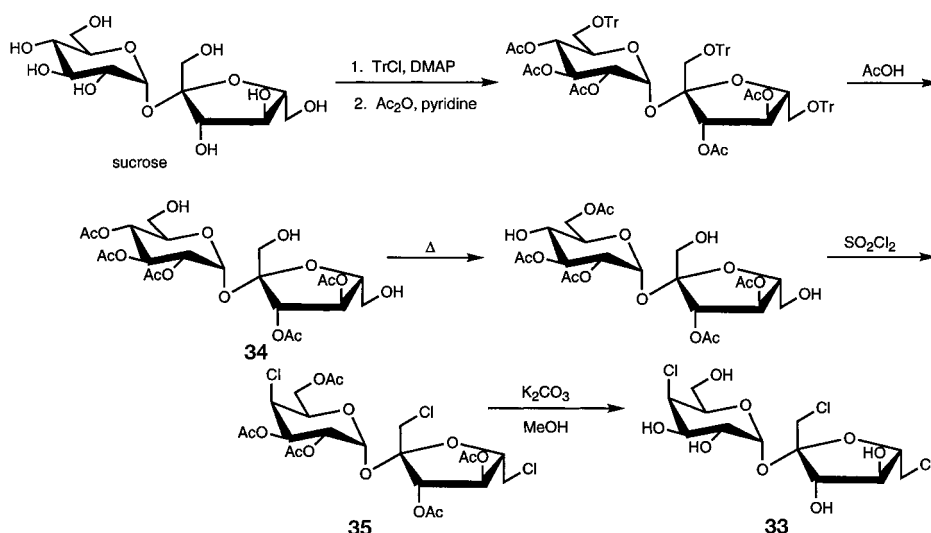
6.1. Chemical Approaches

The synthesis of TGS **33** involves a series of selective protection and deprotection steps so that the 4-hydroxy group can be converted to a chloro atom with inversion of configuration (Scheme 13).^[102, 105] Differentiation between the primary hydroxy groups of the two sugar moieties is also required. The primary hydroxy groups are protected with the

bulky trityl group, and then the secondary hydroxy groups are acetylated with acetic anhydride or acetyl chloride.^[107] Deprotection of the primary hydroxy groups provides **34**. The acetyl group at the C-4 position of the glucose moiety migrates to the primary hydroxy group of the glucose moiety when **34** is heated under reflux at 125 °C in 4-methyl-pentan-2-one and acetic acid. This key migration allows the primary hydroxy group of the glucose unit to be protected in the subsequent chlorination step and also provides for the selective deprotection of the secondary hydroxy group at C-4. Treatment of the free hydroxy groups with sulfuryl chloride affords the corresponding trichloro disaccharide **35** which is then deprotected to give the sucralose.^[108] Since there is a stereochemical inversion at the C-4 center of the glucose moiety, the product formed is a trichlorogalactosylfructose. Other chlorinating agents, such as phosgene and thionyl chloride in the presence of triphenylphosphane oxide or sulfide, have also been advocated for the chlorination reaction.^[109] The usefulness of sucrose 6-esters in the preparation of sucralose has prompted a number of chemical and enzymatic approaches to these compounds.^[110] The chemical methods are based on regioselective cleavage of a 4,6-orthoester.^[111]

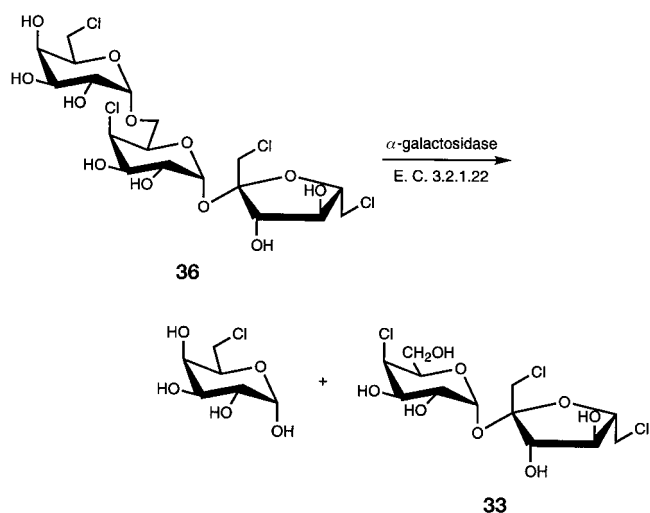
6.2. Enzymatic approaches

Due to the lack of synthetic methodology that offers stereochemical and regioselective control, chemical methods to prepare derivatives of carbohydrates are generally much more difficult than reactions with amino or nucleic acids.^[112] The use of enzymes or microbial cultures to augment synthetic organic chemistry and carry out selected functionalization of complex molecules has been widely documented in the growing field of biocatalysis.^[113] Such regio- and stereochemical control is needed in the synthesis of the synthetic sweetener sucralose **33**.

Scheme 13. Synthesis of TGS **33** from sucrose. The 4-hydroxy group is selectively deprotected by chemical transformations. DMAP = 4-dimethylaminopyridine, Tr = triphenylmethyl (trityl).

6.2.1. Trisaccharide cleavage

This process begins with the trisaccharide raffinose (6-*O*- α -D-galactopyranosyl-sucrose) followed by chemical chlorination with thionyl chloride in the presence of triphenylphosphane and triphenylphosphane oxide to yield tetrachlororaffinose **36** (TCR, *O*- α -D-6-chloro-6-deoxy-galactopyranosyl-(1 $\rightarrow$ 6)- α -D-4-chloro-4-deoxygalactopyranosyl-(1 $\rightarrow$ 2)- β -D-1,6-di-chloro-1,6-dideoxyfructofuranoside)(Scheme 14). The TCR



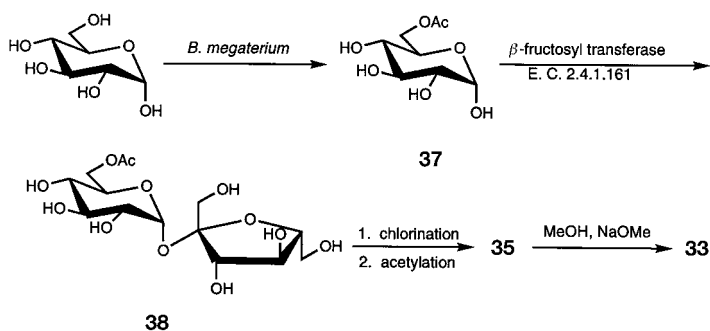
Scheme 14. Cleavage of 6-chloro-6-deoxygalactose by enzymatic hydrolysis with an α -galactosidase.

is isolated as the heptaacetate ester, which after ester hydrolysis, is enzymatically treated with an α -galactosidase to remove the 6-chloro-6-deoxygalactosyl moiety from the 6-position to yield TGS (**33**).^[114, 115]

The α -galactosidase (EC 3.2.1.22) employed here is the same one that is utilized in the sugar beet industry to hydrolyze raffinose in beet sugar molasses to aid in the production of sugar.^[116] This commercial enzyme was derived from the fungal strain *Mortierella vinacea* var. *raffinoseutilizer* (ATCC 20034). In addition to this strain, other fungal strains possessing this activity have also been isolated which include *Circinella muscae*, *Absidia griseola* and *Aspergillus niger*.^[114] Reported conversion of TCR **36** to TGS **33** is in the 60–70 % range, depending on the reaction conditions used.

6.2.2. Bioorganic synthesis^[117]

Another route to TGS utilizes both chemical and biocatalytic transformations.^[118] Glucose was converted to glucose-6-acetate (**37**) by *Bacillus megaterium* with a maximum concentration of 15 g L⁻¹ (Scheme 15). A specific β -fructosyl transferase (EC 2.4.1.161) isolated from *Bacillus subtilis*, using sucrose as the fructosyl donor with **37** as the acceptor, formed sucrose-6-acetate **38** with maximum concentrations of 120 g L⁻¹, representing a yield of 58 %. Following chemical chlorination and acetylation, 4,1',6'-trichloro-4,1',6'-trideoxygalacto-sucrose pentaacetate (**35**) formed with a 39 % molar yield. Chemical deesterification yielded TGS **33** with a 90 % molar yield. Although this route to TGS is comprised of two

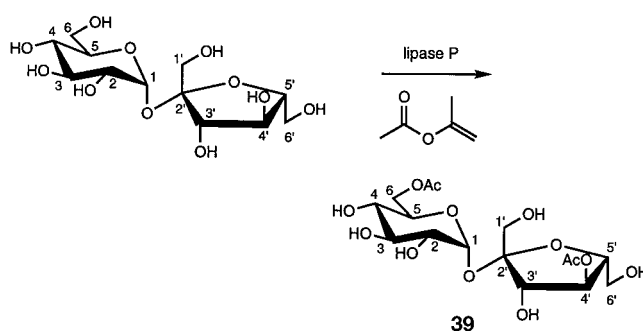


Scheme 15. Synthesis of TGS **33** from glucose through a combination of chemical and biochemical steps.

biocatalytic and two chemical steps, it does show the versatility of combining both approaches into one manufacturing process.^[119]

6.2.3. Regioselective Acylation

As discussed by Klibanov, regioselective chemical reactions of carbohydrates are particularly difficult due to the large number of hydroxyl groups in these types of molecules.^[120] The use of enzymes in organic solvents to catalyze these types of reactions has been well documented and offers the synthetic chemist an alternative approach to this complex type of reaction.^[121] In the case of TGS, Dordick *et al* have described the enzymatic preparation of a useful intermediate **39** from sucrose, (Scheme 16).^[122] In this reaction, lipase P



Scheme 16. Regioacylation of sucrose with isopropenyl acetate to form 4',6-di-O-acetylsucrose.

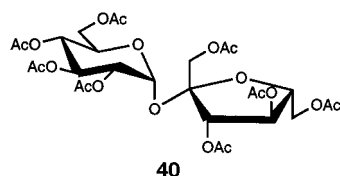
(*Pseudomonas* sp.) from Amano was used with isopropenyl acetate to acylate the 4' and 6 position of sucrose. Chlorination of this intermediate yields TGS **33**.

6.2.4. Regioselective Deacylation

This approach has been used to synthesize intermediates of TGS, described by Palmer and Terradas and Bornemann *et al*.^[122] As shown in Table 2 selected enzymes under specific reaction conditions, i.e. organic solvent and pH, will deacylate sucrose octaacetate **40** regioselectively to produce a number of potential intermediates in the preparation of TGS. These include 2,3,4,6,1',3',6'-heptaacetyl-sucrose, 2,3,4,3',4'-pentaacetyl-sucrose and 2,3,6,3',4'-pentaacetyl-sucrose.

Table 2. Regioselectivity of selected lipases, proteases, and carbohydrases toward **40**.^[123]

Enzyme	Company	Source	Position deacylated
lipases			
AY30	Amano	<i>Candida cylindracea</i>	4', 1'
PPL	Sigma	porcine pancreas	4'
AP12	Amano	<i>Aspergillus niger</i>	4, 6
SP-435	Novo	<i>Candida antarctica</i>	6', 1'
proteases			
alcalase	Novo	<i>Bacillus licheniformis</i>	1', 6'
proleather	Amano	<i>Bacillus subtilis</i>	1', 6'
carbohydrases			
α -galactosidase	Amino	<i>Aspergillus niger</i>	4

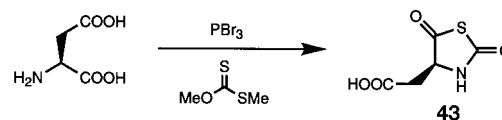


7. Alitame

Alitame **41** is a dipeptide-derived, nutritive sweetener found by Pfizer, through a discovery program, in 1983.^[124–126] It is currently used in Australia, China, and Mexico with approval in the USA pending. Alitame is 2000 times sweeter than sucrose. It has a pleasant sweet taste with no aftertaste. Its time–intensity profile is similar to that of aspartame but is more stable. At pH 2–4, its half-life is twice that of aspartame. It has been reported to develop an occasional off-flavor in soft drinks that can be minimized, or even avoided, by the addition of EDTA.^[127] It has sweetness synergy with saccharin.

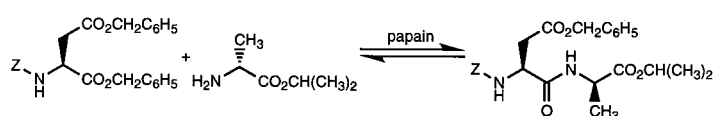
Alitame contains the two amino acids L-aspartic acid and D-alanine and a tetramethylthietane moiety. The synthesis involves the coupling of the two amino acids and thietane moiety by conventional peptide synthesis techniques.^[125] The order in which the three units are coupled is not important. The aminothietane moiety is prepared from diisopropyl ketone (Scheme 17). Diisopropyl ketone is brominated with phosphorus tribromide to give 2,4-dibromo-2,4-dimethylpen-

tane-3-one. This dibromo compound is cyclized by treatment with hydrogen sulfide in presence of sodium methoxide to give 2,2,4,4-tetramethyl-3-oxothietane. The reductive amination of the ketone with ammonium acetate and sodium cyanoborohydride or by heating it in the presence of formamide and formic acid (Leuckart reduction) gives the amino-tetramethylthietane moiety **42**. Scheme 18 shows the activation of the aspartyl unit as the thiocarboxylic anhydride (**43**).^[124, 125, 128]

Scheme 18. Synthesis of the thiocarboxylic anhydride **43** from L-aspartic acid.

7.1. Enzymatic Approaches

For the most part, the synthesis of alitame has generally been carried out by chemical means. However, as alitame is a dipeptide amide this sweetener is a candidate for peptide coupling. A synthetic pathway has been described by Barbas and Wong utilizing the enzyme papain for the synthesis of an alitame precursor (Scheme 19).^[129] Upon hydrogenation, the

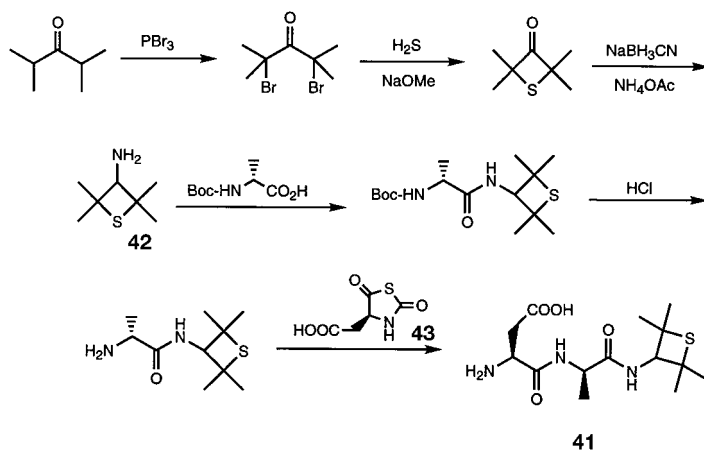


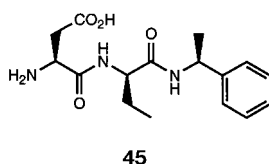
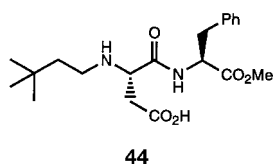
Scheme 19. Coupling of dibenzyl Z-L-aspartate with isopropyl D-alaninate in the synthesis of alitame.

Z- and benzyl-protecting groups are removed and the remaining dipeptide ester, L-Asp-D-Ala(OiPr), can be converted into alitame by chemical coupling to 3-amino-2,2,4,4-tetramethylthietane (**42**, see Scheme 17).

8. Summary and Outlook

A number of companies and universities are still actively pursuing the search for, and development of, new nonnutritive synthetic sweeteners. Economic issues are driving these compounds to be extremely potent on a sweetness-to-weight basis when compared to sucrose. Many of these compounds have not been approved for use in commercial products and their commercial development still has to be seen. Indeed, these potential next-generation sweeteners contain a diverse array of functionality ranging from dipeptide derivatives such as **44** and **45**^[130, 131] to guanidines^[132] and ureas.^[133] Several of the new dipeptide sweeteners have had X-ray structures reported as exemplified by **44** and **45**.^[133] There is still much work to be done before any of these next-generation sweeteners are approved for use. This includes the development of viable processes, although with the significant increases in potencies the volumes at commercial scale are lower significantly relative to the sweeteners discussed above. Refine-

Scheme 17. Synthesis of alitame **41**.



ments in smaller scale processes often have less commercial impact because of the smaller volumes involved.

However, one of these next-generation sweeteners, Neotame **44**, has been submitted to the USA FDA for approval as a tabletop sweetener by Monsanto. This compound is 8000 times sweeter than sucrose and has a clean sweet taste profile. It can be prepared by a reductive alkylation of aspartame (**1**).^[131] This new sweetener also appears to have increased stability under a variety of conditions relative to **1**. These improved properties, as well as the cost advantages, make Neotame **44** a strong commercial, next-generation sweetener candidate.

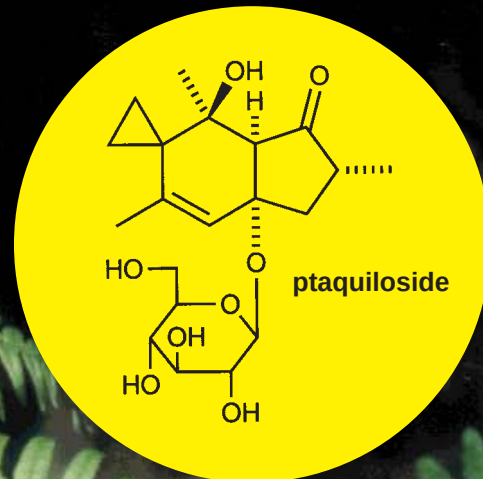
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Isolation, Chemistry, and Biochemistry of Ptaquiloside, a Bracken Carcinogen

Kiyoyuki Yamada,* Makoto Ojika, and Hideo Kigoshi

Bracken (*Pteridium aquilinum*) is a toxic and yet edible plant which is distributed in many parts of the world. The carcinogenicity of bracken has been a long-standing problem. This review provides an account of the extensive studies on a bracken carcinogen. Development of a new and mild extraction method coupled with a carcinogenicity test for rats as a bioassay

led to the discovery and isolation of ptaquiloside; the biological activities of this long-sought carcinogen are described here. The ultimate carcinogen derived from ptaquiloside is so reactive that it not only efficiently alkylates sulfur-containing amino acids and DNA, but also cleaves DNA. The molecular mechanism of this DNA cleavage was determined. Further-

more, both enantiomers as well as artificial analogues of the ultimate carcinogen were synthesized, and their DNA-cleaving activities were evaluated. Related studies on the bracken carcinogen are also briefly described.

Keywords: bioorganic chemistry • DNA cleavage • glycosides • structure elucidation • terpenoids

1. Introduction

The bracken fern, *Pteridium aquilinum* (L. Kuhn), is widely distributed throughout the world and is consumed as a human food in Japan and some other countries. Its toxic effects on livestock have been known since the end of the 19th century; cattle that consumed bracken exhibited cattle bracken poisoning.^[1-3] The major feature of this syndrome is the depression of bone-marrow activity, resulting in severe leucopenia, thrombocytopenia, and the hemorrhagic syndrome. The earliest evidence for the carcinogenicity of the bracken fern was reported by Rosenberger and Heesch, who described the changes in the nature of polypus tumors in the urinary bladder mucosa accompanied by haematuria in cattle that ingested the bracken fern.^[4] The carcinogenicity was unambiguously demonstrated by Evans, who reported that rats fed diets containing the bracken fern developed multiple ileal adenocarcinomas;^[5] this result was confirmed by many research groups. Furthermore, it was shown that the carcinogenicity of young bracken (Figure 1) was greater than that of mature bracken (Figure 2) and that the carcinogenicity of bracken treated with hot water containing sodium bicarbonate or wood ash remarkably decreased.^[2] In spite of the enormous efforts made by many groups in the search for a bracken carcinogen, its isolation was unsuccessful. This was made difficult by two major factors: a) the instability of the



Figure 1. Young bracken used as human food.



Figure 2. Mature bracken.

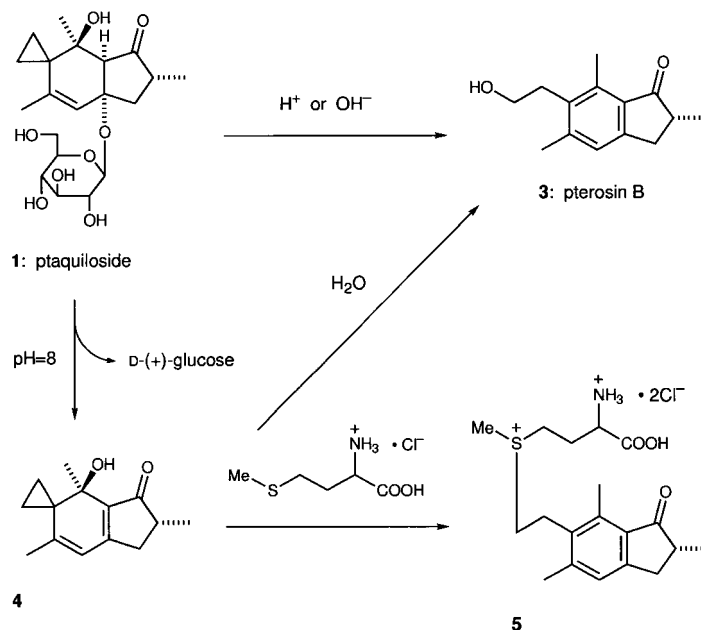
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carcinogen and b) the nature of the assay system; various short-term tests for the bioassay were applied without success.^[2, 6]

2. Isolation and Biological Activities of Ptaquiloside

In 1978 Hirono reported that an aqueous extract obtained by treatment of bracken with boiling water for three minutes was carcinogenic to rats.^[7] We were interested in this result, which clearly showed that the bracken carcinogen could be extracted in boiling water. Therefore, we started to fractionate the aqueous extract of bracken on the basis of the carcinogenicity test for rats, although the test required large amounts of samples and took a long time. After five separation steps employing solvent partitions (water/butanol) and neutral resins (Amberlite XAD-2 and Toyopearl HW-40), the strongly carcinogenic fraction was obtained. This fraction was further separated by repeating normal and reverse-phase chromatography three times to result in the isolation of an unstable new compound termed ptaquiloside (**1**, Scheme 1), which later proved to be the long-sought carcinogen of bracken.^[8, 9]

Ptaquiloside was obtained in low yield (0.2 g from 1 kg of bracken powder) by the bioassay-guided fractionation procedure, as most of the product decomposed, while it was isolated in much better yield (ca. 1 g from 1 kg of bracken powder) by the improved extraction method.^[10] The development of a new and mild extraction method in conjunction with the use



Scheme 1. Reactions of ptaquiloside (**1**) and the ultimate carcinogen **4**.

of the carcinogenicity test for rats as a bioassay was the key to the successful isolation of **1**. In the same year (1983) that we isolated **1**, van der Hoeven et al. reported the isolation and gross structure of a mutagenic compound named aquilide A from bracken which seemed to be identical to ptaquiloside.^[11]

The biological activities of ptaquiloside were evaluated in detail. Thus, **1** was unambiguously shown to be a carcinogen;

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tumors developed in both the ileum and the urinary bladder, target organs of bracken carcinogenicity, of all rats given diets containing **1**.^[12, 13] It was also demonstrated that **1** causes cattle bracken poisoning,^[14] and it proved to be responsible for bright blindness, progressive retinal degeneration (PRD), in sheep.^[15]

3. Structure and Reactivity of Ptaquiloside

3.1. Structure

Ptaquiloside (**1**) is a colorless amorphous compound with the molecular formula $C_{20}H_{30}O_8$.^[8, 16] In aqueous solution **1** gradually converts into pterosisin B (**3**)^[17] and D-glucose. The presence of the partial structures A–G (Figure 3), which

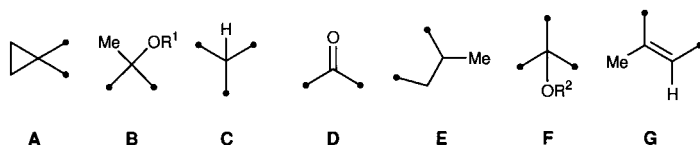
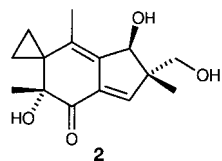


Figure 3. Partial structures of ptaquiloside (**1**).

contain all the carbon atoms of the aglycon part of **1**, was revealed by ^1H and ^{13}C NMR spectroscopy. However, the correlation of these partial structures was difficult with the NMR spectroscopic methods available in the early 1980s, and the elucidation of the gross structure^[8, 16] was first made possible by long-range selective proton decoupling (LSPD) experiments.^[18] The absolute stereostructure of **1** was determined by X-ray crystallographic analysis of ptaquiloside tetraacetate.^[19] Thus, **1** was shown to be a norsesquiterpene glucoside of the illudane type, a new type of carcinogen. In the 1970s, a large number of indanone-type sesquiterpenes—such as pterosisin B (**3**) as characteristic constituents of bracken—were isolated;^[20] they are presumably biosynthesized from the illudane-type precursors such as ptaquiloside. Illudane-type sesquiterpenes occur rather rarely in nature. A representative example is illudin-S (**2**), which is isolated as a toxic compound from a bioluminescent mushroom.^[21] Whereas **1** reveals potent cytotoxicity, **2** is known to have antitumor activity.



3.2. Reactivity

As previously mentioned, ptaquiloside (**1**) is an unstable compound which easily undergoes reaction with acids or bases to give stable aromatic compounds with the indanone skeleton, such as pterosisin B (**3**, Scheme 1).^[16] In a weakly alkaline aqueous solution (pH 8), **1** was readily transformed into the unstable dienone **4** with concomitant liberation of D-glucose (Scheme 1). Dienone **4** gradually reacted to form **3** under alkaline conditions, whereas it was immediately converted into **3** under weakly acidic conditions. Dienone **4** is a

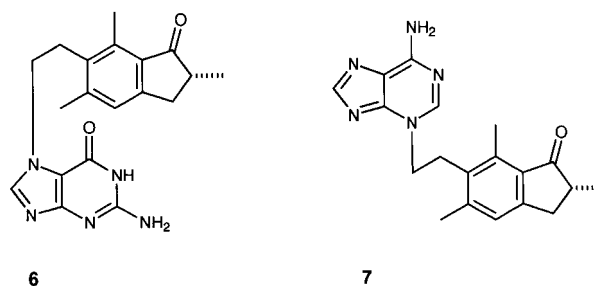
strong electrophile and acts as a powerful alkylating agent toward a variety of nucleophiles such as amino acids. The heteroatoms (oxygen, nitrogen, and sulfur) of amino acids are expected to be alkylated by **4**. Indeed, during the reaction of methionine and **4**, the sulfur atom of the amino acid was selectively alkylated to provide S-alkylmethionine **5**. This result indicates that the toxic indanone **4** is effectively converted into the nontoxic indanone compound by a sulfur-containing amino acid. Since indanone compounds such as pterosisin B show no carcinogenicity,^[20] sulfur-containing amino acids can potentially be used as detoxifying agents for ptaquiloside.

4. DNA Damage by the Ultimate Carcinogen

The covalent binding of carcinogenic alkylating agents with DNA is an important event in the mechanism of action of the agents, and these chemical modifications (damages) of DNA are generally thought to trigger chemical carcinogenesis.^[22] Carcinogens are divided into those that react directly with DNA and/or proteins without enzymatic activation, and those that require metabolic activation to produce reactive electrophiles, termed ultimate carcinogens, which react with DNA and/or proteins.^[22, 23] The chemical properties of ptaquiloside indicate that it is to be classified as a directly acting carcinogen and that the dienone **4** is the ultimate carcinogen, the activated form of **1**. Considering the fact that most natural carcinogens undergo metabolic activation to lead to ultimate carcinogens, **1** is unique in that it produces the ultimate carcinogen **4** without metabolic activation. In the case of carcinogens that require metabolic activation, it is generally difficult to obtain adequate amounts of the ultimate carcinogens necessary for chemical studies. Therefore, it was advantageous that the amount of the ultimate carcinogen **4** sufficient for bioorganic studies was readily available in the case of the bracken carcinogen **1**.

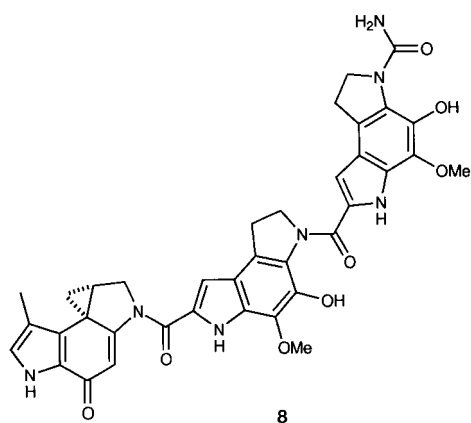
4.1. DNA Alkylation by the Ultimate Carcinogen^[24]

The reaction of salmon sperm DNA with the ultimate carcinogen **4** under physiological conditions (pH 7.5, 37 °C) resulted in the formation of the modified DNA. Thermal hydrolysis of the modified DNA (90 °C, 30 min) produced N-7-alkylguanine **6** (1.8% based on a nucleotide in DNA) and N-3-alkyladenine **7** (0.61%). These results indicated that the thermally unstable sites in DNA were produced by alkylation with **4**.



4.2. DNA Cleavage by the Ultimate Carcinogen^[24, 25]

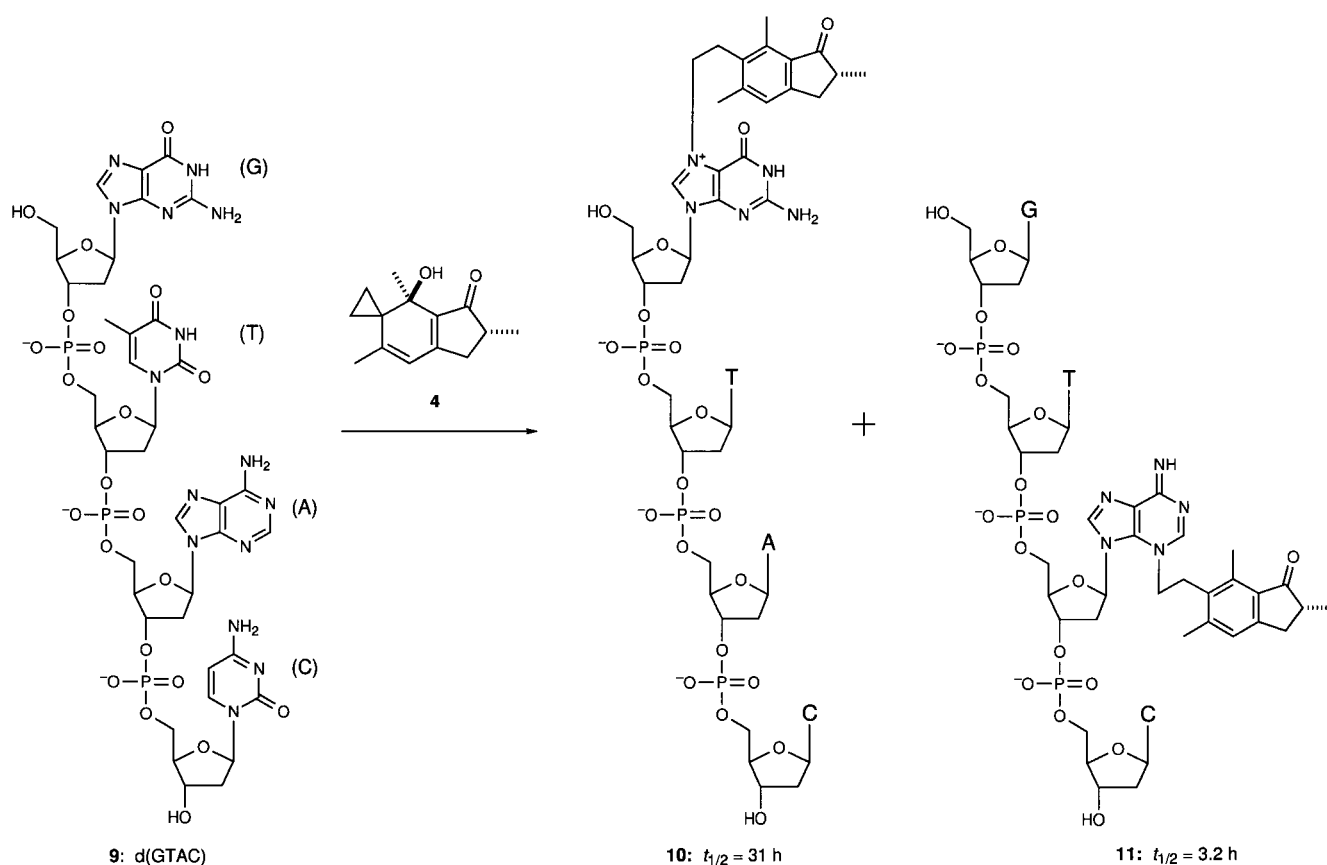
The DNA-cleaving activity of **4** was detected by the topological changes in plasmid pBR322 DNA. With the use of 3'- and 5'-³²P-labeled DNA fragments, it was shown that **4** cleaved DNA at the adenine and guanine residues. The selectivity of the DNA strand breakage was dependent on incubation time: When a DNA sample was incubated with **4** at 37 °C for 25 h, the DNA cleavage predominantly occurred at the adenine residues, while incubation for 130 h gave additional cuttings at the guanine residues. The key structural feature of the antitumor agent CC-1065 (**8**)^[26] is the presence of the cyclopropane ring conjugated with the dienone group. Although the DNA cleavage is postulated to occur by a



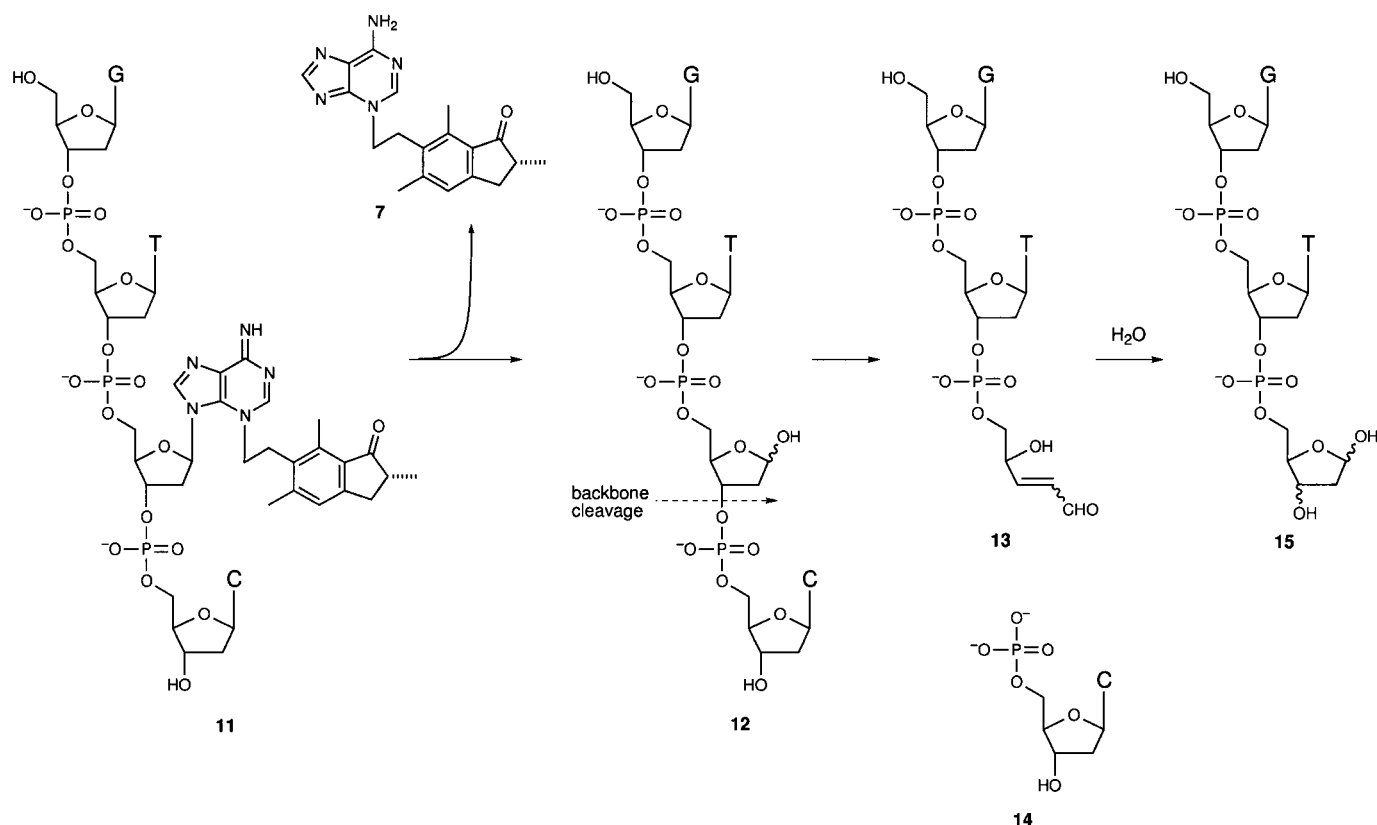
similar mechanism, there are significant differences between DNA damage by **4** and by **8**.^[27] Dieneone **4** forms adducts with guanine residues as well as with adenine residues, while **8** forms adducts only with the adenine residues. Furthermore, **4** causes spontaneous cleavage at the adenine sites under physiological conditions, whereas **8** acts at higher temperatures (> 70 °C).

4.3. Reaction of Deoxytetranucleotide d(GTAC) with the Ultimate Carcinogen: Molecular Mechanism of DNA Cleavage^[25]

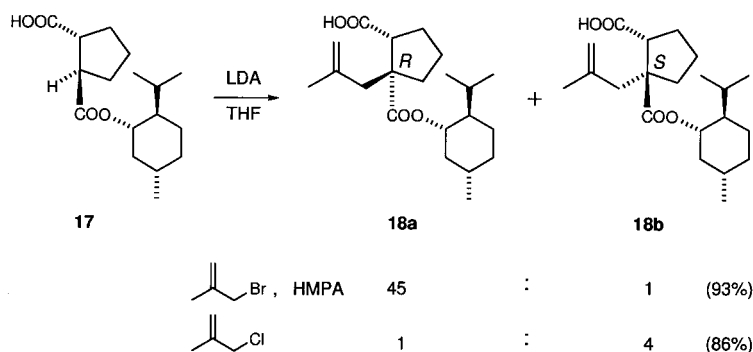
To study the molecular mechanism of DNA cleavage, deoxytetranucleotide d(GTAC) (**9**) was chosen as a model DNA substrate. The reaction of d(GTAC) with the ultimate carcinogen **4** (pH 7.5, 0 °C, 15 h) afforded the two unstable adducts **10** and **11** (Scheme 2). The adduct alkylated at adenine (**11**) was about ten times more unstable than that alkylated at guanine (**10**; $t_{1/2}$ (pH 7.5, 32 °C) = 3.2 and 31 h, respectively).^[28] Adduct **11** was transformed into d(GT-deoxyribose-C) (**12**) with liberation of *N*-3-alkyladenine **7** (Scheme 3). Subsequently, the backbone of **12** was cleaved under physiological conditions (pH 7.5, 32 °C, 29 d) to afford deoxycytidine-5'-phosphate **14** and a mixture of aldehydes **13**. The latter was gradually converted into a mixture of alcohols **15** by the Michael addition of water. Thus, the molecular mechanism of the DNA cleavage by **4** can be depicted as



Scheme 2. Cleavage of deoxytetranucleotide d(GTAC) (**9**) with the ultimate carcinogen **4**—part 1.

Scheme 3. Cleavage of deoxytetranucleotide d(GTAC) (**9**) with the ultimate carcinogen **4**—part 2.

follows: The ultimate carcinogen **4** reacts with DNA to form *N*-3-alkyladenine or *N*-7-alkyl-guanine adducts. Spontaneous cleavage of the *N*-glycosidic linkage then predominantly takes place at the modified adenine (or guanine) residues to produce abasic sites, where the backbone cleavage gradually occurs by a β -elimination reaction.

Scheme 4. Diastereoselective alkylation of the common chiral precursor **17**.

5. Synthesis of Both Enantiomers of the Ultimate Carcinogen and Their DNA-Cleaving Activities^[29]

The challenge of synthesizing ptaquilosin (**16**),^[30] the aglycon of the carcinogen ptaquiloside (**1**), combined with the DNA-cleaving activities of the ultimate carcinogen **4** that is produced by alkali treatment of **16**, prompted us to explore the synthesis and properties of both enantiomers of **16**. To efficiently obtain both enantiomers of **16**, the two diastereomers **18a** and **18b** (*R* and *S* configuration, respectively, at the newly constructed quaternary carbon atom) would be stereoselectively prepared from a common chiral precursor **17** (Scheme 4).^[31] The lithium enolate generated from (+)-menthyl (1*R*,2*R*)-cyclopentane-1,2-dicarboxylate (**17**) was alkylated with methallyl bromide in the presence of hexamethyl phosphoramide (HMPA) at -78°C to almost exclusively afford diastereomer **18a** (Scheme 4). On the other

hand, the same lithium enolate was alkylated with methallyl chloride in the absence of HMPA at -20°C to predominantly provide the other diastereomer **18b**, which was produced by alkylation from the sterically more hindered side of the enolate. The plausible intermediary complex for this contrasteric^[32] alkylation is shown in Figure 4.

The instability of ptaquilosin poses a multitude of serious problems for its synthesis. The presence of the hydroxyl group at C4, which is liable to be dehydrated, is one of the major reasons for the instability of **16**. Therefore, we devised an approach

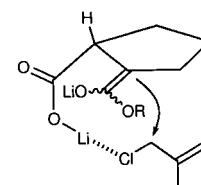


Figure 4. The plausible intermediary complex for the contrasteric alkylation. R = (+)-menthyl.

wherein the angular hydroxyl group is introduced under extremely mild conditions in the very last step. Scheme 5 outlines the synthesis of the natural enantiomer of **16** starting from diastereomer **18a**. The crucial step of the synthesis was deformylative oxidation of aldehyde **27**, which led to **16** via hydroperoxide **28** under sufficiently mild conditions.

The unnatural enantiomer of **16** was synthesized from diastereomer **18b**. With both enantiomers of **16** in hand, we were interested in the problem of whether or not there is a difference in reactivity between the two enantiomers of the ultimate carcinogen **4** toward DNA. The ultimate carcinogen **4** derived from natural ptaquilosin was more efficient (ca. twofold) with respect to DNA cleavage than **4** obtained from unnatural **16**. Other studies directed toward the synthesis of **16** have been reported.^[33, 34]

6. Synthesis of Artificial Analogues of the Ultimate Carcinogen

The strong electrophilicity of the ultimate carcinogen **4** is due to the presence of a reactive cyclopropane ring that is conjugated with the keto group and is part of a cyclopropylcarbinol system. The reactivity of the cyclopropane ring

in **4** seems to be enhanced by the cooperative action of these two structural factors. From the standpoint of the structure–activity relationship, it was of interest to prepare simple analogues of **4** and to compare their DNA-cleaving activities. Furthermore, it was expected that the simple synthetic analogues would be more stable than the labile ultimate carcinogen **4**. Therefore, we synthesized two simple analogues: ketone **29**, which possesses the cyclopropane ring conjugated with a keto group, and alcohol **30**, which only retains the cyclopropylcarbinol system^[35] (Figure 5). Ketone **29** is much

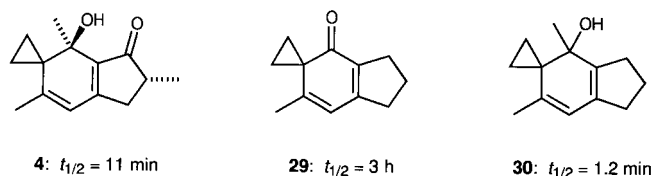
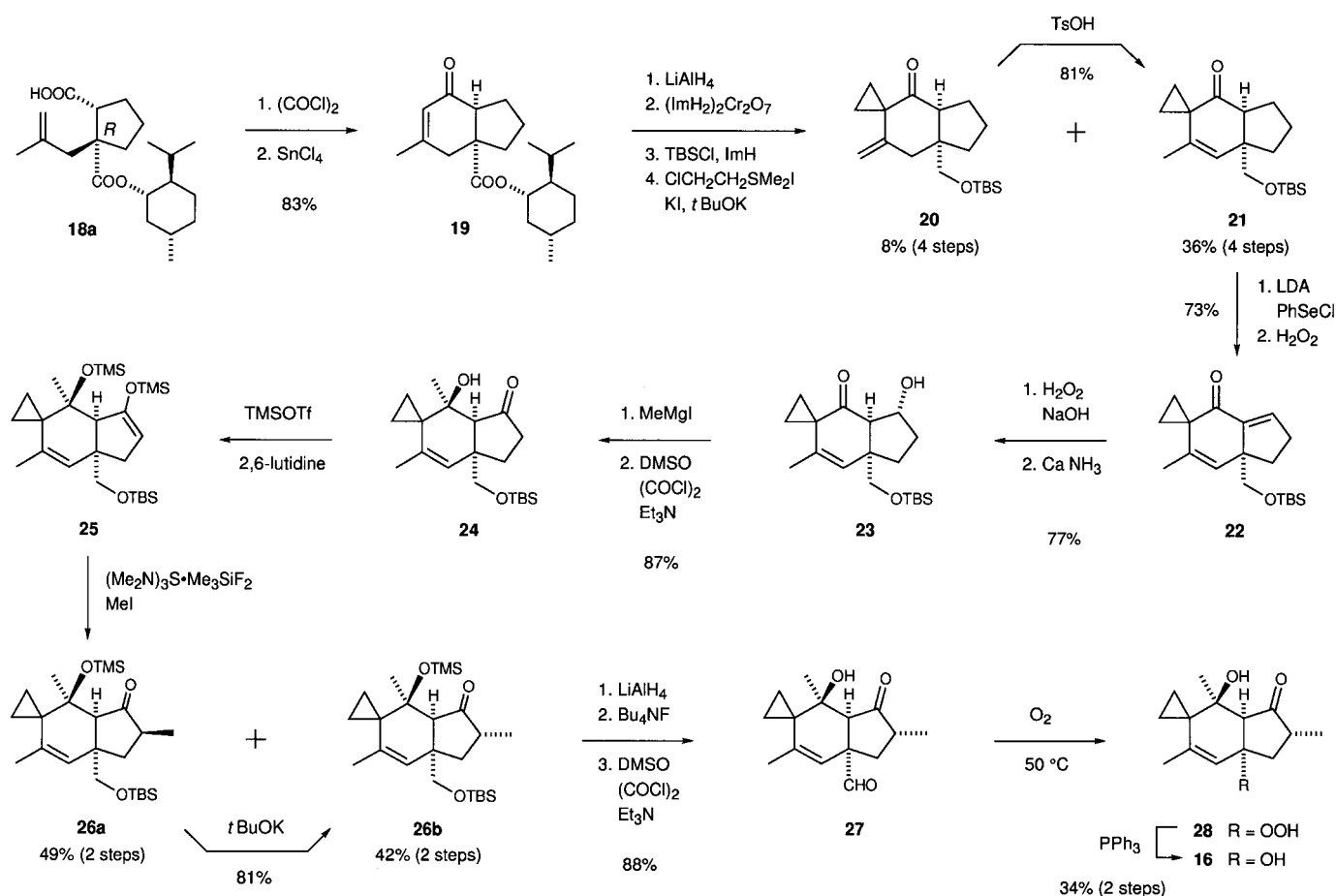


Figure 5. Structures of the ultimate carcinogen **4** and the two artificial analogues **29** and **30**. The half-lives $t_{1/2}$ were measured under physiological conditions (pH 7.5, 26 °C).

more stable than the ultimate carcinogen **4**, whereas alcohol **30** is less stable than **4**. It is remarkable that the artificial analogues **29** and **30** cleaved DNA as effectively as the natural ultimate carcinogen **4**.



Scheme 5. Synthesis of natural ptaquilosin (**16**). TBS = *t*BuMe₂Si, LDA = lithium diisopropylamide, TMS = Me₃Si, Tf = F₃CSO₂.

7. Related Studies on Ptaquiloside

Since we reported the isolation of ptaquiloside from bracken, studies on the qualitative and quantitative analysis of **1** in bracken were performed by a number of groups. For example, Smith et al. reported the presence of **1** in rock fern (*Cheilanthes sieberi*) in New Zealand and Australia,^[36] and Alonso-Amelot et al. described that bracken fern collected in the tropical Andes of Venezuela contained **1**.^[37] Analyses of **1** in bracken fern from England^[38] as well as Costa Rican and Canadian fern^[39] were performed. Natori et al. revealed that while **1** does not show mutagenicity under the standard conditions of the Ames test, the dienone **4** does. Thus, they developed a convenient method for the detection of **1** with a modified Ames test.^[40, 41] Natori et al. investigated the mutagenic constituents in ferns of the *Pteridaceae* family^[42] and isolated mutagenic compounds such as hypolosides A (**31**), B (**32**), and C (**33**)^[43] (Figure 6) as well as dennstoside A^[44] and determined their structures, which are similar to that of **1**.

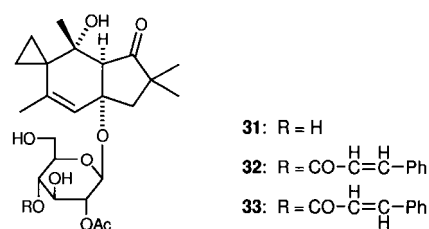


Figure 6. Structures of hypolosides A (**31**), B (**32**), and C (**33**).

Several groups have pointed out the possible human hazard of a bracken carcinogen, especially the transfer of a bracken carcinogen to milk. There were reports that milk from cows fed bracken is carcinogenic to mice and rats, which led to the suspicion that milk contains a bracken carcinogen.^[45–48] Recently, Alonso-Amelot, Smith et al. revealed that **1** is present in milk from cows fed bracken.^[49]

8. Summary and Outlook

In this review the results of studies on a long-sought carcinogen of a bracken fern are described. A carcinogenicity-guided, mild method for extraction was developed, which enabled us to isolate the unstable carcinogen ptaquiloside (**1**). Ptaquiloside was shown to be responsible for a variety of biological activities including carcinogenicity. The structure of **1** was determined to be a norsesquiterpene glucoside of the illudane type. Under weakly alkaline conditions, **1** transformed into the highly reactive ultimate carcinogen **4**, which alkylates the sulfur atom of sulfur-containing amino acids; this finding provides the possibility of using sulfur-containing amino acids as detoxifying agents for the carcinogen **1**. The ultimate carcinogen **4** not only alkylates the adenine and guanine sites of DNA, but also cleaves DNA; the molecular mechanism of this DNA cleavage was disclosed in detail. Both enantiomers of ptaquilosin (**16**), the aglycon of **1**, were

synthesized, and the DNA-cleaving activities of the natural ultimate carcinogen **4** were shown to be stronger than those of unnatural **4**. Two artificial analogues **29** and **30**, which have simpler structures than the ultimate carcinogen **4**, were prepared. Their DNA-cleaving activities proved to be comparable to those of natural **4**. Since **1** is a potent and unique carcinogen that can now be obtained from the plant in large amounts, there will be opportunities in the future for this compound to be used for investigating the detailed mechanism of chemical carcinogenesis.^[50]

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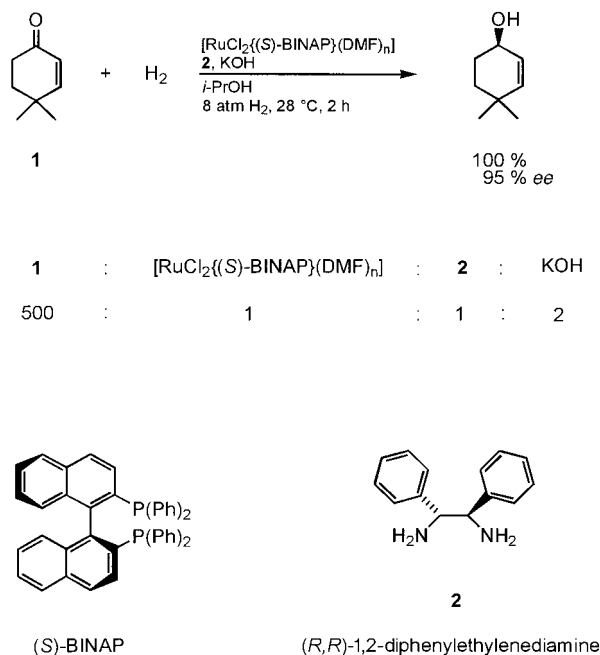
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Highly Enantioselective Complex-Catalyzed Reduction of Ketones— Now with Purely Aliphatic Derivatives Too

Volker Fehring and Rüdiger Selke*

The research group of Zhang at Pennsylvania State University has climbed a mountain that had long defied all attempts at scaling its peak—the complex-catalyzed, highly enantioselective (*ee* values of over 90 %) hydrogenation of purely aliphatic ketones.^[1] Such high *ee* values have up till now remained the exclusive domain of enzymatic methods.^[2]

It has long been possible to asymmetrically hydrogenate a wide range of functionalized ketones with selectivities of over 90 % *ee*. Thus, pharmaceutically important 1,2-amino alcohol derivatives have been available since 1979 with over 95 % *ee* through the hydrogenation of amino ketones. This was achieved by Hayashi et al.^[3] with the use of planar chiral ferrocenebis(phosphanyl)rhodium(i) catalysts and above all by application of the *control concept* developed by Achiwa et al.^[4] with BCPM rhodium(i) catalysts (BCPM = (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(dicyclohexylphosphanyl)-2-(diphenylphosphanylmethyl)pyrrolidine).^[4b] Very high turnover numbers (100 000) can thus be achieved. Likewise, α - and β -ketocarboxylic acid derivatives have been reduced (> 90 % *ee*) to the hydroxy acids or corresponding derivatives with high selectivity.^[4a, 5, 19a] the most impressive results were obtained with chiral, modified heterogeneous catalysts.^[6] Since the pioneering studies of Noyori et al. with BINAP–ruthenium(ii) complexes^[7] (BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl, see Scheme 1), the range of ketones which can be homogeneously hydrogenated with *ee* values of well over 90 % has been expanded to encompass among others γ -keto esters, hydroxy ketones, α - and β -diketones, and even phenyl thio ketones.^[7f] Also the important regioselective hydrogenation of unsaturated, and even cyclic, ketones such as **1** was possible with 95 % *ee* (Scheme 1).^[7d, e] In this case, the otherwise preferred hydrogenation of the olefinic double bond^[7g] is completely suppressed by the addition of a chiral diamine such as (*R,R*)-1,2-diphenylethylenediamine (**2**), which serves as a selectivity-promoting modifier (Scheme 1). Moreover, Noyori et al. have recently shown that the selecting power of the enantiomerically pure diamine **2** is alone sufficient for a successful reaction, as the enantioselectivity

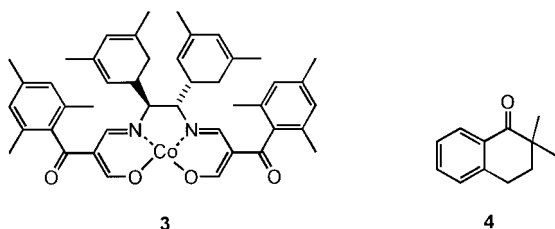


Scheme 1. Regioselective hydrogenation of unsaturated ketones.

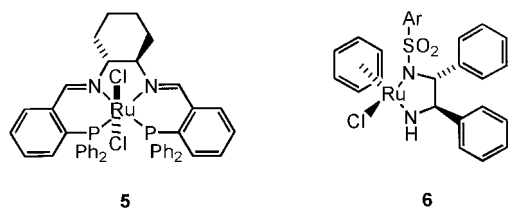
falls only from 96 to 95 % if racemic TOLBINAP^[7h] is used instead of (*R*)-TOLBINAP (TOLBINAP is a BINAP derivative in which the four phenyl groups attached to the phosphorus atoms are replaced by four *p*-tolyl groups).

The transformation of unfunctionalized alkyl aryl ketones such as acetophenone and its analogues to the corresponding chiral alcohols with enantioselectivities of around 95 % was for a long time possible only by asymmetric hydrosilylation^[8] or hydroboration.^[9] However, in 1995 this reaction was accomplished by activation of BINAP–ruthenium catalysts with chiral diamines and KOH.^[10] In its optimized form the reaction needs less than 10^{−4} mol % of catalyst.^[10b] Similarly high selectivities were also reported for cyclic alkyl aryl ketones with BINAP–iridium catalysts.^[11] Use of sodium borohydride as the reductant and the cobalt catalysts **3** with tetradentate ligands derived from Schiff bases afforded reduction of ketone **4** with 94 % *ee*. However, the corresponding reaction with acetophenone was unsatisfactory with only of 68 % *ee*.^[12]

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A successful approach in the field of transfer hydrogenation with formic acid or isopropyl alcohol as the hydrogen source has been developed by Noyori^[13a] through the use of ruthenium catalysts containing chiral N P chelating ligands such as **5** or monosulfonated bis(amine)s such as **6**. This breakthrough is particularly significant in the case of alkyl aryl ketones or ketones with triple bonds in the α position.^[13b] The



excess hydrogen pressure normally necessary for ketone hydrogenations is avoided here by the high concentration of the hydrogen donor. Enantioselectivities of between 95 and 99 % are afforded in most cases for aryl alkanols; such values can otherwise be obtained only with microbiological processes.^[14]

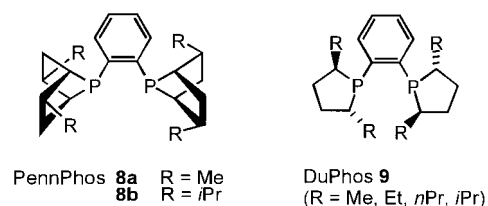
The number of publications describing new ligands that allow the transfer hydrogenation of aromatic ketones with over 90 % *ee* has grown in leaps and bounds since 1996.^[15] In these reactions the use of ruthenium^[15a–f] and iridium^[15g] as the catalytically active metals has recently been augmented by the use of phosphorus-free ligands such as chiral diamines, amino alcohols, and bis(thiourea)s such as **7**.^[15a, c–g] A ruthenium-catalyzed transfer hydrogenation with 92 % *ee* has even been reported for the aliphatic ketone pinacolone (*tert*-butyl methyl ketone).^[16]

One problem that remains unsolved is the complex-catalyzed enantioselective hydrogenation of dialkyl ketones with dihydrogen gas, as these substrates lack the aryl substituent or second functional group necessary for effective enantiofacially selective binding to the catalyst. Corey et al. nevertheless succeeded in reducing pinacolone, in which the steric requirements of the methyl and *tert*-butyl substituents differ quite distinctly, by the hydroboration method with 97 % *ee*.^[9] By contrast, the straight-chain octan-2-one gave an *ee* value of only 72 %, ^[17] compared 94 % *ee* with an alcohol dehydrogenase.^[2]

A particularly successful approach to the catalytic hydrogenation of dialkyl ketones with hydrogen has been the use of the heterogeneous contact catalyst system—Raney nickel chirally modified with tartaric acid.^[18] Here too, selectivity is enhanced by branching of the alkyl substituent in the alkyl

methyl ketones (e.g., 85 % *ee* for the hydrogenation of isopropyl methyl ketone). With straight-chain ketones the highest *ee* values were achieved for hexan-2-one and octan-2-one (80 %). Catalyst selectivity was optimized by the use of pivalic acid as a modifier, which through association clearly blocks one side of the chirality-inducing tartaric acid molecules on the surface of the nickel. Owing to the sterically demanding *tert*-butyl group of the pivalic acid, the range of options for coordination of the ketone to the tartaric acid in the transition state is limited. It is, of course, perfectly conceivable that this differentiation effect is particularly pronounced for alkyl methyl ketones and decreases upon replacement of the methyl group with a larger alkyl moiety.

Ligands of type **8**, known as PennPhos, have given new impetus to the rhodium-catalyzed homogeneous hydrogenation of prochiral ketones.^[1] In **8** the favorable properties of the



strongly basic DuPhos ligands **9**, developed by Burk et al.,^[19] are cleverly enhanced by the incorporation of additional ring-forming bridges into the molecule, in accordance with the established principle of increasing the rigidity in the backbone. This at the same time increases the spatial requirements of the ligands. For the hydrogenations with **8** the enantiomeric excesses obtained are likewise optimized by the use of nonchiral modifiers such as bromides and weak bases. A remarkable feature of this reaction is that bases such as 2-methylimidazole and 2,6-lutidine, if added in substoichiometric amounts to the rhodium catalyst, achieve very similar increases in selectivity, whereas if equimolar quantities are used (base/rhodium catalyst: 1/1) the results obtained differ dramatically (1 % *ee* versus 95 % *ee*, (*S*)-alcohol). Use of triethylamine as the added base even yields the *R* enantiomer. The turnover rate also shows optima that are dependent on the ratio of base to rhodium catalyst. This is viewed by the authors as an opportunity to improve the still unsatisfactory length of time required for hydrogenations with the PennPhos–rhodium catalyst, which in some cases is as long as several days at 30 atm hydrogen pressure and room temperature.

The influence of the alkyl substituents in the substrate on the enantioselectivity of the hydrogenation (Table 1) corresponds to experience from experiments with modified Raney nickel.^[18] According to these, for purely aliphatic ketones the highest enantioselectivities are achieved for methyl ketones with a branched-chain second alkyl substituent. The value of 75 % *ee* obtained with the straight-chain hexan-2-one is, to the best of our knowledge, in any case better than anything achieved to date with nonenzymatic systems and homogeneous catalysis. Higher selectivities have been reported for reductions with stoichiometric amounts of chiral borohydrides (e.g. 80 % *ee* for the reduction of octan-2-one).^[20]

Table 1. Enantioselectivities for the hydrogenation of simple ketones RCOR' .^[a]

R	R'	ee (S) [%]
<i>t</i> Bu	Me	94
C_6H_{11}	Me	92
<i>i</i> Pr	Me	84
<i>n</i> Bu	Me	75
Ph	Me	95 (without KBr)
Ph	Et	93
Ph	<i>i</i> Pr	72

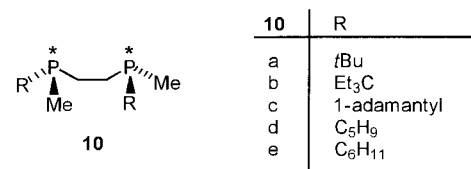
[a] With 0.5 mol % $[\text{Rh}(\text{cod})\text{Cl}]_2$, **8a**, lutidine, and KBr under 30 atm H_2 .^[1]

For alkyl aryl ketones, the use of the novel PennPhos rhodium catalyst afforded enantioselectivities of over 90 %, such as are routinely obtained by transfer hydrogenation,^[13] only for alkyl groups up to C_2 . This is in contrast to microbial reductions, where the selectivity rises with the number of carbon atoms in the alkyl group.^[14] A recent report describes a most spectacular inversion of selectivity for a novel ruthenium-catalyzed transfer hydrogenation of alkyl phenyl ketones with use of the bis(thiourea) ligand **7** derived from (*R,R*)-1,2-diphenylethylenediamine.^[21] In this reaction the following enantioselectivities were obtained as a function of the alkyl group in the substrate molecule: Me: 89 %, (*S*); Et: 91 %, (*S*); *i*Pr: 94 %, (*S*); *t*Bu: 85 %, (*R*). By ordering the substrates according to the magnitude of the selectivities obtained, other studies have likewise demonstrated a marked dependence on the structure of the catalyst.^[10]

The significance for industrial processes is clear. Scheme 2 shows several examples from a survey recently published by

Noyori^[7c] of optically active alcohols that can be used to synthesize biologically important chiral compounds below along with some of relevance to the pharmaceutical industry.^[22] Pheromones constitute a particularly diverse family of chiral aliphatic alcohols.^[23]

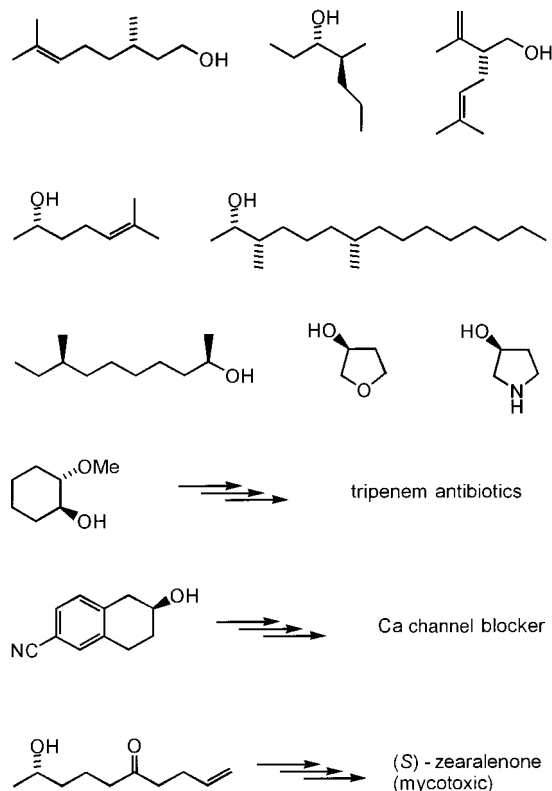
Finally, the bis(trialkylphosphane) ligands **10** developed by Imamoto et al. may, on account of their high basicity, also be suitable for the hydrogenation of ketones. Use of these



ligands, which contain chiral phosphorus centers, affords enantiomeric excesses of over 99 % for the rhodium(I)-catalyzed hydrogenation of *N*-acyl-dehydroamino acids.^[24] The tetrasubstituted substrates, which are generally difficult to hydrogenate enantioselectively, are of particular interest. The partially reversed orders of selectivity for the five ligands described leads us to suspect that high enantiomeric excesses may also be possible for the reduction of ketones. Further advances are conceivable by combining the methods developed by the research groups of Noyori and Zhang, with the use of bases as modifiers.

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Keywords: alcohols • asymmetric catalysis • asymmetric synthesis • hydrogenations • ketones

Scheme 2. Optically active alcohols that can be used to synthesize biologically important chiral compounds.^[7c, 22]

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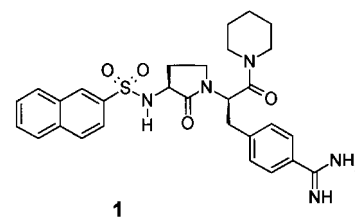
Metal Ions as Co-Inhibitors of Serine Proteases: A New Approach in the Search for Specific High-Affinity Ligands

Tanja Schirmeister*

Serine proteases are key enzymes for a variety of biological processes and are therefore of great importance in the design of new drugs.^[1] The trypsin-like proteases of the blood-clotting cascade, thrombin and factor Xa, are of particular interest in this context.^[2] A common characteristic is their specificity for basic amino acids in P1.^[3] Apart from trypsin, the proteases of fibrinolysis (plasmin, t-PA, urokinase),^[4] those of the complement system (factors C1r, C1s),^[5] and the mast-cell tryptase^[6] belong to this family. Leukocyte elastase is also of therapeutic interest, which, although it uses the same hydrolysis mechanism, possesses a small hydrophobic S1 pocket and thus exhibits only P1 specificity for the short-chain amino acids alanine and valine.^[7] Pathological processes for which serine protease inhibitors could be of therapeutic value include blood-vessel diseases (thrombin), tumors (plasmin, urokinase), infectious processes and autoimmune diseases (tryptase, complement proteases), lung emphysema (elastase), and pancreatitis (trypsin).^[1]

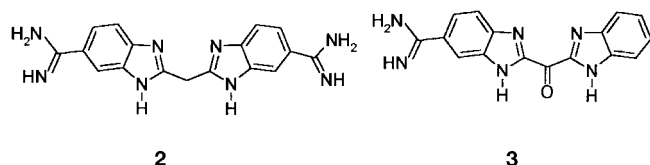
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Up to now, there were three approaches to developing inhibitors for trypsin-like proteases which differed in the type of reaction between the inhibitor and the active site. Compound **1** is one of numerous benzamidines which employ their



positively charged amidinium group to occupy reversibly and noncovalently the S1 pocket of the enzymes; the S1 pocket carries a negative charge due to the amino acid Asp 189.^[8] The petidyl aldehyde GYKI14766 (*N*-Me-D-Phe-Pro-Arg-H),^[9] a potent thrombin inhibitor, additionally reacts reversibly with the serine residue at the active site to yield a hemiacetal. Irreversible inhibitors can be found, for example, in the group of peptidyl chloromethyl ketones (e.g. D-Phe-Pro-Arg-CH₂Cl).^[9]

The recently published discovery by Katz et al.—that the effect of weak inhibitors such as amidinobenzimidazole BABIM (**2**)^[10] can be greatly enhanced by the addition of Zn^{2+} or Co^{2+} ions—represents a new approach for the development of selective, high-affinity serine protease inhibitors.^[11] The activity of the inhibitor **3**, for example, increases

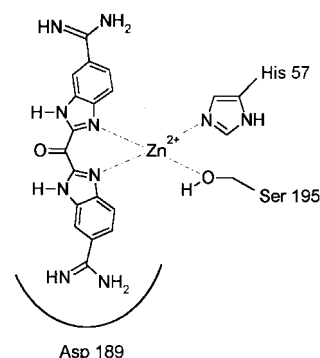


upon the addition of Zn^{2+} from a K_i value in the micromolar range ($87.5\ \mu\text{M}$) by a factor of 17 000 to $K_i = 5.3\ \text{nM}$.^[11] The inhibiting effect of metal cations on proteases has so far only been known for cysteine and aspartate proteases. In these cases, complexation blocks the active site, for aspartate proteases the two catalytically relevant Asp residues and for cysteine proteases the thiolate in the active site. Exceptions in the case of serine proteases are kallikreins^[12] and herpes virus proteases such as the cytomegalovirus protease hCMV.^[13] These are, however, not typical for serine proteases, as they do not utilize Asp/Glu-Ser-His as the catalytic triad, but rather His-Ser-His; this then actually allows the complex formation. In the case of the trypsin-like kallikreins, complexation is made possible by additional histidine-containing loops.

There are also known serine and cysteine proteases which contain an additional Zn^{2+} binding site. However, these do not require Zn^{2+} ions for hydrolytic activity, but rather for the stabilization of the active conformation. Examples are the NS3 protein of the hepatitis C virus (HCV), which is a chymotrypsin-like serine protease, and the 2A proteinases of picornaviruses, a group of chymotrypsin-like cysteine proteases.^[14]

In addition, a number of trypsin mutants have been synthesized. Replacement of different amino acids by histidine allows inhibition, activation, or a change in substrate specificity by Zn^{2+} and other metal cations.^[15]

The enormous increase in the inhibitor activity of the benzamidines of type **2** upon addition of Zn^{2+} ions can be traced to chelation of the metal ion by the amino acids of the active site of the protease (His 157, Ser195) and the nitrogen

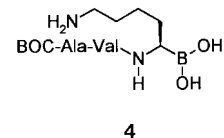


Scheme 1. Binding mode of keto-BABIM to trypsin.

atoms of the two imidazole rings.^[11] The complexation is achieved by the chelating elements of the inhibitor, and not just by histidine residues in the enzyme, as is the case in the above-mentioned metal-dependent trypsin variants or virus proteases. X-ray structure analyses^[19] on keto-BABIM/trypsin (Scheme 1) show that the distance between the S1 recognition

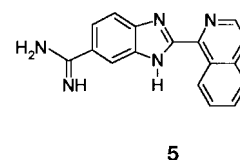
element, the amidinium group, and the chelating element of the inhibitor is of crucial importance for the exhibited high affinity.^[11] Thus, the S1 pocket as well as both catalytically relevant amino acid residues in the enzyme can be blocked.

A similar phenomenon was already observed by Katz et al. for the inhibition of trypsin by peptidylboronates (e.g. **4**; BOC = *tert*-butoxycarbonyl) in combination with alcohols.^[16] The behavior of the enzyme to “select” components from the reaction medium for binding was termed episelection.^[16]



The main problem for the development of new inhibitors, apart from pharmacokinetics (e.g., oral availability), is the lack of selectivity. This can be improved by choosing substituents that take into account not only the P1 specificity of the individual proteases, but also larger substrate sequences. For example, the selectivity between thrombin and trypsin could be significantly increased by exploiting the fact that thrombin, in contrast to trypsin, contains a distinct, lipophilic P3 pocket. This has been realized, for example, in GYKI14766.

Katz et al. were able to show that an improvement in the selectivity can also be achieved by using Zn^{2+} ions as co-inhibitors.^[11] For example, the inhibition of thrombin by inhibitor **5** is increased by a factor of 760 upon the addition of Zn^{2+}



ions ($K_i = 41\ \text{nM}$ with Zn^{2+} , $31\ \mu\text{M}$ without Zn^{2+}), whereas the inhibition of trypsin is barely affected ($K_i = 22.5\ \mu\text{M}$ with Zn^{2+} , $31.2\ \mu\text{M}$ without Zn^{2+}). The selectivity is even a factor of 4750 higher between thrombin and tryptase (for tryptase, $K_i = 54.5\ \mu\text{M}$ with Zn^{2+} , $8.8\ \mu\text{M}$ without Zn^{2+}). Apparently, the chelate formation increases the differences between the individual enzymes at substrate binding sites outside S1.

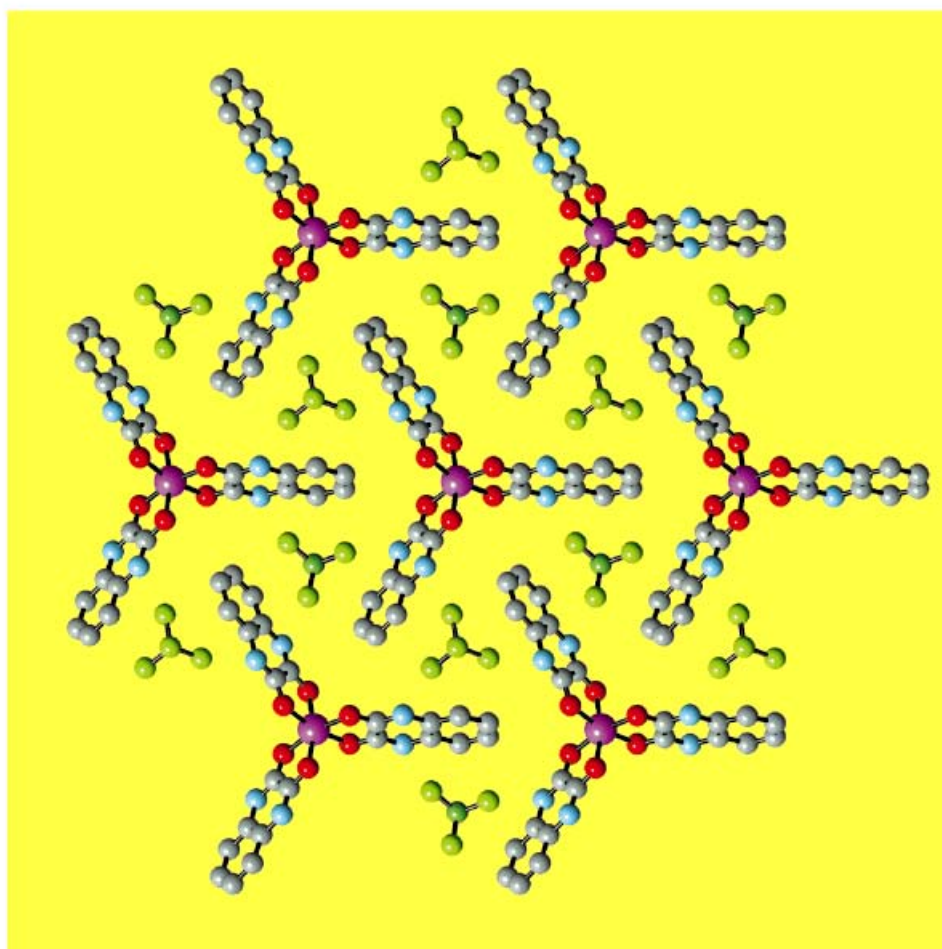
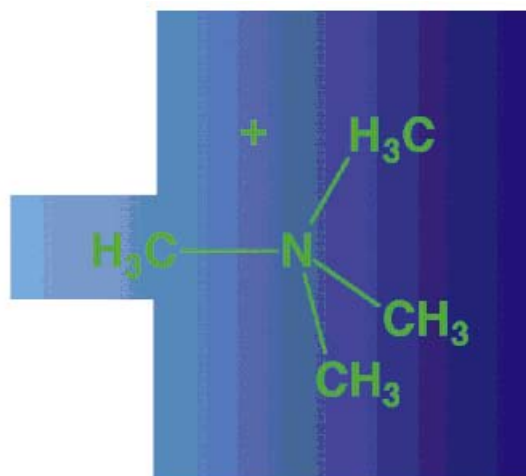
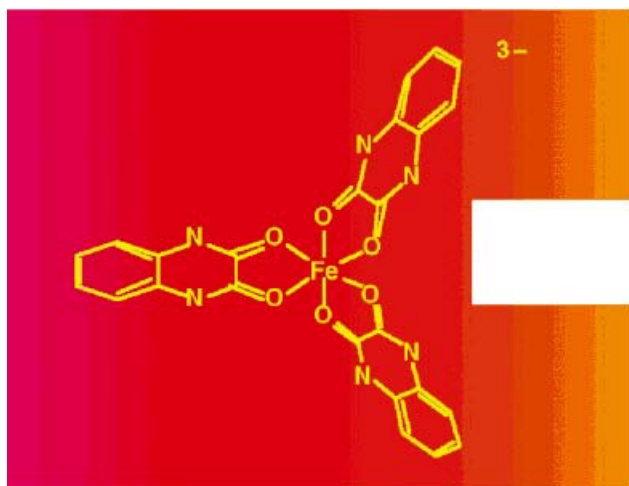
As the increased selectivity and affinity can be observed at Zn^{2+} concentrations of 100 nM (i.e., far below physiological levels), there are promising possibilities for the development of active drugs. On the other hand, it is necessary to critically review the results obtained with inhibitors that contain functional groups that can participate in chelate formation, and which were obtained without the absolute exclusion of complex-forming metal cations.

When applied to other serine proteases, these results imply that the combination of a suitable S1 recognition element—hydrophobic residues for chymotrypsin or short alkyl chains for elastase—and a chelating group can transform weak, unselective ligands into specific, high-affinity inhibitors of low molecular weight by complexation with metal ions. In the case of cysteine proteases, of which the lysosomal cathepsins are especially interesting targets for the therapeutic application of inhibitors,^[17] it must be taken into account that the thiolate at the active site represents a functional group with a stronger tendency for complexation, that the geometry of the active site is of opposite handedness to the structure found for serine proteases,^[18] and that there is a very distinct P2 specificity for hydrophobic amino acids.

German version: *Angew. Chem.* **1998**, *110*, 1930–1932

Keywords: cations • chelates • enzyme inhibitors • serine proteases • zinc

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- [19] Katz et al.^[11] describe three binding modes, which have been crystallographically verified, of BABIM and keto-BABIM to trypsin: 1) with Zn²⁺ or Co²⁺, 2) with SO₄²⁻, 3) without ions.



An esthetically pleasing trigonal network, formed by self-assembly in the crystalline phase from NMe₄⁺ cations and enantiomerically pure Δ and Λ isomers of the anionic iron(III)

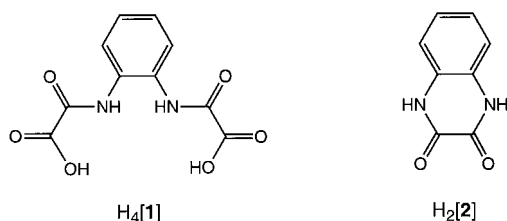
complex presented above on the left, is described by Y. Journaux, M. C. Muñoz, J. R. Pedro, and co-workers on the following pages.

Sheets of Alternating Chirality in the Structure of a Novel Iron(III) Complex with a Cyclic Oxamide Ligand**

M. Carmen Muñoz,* Rafael Ruiz, Maria Traianidis, Ally Aukauloo, Joan Cano, Yves Journaux,* Isabel Fernández, and José R. Pedro*

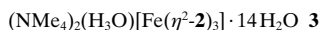
When neutral molecules or ions approach each other to form ordered solid-state structures, highly selective interactions occur between the building blocks which determine the crystal packing. Supramolecular chemistry provides us with a plethora of terms and concepts to describe the basic features of these interactions in the solid state.^[1, 2] In this sense one can speak of supramolecular solid-state chemistry or, equivalently, crystalline supramolecules. Empirical methods are entirely valid in this relatively young area of science, and they often provide the sole approach to crystal engineering.^[3]

Recently we initiated an investigation to assess the possible use of bis-*N*-substituted oxamato ligands such as H₄[1] in the



preparation of iron–amide complexes.^[4] Intriguingly, our results indicate that in basic medium in the presence of ferric ion the ligand Et₂H₂[1] (the diethyl ester of H₄[1]) cyclizes to form the cyclic oxamide ligand H₂[2], which is present in the resulting iron(III) complex in the form of the bidentate 2,3-quinoxalinedione ligand [η²-2]²⁻.^[5] We report here the synthesis, crystal structure, and general physical character-

istics of this new species **3**, one of the rare iron compounds in which an amido ligand is bound to the iron center through an oxygen atom.



The crystal structure of **3** consists of discrete mononuclear [Fe(η²-2)₃]³⁻ complex anions together with tetramethylammonium and oxonium cations and water molecules (Figure 1). Interestingly, parallel planar layers of [Fe(η²-2)₃]³⁻ anions and

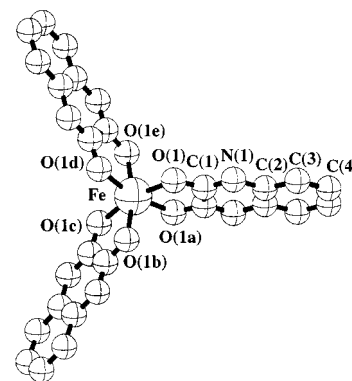


Figure 1. Perspective view of the anionic mononuclear [Fe(η²-2)₃]³⁻ unit of **3** (hydrogen atoms have been omitted for clarity). Selected bond lengths [Å] and angles [°]: Fe–O(1) 2.011(4); O(1)–Fe–O(1a) 80.4(3), O(1)–Fe–O(1b) 90.7(2), O(1)–Fe–O(1c) 166.3(3), O(1)–Fe–O(1d) 90.7(2), O(1)–Fe–O(1e) 99.8(3) [symmetry operations: (a) 2 – x, 1 – x + y, 1/2 – z, (b) 2 – y, 1 + x – y, z; (c) 1 + x – y, 2 – y, 1/2 – z, (d) 1 – x + y, 2 – x, z; (e) y, x, 1/2 – z].

NMe₄⁺ cations alternate in regular fashion in the crystal lattice. Within the anionic layers the iron complex ions are arranged according to a triangular pattern in the *ab* plane (the distance between two iron centers is 12.2 Å; Figure 2, top). The aromatic rings of the ligands associated with one complex anion are arrayed between those of the neighboring molecules such that the edge of each ring interacts with the faces of two aromatic rings from a neighboring molecule. Each phenyl ring projects two of its hydrogen atoms toward the nitrogen atoms of the heteroatom rings from neighboring molecules in such a way that the coulombic attraction H^{δ+} ⋯ N^{δ-} establishes both the directionality of the interaction and most of the energy of attraction. This leads to small tetrahedral cavities with C–H ⋯ N distances that range from 3.63 to 5.24 Å and in which the NMe₄⁺ cations reside. They are located alternately above and below the anionic layers, whereby one of the methyl groups points toward the center of the cavity. Thus, the anionic voids function as a sort of “open hosts.” However, host and guest appear to be held together only by electrostatic attractions in addition to van der Waals forces (the C–H ⋯ N distances range from 3.88 to 4.34 Å).

The layer organization and topology found in crystals of **3**, where one sheet of {[Fe(η²-2)₃]³⁻} octahedra is surrounded by two sheets of {NMe₄⁺} tetrahedra, are reminiscent of those in the phyllosilicate minerals, which belong to the important class of clays. In the latter case, layers of corner-sharing {SiO₄} tetrahedra are linked with layers of edge-sharing {M(O,OH)₆} octahedra (M = Mg, Al), with alternating tetrahedral–octahedral–tetrahedral layers.

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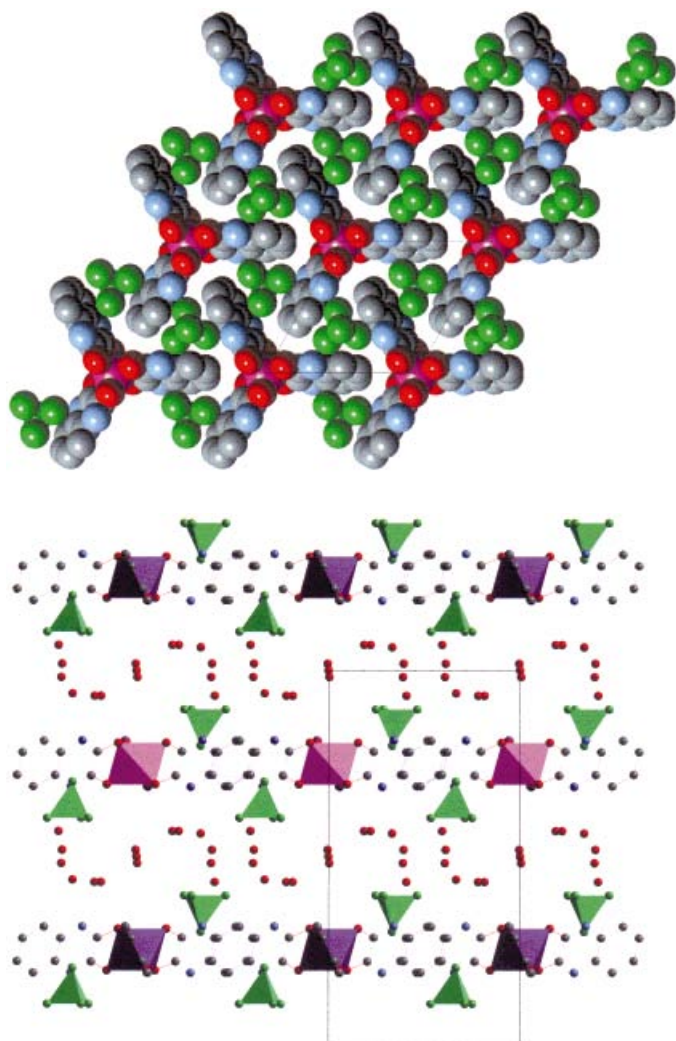


Figure 2. Top: Space-filling model of a portion of the crystal structure of **3**, projected along the *c* axis. Atoms are represented by spheres of arbitrary diameters; iron: violet, oxygen: red, nitrogen: blue, carbon: gray or green. Bottom: Projection of the structure of **3** along the *a* axis. The tetrahedrally arranged carbon atoms of the tetramethylammonium ions are depicted in green, and iron octahedra from the distinctive chiral layers are in dark and light violet.

The superposition of mixed layers along the *c* axis results in a large interplanar separation of 10.3 Å because of the presence of charge-balancing oxonium cations and a significant number of water molecules in the space between the layers (Figure 2, bottom). A very unusual two-dimensional framework of hydrogen bonds is apparent between the solvent water molecules themselves, with O⋯H distances ranging from 2.76 to 2.83 Å. Surprisingly, there are no hydrogen bonds to the oxonium ions (Figure 3, top). The oxygen atoms of the water molecules form a puckered network of edge-sharing, bent, five-membered rings interrupted by twelve-membered rings in the form of large pores (average radius 4.65 Å). The oxonium ions lie at the centers of these rings composed of twelve hydrogen-bonded water molecules. The layers can therefore be viewed as a two-dimensional model of the three-dimensional clathrates that contain the oxonium ions as guests. The oxonium ions are in turn stabilized by relatively weak electrostatic interactions

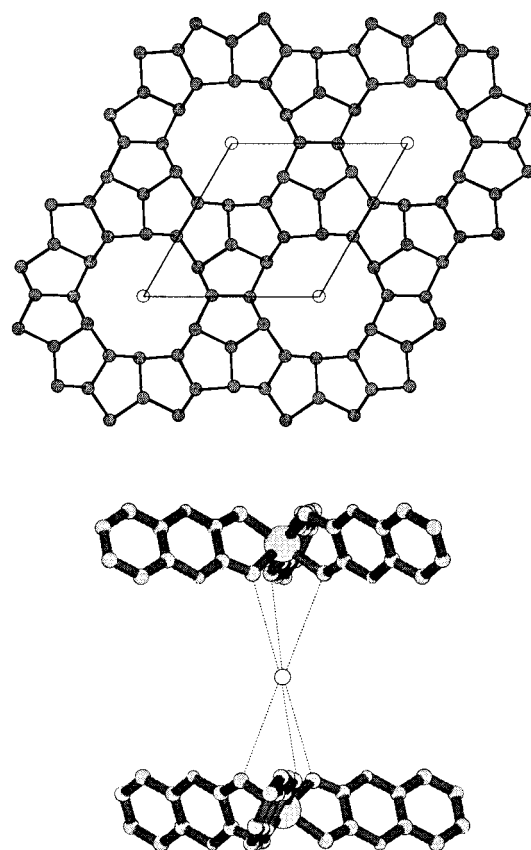


Figure 3. Top: Projection along the *c* axis of oxygen atoms from water molecules involved in the hydrogen-bonding network of **3**. The approximate positions of the hydrogen bonds are indicated. Oxygen atoms from water molecules and oxonium ions are represented by gray and white circles, respectively. Bottom: Perspective view of the octahedral polyhedra around the oxonium ion.

with six negatively charged amido oxygen atoms from two distinct iron complex anions in adjacent layers (see below). This leads to an elongated octahedral polyhedron (O–O distances of 4.32 Å) in which the oxonium ion is encapsulated and thus not available to interact with the H₂O molecules (i.e., it is not solvated; Figure 3, bottom).

The iron center is coordinated to six amido oxygen atoms from the bidentate $[\eta^2\text{-}2]^{2-}$ ligands in a geometry that is approximately trigonally distorted octahedral. A segregated distribution of Δ and Λ isomers occurs between neighboring layers (i.e., alternate layers display opposite chirality), as is nicely shown in the lower part of Figure 2. The angles around the iron center deviate significantly from ideal octahedral geometry as a result of constraints imposed by the five-membered chelate rings (e.g., O(1)–Fe–O(1a) 80.4°). The faces of the triangles, which are perpendicular to the threefold rotational axis, are twisted relative to one another by 51.6° (60° in an ideal octahedron). The iron center of the octahedron displays six equivalent Fe–O_{amido} bond lengths of 2.011 Å, which is surprisingly shorter than that for the only reported iron(III) complex with amido ligands coordinated through oxygen (2.165 Å), where the amido groups are present in neutral form.^[6] The distances are, however, comparable to those of the Fe–O bonds in iron(III) catecholato complexes (2.015 Å),^[7] which suggests an alternative

description for $H_2[2]$ as a 2,3-quinoxalinediolate after substitution of an amido proton by a metal ion.^[8]

Further developments are suggested by the present study with respect to the synthesis of solid-state materials with ordered structures. First, the role played by tetramethylammonium cations in the stabilization of this highly sophisticated structure must be thoroughly examined through the use of other cations of different size and geometry. Second, the question also arises as to whether the mononuclear iron complex anions are able to bind other cations of greater chemical or physical significance than the oxonium ion, such as alkali metal or transition metal cations. We are currently exploring both of these avenues.

Experimental Section

3: A solution of $Et_2H_2[1]$ (1.54 g, 5 mmol) in methanol (100 mL) was treated with a 25% solution of tetramethylammonium hydroxide in methanol (10 mL, 25 mmol), and the resulting light yellow solution was stirred at 60 °C for 30 min. A methanolic solution (50 mL) of $Fe(ClO_4)_3 \cdot H_2O$ (1.77 g, 5 mmol) was then added dropwise through a dropping funnel while the reaction mixture was stirred. The resulting intensely red solution was filtered to eliminate a white precipitate of NH_4ClO_4 , and its volume was reduced to 10 mL with a rotary evaporator. The concentrated solution was treated successively with Et_2O and acetone to give a very hygroscopic product (solid or oil), which was diluted with acetonitrile (300 mL). The resulting suspension was gently heated for 5 h with vigorous stirring and then filtered to eliminate residual solid particles. A polycrystalline red solid precipitated almost immediately when the solution was allowed to cool to room temperature; this was collected by filtration and dried under air (yield: 60.0%). Well-shaped, large, hexagonal prisms of **3** suitable for X-ray structural analysis were obtained by recrystallization from acetonitrile. Complex **3** gave satisfactory elemental analyses (C, H, N, Fe). IR (KBr): $\tilde{\nu} = 3424$ and 1639 (O–H; H_2O and H_3O^+), 1513 and 1462 (C=O), 1379 and 1244 (C–O), 947 cm^{-1} (N–C; NMe_4^+); UV/Vis (CH_3CN): $\lambda_{max}[nm]$ ($\epsilon[L\text{ mol}^{-1}\text{ cm}^{-1}]$) = 230 ($107\,000$), 318 ($43\,000$), 330 (sh), 365 ($12\,000$), 460 (8000); magnetic moment (298 K): $5.9\mu_B$; electrochemical measurements (CH_3CN , 25 °C, 0.1 mol dm^{-3} NEt_4ClO_4): $E_p(Fe^{III}/Fe^{II})$ [V vs. SCE] ($\Delta E_p[mV]$): $-1.38(70)$.

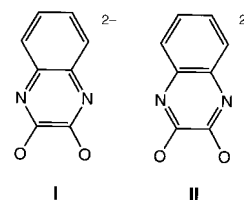
Crystal structure analysis for **3**: Enraf-Nonius CAD-4 diffractometer, $Mo_{K\alpha}$ radiation, $\lambda = 0.71069\text{ Å}$, graphite monochromator, 293 K. Data collection and refinement: $\omega - 2\theta$, corrections for Lorentzian and polarization effects, but no absorption correction ($\mu = 3.58\text{ cm}^{-1}$). The structure was solved with standard Patterson methods and subsequent full-matrix least-squares method refinement. SHELX86, SHELX93.^[9] $C_{32}H_{67}FeN_8O_{21}$, trigonal, space group $P3c1$, $a = b = 12.205(3)$, $c = 20.545(3)\text{ Å}$, $V = 2650(1)\text{ Å}^3$, $Z = 2$, $\rho_{calcd} = 1.20\text{ g cm}^{-3}$, $2 \leq 2\theta \leq 50^\circ$, crystal dimensions $0.10 \times 0.10 \times 0.10\text{ mm}^3$. Of 1568 unique reflections, 1491 were regarded as observed with $I > 2\sigma(I)$. The hydrogen atoms from the water molecules were not located. Furthermore, charge-balance considerations dictate that there be one proton present per Fe atom attached to a water molecule of the solvent (the alternative formulation as iron(IV) is inconsistent with the magnetic measurements). In light of the reported occupancy factors of O(2), O(3), O(4), and O(5) (two, six, six, and one, respectively, for each Fe atom) the proton is unambiguously assigned to the O(5) center (which also occupies a special position in the crystal lattice) rather than integrated into the network of water molecules. The disorder found for the tetramethylammonium and oxonium ions as well as for some of the water molecules is probably enforced by the threefold symmetry of the crystal lattice. Refinement of 103 variables with anisotropic thermal parameters for all atoms except the O(5) atom, which was refined isotropically, resulted in $R = 0.094$, $R_w = 0.108$, $S = 1.2$. Crystal drawings were prepared with the program CRYSTAL MAKER.^[10] 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-100457. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12

Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Symmetry-Driven Rational Design of a Tetrahedral Supramolecular Ti_4L_4 Cluster**

Christian Brückner, Ryan E. Powers, and Kenneth N. Raymond*

Nature provides examples of noncovalently linked molecular clusters of high symmetry which spontaneously self-assemble from their subunits. Examples include the 24-mer apoferritin and the 60-mer human rhinovirus protein coat, of point group symmetry O and I, respectively. Whereas the individual interactions holding the cluster building blocks together (e.g. H bonds and van der Waals interactions) are reasonably well understood, it is less clear what algorithms control the formation of single clusters of defined stoichiometry and high symmetry, rather than the construction of a variety of shapes or random polymers. Can general building principles for synthetic self-assembly structures with well-defined cavities and symmetries be deduced from the natural structures?^[1]

We have answered the question affirmatively by providing a symmetry-based model of cluster formation that both explains the high symmetry clusters found in nature and provides a rational basis for predicting synthetic M_4L_6 clusters.^[2a] The building principle of incommensurate coordination numbers rationalizes construction of a M_4L_6 tetrahedron by combination of a ligand of twofold symmetry (tetrahedron edges) and an octahedral metal center with threefold symmetry (tetrahedron vertices).^[2]

Here we describe an alternative approach to the formation of symmetric tetrahedral clusters, in which the pseudo-octahedral metal centers (threefold axis) occupy the vertices of the tetrahedron and trigonally symmetric tris-bidentate ligands (threefold axis) occupy the faces. Consider the geometric information of a ligand–metal interaction (Figure 1a). Metals such as Ga^{III} and Ti^{IV} require three bidentate chelating groups in order to satisfy their coordination sphere. In a coordination geometry between octahedral and trigonal-prismatic, these three ligands generate a threefold axis at the metal center. While the geometry of such a complex is often described by the twist angle,^[3] here it is convenient to describe this geometry with respect to the orientation of each bidentate ligand. The *approach angle* is defined as the angle between the axis determined by the two donor atoms and the threefold axis of the pseudo-octahedron. An approach angle of 0° corresponds to a trigonal prism, and an angle of 35.3° is typical of “octahedral” tris-catecholate complexes.

With these geometric considerations in mind, the problem of designing a supramolecular assembly based on metal

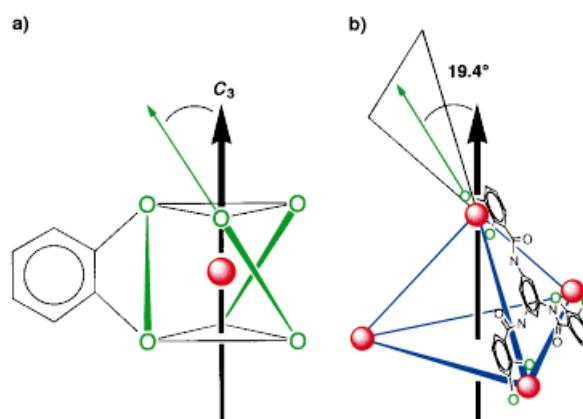


Figure 1. a) Schematic representation of the octahedral coordination environment provided by three bidentate ligands (catecholates). Illustration of the approach angle as defined by the angle between the threefold axis of the octahedron and the axis generated by the two donor atoms of each chelate. b) Identification of this approach angle in a tetrahedral M_4L_4 cluster as the result of the interaction of the planar ligand **4** and metal ions located at the vertices.

complexes can be reduced to designing an n -fold symmetric ligand that positions its multiple chelate vectors correctly for a cluster of given symmetry, provided that the ligands also satisfy the coordination requirements of the metal of choice: The ligand must allow for the preferred coordination geometry as defined by spatial position—expressed by the approach angles—and the absolute number of the donor groups.^[4] In addition, the multifunctional ligand must be designed to avoid multiple coordination to any one metal, since this could result in the formation of complexes of lower stoichiometry.

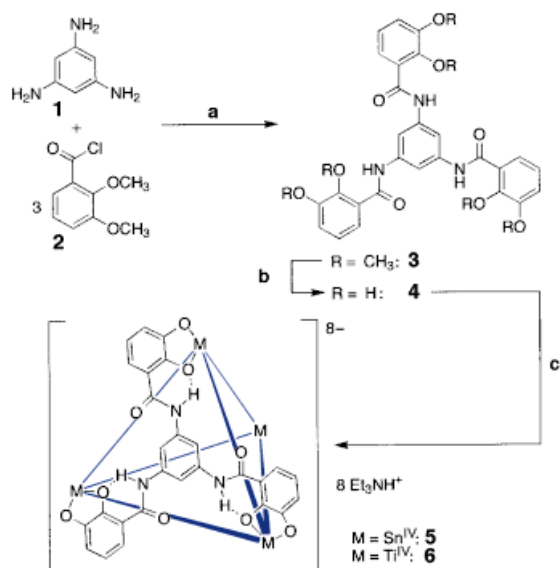
A schematic representation of a tetrahedral M_4L_4 cluster in which the faces of the tetrahedron are made up of strictly planar threefold symmetric ligands, and the vertices are made up of pseudo-octahedrally coordinated metal atoms is depicted in Figure 1b. The angle between a threefold axis and the associated faces in a tetrahedron is 19.4° . If the bound ligands are planar and coordinate as shown, this angle corresponds to the approach angle. The experimentally obtained approach angles for Ti^{IV} tris-catecholates are approximately 23.0° .^[5] This, in turn, implies that the planar ligand to be used in the formation of a tetrahedral cluster is required to distort only a few degrees from planarity to comply with the ideal approach angle at the Ti^{IV} centers.

Based on the foregoing, the threefold symmetric ligand **4** was designed. The hydrogen bond formed between the amide hydrogen and the coordinating *o*-hydroxy oxygen atom imposes a coplanar arrangement of the amide bond with the catecholate unit.^[6] This constraint and the favored coplanarity of the amide group with the central phenyl group produces a rigid system that predisposes the coordinating groups toward the cluster geometry.

The synthesis of **4** followed established routes (Scheme 1). 1,3,5-Triaminobenzene (**1**), derived from the reduction of 3,5-dinitroaniline,^[7] was combined with 2,3-dimethoxybenzoyl chloride (**2**),^[8] to produce the intermediate **3**. Deprotection of the phenolic hydroxy groups with BBr_3 provided ligand **4** in good yield ($> 80\%$ over all steps).

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Scheme 1. Synthesis of the tetrahedral cluster. a) $\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$. b) 1. $\text{BBr}_3/\text{CH}_2\text{Cl}_2$, 2. MeOH . c) 1 equiv $[\text{Ti}(\text{OnBu})_4]$ or SnCl_4 , Et_3N .

Ligand **4** reacts with Al^{III} , Fe^{III} , or Ga^{III} under basic conditions to give precipitates whose ^1H NMR and mass spectra indicated the expected tetrahedral M_4L_4 species.^[9] However, the high charge (12^-) of these anions apparently forestalled the formation of diffraction quality single crystals. The overall charge of the cluster is reduced with higher oxidation state metals. Pseudo-octahedral tris-catecholate complexes of both Sn^{IV} and Ti^{IV} are known;^[5,10] these cations form tetrahedra **5** and **6**, respectively, but only the Ti^{IV} compound provided crystals of diffraction quality. For brevity this report will be restricted to describing the Ti^{IV} complex **6**.

A solution of $[\text{Ti}(\text{OnBu})_4]$ in MeOH was combined with **4** in $\text{MeOH}/\text{Et}_3\text{N}$. After 12 hours, a gelatinous orange precipitation had formed. The ^1H NMR of an $[\text{D}_6]\text{DMSO}$ extract of this precipitate taken at 25°C shows the presence of a mixture of (polymeric) compounds. Heating of the sample to 120°C results, in the course of several hours, in a partial simplification of the spectrum. Dissolution of the precipitate in DMF under reflux for 12 hours resulted in a rearrangement of the kinetic product mixture into one thermodynamic product. Gas phase diffusion of MeOH into this DMF solution produced orange crystals of **6**.

Electrospray (ES) mass spectrometry has been useful in the characterization of the supramolecular clusters in solution.^[11] Here the well resolved traces of positive ion ES mass spectrometric analysis provided proof of the existence of complex **6** in CH_3CN solution. Furthermore, the spectra showed no species of higher or lower oligomerization than Ti_4L_4 . The ^1H NMR of **6** displays its high symmetry. All signals corresponding to the ligand framework are slightly shifted relative to those observed in the uncomplexed ligand.

The single crystal structure provided the ultimate proof of the proposed tetrahedral

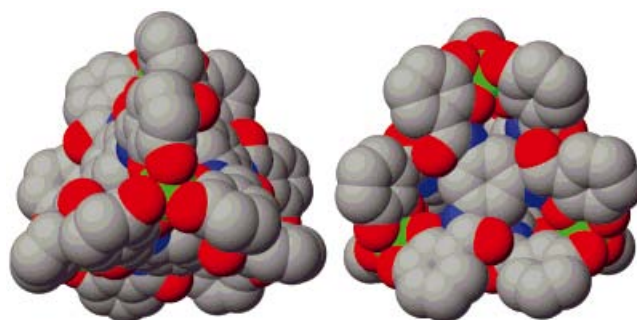


Figure 2. Space-filling model of **6** calculated from the X-ray crystal data and as viewed down the pseudo-threefold axis. Counteranions and hydrogen atoms have been omitted for clarity.

cluster;^[12] a space filling representation is shown in Figure 2. The cluster lies on a crystallographic threefold axis but has molecular symmetry of the rotation group T , such that all the metal ions have the same chirality (all Δ or Λ). Hence, the compound crystallizes as a racemate. The eight triethylammonium counterions are highly disordered, and hydrogen-bonded to either the carbonyl or phenolic oxygens of the cluster. There is no evidence that the small cavity of the tetrahedron contains a guest, as observed in some larger M_4L_6 tetrahedra.^[2d,2f,13] Despite hydrogen bonds between the amide hydrogen and the phenolic oxygens the catechol amides are more distorted from planarity than required by the design of the cluster. We attribute this to the compulsion of the system to minimize the empty volume of the cavity. This may also be the reason for the larger than expected approach angle of 28° . The distortion of the ligands is best visualized in Figure 3.

One related tetrahedral M_4L_4 cluster has appeared in the literature.^[14] Although the formation of this cluster was serendipitous, its structure and formation highlights the building principles exemplified here.

In summary, the threefold axis of a pseudo-octahedral metal center coordinated by three bidentate chelates has been combined with a rigid ligand system of threefold symmetry to drive the formation of a tetrahedral cluster of the stoichiometry Ti_4L_4 . This is another example showing that symmetry-driven cluster formation provides access to predesigned three-dimensional and highly symmetric clusters.

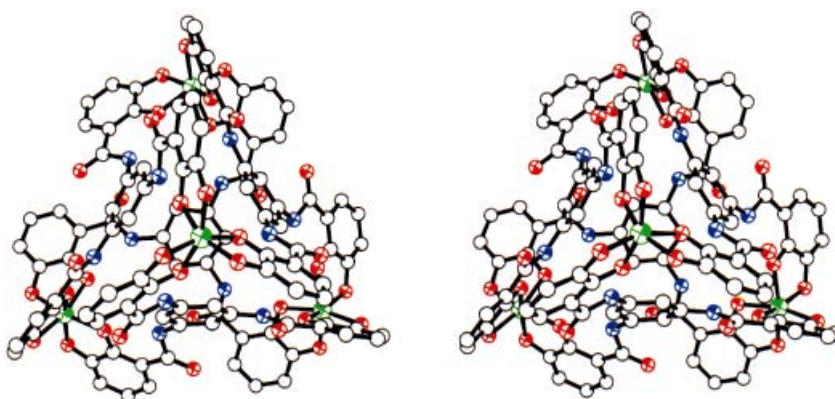


Figure 3. Stereoscopic view of the crystal structure of **6** along the crystallographically imposed threefold axis. Counteranions and hydrogen atoms have been omitted for clarity.

Experimental Section

3 and 4: The intermediate **3** was synthesized from freshly prepared **2** and **1**. Ligand **4** was prepared on a 0.1 M scale and in overall > 80% yield by BBr_3 deprotection according to literature procedures.^[7,8] Correct elemental analyses for **3** and **4** were obtained.

4: ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 25°C , TMS): δ = 11.50 (br. s, 1 H OH), 10.44 (s, 1 H, NH), 9.3 (s, 1 H, OH), 7.99 (s, 1 H, CHCN), 7.42 (d, 1 H, $^3J(\text{H,H})$ = 7.8 Hz, COCHCH), 6.99 (d, 1 H, $^3J(\text{H,H})$ = 7.8, COCHCH), 6.71 (t, 1 H, $^3J(\text{H,H})$ = 7.8 Hz, CHCHCH); ^{13}C NMR (75 MHz $[\text{D}_6]\text{DMSO}$, 25°C , TMS): δ = 167.7 (C=O), 148.2, 146.3, 138.7, 119.3, 118.8, 118.6, 117.4, 110.2.

6: A freshly prepared solution of $[\text{Ti}(\text{OnBu})_4]$ (107 mg, 3.1×10^{-4} mol) in MeOH (20 mL) was added to a solution of ligand **4** (165 mg, 1 equiv) in a mixture of MeOH (20 mL) and Et_3N (1 mL), and the solution was stirred for 12 h at ambient temperature. The orange gelatinous precipitate was removed by centrifugation and suspended in DMF (20 mL). The suspension was heated under N_2 to reflux for 12 h. The resulting solution was filtered through Celite and either evaporated to dryness in vacuo, to produce 190 mg of a microcrystalline solid, or MeOH vapors were allowed to diffuse into this solution at room temperature over several weeks to produce 80 mg (yield 37%, 1st crop) of orange cuboid crystals of analytical purity. ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 25°C , TMS): δ = 11.43 (s, 1 H, NH), 8.2 (br s; 1 H, NH), 7.12 (d, $^3J(\text{H,H})$ = 6.5 Hz, 1 H; COCHCH), 6.84 (s, 1 H, CHCN), 6.45 (t, 1 H, $^3J(\text{H,H})$ = 7.8 Hz, CHCHCH), 6.21 (d, 1 H, $^3J(\text{H,H})$ = 7.8, COCHCH); ^{13}C NMR (125 MHz, $[\text{D}_6]\text{DMSO}$, 25°C , TMS): δ = 158.8 (C=O), 140.3, 138.7, 137.5, 118.5, 116.8, 115.4, 114.5, 112.9, 43.3, 8.3; ES-MS (positive-ion detection, 100% CH_3CN) clusters of peaks with isotope distribution patterns indicative of multiply charged ions could be assigned; a typical example is given (Na^+ is ubiquitously present; $\diamond \equiv [\text{Ti}_4\text{L}_4]^{8+}$): 581 ($\diamond + 9\text{Na}^+ + 4\text{Et}_3\text{NH}^+$) $^{5+}$; 620 ($\diamond + 4\text{H}^+ + 8\text{Na}^+$) $^{4+}$; 681 ($\diamond + 10\text{Na}^+ + 2\text{Et}_3\text{NH}^+$) $^{3+}$; 1162 ($\diamond + 9\text{H}^+ + 1\text{Na}^+$) $^{2+}$; 1173 ($\diamond + 8\text{H}^+ + 2\text{Na}^+$) $^{2+}$; 1184 ($\diamond + 7\text{H}^+ + 3\text{Na}^+$) $^{2+}$; 1195 ($\diamond + 6\text{H}^+ + 4\text{Na}^+$) $^{2+}$; 1206 ($\diamond + 5\text{H}^+ + 5\text{Na}^+$) $^{2+}$; 1217 ($\diamond + 4\text{H}^+ + 6\text{Na}^+$) $^{2+}$; 1228 ($\diamond + 3\text{H}^+ + 7\text{Na}^+$) $^{2+}$; 2302 ($\diamond + 9\text{H}^+$) $^{+}$; 2324 ($\diamond + 8\text{H}^+ + 1\text{Na}^+$) $^{+}$; 2346 ($\diamond + 7\text{H}^+ + 2\text{Na}^+$) $^{+}$; 2368 ($\diamond + 6\text{H}^+ + 3\text{Na}^+$) $^{+}$; 2390 ($\diamond + 5\text{H}^+ + 4\text{Na}^+$) $^{+}$; 2421 ($\diamond + 4\text{H}^+ + 5\text{Na}^+$) $^{+}$.

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- [12] A red tablet crystal of $\text{C}_{156}\text{H}_{188}\text{N}_{20}\text{O}_{36}\text{Ti}_4$ of dimension $0.3 \times 0.22 \times 0.07$ mm was grown by vapor diffusion of MeOH into a DMF solution of **6**. Crystal data were collected with a Siemens SMART diffractometer equipped with a CCD area detector with $\text{MoK}\alpha$ = 0.71069 nm.^[15] Point group $R\bar{3}c$ (No. 167), with a = 22.6143(5), c = 106.038(2) Å, V = 46963 Å³, Z = 12, ρ_{calcd} = 1.32 g cm⁻³. Frames corresponding to an arbitrary sphere of data were collected with ω scans of 0.3° counted for a total of 30 s per frame, temperature of measurement $-103(2)^\circ\text{C}$, 49921 reflections, 6019 unique (R_{int} = 0.090). Data in the range of $2 < 2\theta < 41.6^\circ$ were integrated by the SAINT program.^[16] An absorption correction was applied using SADABS (T_{max} = 0.74, T_{min} = 0.56).^[17] The structure was solved by direct methods (SIR92) and expanded with Fourier techniques.^[18] Number of observations $I > 3.00 \sigma(I)$ = 1381, 271 variables, reflection/parameter ratio = 5.1, refined against $|R|$, R = 0.109, R_w = 0.120, R_{all} = 0.191, min/max residual electron density = $-0.40/0.51$, GOF = 4.21. Oxygen and titanium atoms were refined anisotropically, all other non-hydrogen atoms were refined isotropically. Hydrogen atoms were included at calculated positions. All triethylammonium cations are disordered with respect to the conformation of their ethyl arms and their location in the crystal but could invariably be located in H-bond distance to the catecholate oxygens or the carbonyl oxygens; 8/3 Et_3NH^+ cations per asymmetric unit were distributed unequally over all four possible catecholate and all four possible carbonyl oxygen positions. 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-101007. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033, e-mail: deposit@ccdc.cam.ac.uk).
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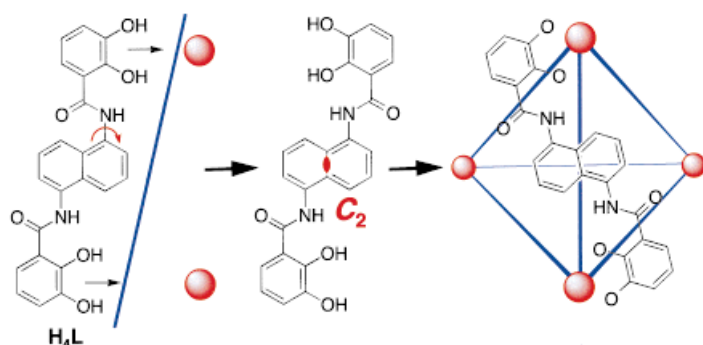
The Self-Assembly of a Predesigned Tetrahedral M_4L_6 Supramolecular Cluster**

Dana L. Caulder, Ryan E. Powers, Tatjana N. Parac, and Kenneth N. Raymond*

We have described the design principles of high symmetry natural clusters, such as ferritin and the human rhinovirus, based on incommensurate interactions.^[1a,b] We have extended this interpretation and shown that it provides a systematic method for the design and synthesis of analogues of these natural clusters using metal–ligand interactions.^[1, 2] Here we present an example of the rational design of a M_4L_6 tetrahedral cluster that exhibits dynamic exchange of guests within the supramolecular cluster cavity.^[3]

If the high symmetry clusters are viewed as truncated polyhedra, the interactions of the subunits must conform to the angles between the planes of the polyhedra, if a high symmetry cluster is to form. Synthesis of an M_4L_6 cluster with tetrahedral symmetry requires that the incommensurate two- and threefold axes be rigidly fixed by the design.^[4] A twofold symmetric bis-bidentate ligand interacting with an octahedral metal center (which generates the threefold axis) can lead to the formation of an M_2L_3 helix (point group D_3) if the angle between the threefold and twofold axes can approach 90° .^[1c–e, 5] Entropic considerations dictate that if the lower stoichiometry M_2L_3 complex can form, it will.^[1c] Therefore, in order to favor the M_4L_6 tetrahedron the geometry of the designed ligand must be correct and inflexible.

The selectivity in the ligand H_4L is achieved by a naphthalene spacer, which causes the two catechol binding units to be offset from one another when the ligand is in the conformation required for helicate formation (Scheme 1).^[1e]



Scheme 1. Helicate formation is disfavored by the use of a naphthalene spacer in the ligand H_4L .

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Thus, the formation of a helicate becomes impossible, and the formation of the M_4L_6 tetrahedron (Figure 1) enabled. Computer modeling^[6] of the M_4L_6 cluster indicated that it would have T symmetry (all metal centers with the same chirality, all Δ or all Λ) and that there would be a substantial cavity inside the cluster.

In this cluster design the planes of the ligands are coincident with the twofold planes of the truncated tetrahedron. As such, the elevation angle of the threefold axis (through the metal center) with the extended twofold ligand plane corresponds to the “approach angle” (Figure 1).^[1f] This angle is calculated to be 35.3° and corresponds to the approach angle of a perfect

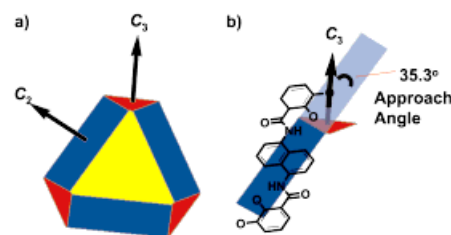


Figure 1. a) An M_4L_6 cluster can be thought of as a truncated tetrahedron with the planes of the polyhedron perpendicular to the symmetry axes. b) If a ligand is designed to lie on the twofold (blue) plane, then the elevation angle of the C_3 axis with the extended twofold plane represents the “approach angle”.

octahedral metal complex. While catechol complexes of Ga^{III} , Fe^{III} , and Al^{III} are typically distorted towards trigonal-prismatic geometries^[7] corresponding to an approach angle of 23° , molecular mechanics calculations^[6] indicated that slight out-of-plane twists in the ligand would compensate for this angle.

The ligand H_4L was synthesized in 75% overall yield according to established methods.^[1c–e] Overnight stirring of a methanol solution containing four equivalents of $[Ga(acac)_3]$, six equivalents of H_4L , twelve equivalents of KOH , and twelve equivalents of Et_4NCl produced a yellow microcrystalline precipitate of $K_5[Et_4N]_7[Ga_4L_6] \cdot 8H_2O$. Although the complex was isolated in 78% yield, the reaction was quantitative as observed by ^1H NMR spectroscopy. The ^1H NMR spectrum (300 MHz, D_2O) of the dissolved precipitate showed all of the signals and shifts expected for the formation of the desired cluster: signals for the backbone and the catechol units, a low field shifted NH signal indicative of complex formation, and signals for the counterions. Remarkably, however, the signals of the seven Et_4N^+ ions are split into two sets in a 6:1 ratio. The larger set ($\delta = 2.42$ (q), 0.68 (t)) is shifted slightly upfield from free Et_4N^+ in solution ($\delta = 3.26$ (q), 1.27 (t)), while the smaller set is dramatically shifted upfield ($\delta = -0.68$ (m), -1.58 (t)). The extreme upfield shift of the Et_4N^+ protons in the complex can be interpreted as a direct indication of the encapsulation of one Et_4N^+ by the tetrahedral cluster $[Ga_4L_6]^{12-}$.^[3b,c, 8] In turn, this encapsulation may be taken as an indication of the successful formation of the cluster.

In addition, the methylene resonance of the encapsulated Et_4N^+ is not a quartet but rather a complex multiplet, indicating that the two protons are inequivalent. This evidence is consistent with an encapsulated Et_4N^+ that is

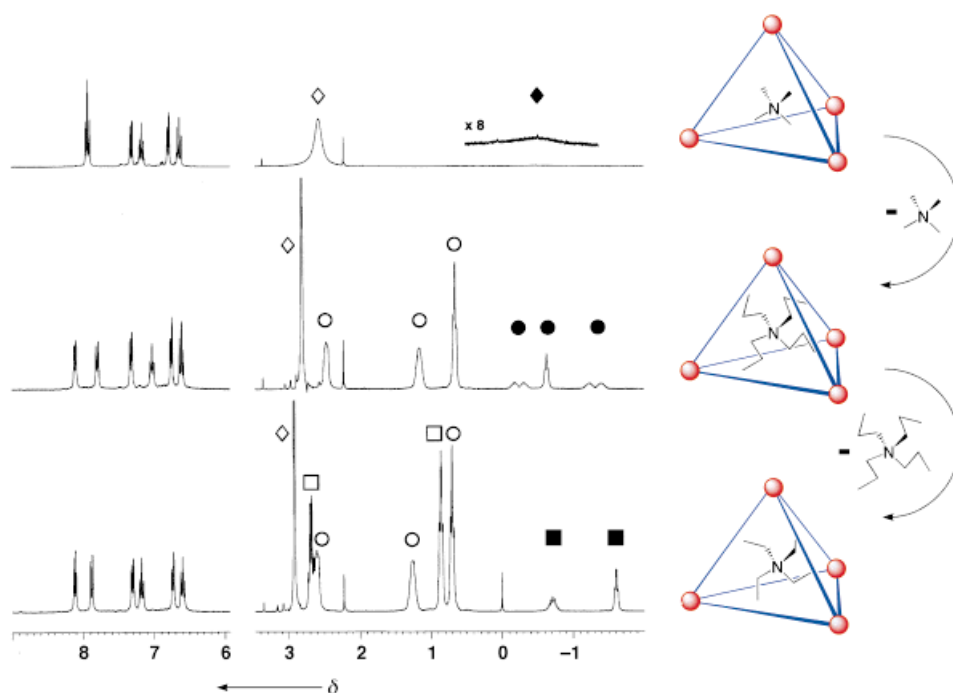


Figure 2. ^1H NMR spectra (300 MHz, D_2O) showing stepwise exchange of counterions in the tetrahedral cluster cavity. Exterior (Δ) and interior ($\blacklozenge$) Me_4N^+ . Exterior ($\circ$) and interior ($\circ$) Pr_4N^+ . Exterior ($\square$) and interior ($\blacksquare$) Et_4N^+ .

sensitive to a chiral environment^[3a] and supports the characterization of the cluster as a racemic mixture of *T* symmetric homochiral complexes. Variable temperature ^1H NMR (300 MHz, D_2O) experiments indicate that the interior and exterior Et_4N^+ resonances do not coalesce below 100°C .

The tetrahedral complex can be synthesized with the smaller Me_4N^+ counterion in an analogous fashion. The ^1H NMR spectrum (500 MHz, D_2O) of the species $\text{K}_6[\text{Me}_4\text{N}]_6[\text{Ga}_4\text{L}_6]$ shows evidence of fast exchange between Me_4N^+ ions in two different chemical environments (Figure 2 top). The major peak is a broad singlet ($\nu_{1/2} = 40$ Hz) located at $\delta = 2.6$ while the minor peak is shifted far upfield to $\delta = -0.5$ ($\nu_{1/2} = 215$ Hz).

Remarkably, the cluster shows a marked preference for the inclusion of Et_4N^+ over the smaller Me_4N^+ and the larger Pr_4N^+ (Figure 2). If Pr_4NCl is added to an NMR tube containing a solution of $\text{K}_6[\text{Me}_4\text{N}]_6[\text{Ga}_4\text{L}_6]$ (Figure 2, top), the Pr_4N^+ quickly (< 1 min) and quantitatively is incorporated into the cluster cavity, displacing the Me_4N^+ (Figure 2, middle). Previously two broad peaks, the Me_4N^+ resonance is subsequently one sharp peak at $\delta = 2.82$ and one equivalent of Pr_4N^+ is found incorporated into the cavity. Again, the resonances of the methylene protons on the encapsulated Pr_4N^+ show substantial diastereotopic splittings (48 and 42 Hz). When Et_4NCl is added to this same NMR tube (Figure 2, bottom), the Et_4N^+ in turn displaces the Pr_4N^+ rapidly (< 1 min) and quantitatively! When given the choice of either Me_4N^+ , Et_4N^+ , or Pr_4N^+ , the tetrahedral cluster host preferentially chooses to encapsulate the Et_4N^+ . No mixtures are observed by ^1H NMR spectroscopy.

The equilibrium constants (K_{eq}) for the inclusion of Et_4N^+ and Pr_4N^+ were determined by ^1H NMR experiments relative

to K^+ ; their respective values are $196 \times 10^2 \text{ M}^{-1}$ and $1.11 \times 10^2 \text{ M}^{-1}$.^[9] The nearly 200-fold difference in the equilibrium constants explains the observation that Et_4N^+ quantitatively replaces encapsulated Pr_4N^+ . Since the inner and outer Me_4N^+ ions are in rapid exchange, the equilibrium constant for the inclusion of Me_4N^+ could not be determined by the same method. However, K_{eq} can be estimated to be very much smaller than $1.11 \times 10^2 \text{ M}^{-1}$, given that Pr_4N^+ quantitatively replaces the encapsulated Me_4N^+ . Detailed investigations of the factors affecting encapsulation and the dynamics of guest exchange are in progress.

The ultimate proof for the formation of the homochiral target cluster and the presence of a host–guest complex is provided by single crystal X-ray diffraction. Suitable crystals

were grown of the similar Fe^{III} complex, $\text{K}_5[\text{Et}_4\text{N}]_7[\text{Fe}_4\text{L}_6]$.^[10] The $[\text{Fe}_4\text{L}_6]^{12-}$ cluster lies on a crystallographic threefold axis with nearly *T* molecular symmetry. Hence the crystal is a racemic mixture of tetrahedra that have homochiral (all Δ or all Λ) iron centers. One of the Et_4N^+ counterions is located inside of the cluster cavity (Figure 3). The cluster is a tightly closed box, with no aperture in the surface, as shown by a space filling model (Figure 4).

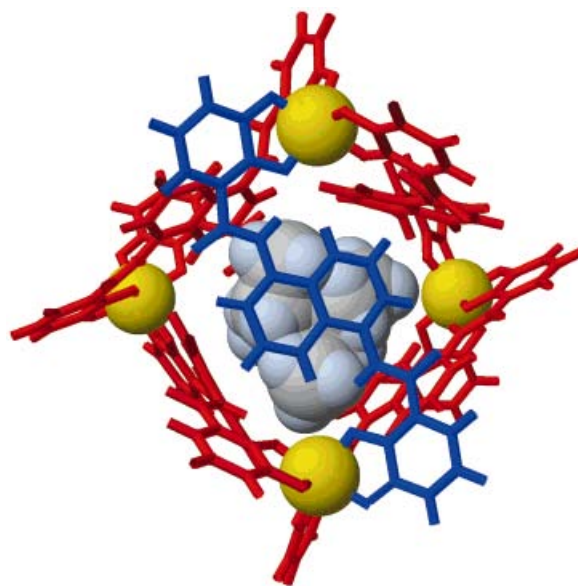


Figure 3. Schematic representation of the structure of $\text{K}_5[\text{Et}_4\text{N}]_7[\text{Fe}_4\text{L}_6]$ in the crystal showing the encapsulated Et_4N^+ . The other cations have been removed and the front ligand is highlighted in blue for clarity.

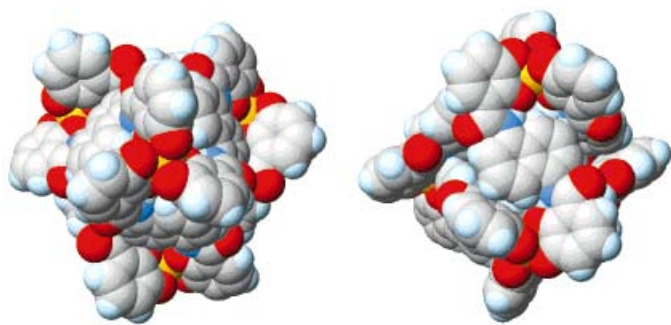


Figure 4. Space-filling views of the crystal structure of $[\text{Fe}_4\text{L}_6]^{12-}$ looking down the crystallographic threefold and pseudo twofold axis of the tetrahedron (right).

The Fe–Fe distances in the cluster are on average 12.8 Å, bringing the cluster just into the nanometer region. The naphthalene rings are twisted along the arene–N bond, so that they bend into the cavity. We interpret this as due to van der Waals interaction between the cluster and the encapsulated Et_4N^+ .

In summary, we have demonstrated that a strict geometric analysis can be employed in the rational design and synthesis of a homochiral M_4L_6 tetrahedral cluster. We have also shown for the first time that assemblies of this nature can be used to selectively encapsulate guests with remarkable discrimination. The supermolecular design rationale presented here is conceived to be general and applicable to other clusters of different size, symmetry, and stoichiometry.

Experimental Section

All NMR spectra were measured with a Bruker 300, 400, or 500 MHz spectrometer. Chemical shifts are reported as δ downfield from sodium $[2,2,3,3\text{-D}_4]3$ -trimethylsilylpropionate in D_2O . Both the methyl protected ligand **1** and the ligand H_4L were fully characterized by ^1H and ^{13}C NMR spectroscopy, FAB-MS, and elemental analysis.

1: 2,3-Dimethoxybenzoyl chloride^[11] (11.80 g, 58.8 mmol) and 1,5-diaminonaphthalene (4.43 g, 28.0 mmol) were dissolved in CH_2Cl_2 (400 mL). An excess of Et_3N (10 mL) was added and the reaction mixture stirred for one hour. The solution was washed with 1N HCl (200 mL) followed by 1N NaOH (200 mL). The organic layer was dried over MgSO_4 and concentrated by rotary evaporation. Diethyl ether was added to precipitate **1** as tan needle crystals, which were collected by filtration and air dried (9.38 g). A second crop of crystals was collected (1.86 g) to give a combined yield of 82.5%.

H_4L : BBr_3 (5 mL, 48.7 mmol) was added by syringe to a solution of **1** (1.48 g, 3.04 mmol) in CH_2Cl_2 (100 mL) at -78°C . The reaction mixture was allowed to warm to room temperature and stirred overnight. Volatiles were removed under vacuum, and the remaining orange-yellow residue was stirred in water for 2 h at 100°C . The colorless precipitate was collected by filtration and dried under vacuum at 70°C for 6 h (1.16 g, 2.70 mmol, 89%). ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 11.93 (s, 2H); 10.91 (s, 2H); 9.52 (s, 2H); 7.92 (d, J = 8.5 Hz, 2H); 7.87 (d, J = 7.3 Hz, 2H); 7.64–7.59 (m, 4H); 7.03 (dd, J = 1.7, 7.9 Hz, 2H); 6.84 (t, J = 7.9 Hz, 2H).

$\text{K}_5(\text{Et}_4\text{N})_7[\text{Ga}_4\text{L}_6]$: The ligand H_4L (0.100 g, 0.232 mmol) was suspended under oxygen-free conditions in distilled MeOH (30 mL). A 0.497N solution of KOH in MeOH (935 μL , 0.464 mmol) was added by micropipette. The ligand dissolved after about 5 min with stirring, after which a 0.280M solution of Et_4NCl in MeOH (1.660 mL, 0.465 mmol) was added by micropipette. $(\text{Ga}(\text{acac})_3)$ (0.056 g, 0.154 mmol) was then added to the solution as a powder. Within seconds the $\text{Ga}(\text{acac})_3$ dissolved, and the solution changed from colorless to yellow. While the reaction mixture was stirred at room temperature overnight, the product precipitated as a yellow

silky powder. This was isolated by centrifugation and dried under vacuum (0.120 g, 0.029 mmol, 76%). ^1H NMR (300 MHz, D_2O): δ = 13.60 (s, 12H; NH), 8.15 (d, J = 7.8 Hz, 12H, Ar_H), 7.91 (d, J = 8.6 Hz, 12H, Ar_H), 7.35 (dd, J = 1.5 Hz, 8.2 Hz, 12H, Ar_H), 7.20 (t, J = 8.2 Hz, 12H, Ar_H), 6.78 (dd, J = 1.5 Hz, 7.3 Hz, 12H, Ar_H), 6.63 (t, J = 7.9 Hz, 12H, Ar_H), 2.42 (q, J = 7.2 Hz, 48H, $\text{CH}_{2(\text{out})}$), 0.68 (t, J = 7.2 Hz, 72H, $\text{CH}_{3(\text{out})}$), -0.68 (m, 8H, $\text{CH}_{2(\text{in})}$), -1.58 (t, J = 6.9 Hz, 12H, $\text{CH}_{3(\text{in})}$). ^{13}C NMR (125 MHz, D_2O) δ = (C) 172.4, 161.4, 157.7, 136.9, 117.4; (CH) 129.4, 121.5, 120.3, 118.3, 117.8, 117.7; (CH_2) 54.5, 52.9; (CH_3) 9.1, 7.0; ES-MS (negative-ion detection, $\text{H}_2\text{O}/\text{CH}_3\text{OH}$ 10:90) $\diamond \equiv [\text{Ga}_4\text{L}_6]^{12-}$: m/z : 859.4 [$\diamond + 4\text{Et}_4\text{N}^+ + 2\text{K}^+ + 2\text{H}^+$] $^{4-}$, 868.9 [$\diamond + 4\text{Et}_4\text{N}^+ + 3\text{K}^+ + 1\text{H}^+$] $^{4-}$, 882.2 [$\diamond + 5\text{Et}_4\text{N}^+ + 1\text{K}^+ + 2\text{H}^+$] $^{4-}$, 891.8 [$\diamond + 5\text{Et}_4\text{N}^+ + 2\text{K}^+ + 1\text{H}^+$] $^{4-}$, 914.8 [$\diamond + 6\text{Et}_4\text{N}^+ + 1\text{K}^+ + 1\text{H}^+$] $^{4-}$, 924.2 [$\diamond + 6\text{Et}_4\text{N}^+ + 2\text{K}^+$] $^{4-}$, 937.4 [$\diamond + 7\text{Et}_4\text{N}^+ + 1\text{H}^+$] $^{4-}$, 946.9 [$\diamond + 7\text{Et}_4\text{N}^+ + 1\text{K}^+$] $^{4-}$, 1189.7 [$\diamond + 5\text{Et}_4\text{N}^+ + 2\text{K}^+ + 2\text{H}^+$] $^{3-}$, 1202.3 [$\diamond + 5\text{Et}_4\text{N}^+ + 3\text{K}^+ + 1\text{H}^+$] $^{3-}$, 1219.8 [$\diamond + 6\text{Et}_4\text{N}^+ + 1\text{K}^+ + 2\text{H}^+$] $^{3-}$, 1232.7 [$\diamond + 6\text{Et}_4\text{N}^+ + 2\text{K}^+ + 1\text{H}^+$] $^{3-}$, 1250.2 [$\diamond + 7\text{Et}_4\text{N}^+ + 2\text{H}^+$] $^{3-}$, 1263.0 [$\diamond + 7\text{Et}_4\text{N}^+ + 1\text{K}^+ + 1\text{H}^+$] $^{3-}$, 1275.7 [$\diamond + 7\text{Et}_4\text{N}^+ + 2\text{K}^+$] $^{3-}$, 1293.5 [$\diamond + 8\text{Et}_4\text{N}^+ + 1\text{H}^+$] $^{3-}$, 1306.0 [$\diamond + 8\text{Et}_4\text{N}^+ + 1\text{K}^+$] $^{3-}$; elemental analysis calcd for $\text{K}_5\text{Ga}_4\text{C}_{200}\text{H}_{224}\text{N}_{19}\text{O}_{36} \cdot 8\text{H}_2\text{O}$: C 58.75, H 5.92, N 6.51; found C 58.43, H 5.65, N 6.19.

$\text{K}_6[\text{Me}_4\text{N}]_6[\text{Ga}_4\text{L}_6]$: The complex was synthesized in a manner similar to $\text{K}_5(\text{Et}_4\text{N})_7[\text{Ga}_4\text{L}_6]$ using Me_4NCl . Within 10 min of stirring at room temperature the product precipitated as a yellow powder (88%). ^1H NMR (500 MHz, D_2O): δ = 7.91 (d, J = 7.5 Hz, 12H, Ar_H), 7.88 (d, J = 8.5 Hz, 12H, Ar_H), 7.29 (d, J = 8.3 Hz, 12H, Ar_H), 7.14 (t, J = 8.2 Hz, 12H, Ar_H), 6.77 (d, J = 7.4 Hz, 12H, Ar_H), 6.61 (t, J = 7.8 Hz, 12H, Ar_H), 2.59 (br.s, $\nu_{1/2}$ = 40 Hz, 32.4 H, $\text{CH}_{3(\text{out})}$), -0.50 (br.s, $\nu_{1/2}$ = 215 Hz, 3.6 H, $\text{CH}_{3(\text{in})}$); ESMS (anion detection, $\text{H}_2\text{O}/\text{CH}_3\text{OH}$ 10:90; $\diamond \equiv [\text{Ga}_4\text{L}_6]^{12-}$): m/z : 821.4 [$\diamond + 6\text{Me}_4\text{N}^+ + 2\text{H}^+$] $^{4-}$, 830.7 [$\diamond + 6\text{Me}_4\text{N}^+ + 1\text{K}^+ + 1\text{H}^+$] $^{4-}$, 839.7 [$\diamond + 6\text{Me}_4\text{N}^+ + 2\text{K}^+$] $^{4-}$, 1096.2 [$\diamond + 3\text{Me}_4\text{N}^+ + 6\text{K}^+$] $^{3-}$, 1108.4 [$\diamond + 4\text{Me}_4\text{N}^+ + 5\text{K}^+$] $^{3-}$, 1120.4 [$\diamond + 5\text{Me}_4\text{N}^+ + 4\text{K}^+$] $^{3-}$, 1132.5 [$\diamond + 7\text{Me}_4\text{N}^+ + 2\text{K}^+$] $^{3-}$, 1144.5 [$\diamond + 7\text{Me}_4\text{N}^+ + 2\text{K}^+$] $^{3-}$; elemental analysis calcd for $\text{K}_6\text{Ga}_4\text{C}_{168}\text{H}_{156}\text{N}_{18}\text{O}_{36} \cdot 4\text{H}_2\text{O}$: C 56.23, H 4.61, N 7.03; found: C 56.22, H 4.31, N 7.03.

$\text{K}_5(\text{Et}_4\text{N})_7[\text{Fe}_4\text{L}_6]$: The complex was synthesized in a manner similar to $\text{K}_5(\text{Et}_4\text{N})_7[\text{Ga}_4\text{L}_6]$ on use of $[\text{Fe}(\text{acac})_3]$ (79%). Crystals suitable for analysis by X-ray diffraction grew at room temperature over two weeks by gas phase diffusion of acetone into a methanol/water solution of the complex. ESMS (anion detection, $\text{H}_2\text{O}/\text{CH}_3\text{OH}$ 10:90; $\diamond \equiv [\text{Fe}_4\text{L}_6]^{12-}$): m/z : 613.8 [$\diamond + 2\text{Et}_4\text{N}^+ + 1\text{Na}^+ + 4\text{H}^+$] $^{5-}$, 641.7 [$\diamond + 2\text{Et}_4\text{N}^+ + 3\text{K}^+ + 2\text{Na}^+$] $^{5-}$, 788.4 [$\diamond + 2\text{Et}_4\text{N}^+ + 1\text{K}^+ + 3\text{Na}^+ + 2\text{H}^+$] $^{4-}$, 1094.5 [$\diamond + 2\text{Et}_4\text{N}^+ + 5\text{K}^+ + 2\text{Na}^+$] $^{3-}$, 1123.4 [$\diamond + 3\text{Et}_4\text{N}^+ + 5\text{K}^+ + 1\text{H}^+$] $^{3-}$, 1183.8 [$\diamond + 5\text{Et}_4\text{N}^+ + 3\text{K}^+ + 1\text{H}^+$] $^{3-}$, 1214.2 [$\diamond + 6\text{Et}_4\text{N}^+ + 2\text{K}^+ + 1\text{H}^+$] $^{3-}$, 1244.7 [$\diamond + 7\text{Et}_4\text{N}^+ + 1\text{K}^+ + 1\text{H}^+$] $^{3-}$, 1490.9 [$\diamond + 1\text{Et}_4\text{N}^+ + 1\text{K}^+ + 1\text{Na}^+ + 7\text{H}^+$] $^{2-}$; elemental analysis calcd for $\text{K}_5\text{Fe}_4\text{C}_{200}\text{H}_{224}\text{N}_{19}\text{O}_{36} \cdot 4\text{H}_2\text{O}$: C 60.65, H 5.90, N 6.72; found: C 60.38, H 5.83, N 6.44.

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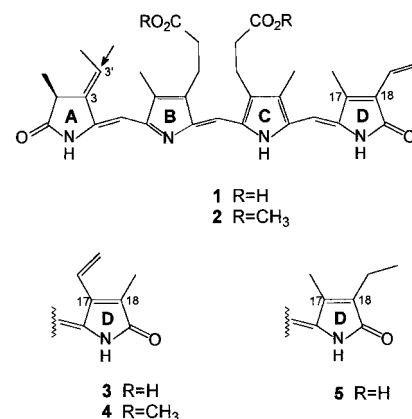
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- [10] Crystal data for $\text{K}_5[\text{Et}_4\text{N}]_7[\text{Fe}_4\text{L}_6] \cdot 8\text{H}_2\text{O} \cdot 3\text{CH}_3\text{OH}$ were collected with a Siemens SMART diffractometer equipped with a CCD area detector;^[12] crystal size $0.25 \times 0.23 \times 0.10$ mm; $T = -120^\circ\text{C}$, $\lambda\text{MoK}\alpha = 0.71073$ Å; point group $I\bar{4}3d$ (No. 220), $a = 43.706(8)$ Å, $V = 83488$ Å³, $Z = 16$, $\mu = 0.45$ mm⁻¹, $F(000) = 35808$, $\rho_{\text{calc}} = 1.333$ Mg m⁻³, $2\theta_{\text{max}} = 41.67^\circ$. Of the 136 092 reflections collected 7336 were unique ($R_{\text{int}} = 0.214$). The structure was solved by direct methods and was refined on F^2 using SHELXTL.^[13] Data were corrected for Lorentz and polarization effects. An empirical absorption correction was applied using XPREP^[13] (ellipsoidal model, $R_{\text{int}} = 0.036$, $T_{\text{max}} = 0.895$, $T_{\text{min}} = 0.834$). The iron atoms, oxygen and nitrogen atoms of the ligands, the half-occupancy potassium, and the nitrogen and carbon atoms of the full occupancy Et_4N^+ counterion were refined anisotropically. Hydrogen atoms were included as riding on their respective carbon and nitrogen atoms for all but the disordered counterions and solvent molecules. Not all carbon atoms were found for the disordered Et_4N^+ counterions. The N–C and C–C distances for these disordered ions were set to target values of 1.4 and 1.5 Å. An antibumping restraint was applied to carbon atoms of the disordered Et_4N^+ on the interior of the tetrahedral cluster. Weighting scheme: $1/[\sigma^2 F_o^2 + (0.1660p)^2 + 779.981p]$, where $p = ((F_{o,0}^2)_{\text{max}} + 2 F_o^2)/3$. Final $R_1 = 0.0978$ for 4672 reflections with $F_o > 4\sigma(F_o)$; 4672 Friedel unique data, 542 parameters, 14 restraints, $3.75^\circ < 2\theta < 34.58^\circ$; for all 7336 data, $wR_2 = 0.3288$, $\text{GOF} = 1.205$; max/min residual density $+0.62/-0.32$ e Å⁻³, Flack parameter $= 0.03(5)$.^[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-100947. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
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A Novel Chromophore Selectively Modifies the Spectral Properties of One of the Two Stable States of the Plant Photoreceptor Phytochrome**

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Phytochromes are plant photoreceptors that consist of a protein (125–140 kDa) covalently bound to the open-chain tetrapyrrole chromophore phytychromobilin (**1**, Scheme 1).



Scheme 1. Structural formulas of the native phytochrome chromophore phytychromobilin (**1**), the isomer “iso”-phytychromobilin (**3**, described here for the first time), the corresponding methyl esters **2** and **4**, and phycocyanobilin (**5**). The arrow marks the 3' position on ring A of **1**, which is covalently attached to the apoprotein through nucleophilic attack by a cystein thiol group. The B/C tautomeric form shown here was selected in analogy to the crystal structure of a 2,3-dihydrobilatriene abc model compound.^[20]

Initiated by $Z \rightleftharpoons E$ photoisomerization of a double bond of **1**,^[1] the phytochrome undergoes a multistep rearrangement steered by subtle chromophore–protein interactions. This ultimately leads to a biological signal transduction and control of a wide array of physiological processes as a function of wavelength and intensity of the absorbed light.^[2] Accordingly, effects on absorption and photochemical properties upon selective modifications of the protein and chromophore components may significantly contribute to the understanding of the light-induced phytochrome transformations.

The synthesis of native and mutated forms of the phytochrome apoprotein (i.e., chromophore-free protein) has been accomplished previously,^[3] as has the assembly of the apoproteins with native **1** and with phycocyanobilin (**5**).^[1c, 3] However, the amount of **1** isolable from algae^[4] has been

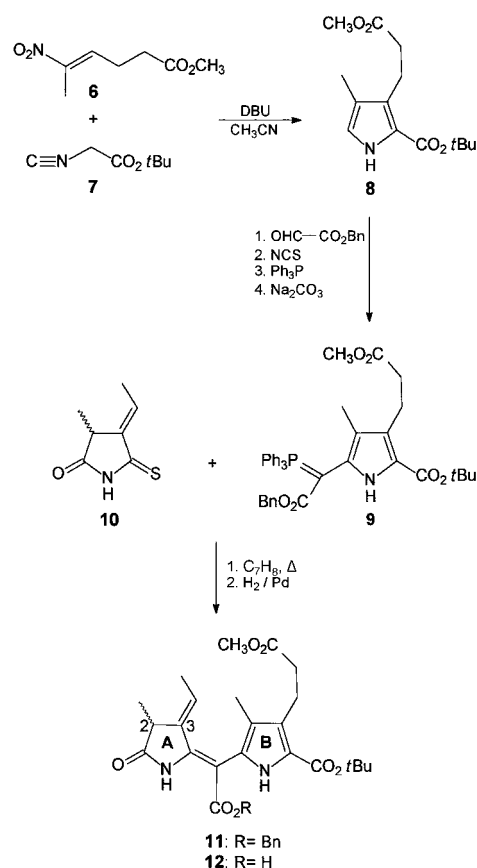
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insufficient for detailed spectroscopic investigations. More efficient and variable syntheses of **1**^[5] and of modified tetrapyrrole chromophores (including substitutional isomers and isotopomers^[7]) are therefore urgently needed.

We now report new syntheses of **1** and a substitutional isomer, "iso"-phytychromobilin (**3**, Scheme 1), based in part on previous work. Whereas Gossauer and collaborators^[8] synthesized only the dimethyl esters of several open-chain tetrapyrroles, we present here the very labile free acids **1** and **3**, and document the ability of these compounds to form functional chromoproteins with heterologously produced phytyochrome apoprotein.

Racemic thiosuccinimide **10** (ring A) was prepared by a known route.^[8b] The conditions for the subsequent thio-Wittig reaction must be chosen such that the 3-ethylidene structure, which is essential for covalent binding to the protein,^[9] does not rearrange to the more stable 2,3-dehydro structure with an unsaturated ring A. In contrast to the earlier synthesis, ring B was prepared by cyclization^[10] of nitroolefin **6**^[11] with isocyanide **7**^[12] to form **8** (Scheme 2), rather than by a Paal–Knorr condensation. Substitution of the free α position of **8**

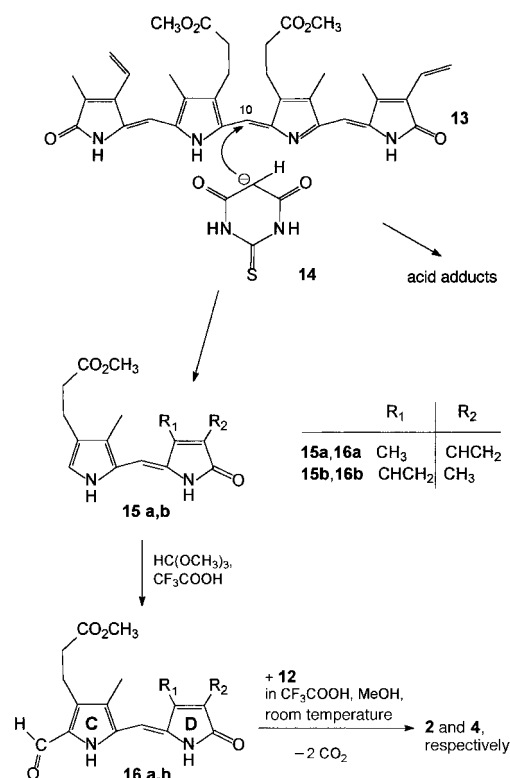


Scheme 2. Synthesis of phosphorus ylid **9** (ring B) and coupling with separately prepared **10** (ring A)^[8b] to give dipyrromethene **11**. Bn = benzyl, *t*Bu = *tert*-butyl, NCS = *N*-chlorosuccinimide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

with a benzyloxycarbonyl(hydroxy)methyl group was followed by chlorination and reaction with triphenylphosphane to provide ylid **9**,^[13] which was combined with **10** in a thio-Wittig reaction to afford **11**. Hydrogenolysis of the benzyl ester

group of **11** gave dipyrromethene **12**. All products gave the expected elemental analyses. Since rings B and C in **1** are identical, and since several syntheses are known for ring D,^[14] the present choice of a stepwise construction of the ring system allows for a broad variation in the substitution pattern and for the introduction of stable isotope labels. The latter are of decisive importance for the interpretation of the complex vibrational spectra of the chromophore in phytyochrome.^[3g]

Instead of a stepwise assembly by annelation of rings C and D, we chose the more efficient cleavage at C10 of biliverdin IX α dimethyl ester (**13**) with the thiobarbiturate anion (**14**).^[15] This alternative affords the two rings already joined in the form of the dipyrromethenones **15a** and **15b** (Scheme 3).



Scheme 3. Cleavage of biliverdin IX α dimethyl ester **13** by thiobarbiturate anion (**14**). The reaction affords both a dipyrromethenone with rings A–B (**15b**) and a thiobarbiturate adduct of rings C–D (not shown) as well as to dipyrromethenone C–D (**15a**) and the corresponding adduct with rings A–B (not shown).

After chromatographic separation (silica gel, chloroform/ethyl acetate 1/1) the two products were formylated separately to **16a** and **16b**, which were used for the construction of **1** and **3**. The two halves, **12** and **16a** or **16b**, were coupled^[6] to the corresponding dimethyl esters **2** and **4**, respectively, in about 40% yield (see Table 1). The structural assignment of **4** is based on ¹H NMR spectra of the two esters, in which the ABX and AMX signal groups unequivocally establish C17 (**4**) and C18 (**2**) to be the positions of the vinyl substituents.^[16] Synthesis of the acids **1** and **3** from the corresponding esters proved difficult because of the instability of the products; it was achieved only by hydrolysis on an acidified ion-exchange resin (Dowex-50WX8-200, 40% trifluoroacetic acid, 48 h, room temperature, chromatographic purification, and crys-

Table 1. Physical and spectroscopic data for **3**, **4**, and **16b**.

3: ^1H NMR (400 MHz, $[\text{D}_5]\text{pyridine}$): δ = 1.50 (d, 3H, J = 7.51 Hz), 1.69 (d, 3H, J = 7.26 Hz), 2.02, 2.10, 2.16 (3s, each 1H), 2.85 (m, 4H), 3.10 (t, 2H, J = 7.23 Hz), 3.18 (t, 2H, J = 7.35 Hz), 3.32 (q, 1H, J = 8.20 Hz), 5.59–5.76 (AB, 2H, partially overlapped by the H_2O peak), 5.87 (s, 1H), 6.26 (s, 1H), 6.32 (q, 1H, J = 7.31 Hz), 6.87 (m, X), 7.35 (s, 1H)

4: M.p. 208 °C; ^1H NMR (400 MHz, CDCl_3): δ = 1.30 (d, 3H, J = 7.54 Hz), 1.84 (d, 3H, J = 6.73 Hz), 1.88, 2.00, 2.08 (3s, each 3H), 2.52 (t, 2H, J = 7.80 Hz), 2.53 (t, 2H, J = 7.55 Hz), 2.87 (t, 2H, J = 7.82 Hz), 2.91 (t, 2H, J = 7.53 Hz), 3.09 (q, 1H, J = 7.38 Hz), 3.65, 3.66 (s, each 3H), 5.62 + 5.64 (AB, J_{AB} = 1.61, J_{AX} = 17.86, J_{BX} = 11.51 Hz), 5.76 (s, 1H), 6.09 (s, 1H), 6.33 (q, 1H, J = 7.35 Hz), 6.59 (s, 1H), 6.59–6.70 (X, 1H); UV/Vis (MeOH, 0.5% NEt_3): λ_{max} (ϵ) = 366 (42000), 617 nm (16100); FT-IR (CCl_4): $\tilde{\nu}$ = 3435, 3343, 2987–2915, 1742, 1733, 1698, 1666, 1619, 1590, 1436, 1252, 1165, 986, 954, 917 cm^{-1} ; FAB-MS: m/z (%) = 613 (18) [M^+], 586 (7), 502 (19), 467 (19), 418 (14), 391 (12), 348 (39), 334 (100); HR-FAB-MS ($\text{C}_{35}\text{H}_{41}\text{N}_4\text{O}_6$): calcd 613.3026, found 613.3034

16b: M.p. 235–237 °C; ^1H NMR (400 MHz, CDCl_3): δ = 2.09, 2.11 (2s, each 3H), 2.58 (t, 2H, J = 7.65 Hz), 3.06 (t, 2H, J = 7.64 Hz), 3.65 (s, 3H), 5.65 + 5.68 (AB, 2H, J_{AB} = 1.60, J_{AX} = 20.20, J_{BX} = 13.83 Hz), 6.10 (s, 1H), 6.59–6.66 (X, 1H), 9.75 (s, 1H), 10.55 (brs, 1H), 10.75 (brs, 1H); UV/Vis (MeOH): λ_{max} (ϵ) = 405 (24250), 271 (11500), 243 nm (11800); FT-IR (KBr): $\tilde{\nu}$ = 3335, 2949–2858, 1734, 1675, 1559, 1443, 1340, 1302, 1250, 1173, 1057, 993, 761 cm^{-1} ; EI-MS: m/z (%) = 328 (100) [M^+], 313 (7), 299 (18), 269 (15), 241 (19), 225 (20), 197 (5), 183 (4), 134 (5), 120 (4), 106 (3); HR-MS ($\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4$): calcd 328.1423, found 328.1421

tallization from chloroform/1 % methanol/*n*-hexane). In view of their instability, the free acids were used in the assembly experiments (see below) immediately after their ^1H NMR spectra were recorded. The syntheses described offer the first approach to acids **1** and **3** and related compounds in quantities sufficient for spectroscopic investigation after incorporation into protein. However, the overall yield is still relatively modest.

Acids **1** and **3** were incubated with recombinant oat apophytochrome^[17] under standard conditions in order to test, in the case of **1**, the reproducibility of the phytochrome absorption values for the native chromoprotein (λ_{max} = 667 nm for P_r and 730 nm for P_{fr})^[18] and, in the case of **3**, to search for any effect of the modified substitution pattern of ring D on the spectral properties. The maxima in the difference spectrum (Figure 1) for chromoprotein constructed with **1** (λ_{max} = 665 nm for P_r and 728 nm for P_{fr}) are in accord with values obtained for native phytochrome extracted from etiolated oat. Based on our experience,^[3d] the hypsochromic shift by a few nanometers may result from a slightly altered conformation of the apoprotein owing to the heterologous expression in yeast.^[19] Recombinant apophytochrome can also be assembled with phycocyanobilin (**5**) obtained by extraction of algae. Tetrapyrrole **5** differs from the native chromophore **1** only with regard to saturation of the vinyl substituent on ring D (18-ethyl instead of 18-vinyl; Scheme 1); because of the shortened π -electron system, both maxima in the chromoprotein are shifted hypsochromically by about 14 nm (λ_{max} = 653 nm for P_r and 717 nm for P_{fr} ; see also curve “PCB” in Figure 1; for the absorption maxima for the various phytochromes, see Table 2).

The P_r form of chromoprotein assembled with the “iso”-phytochromobilin **3** displays an absorption maximum practically identical to that of the native chromophore **1** (λ_{max} = 663 nm). In contrast, in the P_{fr} form, and also in the

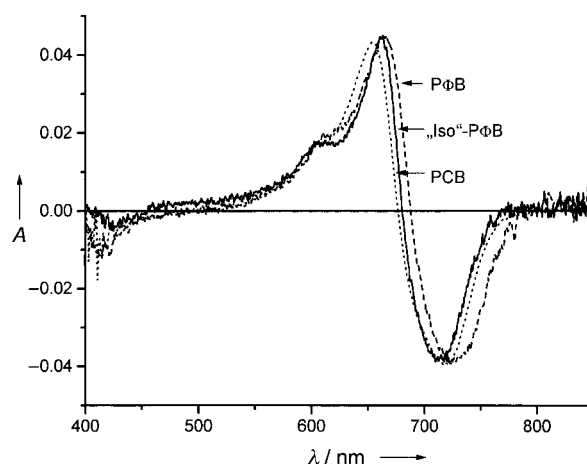


Figure 1. P_r – P_{fr} Difference spectra of the recombinant phytochromes obtained by assembly of the heterologously expressed apoprotein with phytochromobilin (**1**; PΦB) and with “iso”-phytochromobilin (**3**; “iso”-PΦB). The difference spectrum for recombinant phytochrome assembled with phycocyanobilin (**5**, PCB)^[17] is also shown. The absorption values on the ordinate refer to the spectra of the chromoproteins obtained by assembly with **1** and **3**. The amplitude of the shorter wavelength maximum of **5** was normalized to that of **1**.

Table 2. Absorption maxima for native and recombinant phytochromes.

Phytochrome type	Chromophore	λ_{max} [nm]; P_r , P_{fr}
native phytochrome ^[a]	1	667, 730
recombinant phytochrome	1 ^[b, c]	665, 728
recombinant phytochrome	3 ^[b]	663, 714
recombinant phytochrome	5 ^[c]	653, 717

[a] Prepared from yeast. [b] Synthetically prepared compound. [c] From material extracted from algae.

chromoprotein assembled with phycocyanobilin **5**, absorption is shifted hypsochromically to 714 nm.^[17]

The positions of the absorption maxima indicate that the protein surface of the chromophore pocket tolerates the

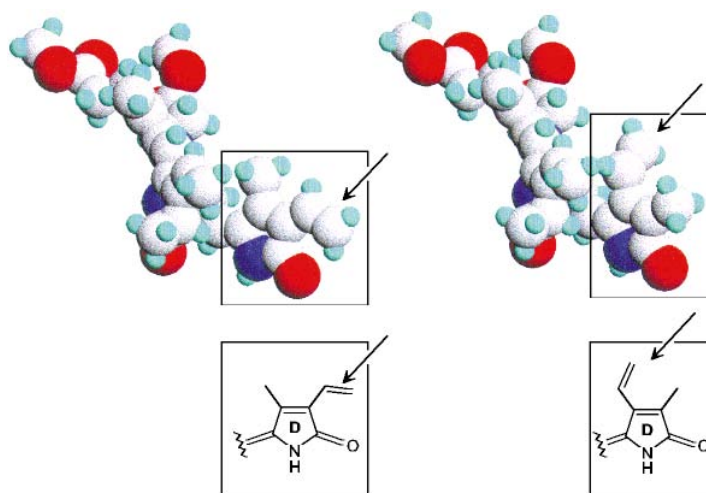


Figure 2. Structures of the *Z,Z,E* configured compounds **1** and **3** optimized at the PM3/MM⁺ level (Hyperchem, version 4.0). Note that the differing conformations in ring D were generated without regard to interactions with the protein pocket of the phytochrome. Arrows indicate the positions of the vinyl substituents.

altered substitution on ring D of **3** in the P_r form, whereas in the P_{fr} form the chromophore–protein interactions discriminate between the substitution patterns of **1** and **3**. There remains the question of whether this selectivity of the chromophore–protein interactions reflects either steric and/or electronic effects (see Figure 2).

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Tweezers with Different Bite: Increasing the Affinity of Synthetic Receptors by Varying the Hinge Part**

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Despite the tremendous progress in the design and synthesis of receptor molecules with predicted binding properties, it remains a difficult task to design a molecule capable of binding to a particular ligand. Therefore, recent efforts have turned to the more “biomimetic approach” of combinatorial chemistry for the generation of libraries of synthetic receptors capable of binding certain desired ligands. The approach is inspired by nature’s very own combinatorial approach so clearly demonstrated by the immune system.

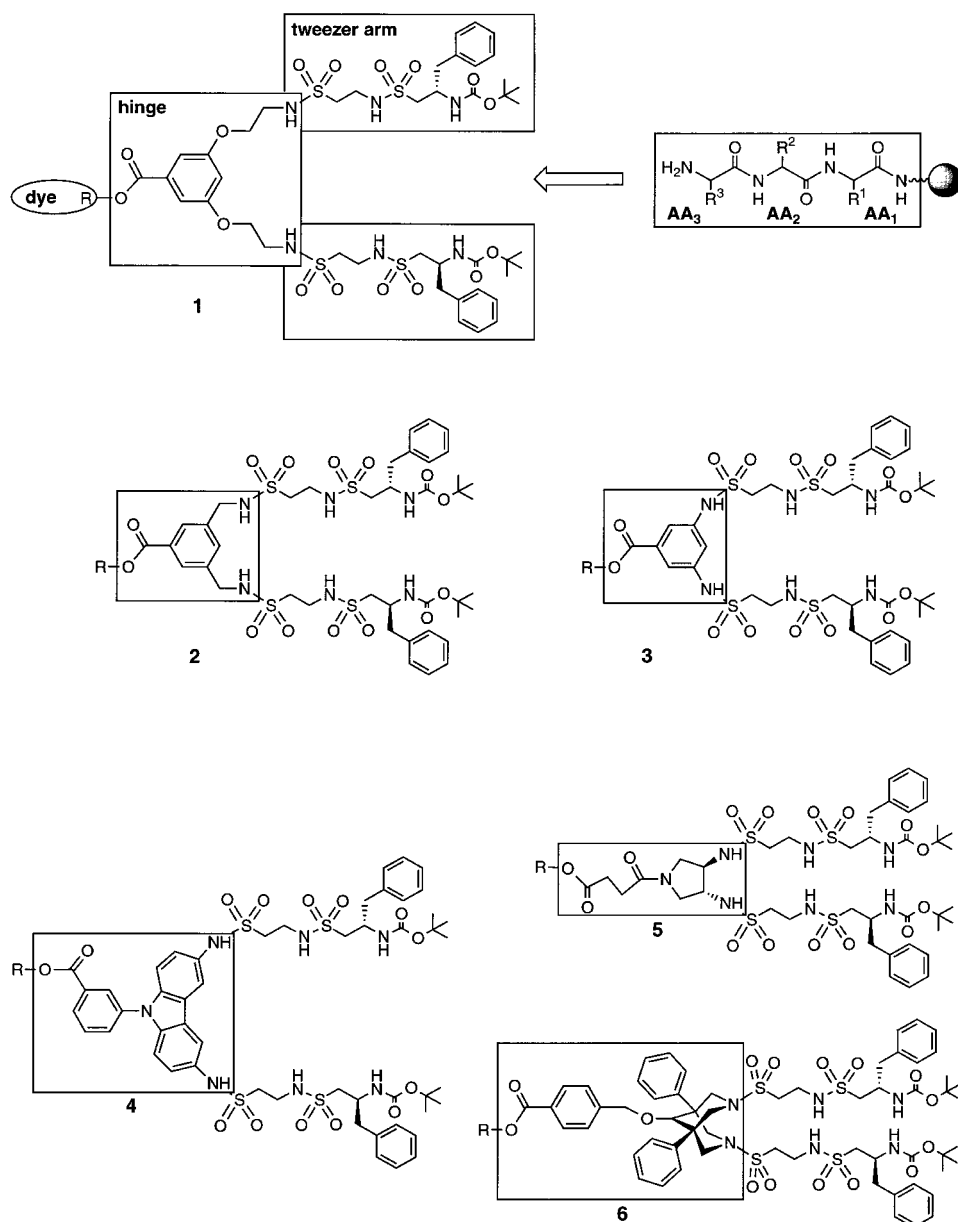
Based on the successful concept of “tweezerlike” two armed synthetic receptors,^[1] we have developed synthetic receptors consisting of peptidosulfonamide peptidomimetics.^[2] We would like to prepare libraries of tweezerlike receptors that can be screened for their binding affinity to a variety of ligands, peptides, other biomolecules (for example, those that are present on pathogenic organisms), drugs, and signaling molecules. Although our present synthetic receptor showed a remarkable binding selectivity,^[2] to have further possible applications its binding affinity with ligands had to be increased. We now describe the results of incorporating less flexible “hinges” in tweezerlike synthetic receptors.

Our present “tweezerlike” synthetic receptors consist of three different parts (Scheme 1): A hinge to which the tweezer arms are attached; a dye or a solid-phase bead attached to this hinge; and two binding arms, which at present consist of peptidosulfonamide peptidomimetics. Based on the original hinge in tweezer **1**, hinges in tweezers **2–6** were selected to gradually vary the flexibility and interchain distance, or both, between the amino nitrogen atoms.

The route for the preparation of the tweezerlike synthetic receptors is exemplified by the preparation of tweezers **2** and **5** in Schemes 2 and 3. The bis(aminomethyl)benzoic acid hinge present in receptor **2** was synthesized from 3,5-dimethylbenzoic acid (**7**).^[3] We took advantage from the fact

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Scheme 1. Structures of tweezerlike synthetic receptor: R = Disperse Red 1; the hinge parts are shown in the frames; AA_{1-3} .^[12]

that some monobrominated product **10** always occurred on bromination of **8** by using **10** for the preparation of the so-called amputated tweezer containing only one arm (**2a**, see above). After removal of the Boc protecting groups in **11**, the peptidosulfonamide arms were introduced through the sulfonyl chloride approach.^[4] Saponification of the methyl ester followed by coupling to Disperse Red 1 (DispR) completed the synthesis of the intensely blood-red synthetic receptor **2**. The amputated receptor **2a** was prepared analogously (Scheme 2).

The pyrrolidine hinge^[5] in tweezer **5** was prepared from L-tartaric acid (Scheme 3). The pyrrolidine diol **14** was prepared according to Nagel et al.^[6] This diol was converted into the diazide,^[7] then reduced, and the resulting amino groups protected to afford **15**. The dye was attached to a spacer group by hydrogenolysis of the benzyl group.^[8] Subsequently, the

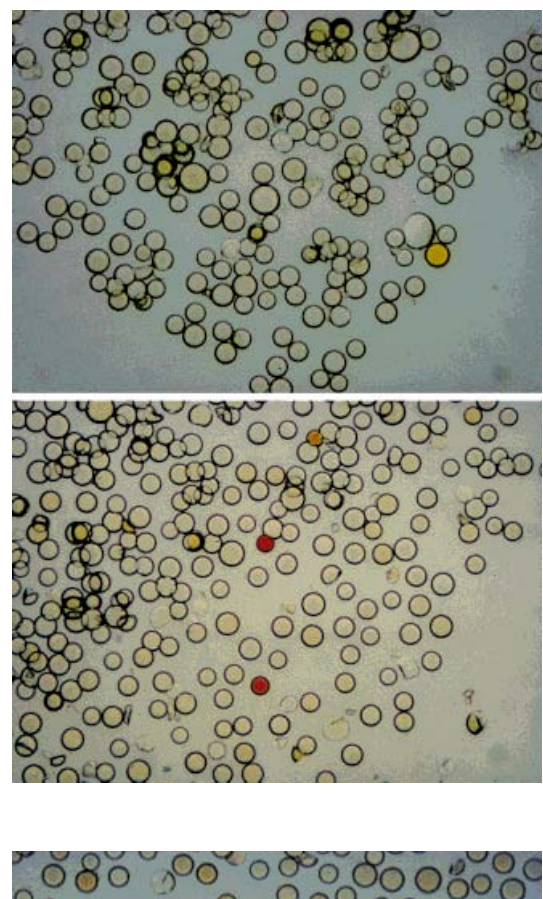
Boc protecting groups in **16** were removed and introduction of the peptidosulfonamide arms by the sulfonyl chloride approach completed the synthesis of **5**.

In synthetic receptor **3** the commercially available diamino-nobenzoic acid hinge was used. The carbazole hinge present in tweezer **4** was prepared according to Rebek et al.^[9] The choice for the preorganized tweezer hinge present in receptor **6** was inspired by the work of Diederich et al.^[10] and this hinge was obtained after reduction and attachment of the dye part.^[11]

The thus obtained receptors **1–6** were screened for binding against a 24389 (= 29^3) member encoded sidechain-deprotected tripeptide library on TentaGel ($AA_3-AA_2-AA_1-N(H)-TentaGel$).^[12] The bead-supported tripeptide library was equilibrated in a chloroform solution of the receptor (Figure 1).^[13] Immediately it can be seen that receptors **2**, **3**, and **4** showed an increased binding affinity, since the concentration for binding of these receptors to the beads was lower than the concentration for binding of the original receptor (Table 1). The binding by the pyrrolidine receptor **5** is comparable to that of the original receptor **1**, and clearly two tweezer arms are needed for a significant binding, since the

“amputated” receptor having one arm (**2a**) does not give rise to an appreciable binding even at a concentration of 425 μM . At first glance the absence of any binding whatsoever by receptor **6** was surprising. However, we reasoned that repulsion between the lone pairs on the oxygen atoms of the sulfonamide groups attached to the diazobicyclonane system might disfavor the chair–chair shape and as a consequence favor the formation of a boat–chair conformation and lead to the opening of the tweezerlike structure.^[14]

After 72 h equilibration the colored beads were separated and decoded by photolytic release of the molecular tags, as monitored by electron-capture gas chromatography (EC-GC).^[15] The number of beads which were decoded for each synthetic receptor are shown in Table 1. This table also shows the consensus sequences bound by each receptor, the frequencies with which they were found among the decoded



synthetic receptor **1**, both the diamino receptor **3** and the pyrrolidine receptor **5** show some degree of diastereoselectivity since L-Glu-D-His or D-Glu-L-His are found, but not the corresponding diastereomeric sequences L-Glu-L-His or

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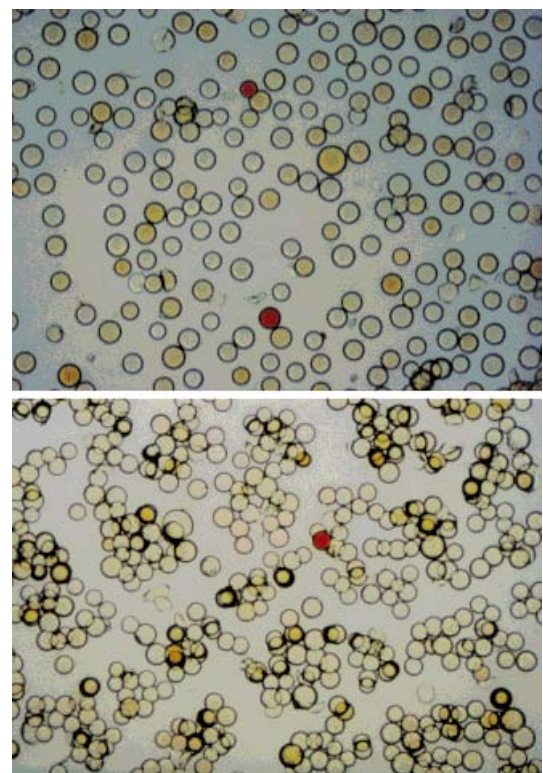


Figure 1. Photographs of the screening assays of tweezer receptors **1**, **2**, **3**, and **5** for binding to the bead-supported tripeptide library.

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Table 1. Binding selectivity of receptors **1–6** for tripeptides in a 24389 (=29³) member encoded sidechain-deprotected tripeptide library on TentaGel (AA₃–AA₂–AA₁–N(H)–TentaGel).

Receptor	Equilibrium concentration [μM]	Decoded beads number	Consensus sequence AA ₃ –AA ₂ –AA ₁	Found frequency [%] ^[a]	Library member frequency [%] ^[b]
1 ^[e]	70	34	L/D-Ala-D/L-Asp-L/b-Xxx ^[d]	50	0.1
			L-Glu-D-His/Asn-Xxx	20	0.3
2	40	28	Glu-Xxx-Xxx ^[c]	61	6.9
			L/b-Glu-D/L-His-Xxx ^[d]	32	0.2
			L/b-Glu-Xxx-L/b-Val	21	0.2
			Gly-Asn/His-Asp/Glu	21	0.07
2a	425	3	Glu/Asp-Xxx-Xxx	100	14
3	20	33	Glu-Xxx-Xxx	64	6.9
			Xxx-His-Xxx	70	6.9
			Xxx-Xxx-Asp	27	6.9
			L/D-Glu-D/L-His-Xxx ^[d]	61	0.2
4	40	16	Glu-Xxx-Xxx	63	6.9
			Xxx-His-Xxx	56	6.9
			L/b-Glu-D/L-His-Xxx ^[d]	38	0.2
5	80	19	L/b-Glu-D/L-His-Xxx	95	0.2
			L/b-Glu-D/L-His-Phe ^[d]	26	0.02
6	500	none	none		

[a] Only consensus sequences found in ≥20% of the beads are listed here. [b] Frequency with which these are actually present in the tripeptide library. [c] No prefix L- or D- indicates no preference for either enantiomer by the synthetic receptor. [d] The prefixes L- and D- placed in this manner indicate that, for example, L-Glu-D-His-Xxx and D-Glu-L-His-Xxx are found but not L-Glu-L-His-Xxx or D-Glu-D-His-Xxx. [e] See reference [2].

D-Glu-D-His. This diastereoselectivity is also shown, albeit less clearly, by the other two receptors **2** and **4** that were capable of recognizing the Glu-His sequence. As was the case with the original receptor **1**, most variability is found in the amino acid residue that is nearest to the polymer support (AA₁). However, in the original receptor **1** this is predominantly a polar amino acid residue while in the receptors **2** and **3** (which contain less flexible hinges than the hinge of **1**) and in the carbazole receptor **4** the distribution of polar to nonpolar amino acids in AA₁ is about equal whereas in the pyrrolidine-based receptor **5** there is a shift to an apolar amino acid for AA₁.

Although the trends are clear and we seem to be on our way towards realizing our main aim with an increase in the binding affinity, binding of the peptide sequences determined by decoding the beads had to be verified by binding experiments with these peptides obtained by independent synthesis and determination of some representative binding constants.

Based on the sequences found from the decoding experiments we selected the indicated sequences for resynthesis (Table 2). Several binding constants were determined. Indeed, the binding affinity of the sequence D-Ala-L-Asp-D-Ser that bound with high selectivity to the original receptor **1** was increased more than tenfold (from 330 to 4100 M⁻¹) with synthetic receptor **2**. An increasing affinity was also observed with the sequence L-Glu-D-Asn-L-Val that bound with a lower affinity to the original receptor (95 M⁻¹) but that bound to tweezer **2** with a respectable affinity of K_a=1680 M⁻¹. A twofold increase in binding affinity of D-Ala-L-Asp-D-Ser

was observed on using the more rigid tweezer **3**, a receptor that has less space between the peptidosulfonamide arms. This tweezer, like the previous tweezer **2**, also improved the binding affinity of similar tripeptides, for example L-Glu-D-His-L-Val, which bound to the original tweezer **1**. Although a coloring of the tripeptide containing beads comparable to that with the benzyl tweezer **2** took place upon incubation with a concentration of the carbazole tweezer **4**, none of the beads were dark orange or red. Therefore, the binding affinity was considered not be significantly enhanced relative to the original receptor **1**. Apparently, despite the rigid character of the carbazole hinge the distance between the arms is too large for a clear increase in the binding affinity. The pyrrolidine hinge seemed a very attractive one with respect to rigidity and chirality, and the selectivity of binding of the tweezer containing this hinge was very high. In 95 % of the decoded beads the sequence L/b-Glu-D/L-His-Xxx was found. Moreover L-Glu-D-His-Xxx and D-Glu-L-His-Xxx were found, but not the corresponding diastereomeric sequences L-Glu-L-His-Xxx or D-Glu-D-His-Xxx (Table 1). However, the binding affinity was a little disappointing. Apparently, the tweezer arms point too far away from each other for a significant increase of binding to occur.

Table 2. Binding affinity of receptors **1–6** for peptides, which were synthesized according to the sequences found by decoding.

Receptor	Resynthesized peptide	Screening affinity ^[a]	Binding affinity ^[b]	K _a [M ⁻¹] ^[c]	ΔG [kJ mol ⁻¹]
1	D-Ala-L-Asp-D-Ser	+	++	320	-14.2
	L-Glu-D-Asn-L-Val	+	+	95	-11.2
2	D-Ala-L-Asp-D-Ser	[f]	+++	4100	-20.5
	L-Glu-D-Asn-L-Val	+++	+++	1680	-18.3
3	D-Ala-L-Asp-D-Ser	[e]	++	760	-16.4
	L-Glu-D-Asn-L-Val	[e]	+	[d]	[d]
	L-Glu-D-His-L-Val	++	+++	210	-13.2
	Gly-L-His-L-Asp	++	+++	[d]	[d]
4	Gly-L-His-L-Asp	+	+	[d]	[d]
5	D-Ala-L-Asp-D-Ser	[e]	++	~40	~-9
	L-Glu-D-His-L-Val	+++	++	80	-10.8

[a] As determined from incubation with the bead-supported tripeptide library: +++ red beads; ++ dark orange to red beads; + dark orange beads. [b] By incubation in chloroform of the resynthesized peptide on the bead with the colored receptor. [c] As derived from UV measurements, the error is ±10 %, with the exception of 4100 M⁻¹: ±5 % and 210 and 40 M⁻¹, each ±15 %. [d] Not determined. [e] Not found. [f] Not found, however the related sequence D-Ala-L-Asp-D-Thr was found.

In conclusion, we have shown that by varying the hinge part of tweezerlike synthetic receptor molecules it is possible to increase the binding affinity of tripeptides significantly while maintaining the selectivity. The availability of a variety of hinges or scaffolds and building blocks inspired by “natural diversity” will provide access to all sorts of required libraries capable of binding compounds other than peptides.

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- [12] AA₁₋₃: Gly, D- and L-Ala, D- and L-Val, D- and L-Leu, D- and L-Phe, D- and L-Pro, D- and L-Ser, D- and L-Thr, D- and L-Asn, D- and L-Gln, D- and L-Asp, D- and L-Glu, D- and L-His, D- and L-Lys, D- and L-Arg.
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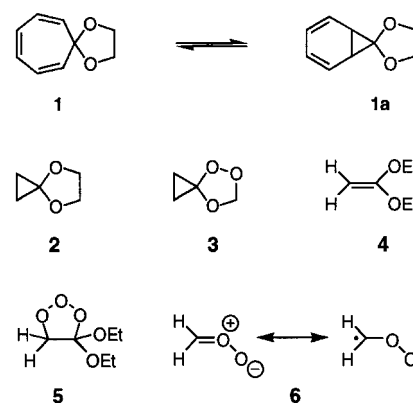
A Spontaneous Fragmentation: From the Criegee Zwitterion to Coarctate Möbius Aromaticity**

Christian Berger, Christian Bresler, Ulrich Dilger, Daniel Geuenich, Rainer Herges,* Herbert Röttele, and Gerhard Schröder*

Dedicated to Professor William von E. Doering on the occasion of his 80th birthday

Coarctate reactions^[1] are defined as those in which two bonds are simultaneously formed and broken at one or more atoms. Like the pericyclic reactions, they form an independent and coherent class of concerted reactions. Rules are available for predicting the stereochemical course of coarctate reactions,^[1] similar to the Woodward–Hoffmann rules for pericyclic reactions. We now describe an unusual fragmentation reaction which is in accordance with these stereochemical rules and for which such a coarctate transition state was confirmed by theoretical calculations.

Tropone ethylene acetal (**1**) is in equilibrium with the norcaradiene derivative **1a**. Above 100 °C **1** undergoes sigmatropic rearrangements ($E_a = 23.9 \text{ kcal mol}^{-1}$).^[2] Moreover, above 110 °C **1** decomposes via **1a** to give carbon dioxide, benzene, and ethene ($E_a = 31.6 \text{ kcal mol}^{-1}$).^[2] The fragmentation of **1a** was interpreted as a chelotropic cycloreversion to give benzene and 2-carbena-1,3-dioxolane. The authors speculate that the decomposition of the 2-carbena-1,3-dioxolane and the chelotropic cycloreversion might be part of a single concerted step.^[2] The parent structural element in the fragmentation of **1a** is the 4,7-dioxaspiro[2.4]heptane **2**. If a C–O bond in **2** is replaced by a O–O bond (**3**),



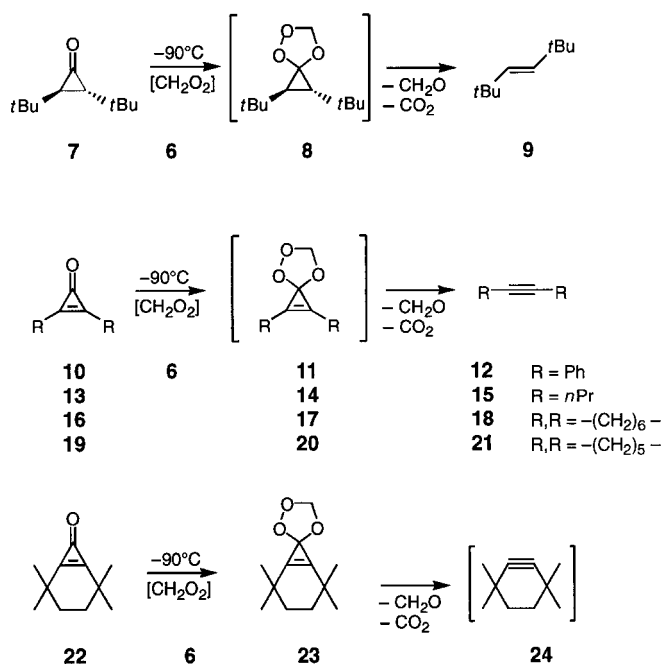
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the activation barrier for a concerted fragmentation should be lowered considerably relative to **1** or **2**. The bond energy of a C–O bond is about 85 kcal mol^{−1},^[3] and that of an O–O bond only 40 kcal mol^{−1}.^[4] Derivatives of **3** are generally accessible by 1,3-dipolar cycloaddition of formaldehyde *O*-oxide (**6**) to three-membered ring ketones under ozone-free conditions.^[5a] The primary ozonide **5**, generated from ozone and ketene diethyl acetal (**4**) at −110 °C was used as a source of **6**. Compound **5** decomposes between −90 and −80 °C in a [3+2] cycloreversion to give **6** and inert diethyl carbonate ($E_a = 12.5$ kcal mol^{−1}, $\Delta H^\ddagger = 11.5$ kcal mol^{−1}).^[5b]

The three-membered ring ketones **7**, **10**, **13**, **16**, **19**, and **22** are known. They were added at −110 °C to the primary



ozonide **5**, which was identified in the ¹H NMR spectrum at −110 °C by means of the methylene signal of the 1,2,3-trioxolane ring at $\delta = 4.35$ (s, 2H, in [D₁₄]methylcyclohexane), 3.9 (in [D₁₄]methylcyclohexane/[D₈]toluene 2/1), and 4.68 (in [D₁₀]diethyl ether). The [3+2] cycloreversion of **5**, which begins at −90 °C, can be monitored by following the decrease in intensity of this signal. We suggest^[6] that **6** reacts with **7**, **10**, **13**, **16**, **19**, and **22** to form the spiroozonides **8**, **11**, **14**, **17**, **20**, and **23**, which with the exception of **23** (see below) decompose spontaneously to carbon dioxide, formaldehyde, and the alkene **9** or the alkynes **12**, **15**, **18**, and **21**. Carbon dioxide can be extracted from the reaction mixture with a stream of nitrogen and precipitated as barium carbonate by passing it through a solution of barium hydroxide. Formaldehyde could not be detected by ¹H NMR spectroscopy.^[7] The characterization of the hydrocarbon products **9**, **12**, **15**, **18**, and **21** is described in the Experimental Section. The reactions of **7**, **10**, **13**, and **22** with **6**, which was generated from **5**, were monitored by low-temperature ¹H NMR spectroscopy. Results for the temperature range −90 to −80 °C are discussed below.

In the reaction of **7** with **6** in [D₁₄]methylcyclohexane,^[8] the decrease in the methylene proton signal of **5** at $\delta = 4.35$ (s, 2H) corresponds to the increase in the olefin proton signal at $\delta = 5.3$ (s, 2H) of *trans*-di-*tert*-butylethene (**9**). In the reaction of **10** with **6** in [D₁₀]diethyl ether/CD₂Cl₂ (8/1), the decrease in the signal for the *o,o'*-protons of **10** at $\delta = 8.05$ (sym. m, 4H) is in agreement with the increase in the signal for the *o,o'*-protons of the toluene **12** at $\delta = 7.53$ (sym. m, 4H). The reaction of **13** with **6** in [D₁₀]diethyl ether can be unambiguously monitored by means of the signals of the α -methylene protons of the *n*-propyl groups of the starting material **13** [$\delta = 2.62$ (t, 4H)] and of the product **15** [$\delta = 2.1$ (t, 4H)]. Decrease and increase of these signals are in agreement.

When **22** was treated with **6** in [D₁₄]methylcyclohexane/[D₈]toluene (2/1), we could not assign any ¹H NMR signals to 3,3,6,6-tetramethylcyclohex-1-yne (**24**) between −90 and −80 °C. This is in agreement with the literature.^[9] The behavior of **24** under the reaction conditions (in the presence of peroxide) was not investigated. In the presence of tetraphenylcyclopentadienone, no Diels–Alder product was formed. Above −90 °C the decrease in the methylene signal of **5** at $\delta = 3.9$ (s, 2H) was accompanied by an increase in a signal at $\delta = 4.88$ (s, 2H). After about 15 min a relative intensity maximum was reached at −85 °C (about 15%, relative to the four methylene protons of diethyl carbonate at 20 °C). At −80 °C the intensity of the signal at $\delta = 4.88$ decreases faster than that of the signal of **5** at $\delta = 3.9$. We interpret the former as unambiguous evidence for the intermediate spiroozonide **23**, the fragmentation of which forms the highly strained alkyne **24**. Therefore, **23** is more stable than the spiroozonides **8**, **11**, and **14**.

The substantially lower thermal stability which was expected for **3** relative to **2** was proved to be correct. The spiroozonides **8**, **11**, **14**, **17**, and **20** with the structural elements of 4,5,7-trioxaspiro[2.4]heptane (**3**) and of a 4,5,7-trioxaspiro[2.4]hept-1-ene undergo spontaneous fragmentation between −90 and −80 °C.^[10] The fragmentation of the spiroozonides fulfils the formal criteria for reactions with a coarctate transition state. In the course of the reaction two C–C bonds of the three-membered ring are broken at the central spiro C atom, and two C–O bonds are formed to generate CO₂. Eight electrons are involved in the reaction (the mechanism can be formally written with four electron-pushing arrows). A topological analysis shows that the transition state of the reaction is stabilized by coarctate Möbius aromaticity. According to the stereochemical rules of coarctate reactions, the π systems of the two terminators must be orthogonal in the transition state (Figure 1). This is realized in an ideal manner in the spiro arrangement of the three- and five-membered rings in the spiroozonides **8**, **11**, **14**, **17**, **20**, and **23**. In our nomenclature^[11] the fragmentation should be denoted as a [$\pi^2 + \chi^2 + \pi^4$] coarctate reaction.

The fragmentation of cyclopent-3-ene-1-one spiroozonide (1,2,4-trioxaspiro[4.4]non-7-ene) is homologous to that of the cyclopropanone spiroozonide **3** (4,5,7-trioxaspiro[2.4]heptane). According to the stereochemical rules of coarctate reactions involving ten electrons, this reaction must proceed via a flat transition state, which can not be realized in the spiro

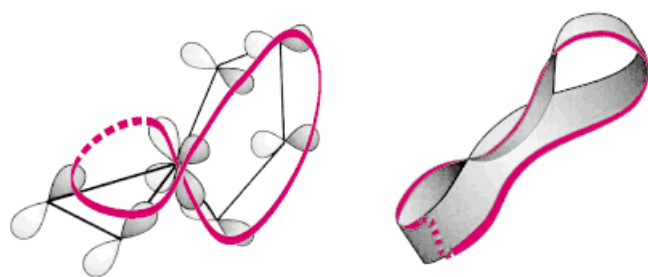


Figure 1. Orbital basis (left) and topology (right) of the transition state of the spiroozonide fragmentation. The orbital basis contains eight electrons in eight orbitals. The spiro C atom (coarctate center) participates in two basis orbitals, because two bonds are formed and broken simultaneously at this atom. The topology of orbital overlap is equivalent to a coarctate Möbius strip. For the resulting consequences for the stereochemical course of the reaction, see the text.

system. As a consequence, a coarctate fragmentation was not observed in this system.^[10]

We performed quantum-chemical calculations with semiempirical, ab initio, and density functional theory (DFT) methods^[12] (PM3,^[13] QCISD/6-31G, B3LYP/6-31G, B3LYP/6-31 + G*^[14, 15]) on the parent systems of the reactions presented above. We found such a transition state at all levels of theory. The transition states were characterized as first-order stationary points by harmonic frequency calculations (one imaginary frequency per transition state), and they were confirmed to be saddle points of a concerted fragmentation by intrinsic reaction coordinate (IRC) calculations. Figure 2

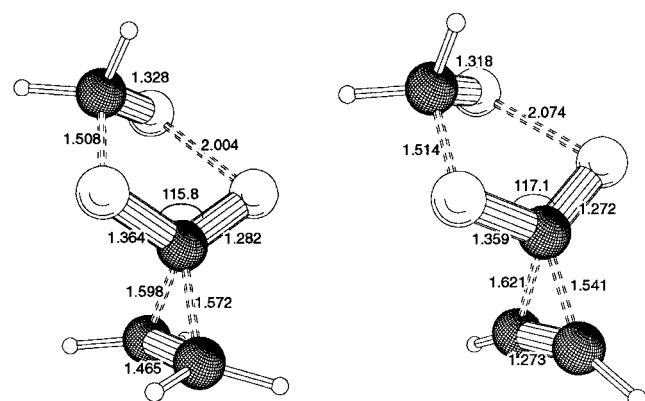


Figure 2. Transition state structures of both parent systems of the spiroozonide fragmentation calculated at the B3LYP/6-31 + G* level with bond lengths [Å] and angles [°].

shows the geometry of the two transition states, and Table 1 lists the energies of the starting materials, transition states, and products for the highest and most reliable theoretical level of the calculations. The transition states are not symmetrical. The calculated course of the reaction is not synchronous but concerted.^[16] A barrier of $\Delta H^\ddagger =$

11.3 kcal mol⁻¹ was calculated for the fragmentation of the spirocyclopropane, and $\Delta H^\ddagger = 16.4$ kcal mol⁻¹ for the fragmentation of the spirocyclopropene. As expected, the reactions are strongly exothermic: $\Delta H^\circ = -85.2$ and -84.8 kcal mol⁻¹, respectively.

Alternatively, the following two-step reaction is conceivable: In the first step the olefin or alkyne is eliminated, and in the second step the carbene (1,2,4-trioxolane-3-ylidene) fragments to give CO₂ and CH₂O. We did not find a stationary point corresponding to the carbene at any of the above-mentioned levels of theory. The corresponding structures fragment without a barrier to give CO₂ and CH₂O. The two-step mechanism therefore can be excluded with a high degree of certainty.

Table 1. Energies of the starting materials, transition states, and products of the fragmentation of both parent systems of the spiroozonide fragmentation calculated at the B3LYP/6-31 + G* level.^[a]

E_{abs} [a.u.]	-381.56811	-381.54647	-381.69250	-380.30805	-380.27665	-380.43233
ZPE [a.u.]	0.100789	0.09079	0.089423	0.076021	0.070694	0.065092
N_{imag}	0	1	0	0	1	0
$\tilde{\nu}$ [cm ⁻¹]	—	-397.5	—	—	-440.1	—
E_{rel} [kcal mol ⁻¹]	0.0	11.3	-85.2	0.0	16.4	-84.8

[a] E_{abs} = absolute energy, ZPE = zero-point energy, N_{imag} = number of imaginary frequencies according to a normal coordinate analysis, $\tilde{\nu}$ = wavenumber of the imaginary frequency, E_{rel} = energy relative to the starting materials.

The back reaction of the spontaneous fragmentation is a termolecular $[\pi^2 + \chi^2 + \pi^4]$ reaction, which will be difficult to realize unless preorganization of the components and high pressure are used.

Experimental Section

Procedure for the low-temperature ¹H NMR experiments: An excess of ozone was passed into a solution of ketene diethyl acetal **4** in a NMR tube at -110°C through a capillary. The precooled gas stream was adjusted such that single gas bubbles passed through the solution. After ozonization, a precooled stream of nitrogen was passed through the NMR tube until a moistened KI/starch paper remained colorless. A storage bottle, in which a solution of the three-membered ring ketone was precooled to -110°C , was connected to the glass joint on the top of the NMR tube. The contents were discharged by nitrogen pressure into the NMR tube, which was immediately introduced into the precooled ¹H NMR measuring cell.

7 + 6: 4 (14.1 mg, 0.121 mmol) in [D₁₄]methylcyclohexane (0.5 mL), **7** (7.4 mg, 0.044 mmol) in [D₁₄]methylcyclohexane (0.4 mL); **10 + 6: 4** (20.8 mg, 0.171 mmol) in [D₁₀]diethyl ether (0.45 mL), **10** (7.4 mg, 0.036 mmol) in [D₁₀]diethyl ether (0.35 mL) and CD₂Cl₂ (0.1 mL); **13 + 6: 4** (23.5 mg, 0.20 mmol) in [D₁₀]diethyl ether (0.45 mL), **13** (7.0 mg, 0.05 mmol) in [D₁₀]diethyl ether (0.45 mL); **22 + 6: 4** (18.2 mg, 0.157 mmol) in [D₁₄]methylcyclohexane (0.45 mL), **22** (8.2 mg, 0.05 mmol) in [D₁₄]methylcyclohexane (0.12 mL) and [D₈]toluene (0.33 mL).

The [3+2] cycloaddition of **6** with the three-membered ring ketones on a preparative scale is similar to the low-temperature ¹H NMR procedure. Ozonization was carried out in cold traps with an additional side flask.^[5] A precooled stream of ozone was passed through the solution of **4** at -110°C until the mixture turned blue. Excess ozone was expelled with a precooled

stream of nitrogen until a moistened KI/starch paper remained colorless. The solution of the ketone was transferred with a pipette into the side flask. After temperature equalization (5 min), the cold solution was discharged into the main flask with nitrogen pressure. During warm up above -65°C , a gentle stream of nitrogen was passed through the solution. In all cases, above -60°C we observed slight and above -50°C pronounced precipitation of barium carbonate on passing the gas through an aqueous solution of barium hydroxide.

7 + 6: 4 (132.4 mg, 1.14 mmol) in pentane (7 mL), **7** (63.0 mg, 0.37 mmol) in pentane (7 mL). The solvent was removed at 20°C and 200 mbar on a rotary evaporator. The residue was purified by chromatography (SiO_2 ; pentane/diethyl ether, 20/1) to give **9** (13.6 mg, 0.1 mmol, 26%). The ^1H NMR data were in agreement with the literature data.^[17] A yield of 51% was determined by ^1H NMR spectroscopy of the crude product (benzene as standard).

10 + 6: 4 (132.9 mg, 1.14 mmol) in diethyl ether (6 mL), **10** (47.2 mg, 0.23 mmol) in diethyl ether (5 mL) and CH_2Cl_2 (3 mL); for the workup, see above; the pressure was reduced to about 1 mbar. The residue was purified by chromatography (SiO_2 , CH_2Cl_2) to give colorless crystals (23.6 mg, 0.13 mmol, 58%) of the tolane **12**, m.p. 63°C (methanol). The yield of the crude product was 76%, as determined by ^1H NMR spectroscopy with toluene as standard.

13 + 6: 4 (149.0 mg, 1.28 mmol) in diethyl ether (7 mL), **13** (42.4 mg, 0.31 mmol) in diethyl ether (5 mL). The yield of the crude product was 67%, as determined by ^1H NMR spectroscopy with benzene as standard. The ^1H NMR data of **15** are in agreement with those of an independently synthesized sample.

16 + 6: 4 (165.3 mg, 1.42 mmol) in diethyl ether (6 mL), **16** (63.0 mg, 0.46 mmol) in diethyl ether (6 mL). The yield of the crude product was 83%, as determined by ^1H NMR spectroscopy with benzene as standard. The ^1H NMR data of **18** are in agreement with the literature data.^[18]

16 + 6 + tetraphenylcyclopentadienone: 4 (192.0 mg, 1.65 mmol) in pentane (13 mL), **16** (72.9 mg, 0.54 mmol) in pentane (6 mL) and toluene (2.5 mL). At 20°C tetraphenylcyclopentadienone (205.9 mg, 0.54 mmol) in CH_2Cl_2 (8 mL) was added, and the mixture stirred for 48 h. After the usual workup, the product was purified by chromatography (Al_2O_3 , activity level I, petroleum ether (b.p. $100\text{--}140^{\circ}\text{C}$)/benzene (7/3)) as colorless crystals (166 mg, 0.36 mmol, 67%), m.p. $222\text{--}223^{\circ}\text{C}$ (pentane/diethyl ether, 2/1; $224\text{--}225^{\circ}\text{C}$ ^[19]). The ^1H NMR data of the cyclooctanetetraphenylbenzene are in agreement with the literature data.^[19]

19 + 6: 4 (241.0 mg, 2.07 mmol) in pentane (14 mL) was ozonized at -110°C . Then **19** (62.7 mg, 0.51 mmol) in pentane (2 mL) and toluene (6 mL) was added, and the reaction flask was immersed in a cold bath at -78°C . After 15 min tetraphenylcyclopentadienone (200 mg, 0.52 mmol) in CH_2Cl_2 (8 mL) was introduced into the reaction flask from a separate flask with N_2 pressure. The mixture was kept for 48 h at -78°C , worked up as usual, and purified by chromatography as described above. Colorless crystals (120 mg, 0.27 mmol, 52%), m.p. $221\text{--}222^{\circ}\text{C}$ (petroleum ether); $222\text{--}223^{\circ}\text{C}$.^[20a] The ^1H NMR data of the cycloheptanetetraphenylbenzene are in agreement with the literature data.^[20b]

22 + 6: 4 (214 mg, 1.83 mmol) in pentane (8 mL), **22** (75.3 mg, 0.46 mmol) in pentane (2 mL) and toluene (6 mL). There were no ^1H NMR signals that could be assigned to 3,3,6,6-tetramethyl-1-(3,3,6-trimethyl-hept-6-en-1-ynyl)cyclohexene (isomer of the dimer of **24**)^[21] in the spectrum of the crude product.

22 + 6 + tetraphenylcyclopentadienone: 4 (239.5 mg, 2.06 mmol) in pentane (8 mL), **22** (84.4 mg, 0.51 mmol) and tetraphenylcyclopentadienone (202.4 mg, 0.53 mmol) both in pentane (2 mL) and toluene (6 mL). The mixture was kept for 15 min at -78°C and worked up as usual. There are no signals in the ^1H NMR spectrum that could be assigned to the Diels–Alder product. According to a control experiment, tetraphenylcyclopentadienone is virtually inert towards **6**.

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Thermal Behavior of Spiroozonides from Formaldehyde-*O*-oxide and Tropones Derivatives: A Coarctate Reaction

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In memory of Rudolf Criegee

Spiroozonides generated from cyclopropanones and cyclopropanones already fragment at temperatures below -80°C to give alkenes and alkynes, respectively, carbon dioxide, and formaldehyde.^[1] The surprisingly low activation barrier is explained by stabilization of the transition state by *coarctate* Möbius aromaticity.^[2,3] The spiro geometry of the starting materials and transition states is consistent with the stereochemical rules of coarctate reactions. We have included the thermal behavior of the spiroozonides from tropones and **1** in our investigations of this class of reactions. In analogy to the cyclopropane derivatives^[1] the valence isomeric spiroozonides with a norcaradiene structure should undergo spontaneous fragmentation to give carbon dioxide, formaldehyde, and benzene derivatives. The driving force of the reaction is increased over that of the parent system because an aromatic ring is formed as a product.

Under ozone-free conditions^[1,4] the spiroozonides are accessible by [3+2] cycloaddition of **1** and tropones (Scheme 1). The spiroozonides **3**, **7**, **11**, **15**, **19**, **23**, **27**, **31**, **35**, **39**, **43**, **47** from the tropones **2**, **6**, **10**, **14**, **18**, **22**, **26**, **30**, **34**, **38**,

42, and **46**, respectively, and formaldehyde-*O*-oxide (**1**) were unambiguously characterized by low-temperature ^1H NMR spectroscopy. The decomposition kinetics were determined by ^1H NMR spectroscopy following literature methods^[5] for 1,2,3-trioxolanes. Spiroozonides and 1,2,3-trioxolanes decompose according to a first-order rate law. The quantitative evaluation of suitable, temperature-dependent ^1H NMR signals allows the determination of the half-lives $t_{1/2}$ of all spiroozonides at a given temperature ($t_{1/2}$ varies between 9 min at -56°C for **11** and 38 min at $+72^{\circ}\text{C}$ for **47**). The kinetic parameters of decomposition $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and ΔE_a of all spiroozonides except **23**, **31**, and **35** were experimentally determined. The results and product yields are summarized in Table 1.

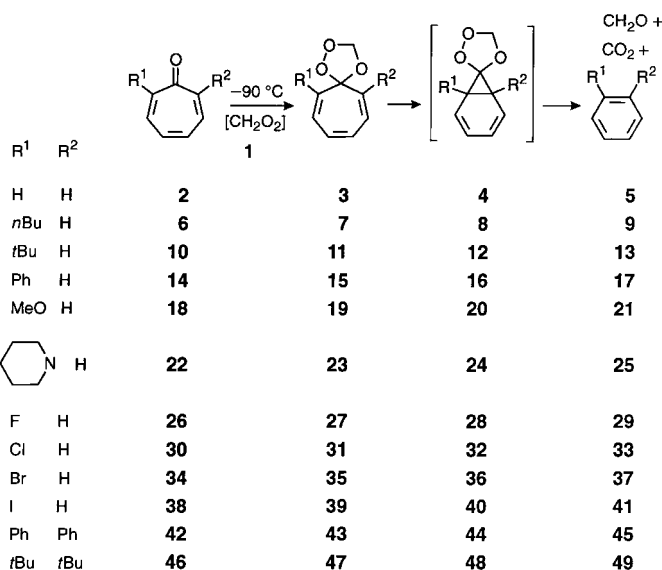
Table 1. Kinetic data and product yields of the decomposition of the spiroozonides generated from **1** and tropones.

Spiro- ozonide	$t_{1/2}$ (T) [min] [$^{\circ}\text{C}$]	$\Delta G^{\ddagger}$ (T) [kcal · mol $^{-1}$] [K]	$\Delta H^{\ddagger}$ [kcal · mol $^{-1}$]	$\Delta S^{\ddagger}$ [cal K $^{-1}$ · mol $^{-1}$]	ΔE_a [kcal · mol $^{-1}$]	Product/ Yield [%]
3 ^[a]	32 (−22)	19 (257)	16	−12	16	5 / >90 ^[f]
7 ^[a]	11 (−24)	18 (245)	17	−1	18	9 / >90 ^[f]
11 ^[a]	9 (−56)	16 (222)	7	−37	8	13 / >90 ^[f]
15 ^[a]	18 (−25)	18 (253)	13	−21	13	17 /65 ^[g]
19 ^[a]	16 (+25)	22 (294)	11	−37	11	21 / >90 ^[f]
23 ^[a]	32 (−24)	— ^[e]	— ^[e]	— ^[e]	— ^[e]	25 /43 ^[g]
27 ^[a]	49 (+5)	21 (278)	16	−17	17	29 ^[h]
31 ^[a]	34 (−5)	— ^[e]	— ^[e]	— ^[e]	— ^[e]	33 ^[h]
35 ^[a]	33 (−15)	— ^[e]	— ^[e]	— ^[e]	— ^[e]	37 ^[h]
39 ^[a]	22 (−15)	19 (248)	14	−18	15	41 ^[h]
43 ^[a]	35 (+14)	21 (283)	14	−27	14	45 /75 ^[g]
47 ^[b]	35 (+25)	22 (309)	23	2	23	49 /66 ^[g]
47 ^[c]	34 (+40)	23 (308)	19	−15	19	49 ^[e]
47 ^[d]	38 (+72)	26 (349)	43	49	44	50 /60 ^[g]

[a] Fragmentation in $[\text{D}_{10}]$ diethyl ether/ CD_2Cl_2 5:1. [b] Fragmentation in CD_3OD . [c] Fragmentation in CDCl_3 . [d] Fragmentation in $[\text{D}_{12}]$ cyclohexane. [e] Not determined. [f] Yield in the raw product. [g] Yield for the isolated product. [h] ^1H NMR spectrum exhibits only product and no signals for the starting materials.

Spiroozonides of tropones with suitable structures undergo spontaneous fragmentations. Besides the aromatic leaving groups **5**, **9**, **13**, **17**, **21**, **25**, **29**, **33**, **37**, **41**, **45**, **49**, carbon dioxide and formaldehyde are formed. The qualitative detection of carbon dioxide by passing a stream of nitrogen through the reaction mixture and then through a solution of barium hydroxide is temperature-dependent (see Experimental Section). Formaldehyde cannot be detected by ^1H NMR spectroscopy. However, convincing evidence of its intermediacy was provided by the thermal treatment of the crystalline spiroozonide **47** in CD_3OD . The increase of the ^1H NMR signals of *o*-di-*tert*-butylbenzene (**49**) is accompanied by the growth of a singlet at $\delta = 4.6$, which can be assigned to the methylene protons of the semiacetal $\text{CD}_3\text{OCH}_2\text{OD}(\text{H})$.

The spontaneous fragmentation is an example of a coarctate reaction. At the spiro-C atom two bonds are made (two $\text{C}=\text{O}$ bonds in CO_2) and two bonds are broken (two $\text{C}-\text{C}$ bonds in the three-membered ring) simultaneously. With eight electrons involved, the reaction has to proceed via a coarctate



Scheme 1. [3+2] cycloaddition of **1** and tropones derivatives.

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Möbius transition state, which must have a spiro geometry. The suitable stereoelectronic prerequisites are realized in the spiro geometry of the starting material and the reaction therefore is favored.

We performed density functional theory calculations^[6] with the B3LYP^[7,8] combination of functionals and the 6-31G* basis set to obtain quantitative information on the parent system (Figure 1 and Table 2).^[9] According to these calculations the rate-determining step of the reaction is not the

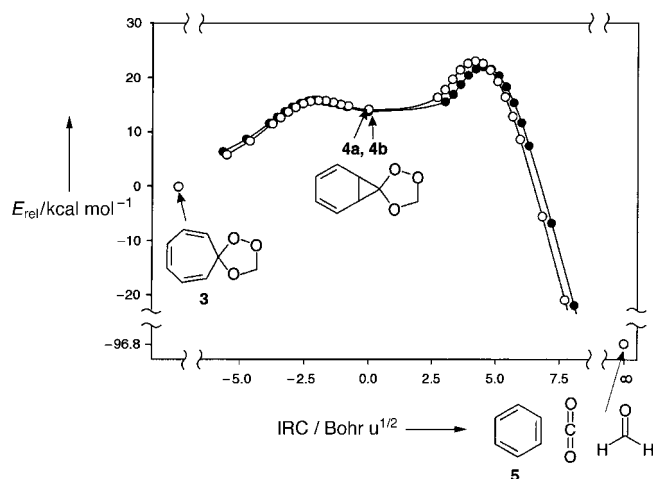


Figure 1. Relative energies E_{rel} in the course of the fragmentation of the spiroozonide **3** calculated at the B3LYP/6-31G* level (IRC = intrinsic reaction coordinate). The values of the IRC are relative to the norcaradiene intermediates **4a** and **4b**.

coarctate fragmentation but the electrocyclic ring closure to give the norcaradiene.^[10,11] Interestingly, the spiroozonide **3** has a planar seven-membered ring^[12,13] in contrast to cycloheptatriene and most of its derivatives. Two diastereomeric forms **4a** and **4b** are possible for the nonplanar structure of the intermediate norcaradiene, which both fragment to give the same products. The activation enthalpy for the electrocyclic ring closure of **3** to **4a** and **4b** is 14.7 kcal mol⁻¹ in both cases. The norcaradienes **4a** and **4b** are flat minima that isomerize back to the cycloheptatrienes with an activation barrier of 1.3 and 0.9 kcal mol⁻¹ or fragment to give the products benzene, carbon dioxide, and formaldehyde with a barrier of 6.6 and 7.1 kcal mol⁻¹. Figure 1 shows the relative

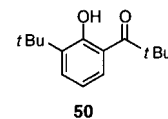
energies of the structures along the intrinsic reaction coordinate (IRC)^[14,15] of the reaction.^[16]

The remarkable dependency of the activation parameter on the substitution of the cycloheptatriene ring is inter alia attributed to steric effects that affect the cycloheptatriene/norcaradiene isomerization and not the subsequent coarctate fragmentation. Semiempirical PM3^[17] calculations indicate that the *tert*-butyl-substituted cycloheptatriene **11** is more sterically hindered than the corresponding norcaradiene **12**, whereas the situation in the di-*tert*-butyl-substituted systems **47** and **48** is reverse. Norcaradiene **48** exhibits strong sterical interactions between the neighboring *tert*-butyl groups. Consequently, in the first case the activation barrier is lowered and in the second case the barrier is raised. The PM3 calculations correctly reproduce this trend qualitatively (Table 3).

Table 3. PM3-calculated energies [kcal mol⁻¹] of the stationary points (minima and transition states) of the fragmentation of the spiroozonides **3**, **11**, and **47**.

Compound	R ¹	R ²	Cycloheptatriene derivative	TS1	Norcaradiene derivative	TS2	Products
3	H	H	0.0	22.7	8.1	26.0	-92.7
11	<i>t</i> Bu	H	0.0	20.9	6.9	24.7	-99.4
47	<i>t</i> Bu	<i>t</i> Bu	0.0	26.3	21.8	40.4	-88.8

The reactivity of **47** is solvent-dependent. In CD₃OD and CDCl₃ at different temperatures *o*-di-*tert*-butylbenzene (**49**), carbon dioxide, and formaldehyde are formed. In cyclohexane (80 °C/1 h), **49**, **46**, and 2-hydroxy-3-*tert*-butylpivalophenone (**50**) in a ratio of 1:1.2:2 were detected. In methylcyclohexane (100 °C/1 h) the product ratio is 1.5:1:6. The maximum yield of **50** is 60%. The formation of **50** can be explained by the intermediacy of the isomeric 2,7-di-*tert*-butyltropone-*O*-oxide. In contrast to the thermolysis of **47** that of the spiroozonide **27** is only weakly dependent on the solvent polarity.



Interestingly, the observations are not transferable to the next higher homologue of **1**: acetaldehyde-*O*-oxide^[4] does not react with the tropone derivatives **18** and **46**.^[18] Colchicines belong to the tropone derivatives. The fragmentation of the

Table 2. Density functional theory (B3LYP/6-31G*) calculated energies of the stationary points (minima and transition states) of the fragmentation of the spiroozonide **3** to benzene, carbon dioxide, and formaldehyde. Absolute energies (E_{abs}) and zero-point energies (ZPE) in Hartree per particle, NIMAG = number of imaginary frequencies according to a normal coordinate analysis, $\tilde{\nu}$ = wavenumber [cm⁻¹] of the imaginary frequency, E_{rel} = relative energy of the stationary points relative to the starting material **3**.

	3	[3 → 4a][‡]	4a	[4a → Prod.][‡]	[3 → 4b][‡]	4b	[4b → Prod.][‡]	Prod.
E_{abs}	-535.17585	-535.15072	-535.15397	-535.14082	-535.15073	-535.15336	-535.13918	-535.33007
ZPE	0.148084	0.146351	0.147524	0.144865	0.146455	0.147529	0.144675	0.139171
NIMAG	0	1	0	1	1	0	1	0
$\tilde{\nu}$	-	-405	-	-506	-399	-	-512	-
E_{rel}	0.0	14.7	13.4	20.0	14.7	13.8	20.9	-102.4

spiroozonides from **1** and colchicines provides an elegant access to the class of allocolchicines.^[19]

Experimental Section

Procedure for trapping formaldehyde-*O*-oxide **1** with tropones:

Ketene diethylacetal (1.20 mmol) in ether (5 mL) was treated with ozone at -116°C until the solution started to turn blue. After removal of the ozone in a stream of nitrogen, a cold solution of the tropone (0.30 mmol) in ether/dichloromethane (2:1, 5 mL) was added. The solvent was removed at room temperature in a rotatory evaporator at 300 mbar. The less volatile benzene derivatives **17**, **25**, **45**, and **49** could be isolated after purification by chromatography. The physical data of the benzene derivatives are in agreement with authentic samples. The yields of the volatile benzene derivatives **5**, **9**, **13**, and **21** were determined by ^1H NMR spectroscopy relative to an inert standard.

Procedure for the low-temperature ^1H NMR measurements:^[1]

Ketene diethylacetal (0.20 mmol) was dissolved in $[\text{D}_{10}]$ diethyl ether (0.40 mL) and thoroughly ozonized in an NMR tube at -116°C by using a capillary. After ozonization a precooled stream of nitrogen was passed through the NMR tube until a moistened KI starch paper remained colorless. Then a precooled solution of the tropone (0.050 mmol) in $[\text{D}_{10}]$ diethyl ether/ CD_2Cl_2 (2:1; 0.40 mL) was added. The tube was immediately introduced into the precooled ^1H NMR measuring cell. The reaction temperature was determined by using the $\Delta\delta$ -value of methanol.^[20]

Results: a) ^1H NMR data of the spiroozonides; signals whose decrease is monitored are marked with the symbol †. The spiroozonides **7**, **15**, **23**, and **43** exhibit ^1H NMR signals for the substituents that are almost identical with those of the products **9**, **17**, **25**, and **45**; b) value of the temperature range for the qualitative detection of CO_2 ; c) half-lives $t_{1/2}$ for different temperatures.

2 + 1: a) 1,2,4-Trioxaspiro[4.6]undeca-6,8,10-triene (**3**): ^1H NMR (500 MHz, -22°C): $\delta = 5.20$ (s, 2H, OCH_2OO), 5.83 (d, 2H, $J = 10.5$ Hz, olefin. H), 6.50–6.59 (m, 4H, olefin. H)†; b) -22 to -15°C ; c) 33 min (-22°C), 16 min (-16°C), 8.3 min (-11°C).

6^[21] + 1: a) 6-*n*-Butyl-1,2,4-trioxaspiro[4.6]undeca-6,8,10-triene (**7**): ^1H NMR (500 MHz, -34°C): $\delta = 2.35$ –2.52 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 5.09 (s, 1H, OCH_2OO), 5.50 (s, 1H, OCH_2OO), 5.74 (d, 1H, $J = 10.7$ Hz, olefin. H), 6.41 (d, 1H, $J = 6.8$, olefin. H)†, 6.43–6.49 (m, 1H, olefin. H)†, 6.51–6.61 (m, 2H, olefin. H)†; b) -21 to -15°C ; c) 51 min (-34°C), 27 min (-28°C), 11 min (-24°C).

10: 2-*tert*-Butyltropone (**10**) was prepared analogously to the literature procedure^[21] by using *tert*-butyllithium (16.0 mmol, 10 mL of a 1.6M solution in pentane) and tropolone (7.0 mmol, 0.86 g in ether). The by-products were separated from **10** by chromatography on silica gel with pentane/ether (40:1). Compound **10** was eluted with ether. After microdistillation (70°C ; $p = 0.5$ mbar) **10** was obtained as a colorless oil. Yield: 96 mg (12%). ^1H NMR (250 MHz, CDCl_3): $\delta = 1.31$ (s, 9H, $\text{C}(\text{CH}_3)_3$), 6.71–6.92 (m, 4H, olefin. H), 7.19 (d, 1H, $J = 9.1$ Hz, olefin. H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 29.87$, 37.98, 130.89, 131.83, 132.92, 132.93, 138.33, 160.46, 188.80; IR (KBr): $\tilde{\nu} = 1458$, 1588, 1632, 2956, 3002 cm^{-1} ; UV/Vis (*n*-hexane): λ_{max} (lg ϵ) = 205.0 (4.01), 230.0 (4.21), 297.0 nm (3.71); HRMS calcd. for $\text{C}_{11}\text{H}_{14}\text{O}$: 162.1045; found 162.1057.

10 + 1: a) 6-*tert*-Butyl-1,2,4-trioxaspiro[4.6]undeca-6,8,10-triene (**11**): ^1H NMR (500 MHz, -56°C): $\delta = 1.30$ (s, 9H, $\text{C}(\text{CH}_3)_3$), 4.95 (s, 1H, OCH_2OO), 5.47 (s, 1H, OCH_2OO), 5.71 (d, 1H, $J = 10.4$ Hz, olefin. H), 6.36–6.41 (m, 1H, olefin. H)†, 6.51 (d, 1H, $J = 7.1$ Hz, olefin. H)†, 6.57–6.67 (m, 2H, olefin. H)†; b) -42 to -32°C ; c) 9.2 min (-56°C), 7.3 min (-52°C), 3.7 min (-46°C).

14^[21] + 1: a) 6-Phenyl-1,2,4-trioxaspiro[4.6]undeca-6,8,10-triene (**15**): ^1H NMR (500 MHz, -16°C): $\delta = 4.95$ (s, 1H, OCH_2OO), 5.17 (s, 1H, OCH_2OO), 5.96 (d, 1H, $J = 10.9$ Hz, olefin. H)†, 6.56–6.62 (m, 2H, olefin. H), 6.64–6.70 (m, 1H, olefin. H); b) -16 to -12°C ; c) 18 min (-25°C), 13 min (-20°C), 6 min (-15°C).

18^[22] + 1: a) 6-Methoxy-1,2,4-trioxaspiro[4.6]undeca-6,8,10-triene (**19**): ^1H NMR (500 MHz, $+25^{\circ}\text{C}$): $\delta = 3.69$ (s, 3H, OCH_3), 5.14 (s, 1H, OCH_2OO), 5.26 (s, 1H, OCH_2OO), 5.71 (d, 1H, $J = 10.9$ Hz, olefin. H), 5.80 (d, 1H, $J =$

8.3 Hz, olefin. H), 6.28–6.32 (m, 1H, olefin. H)†, 6.50–6.56 (m, 2H, olefin. H); b) $+8$ to $+12^{\circ}\text{C}$; c) 26 min ($+18^{\circ}\text{C}$), 23 min ($+21^{\circ}\text{C}$), 16 min ($+25^{\circ}\text{C}$).

22^[22] + 1: a) 1-(1,2,4-Trioxaspiro[4.6]undeca-6,8,10-trien-6-yl)piperidine (**23**): ^1H NMR (500 MHz, -30°C): $\delta = 5.17$ (s, 1H, OCH_2OO), 5.40 (s, 1H, OCH_2OO), 5.56 (d, 1H, $J = 10.0$ Hz, olefin. H), 5.91 (d, 1H, $J = 8.1$ Hz, olefin. H)†, 6.36–6.48 (m, 2H, olefin. H), 6.57–6.62 (m, 1H, olefin. H); b) -30 to -24°C ; c) 50 min (-30°C), 32 min (-24°C).

26^[22] + 1: a) 6-Fluoro-1,2,4-trioxaspiro[4.6]undeca-6,8,10-triene (**27**): ^1H NMR (400 MHz, $+10^{\circ}\text{C}$): $\delta = 5.24$ (s, 1H, OCH_2OO), 5.37 (s, 1H, OCH_2OO), 5.87 (dd, 1H, $J = 11.4$, 6.8 Hz, olefin. H)†, 6.31–6.49 (m, 3H, olefin. H)†, 6.62 (dd, 1H, $J = 11.7$, 7.3 Hz, olefin. H)†; b) -2 to $+4^{\circ}\text{C}$ (methanol), $+4$ to $+10^{\circ}\text{C}$ (diethyl ether/dichloromethane), $+7$ to $+12^{\circ}\text{C}$ (toluene); c) 49 min ($+5^{\circ}\text{C}$), 25 min ($+10^{\circ}\text{C}$), 17 min ($+15^{\circ}\text{C}$).

30^[21] + 1: a) 6-Chloro-1,2,4-trioxaspiro[4.6]undeca-6,8,10-triene (**31**): ^1H NMR (400 MHz, -5°C): $\delta = 5.19$ (s, 1H, OCH_2OO), 5.40 (s, 1H, OCH_2OO), 5.86 (pseudo-d, 1H, olefin. H)†, 6.45–6.53 (m, 1H, olefin. H)†, 6.59–6.65 (m, 2H, olefin. H)†, 6.86 (d, 1H, $J = 7.8$ Hz, olefin. H)†; b) -5 to 0°C ; c) 34 min (-5°C).

34^[21] + 1: a) 6-Bromo-1,2,4-trioxaspiro[4.6]undeca-6,8,10-triene (**35**): ^1H NMR (400 MHz, -15°C): $\delta = 5.17$ (s, 1H, OCH_2OO), 5.41 (s, 1H, OCH_2OO), 5.85 (d, 1H, $J = 10.7$ Hz, olefin. H)†, 6.41–6.47 (m, 1H, olefin. H)†, 6.58–6.70 (m, 2H, olefin. H)†, 7.11 (d, 1H, $J = 7.8$ Hz, olefin. H); b) -15 to -10°C ; c) 33 min (-15°C).

38^[21] + 1: a) 6-Iodo-1,2,4-trioxaspiro[4.6]undeca-6,8,10-triene (**39**): ^1H NMR (400 MHz, -15°C): $\delta = 5.17$ (s, 1H, OCH_2OO), 5.41 (s, 1H, OCH_2OO), 5.77 (d, 1H, $J = 11.0$ Hz, olefin. H)†, 6.31–6.37 (m, 1H, olefin. H)†, 6.56–6.72 (m, 2H, olefin. H), 7.40 (d, 1H, $J = 7.6$ Hz, olefin. H); b) -20 to -15°C ; c) 72 min (-25°C), 57 min (-20°C), 22 min (-15°C).

42^[23] + 1: a) 6,11-Diphenyl-1,2,4-trioxaspiro[4.6]undeca-6,8,10-triene (**43**): ^1H NMR (500 MHz, $+10^{\circ}\text{C}$): $\delta = 5.00$ (s, 2H, OCH_2OO), 6.59–6.66 (m, 2H, olefin. H)†, 6.73–6.78 (m, 2H, olefin. H)†; b) $+8$ to $+12^{\circ}\text{C}$; c) 50 min ($+10^{\circ}\text{C}$), 35 min ($+14^{\circ}\text{C}$).

46^[24] + 1: 2,7-Di-*tert*-butyltropone (**46**) (60 mg, 0.28 mmol) in pentane (5 mL) was added to the primary ozonide generated from ketene diethylacetal (160 mg, 1.38 mmol) dissolved in pentane (5 mL) at -110°C . The reaction mixture was allowed to warm up to 0°C , the solution was decanted from the polymeric peroxides and then concentrated. Compound **47** was obtained as colorless crystals (55 mg, 76%). a) 6,11-Di-*tert*-butyl-1,2,4-trioxaspiro[4.6]undeca-6,8,10-triene **47**: m.p. (pentane) 78 – 79°C (decomp), ^1H NMR (250 MHz, $+20^{\circ}\text{C}$, CDCl_3): $\delta = 1.37$ (s, 18H, $\text{C}(\text{CH}_3)_3$), 5.26 (s, 2H, OCH_2OO), 6.45–6.63 (m, 4H, olefin. H); ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 32.36$, 37.66, 93.95, 110.22, 123.20, 128.42, 144.71; IR (KBr): $\tilde{\nu} = 743$, 987, 1053, 1117, 1250, 1357, 1370, 1463, 1481, 2903, 2956 cm^{-1} ; UV/Vis (ether): λ_{max} (lg ϵ) = 271.6 nm (3.85); HRMS calcd. for $\text{C}_{16}\text{H}_{24}\text{O}_3$: 264.1725, found 264.1695; C,H analysis for $\text{C}_{16}\text{H}_{24}\text{O}_3$: calcd. C 72.69, H 9.15; found C 72.24, H 8.67, b) not measured, c) in CD_3OD : 35 min ($+25^{\circ}\text{C}$), 15 min ($+32^{\circ}\text{C}$), 7.6 min ($+36^{\circ}\text{C}$), 5.8 min ($+40^{\circ}\text{C}$); in CDCl_3 : 57 min ($+35^{\circ}\text{C}$), 34 min ($+40^{\circ}\text{C}$), 21 min ($+45^{\circ}\text{C}$); in $[\text{D}_{12}]$ cyclohexane: 38 min ($+72^{\circ}\text{C}$), 25 min ($+76^{\circ}\text{C}$), 8.9 min ($+80^{\circ}\text{C}$).

Warming of **47** in methylcyclohexane: Compound **47** (446 mg, 1.69 mmol) was warmed to 100°C in methylcyclohexane (3 mL) for 1 h. From the crude product 1,2-di-*tert*-butylbenzene (**49**) (19 mg, 6%) and 2-hydroxy-3-*tert*-butylpivalophenone (**50**)^[25] (240 mg, 60%) were separated by chromatography with pentane as eluant. If the eluting solvent was changed to pentane/ether (5:1), 2,7-di-*tert*-butyltropone (**46**) (48 mg, 13%) was isolated.

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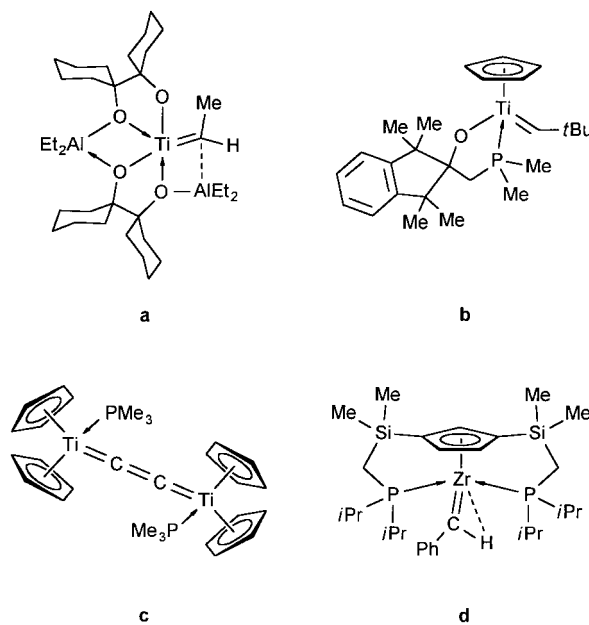
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α -Hydrogen Elimination from (1-Aza-1,3-diene)titanium Complexes: Synthesis of Metallacyclic Titanium–Alkylidene Complexes**

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Alkylidene–metal intermediates play a key role in several important reactions such as transition metal catalyzed olefin and alkyne polymerization, olefin metathesis, or olefination of carbonyl compounds. Therefore there is a great deal of interest in model studies with defined and isolable alkylidene complexes, and several methods for the synthesis of such compounds have already been developed.^[1] Among the alkylidene–metal complexes of the titanium group, the methylidene titanocene [$\text{Cp}_2\text{Ti}=\text{CH}_2$] has gained special significance. Its application in organic synthesis^[2] is attributed to the fact that it is relatively readily generated in situ from different compounds such as bis(cyclopentadienyl)titanacyclobutane complexes,^[3] dimethyltitanocene,^[4] or [$\text{Cp}_2\text{TiCH}_2 \cdot \text{Me}_2\text{AlCl}$] (Tebbe reagent).^[5] To date, however, very few alkylidene–metal complexes of the titanium group have been isolated and characterized by X-ray structure analysis (Scheme 1).^[6–9]



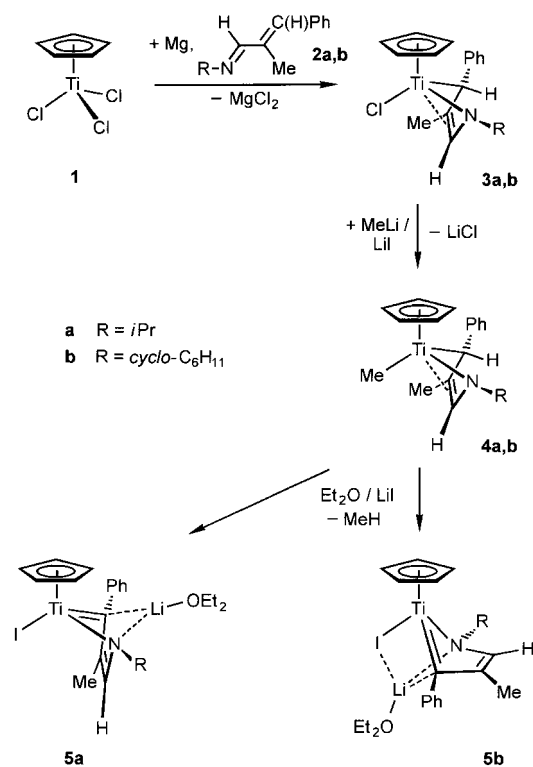
Scheme 1. Selected, structurally characterized alkylidene complexes of titanium and zirconium complexes. **a**: Ti–C 1.933(6) Å, $\delta(\text{Ti}=\text{C}) = 202.1$ (main components);^[6] **b**: Ti–C 1.911(3) Å, $\delta(\text{Ti}=\text{C}) = 278.1$;^[7] **c**: Ti–C 2.051(2) Å, $\delta(\text{Ti}=\text{C}) = 258.1$;^[8] **d**: Zr–C 2.024(4) Å, $\delta(\text{Zr}=\text{C}) = 229.4$.^[9]

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In our studies on 1-aza-1,3-diene complexes of the early transition metals^[10] we have established that (1-aza-1,3-diene)titanium complexes exhibit favorable prerequisites for the preparation of titanium–alkylidene complexes: In the 1-aza-1,3-diene complexes the heterodienes are bound to the metal atom as 1-aza-but-2-ene-1,4-diyl dianions and form with these a $\text{Ti}[\text{CH}(\text{R})\text{CH}=\text{CHNR}]$ ring.^[11] An α -hydrogen elimination at the TiCH group, initiated by the introduction of a neighboring carbanionic methyl group,^[12] would lead to a Ti=C alkylidene function, which might be additionally stabilized by conjugation with the C=C bond of the coordinated 1-aza-1,3-diene ligand. We have established that this concept can be applied successfully and report here on the synthesis and structure of novel metallacyclic titanium–alkylidene complexes.

The 1-aza-1,3-diene complexes **3a** and **3b** are formed in the reduction of $[\text{CpTiCl}_3]$ with magnesium in the presence of the 1-aza-1,3-dienes **2a** and **2b**, respectively (Scheme 2).^[11] They



Scheme 2. Synthesis of the titanacyclic alkylidene complexes **5a** and **5b**.

can be isolated as air-sensitive green-brown crystals (**3a**, m.p. 84 °C; **3b**, m.p. 119–122 °C) in yields of up to 67%; the EI mass spectra of the compounds contain intense peaks for the molecular ions.

Their constitution can be deduced unambiguously from the characteristic NMR spectra (Table 1). In each case the 1-aza-1,3-diene is formally reduced to the dianion and bound in the chelate form to the titanium atom, resulting in a 1-aza-2-titanacyclopent-4-ene ring. Furthermore, a crystal structure analysis of **3b**^[13] revealed that this $\text{Ti}(\text{C3}-\text{C2}=\text{C1}-\text{N})$ ring is folded along the C3–N axis (fold angle $\theta = 67.0(2)^\circ$); the open side of the *cis*-configured heterodiene points in the direction

Table 1. NMR spectroscopic data of **3a**, **3b**, **4b**, **5a**, and **5b**.^[a]

3a: ¹H NMR: $\delta = 7.18$ (t, 2H; *m*-Ph), 7.01 (t, 1H; *p*-Ph), 6.83 (s, 1H; =CH), 6.81 (d, 2H; *o*-Ph), 6.13 (s, 5H; Cp), 4.16 (sept., ³J(H,H) = 6.5 Hz, 1H; *i*-C₃H₇), 2.03 (s, 3H; =CMe), 1.27 (d, ³J(H,H) = 6.5 Hz, 3H; *i*-C₃H₇), 1.15 (d, ³J(H,H) = 6.5 Hz, 3H; *i*-C₃H₇), 0.42 (s, 1H; TiCH); ¹³C NMR: $\delta = 143.11$ (s; *ipso*-Ph), 128.90 (d, ¹J(C,H) = 156 Hz; *o/m*-Ph), 128.52 (d, ¹J(C,H) = 156 Hz; *o/m*-Ph), 125.39 (d, ¹J(C,H) = 156.5 Hz; *p*-Ph), 118.61 (d, ¹J(C,H) = 172.8 Hz; =CH), 116.12 (s, =CMe), 112.97 (d, ¹J(C,H) = 174.4 Hz; Cp), 101.50 (d, ¹J(C,H) = 136.9 Hz; TiCH), 59.66 (d, ¹J(C,H) = 138.5 Hz; *i*-C₃H₇), 25.53 (q, ¹J(C,H) = 125.5 Hz; *i*-C₃H₇), 23.31 (q, ¹J(C,H) = 127.1 Hz; *i*-C₃H₇), 18.55 (q, ¹J(C,H) = 127.1 Hz; =CMe)

3b: ¹H NMR: $\delta = 7.18$ (t, 2H; *m*-Ph), 7.01 (t, 1H; *p*-Ph), 6.83 (s, 1H; =CH), 6.80 (d, 2H; *o*-Ph), 6.12 (s, 5H; Cp), 3.70 (m, 1H; *cyclo*-C₆H₁₁), 2.02 (s, 3H; =CMe), 1.90–1.15 (m, 10H; *cyclo*-C₆H₁₁), 0.43 (s, 1H; TiCH); ¹³C NMR: $\delta = 143.19$ (s; *ipso*-Ph), 128.90 (d, ¹J(C,H) = 157.7 Hz; *o/m*-Ph), 128.49 (d, ¹J(C,H) = 158.2 Hz; *o/m*-Ph), 125.36 (d, ¹J(C,H) = 160.9 Hz; *p*-Ph), 119.49 (d, ¹J(C,H) = 173.4 Hz; =CH), 115.77 (s; =CMe), 112.97 (d, ¹J(C,H) = 174.1 Hz; Cp), 101.56 (d, ¹J(C,H) = 138.0 Hz; TiCH), 68.32 (d, ¹J(C,H) = 135.4 Hz; *cyclo*-C₆H₁₁), 37.03 (t, ¹J(C,H) = 128.9 Hz; *cyclo*-C₆H₁₁), 34.88 (t, ¹J(C,H) = 125.5 Hz; *cyclo*-C₆H₁₁), 26.68 (t, *cyclo*-C₆H₁₁), 26.59 (t, *cyclo*-C₆H₁₁), 26.36 (t; *cyclo*-C₆H₁₁), 18.46 (q, ¹J(C,H) = 128.0 Hz; =CMe)

4b: ¹H NMR: $\delta = 7.12$ (t, 2H; *m*-Ph), 9.93 (t, 1H; *p*-Ph), 6.75 (s, 1H; =CH), 6.69 (d, 2H; *o*-Ph), 5.98 (s, 5H; Cp), 3.53 (m, 1H; *cyclo*-C₆H₁₁), 2.02 (s, 3H; =CMe), 1.95–1.15 (m, 10H; *cyclo*-C₆H₁₁), –0.17 (s, 1H; TiCH), –1.31 (s, 3H; TiMe); ¹³C NMR: $\delta = 144.27$ (s; *ipso*-Ph), 128.33 (d, ¹J(C,H) = 158.0 Hz; *o/m*-Ph), 127.87 (d, ¹J(C,H) = 156.7 Hz; *o/m*-Ph), 124.25 (d, ¹J(C,H) = 161.0 Hz; *p*-Ph), 120.74 (d, ¹J(C,H) = 170.6 Hz; =CH), 112.65 (s; =CMe), 111.00 (d, ¹J(C,H) = 172.4 Hz; Cp), 97.87 (d, ¹J(C,H) = 135.9 Hz; TiCH), 67.15 (d; *cyclo*-C₆H₁₁), 39.72 (q, ¹J(C,H) = 118.1 Hz; TiMe), 37.17 (t, ¹J(C,H) = 125.0 Hz; *cyclo*-C₆H₁₁), 35.66 (t, ¹J(C,H) = 123.1 Hz; *cyclo*-C₆H₁₁), 26.57 (t; *cyclo*-C₆H₁₁), 26.44 (t; *cyclo*-C₆H₁₁), 26.34 (t; *cyclo*-C₆H₁₁), 18.73 (q, ¹J(C,H) = 123.0 Hz; =CMe)

5a: ¹H NMR: $\delta = 6.95$ (t, 2H; *m*-Ph), 6.82 (d, 2H; *o*-Ph), 6.51 (t, 1H; *p*-Ph), 6.17 (s, 1H; =CH), 6.04 (s, 5H; Cp), 4.14 (sept., ³J(H,H) = 6.5 Hz, 1H; *i*-C₃H₇), 3.37 (q, ³J(H,H) = 7.0 Hz, 4H; OCH₂CH₃), 2.16 (s, 3H; =CMe), 1.20 (d, ³J(H,H) = 6.5 Hz, 6H; *i*-C₃H₇), 1.10 (t, ³J(H,H) = 7.0 Hz, 4H; OCH₂CH₃); ¹³C NMR: $\delta = 244.69$ (s; Ti=C), 146.25 (s; *ipso*-Ph), 127.91 (d, ¹J(C,H) = 157.8 Hz; =CH), 127.53 (d, ¹J(C,H) = 154.3 Hz; *o/m*-Ph), 126.26 (d, ¹J(C,H) = 156.0 Hz; *o/m*-Ph), 119.45 (d, ¹J(C,H) = 152.8 Hz; *p*-Ph), 106.14 (d, ¹J(C,H) = 170.1 Hz; Cp), 101.53 (br. s; =CMe), 66.05 (t; OCH₂CH₃), 58.23 (d, ¹J(C,H) = 133.3 Hz; *i*-C₃H₇), 26.55 (q, ¹J(C,H) = 125.9 Hz; *i*-C₃H₇), 18.38 (q, ¹J(C,H) = 125.2 Hz; =CMe), 15.54 (q, ¹J(C,H) = 126.3 Hz; OCH₂CH₃)

5b: ¹H NMR: $\delta = 6.96$ (t, 2H; *m*-Ph), 6.82 (d, 2H; *o*-Ph), 6.52 (t, 1H; *p*-Ph), 6.18 (s, 1H; =CH), 6.06 (s, 5H; Cp), 3.67 (m, 1H; *cyclo*-C₆H₁₁), 3.38 (q, ³J(H,H) = 6.9 Hz, 4H; OCH₂CH₃), 2.15 (s, 3H; =CMe), 1.92–1.18 (m, 10H; *cyclo*-C₆H₁₁), 1.11 (t, ³J(H,H) = 6.9 Hz, 4H; OCH₂CH₃); ¹³C NMR: $\delta = 244.62$ (s; Ti=C), 146.42 (s; *ipso*-Ph), 128.02 (d, ¹J(C,H) = 158.4 Hz; =CH), 127.65 (d, ¹J(C,H) = 164.1 Hz; *o/m*-Ph), 126.45 (d, ¹J(C,H) = 156.2 Hz; *o/m*-Ph), 119.90 (d, ¹J(C,H) = 156.4 Hz; *p*-Ph), 106.40 (d, ¹J(C,H) = 170.9 Hz; Cp), 101.70 (br. s; =CMe), 66.17 (t; OCH₂CH₃), 38.05 (t, ¹J(C,H) = 125.6 Hz; *cyclo*-C₆H₁₁), 37.20 (t, ¹J(C,H) = 127.4 Hz; *cyclo*-C₆H₁₁), 27.23, 27.12, 27.02 (t; *cyclo*-C₆H₁₁), 18.35 (q, ¹J(C,H) = 125.9 Hz; =CMe), 15.59 (q, ¹J(C,H) = 125.5 Hz; OCH₂CH₃)

[a] The NMR spectra were recorded at 25 °C in [D₈]THF at 300.075 (¹H) and 75.462 MHz (¹³C) on a Varian-Gemini-300-BB spectrometer. Correct elemental analyses were obtained for all compounds.

of the Cp ligand (*supine* form, Figure 1).^[14] The Ti–C3 and the Ti–N distances of 2.147(3) and 1.902(3) Å, respectively, lie in the range of normal single bonds.^[15] The short distances between the titanium atom and the olefinic carbon atoms C1 and C2 (2.323(3) and 2.374(3) Å, respectively) likewise indicate a bonding interaction. Thus, overall the bonding mode of the 1-aza-1,3-diene to the CpTiCl core is best described by the $\sigma^2\pi$ structure type.^[16] For the proposed α -

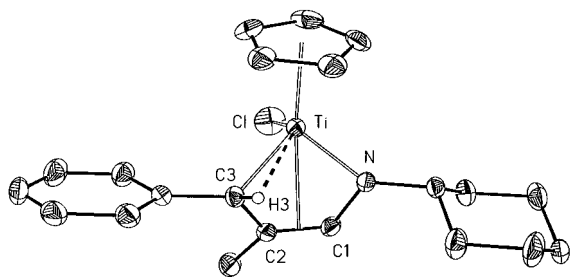


Figure 1. Structure of **3b** in the crystal (ellipsoids are drawn at 40% probability level; all H atoms except H3 were omitted for clarity). Selected bond lengths [Å] and angles [°]: Ti–Cl 2.310(1), Ti–N 1.902(3), Ti–C1 2.323(3), Ti–C2 2.374(3), Ti–C3 2.147(3), C1–C2 1.394(4), C2–C3 1.449(4), C1–N 1.376(4), Ti–H3 2.39(3); N–Ti–C3 87.3(1), N–Ti–Cl 113.76(8), C3–Ti–Cl 109.38(9), Ti–N–C1 88.7(2), Ti–C3–C2 80.1(2), Ti–C3–H3 93(2); sum of angles at N: 356.9(2); fold angle θ : (Ti–N–C3)–(N–C1–C2–C3) = 67.0(2)°.

hydrogen transfer it is particularly interesting that the Ti–C3–H3 group shows structural features that are even indicative of an agostic Ti $\leftarrow$ H–C interaction (Ti–H3 2.39(3) Å, Ti–C3–H3 93(2)°).^[17]

Treatment of the 1-aza-1,3-diene complexes **3a** and **3b** with methyllithium (one equivalent in each case), which was prepared from methyl iodide and lithium,^[18] leads initially to the methyl compounds **4a** and **4b**, respectively. However, these can only be detected, and in the case of **4b** isolated, if the temperature during the reaction is kept below 0 °C. At room temperature the reaction surprisingly leads directly to the new metallacyclic titanium–alkylidene complexes **5a** and **5b**, respectively (Scheme 2). Evidently the methane elimination from methyl compounds **4a** and **4b** proceeds without additional activation under very mild conditions. Compounds **5a** and **5b** are air-sensitive red-brown crystalline solids, which are well soluble, for example, in diethyl ether and *n*-pentane, and decompose first above 200 °C. Already on the basis of ¹³C NMR spectra it was possible to conclude the presence of alkylidene complexes: for instance, the signals of the metal-bound heterodiene carbon atoms are shifted dramatically to low field (δ = 244.69 (**5a**), 244.62 (**5b**)) compared to those of **3a** and **3b**. They lie in a region that is characteristic for carbene-carbon atoms (see Scheme 1).^[19] However, in order to explain how the lithium iodide (initially only detected by elemental analysis) is incorporated in these complexes and with a view to the first characterization of the structure of these metallacyclic titanium–alkylidene complexes, crystal structure determinations of **5a** and **5b** were carried out.^[20] The two compounds appear to be similar at least in solution, since their NMR spectra are almost identical (Table 1). Surprisingly, however, the same is not true for the solid-state structures (Figures 2 and 3).

The central building block of **5a** and **5b** is a five-membered titanacycle CpTi(C3–C2=C1–N), which, as for **3b**, is folded along the C3–N axis. However, the orientations of the folds differ: in **5b** the titanacycle displays a *prone*-analogous geometry, it is thus bent towards the Cp ligand (θ = 68.2(2)°); in contrast, in **5a** the five-membered ring is folded away from the Cp ligand (θ = 62.3(2)°), which leads to a *supine* conformation.^[14] In both cases the titanium atom is

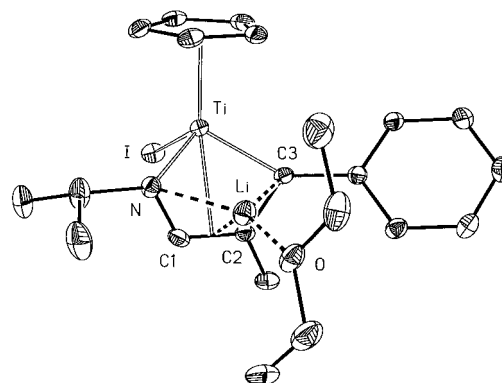


Figure 2. Structure of **5a** in the crystal (ellipsoids are drawn at the 40% probability level; all H atoms were omitted for clarity). Selected bond lengths [Å] and angles [°]: Ti–I 2.7893(6), Ti–N 1.949(3), Ti–C1 2.331(3), Ti–C2 2.358(3), Ti–C3 1.958(3), Li–N 2.074(6), Li–O 1.876(6), Li–C1 2.214(7), Li–C2 2.260(7), Li–C3 2.217(6), C1–C2 1.397(5), C2–C3 1.447(4), C1–N 1.381(4); N–Ti–C3 90.3(1), N–Li–C3 80.3(2), N–Ti–I 106.80(8), C3–Ti–I 110.61(9), Ti–N–C1 87.1(2), Ti–C3–C2 86.3(2); sum of angles at C3: 359.4(2); sum of angles at N: 349.0(2); fold angle θ : (Ti–N–C3)–(N–C1–C2–C3) = 62.3(2)°.

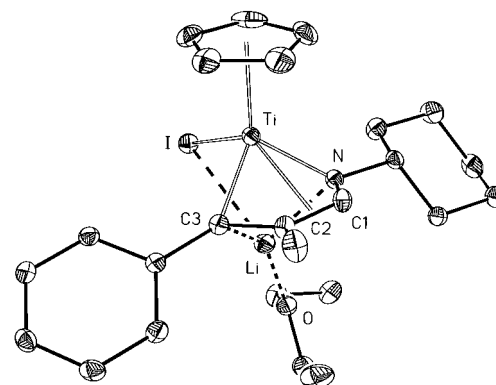


Figure 3. Structure of **5b** in the crystal (ellipsoids are drawn at the 40% probability level; all H atoms were omitted for clarity). Selected bond lengths [Å] and angles [°]: Ti–I 2.8012(7), Ti–N 1.993(2), Ti–C1 2.274(3), Ti–C2 2.324(3), Ti–C3 1.979(3), Li–N 2.127(6), Li–O 1.894(6), Li–I 2.874(6), Li–C1 2.764(7), Li–C2 2.851(6), Li–C3 2.334(6), Ti–Li 2.694(6), C1–C2 1.400(4), C2–C3 1.431(4), C1–N 1.377(4); N–Ti–C3 88.8(1), N–Li–C3 76.9(2), N–Ti–I 96.11(8), C3–Ti–I 95.94(9), Ti–N–C1 82.7(2), Ti–C3–C2 84.3(2); sum of angles at C3: 351.0(2); sum of angles at N: 335.4(2); fold angle θ : (Ti–N–C3)–(N–C1–C2–C3) = 68.2(2)°.

bound to the nitrogen atoms through normal Ti–N σ bonds (Ti–N 1.949(3) (**5a**), 1.993(3) Å (**5b**)).^[15] In addition, there are π interactions to the 1-aza-1,3-diene carbon atoms C1 and C2 (2.331(3), 2.358(3) Å (**5a**); 2.274(3), 2.324(3) Å (**5b**)). The most important structural element of **5a** and **5b** is the Ti=C3 bond (1.958(3) (**5a**), 1.973(4) Å (**5b**)). As expected it is shorter than the Ti–C3 single bond of **3b**, and its length approximately corresponds to those of the Ti=C double bonds of the titanium–alkylidene complexes given in Scheme 1.

An important role in the syntheses of these titanium–alkylidene complexes is evidently played by lithium iodide which is generated in the preparation of methyllithium and is present in the reaction mixture.^[18] Both in **5a** as well as in **5b** the I[−] ion occupies the coordination site at the titanium atom that becomes vacant during the methane elimination so that the piano stool arrangement remains intact in the ligand

sphere of the transition metal atom.^[21] In **5b** the titanium atom and the Li⁺ ion are additionally bridged by the I[−] ion (Li–I 2.874(6) Å). The Li⁺ ion is furthermore bound over large distances to the heterodiene termini C3 and N (Li–C3 2.334(6), Li–N 2.127(6) Å) and is coordinatively saturated by a molecule of diethyl ether.^[22] In **5a** the *supine* conformation of the CpTi(=C3–C2=C1–N) five-membered ring prevents a bond between the Li⁺ and the I[−] ion. This missing interaction is compensated by a shorter bond between the Li⁺ ion and the nitrogen atom (Li–N 2.074(6) Å) and a π interaction with all three carbon atoms of the heterodiene skeleton (Li–C1 2.217(6), Li–C2 2.260(7), Li–C3 2.214(7) Å). Consequently bonding similar to that in the (1,3-diene)dilithium or (1,4-diaza-1,3-diene)dilithium compounds can be assumed here.^[23]

The folding of the CpTi(=C3–C2=C1–N), five-membered ring of **5a** and **5b** prevents the desired conjugation of the Ti=C bond with the C=C bond within the metallacycle, which could additionally stabilize the alkylidene function. Despite this the simple preparation of **5a** and **5b** indicates that stable alkylidene complexes are accessible from (1-aza-1,3-diene)titanium complexes under very mild conditions by α -hydrogen elimination. It still remains unclear why in the formation of **5a** and **5b** lithium iodide is formally added and not lithium chloride which is also present in the same amount. Furthermore, it remains to be proven that a *supine-prone* rearrangement of the 1-aza-1,3-diene ligands in **4a** and **4b** is possible at least for the step involving the α -hydrogen elimination.^[24] These questions as well as studies into the reactivity of the new titanium–alkylidene complexes are currently under investigation.

Experimental Section

All work was carried out under argon and in carefully dried, degassed solvents.

3a, 3b: A solution of [CpTiCl₃] **1** (5.00 g, 22.80 mmol) in THF (100 mL) was treated with the appropriate 1-aza-1,3-diene (22.80 mmol: **2a**: 4.27 g; **2b**: 5.18 g) and magnesium (0.554 g, 22.80 mmol) and stirred for 8 h at −20 °C and then for 24 h at room temperature until the metal had completely reacted. Subsequently the solvent was removed under vacuum and the residue was extracted with diethyl ether (100 mL). The extract was concentrated to dryness and the residue was extracted with *n*-pentane (75 mL). After the extract had been left to stand for a long time at −20 °C, **3a** (5.13 g, 67%; m.p. 84 °C) and **3b** (4.37 g, 51%; m.p. 119–122 °C) crystallized in the form of green-brown crystals. The crystals of **3b** suitable for the crystal structure analysis were obtained by repeated recrystallization from diethyl ether.

4b: A solution of **3b** (2.10 g, 5.58 mmol) in diethyl ether (100 mL) was treated dropwise at 0 °C with a solution of methylolithium (6.85 mL of a 0.86 M solution), which had been prepared from methyl iodide and lithium in diethyl ether. The reaction mixture was stirred for 2 h at 0 °C. Subsequently the solvent was removed under vacuum and the residue was extracted in cold (ca. 0 °C) *n*-pentane (100 mL) and separated by filtration from the lithium salts. The filtrate was concentrated to dryness under vacuum to leave a brown microcrystalline solid (1.61 g, 81%; decomposition above 20 °C).

5a and 5b: A solution of **3a** (2.64 g, 7.86 mmol) and **3b**, respectively, (2.95 g, 7.86 mmol) in diethyl ether (100 mL) was treated dropwise at 0 °C with a solution of methylolithium (5.24 mL of a 1.5 M solution), which had been prepared from methyl iodide and lithium. The reaction mixture was stirred for 24 h at room temperature. Subsequently the solvent was removed under vacuum and the residue was extracted with boiling *n*-pentane.

After the extract had been left to stand for a long time at −5 °C, **5a** (2.23 g, 56%; m.p. 165 °C) and **5b** (2.67 g, 62%; m.p. 168 °C) crystallized in the form of red-brown crystals.

Crystals suitable for the crystal structure analyses were obtained by repeated recrystallization from diethyl ether.

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- [15] Typical lengths of Ti–C σ bonds: a) $[Cp_2Ti\{o-(CH_2)C_6H_4\}]$: 2.204(4), 2.202(5) $\text{\AA}$, G. S. Bristow, M. F. Lappert, T. R. Martin, J. L. Atwood, W. F. Hunter, *J. Chem. Soc. Dalton Trans.* **1984**, 399–413; b) $[Cp_2Ti\{CH_2CH(Ph)CH_2\}]$: 2.127(3), 2.113(4) $\text{\AA}$, J. B. Lee, G. J. Gajda, W. P. Schaefer, T. R. Howard, T. Ikariya, D. A. Straus, R. H. Grubbs, *J. Am. Chem. Soc.* **1981**, 103, 7358–7361; c) $[Cp_2TiMe_2]$: 2.170(2), 2.181(2) $\text{\AA}$, U. Thewalt, T. Wöhrle, *J. Organomet. Chem.* **1994**, 464, C17–C19; d) $[(cyclo-C_6H_4)_2N]_2TiMe_2$: 2.111(4), 2.118(3) $\text{\AA}$, L. Scoles, R. Minhas, R. Duchateau, J. Jubb, S. Gambartotta, *Organometallics* **1994**, 13, 4978–4983. Typical lengths of Ti–N σ bonds (titanium amides): 1.939 $\text{\AA}$, F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, S1–S19.
- [16] a) J. W. Lauher, R. Hoffmann, *J. Am. Chem. Soc.* **1976**, 98, 1729–1742; b) P. Hofmann, M. Frede, P. Stauffert, W. Lasser, U. Thewalt, *Angew. Chem.* **1985**, 97, 693–694; *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 712–713.
- [17] Examples for agostic Ti–H–C interactions: a) $[MeTiCl_2(dmpe)]$: Ti–H 2.447(3) $\text{\AA}$, Ti–C–H 93.5(2)°, Z. Dawoodi, M. L. H. Green, V. S. B. Mtetwa, K. Prout, A. J. Schultz, J. M. Williams, T. F. Koetzle, *J. Chem. Soc. Dalton Trans.* **1986**, 1629–1637; b) $[Cp^*Ti(CH_2Ph)_3]$: Ti–H 2.32, 2.37 $\text{\AA}$, M. Mena, M. A. Pellinghelli, P. Royo, R. Serrano, A. Tiripiccio, *J. Chem. Soc. Chem. Commun.* **1986**, 1118–1119; c) $[(\mu-\eta^5-\eta^5-C_{10}H_8)\{Ti(CH_2Ph)_2\}]$: Ti–H: 2.46, 2.45, 2.48, 2.59 $\text{\AA}$, L. M. Alvaro, T. Cuenca, J. C. Flores, P. Royo, M. A. Pellinghelli, A. Tiripiccio, *Organometallics* **1992**, 11, 3301–3306; d) $[CpCp^*Ti(CH_2PPh_2)_2]$: Ti–H 2.46(2) $\text{\AA}$, Ti–C–H 93(1)°, T. Cuenca, J. C. Flores, P. Royo, A.-M. Larssonneur, R. Choukroun, F. Dahan, *Organometallics* **1992**, 11, 777–780; e) $[Cp^*Ti(CH_2SiMe_3)_2(\mu-O)]$: Ti–H 2.422, 2.489 $\text{\AA}$, P. Gómez-Sal, M. Mena, F. Palacios, P. Royo, S. M. Carreras, *J. Organomet. Chem.* **1989**, 375, 59–65.
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- [19] Examples for the ^{13}C NMR shifts of alkylidene carbon atoms in complexes of the type $[L_nM=CRR']$ can be found in references [1d, h, 3a].
- [20] a) Crystal structure analysis of **5a**: $C_{22}H_{31}NOiLiTi$, $M_r = 507.22$, crystal dimensions $0.40 \times 0.36 \times 0.35 \text{ mm}^3$, $a = 10.039(1)$, $b = 14.934(2)$, $c = 15.517(2) \text{ \AA}$, $\beta = 90.93(1)^\circ$, $V = 2326.0(5) \text{ \AA}^3$, $T = 183(2) \text{ K}$, $\rho_{\text{calcd}} = 1.448 \text{ g cm}^{-3}$, $\mu = 1.705 \text{ mm}^{-1}$, $F(000) = 1024$, $Z = 4$, monoclinic, space group $P2_1/c$ (no. 14), Enraf-Nonius-CAD4 diffractometer, $\lambda = 0.71073 \text{ \AA}$, $\omega/2\theta$ scan, 4989 measured reflections ($-h, +k, \pm l$), $2.44 > \theta > 26.30^\circ$, 4718 independent and 3655 observed reflections [$I > 2\sigma(I)$], 300 refined parameters, direct methods, $R = 0.0328$, $R_w = 0.0529$ [$w = 1/\sigma^2(F_o)$], max. residual electron density $0.677 \text{ e \AA}^{-3}$. Crystal structure analysis of **5b**: $C_{25}H_{35}NOiLiTi$, $M_r = 547.28$, crystal dimensions $0.40 \times 0.36 \times 0.32 \text{ mm}^3$, $a = 10.471(2)$, $b = 12.893(2)$, $c = 19.259(3) \text{ \AA}$, $\beta = 100.13(1)^\circ$, $V = 2559.5(7) \text{ \AA}^3$, $T = 183(2) \text{ K}$, $\rho_{\text{calcd}} = 1.420 \text{ g cm}^{-3}$, $\mu = 1.556 \text{ mm}^{-1}$, $F(000) = 1112$, $Z = 4$, monoclinic, space group $P2_1/n$ (no. 14), Enraf-Nonius-CAD4 diffractometer, $\lambda = 0.71073 \text{ \AA}$, $\omega/2\theta$ scan, 5340 measured reflections ($\pm h, -k, +l$), $2.41 > \theta > 26.32^\circ$, 5186 independent and 3959 observed reflections [$I > 2\sigma(I)$], 276 refined parameters, direct methods, $R = 0.0298$, $R_w = 0.0544$ [$w = 1/\sigma^2(F_o)$], max. residual electron density $0.558 \text{ e \AA}^{-3}$. b) Further details of the crystal structure investigations 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 numbers CSD-407632, CSD-407634, and CSD-407633.
- [21] To date very few Ti–I bond lengths of titanium(IV) iodides have been reported, for example: a) $[(2,6\text{-}t\text{-Bu}_2\text{C}_6\text{H}_3\text{O}_3)_2TiI]$: 2.634(8) $\text{\AA}$, S. L. Latesky, J. Keddington, A. McMullen, I. P. Rothwell, J. C. Huffman, *Inorg. Chem.* **1985**, 24, 995–1001; b) $[(\mu-C_2Me_4)(C_5H_4)_2TiI_2]$: 2.763(4), 2.730(3) $\text{\AA}$, A. J. Edwards, N. J. Burke, C. M. Dobson, K. Prout, S. J. Heyes, *J. Am. Chem. Soc.* **1995**, 117, 4637–4653; c) $[(C_5H_4(SiMe_3))_2TiI_2]$: 2.771(3) $\text{\AA}$, M. G. B. Drew, E. Delgado, E. Hernandez, P. K. Baker, N. Mansilla, *Acta Crystallogr. Sect. C* **1996**, 52, 2168–2170; d) $[(C_5H_4Me)Ti(I)O]_4$: 2.667(4) $\text{\AA}$, C. O. Kienitz, C. Thöne, P. G. Jones, *Acta Crystallogr. Sect. C* **1997**, 53, 843–845; e) $[1,2\text{-(Me}_3\text{SiN)}_2(cyclo-C_6H_{10})TiI_2]$: 2.6321(7) $\text{\AA}$, B. Tsuie, D. C. Swenson, R. F. Jordan, J. L. Petersen, *Organometallics* **1997**, 1392–1400. The Ti–I bond in **5b** (2.8012(7) $\text{\AA}$) is, of course, slightly longer than that in **5a** (2.7893(6) $\text{\AA}$) through the Li–I contact.
- [22] The Li–I distance in **5b** (2.874(6) $\text{\AA}$) is only negligibly longer than that in complexed monomeric lithium iodides: a) $[Li(pmedien)]$ (pmedien = N,N,N',N' -pentamethyldiethyltriethylamine): 2.75(3), 2.67(3) $\text{\AA}$, C. L. Raston, B. W. Skelton, C. R. Whitaker, A. H. White, *J. Chem. Soc. Dalton Trans.* **1988**, 987–990; b) $[Li(NC_3H_5-3,5\text{-Me}_2)_3]$: 2.80(1) $\text{\AA}$, C. L. Raston, C. R. Whitaker, A. H. White, *J. Chem. Soc. Dalton Trans.* **1988**, 991–995. It is, however, unusual that the Li^+ ion is surrounded by four different bonding partners.
- [23] a) $[Li(thf)_2]_2(Me_3Si)CHCH=CHCH(SiMe_3)_2$: M. G. Gardiner, C. L. Raston, F. G. N. Cloke, P. B. Hitchcock, *Organometallics* **1995**, 14, 1339–1353; b) $[Li(tmada)]_2(Me_3Si)CHCH=CHCH(SiMe_3)_2$: L. D. Field, M. G. Gardiner, B. A. Messerle, C. L. Raston *Organometallics* **1992**, 11, 3566–3570; c) $[Li(tmada)]_2(Ph)CHCH=CHCH(Ph)_2$: D. Wilhelm, T. Clark, P. von R. Schleyer, H. Dietrich, W. Mahdi, *J. Organomet. Chem.* **1985**, 280, C6–C10; d) $[Li(thf)_2]_2[(4\text{-MeC}_6\text{H}_4)\text{-NC(Ph)=C(Ph)N(4-MeC}_6\text{H}_4)]$: J. Scholz, B. Richter, R. Goddard, C. Krüger, *Chem. Ber.* **1993**, 126, 57–61.
- [24] D. Devore, F. J. Timmers, D. L. Hasha, R. K. Rosen, T. J. Marks, P. A. Deck, C. L. Stern, *Organometallics* **1995**, 14, 3132–3134.

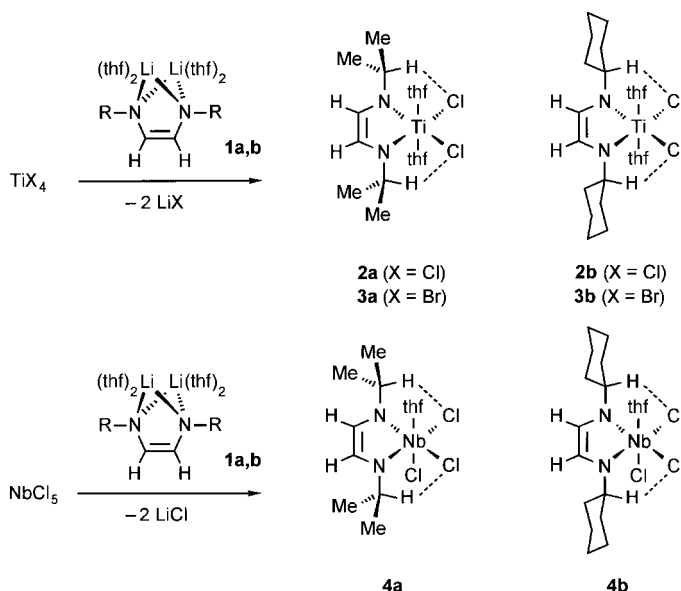
(1,4-Diaza-1,3-diene)titanium and -niobium Halides: Unusual Structures with Intramolecular C–H...Halogen Hydrogen Bonds**

Thomas Spaniel, Helmar Görls, and Joachim Scholz*

In recent years the number of systematic investigations of hydrogen bonds for the development of syntheses for supramolecules and of crystal engineering has risen dramatically.^[1] Hereby, the interest is switching more and more to those hydrogen bonds which do not involve the conventionally strong O–H...O and N–H...O bonds (energies 20–40 kJ mol^{–1}). In many organic and organometallic compounds C–H units frequently function as H-bonding donors and form weak hydrogen bonds (energies < 20 kJ mol^{–1}) with suitable H-bonding acceptors, mainly oxygen (C–H...O) or nitrogen (C–H...N).^[2] However, it is still under debate whether chlorine or other halogen atoms can also be H-bonding acceptors. Whereas on the one hand the existence of C–H...Cl hydrogen bonds has been questioned,^[3] a few individual examples of such interactions have been known since 1982.^[2a] However, nearly all these compounds are saltlike and contain Cl[–] ions. To date there are hardly any compounds known in which chlorine atoms are covalently bound and nevertheless participate in C–H...Cl hydrogen bonds. Most of the C–H...Cl interactions found so far are concerned with intermolecular interactions,^[4] which in addition have only been observed in the crystal.^[2a, 5]

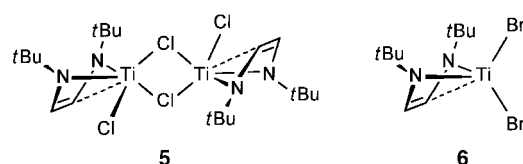
In studies on the chemistry of (1,4-diaza-1,3-diene) halide complexes of the early transition metals we have established that these C–H...Cl hydrogen bonds with covalently bound chlorine do indeed exist and that they can occur not only in the solid state but also in solution.^[6, 7] We report here on the synthesis of bis(isopropyl)glyoxaldiimine- and bis(cyclohexyl)glyoxaldiiminetitanium and -niobium halides and show that intramolecular C–H...halogen hydrogen bonds can even considerably influence the molecular geometry of these 1,4-diaza-1,3-diene complexes.

The new bis(isopropyl)glyoxaldiimine- and bis(cyclohexyl)glyoxaldiiminetitanium- and -niobium halides can be prepared in moderate to good yields by the reaction of the dilithium (1,4-diaza-1,3-diene) compounds **1a, b** with the respective metal halides in a molar ratio of 1:1 (Scheme 1). The titanium chloride and the titanium bromide complexes **2a, b** and **3a, b**, respectively, precipitate as bright red crystalline solids,^[8] and the niobium compounds **4a, b** form amber crystals. They are all air- and moisture-sensitive and are well soluble in THF, less so in diethyl ether, and only sparingly soluble in aliphatic solvents. The ¹H NMR spectra of the new



Scheme 1. Synthesis of the (1,4-diaza-1,3-diene)titanium(IV) and -niobium(V) halides **2a–4a** (R = *i*Pr) and **2b–4b** (R = cyclohexyl).

1,4-diaza-1,3-diene complexes contain few signals, which indicate highly symmetrical molecules (Table 1). However, these signals are difficult to assign. For instance, there is no obvious explanation for the surprisingly strong lowfield shift of the methine proton signals of the isopropyl and the cyclohexyl groups of **2a** and **3a** and **2b** and **3b** ($\delta = 6.99$ – 6.22), respectively.^[9] The highfield shift of the signal for the azomethine protons ($\delta = 4.21$ – 3.75) is also remarkable. In contrast, in the similar bis(*tert*-butyl)glyoxaldiiminetitanium complexes **5** and **6** these signals occur in the olefinic region of the spectra ($\delta = 5.88$ (**5**),^[8] 5.78 (**6**)^[10a]), where they are expected on the basis of the enediamide structure of these compounds.



X-ray crystal structure analyses of **2b** and **4a** were necessary to establish the reasons for these unusual NMR data.^[11] The most prominent structural features of **2b** are without doubt the short distances between the chlorine atoms Cl1 and Cl2 and the hydrogen atoms H3 and H7, respectively, of the cyclohexyl rings (each 2.59(4) Å, Figure 1). They are significantly shorter than the sum of the van der Waals radii of chlorine and hydrogen (1.75 and 1.20 Å, respectively)^[12] and evidently cause the strong deshielding of H3 and H7, which leads to the unexpected lowfield shift of the ¹H NMR signal.

These C–H...Cl hydrogen bonds have significant consequences for the structure of **2b**: The Ti–N distances of 2.034(4) and 2.037(3) Å are large compared to those in other (1,4-diaza-1,3-diene)titanium complexes (Ti–N 1.908(2), 1.910(2) Å (**5**);^[8] Ti–N 1.908(2), 1.910(2) Å (**6**)^[10]) or in titanium amide compounds (average Ti–N distance

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Table 1. NMR spectroscopic data of **2a**, **b**, **3a**, **b**, and **4a**, **b**.^[a]

2a: ¹H NMR: δ = 6.63 (sept., ³J(H,H) = 6.6 Hz, 2H; NCHMe₂), 4.21 (s, 2H; HC=CH), 3.62 (m, 8H; OCH₂, THF), 1.77 (m, 8H; OCH₂CH₂, THF), 1.09 (d, ³J(H,H) = 6.6 Hz, 12H; NCHMe₂). ¹³C NMR: δ = 115.87 (ddd, ¹J(C,H) = 168.4, ²J(C,H) = 10.2, ³J(C,H) = 6.9 Hz; HC=CH), 68.21 (t; OCH₂, THF), 57.59 (d, ¹J(C,H) = 144.3 Hz; NCHMe₂), 26.25 (t; OCH₂CH₂, THF), 24.25 (q, ¹J(C,H) = 125.5 Hz; NCHMe₂)

2b: ¹H NMR: δ = 6.22 (tt, 2H; NCH, *cyclo*-C₆H₁₁), 4.14 (s, 2H; HC=CH), 3.62 (m, 8H; OCH₂, THF), 1.97 (m, 4H; *cyclo*-C₆H₁₁), 1.78 (m, 8H; OCH₂CH₂, THF), 1.77 (m, 4H; *cyclo*-C₆H₁₁), 1.65–1.45 (m, 8H; *cyclo*-C₆H₁₁), 1.00 (m, 4H, *cyclo*-C₆H₁₁); ¹³C NMR: δ = 116.20 (ddd, ¹J(C,H) = 167.9, ²J(C,H) = 9.9, ³J(C,H) = 6.9 Hz; HC=CH), 68.22 (t, OCH₂; THF), 66.77 (d; *cyclo*-C₆H₁₁), 35.28 (t, ¹J(C,H) = 126.8 Hz; *cyclo*-C₆H₁₁), 27.09 (t, ¹J(C,H) = 125.7 Hz; *cyclo*-C₆H₁₁), 26.24 (t, ¹J(C,H) = 130.7 Hz; *cyclo*-C₆H₁₁), 26.33 (t, OCH₂CH₂; THF)

3a: ¹H NMR: δ = 6.99 (sept., ³J(H,H) = 6.7 Hz, 2H; NCHMe₂), 3.86 (s, 2H; HC=CH), 3.62 (m, 8H; OCH₂, THF), 1.77 (m, 8H; OCH₂CH₂, THF), 1.07 (d, ³J(H,H) = 6.7 Hz, 12H; NCHMe₂); ¹³C NMR: δ = 113.10 (ddd, ¹J(C,H) = 169.0, ²J(C,H) = 10.5, ³J(C,H) = 6.9 Hz; HC=CH), 68.22 (t; OCH₂, THF), 58.60 (d, ¹J(C,H) = 143.3 Hz; NCHMe₂), 26.29 (t; OCH₂CH₂, THF), 24.28 (q, ¹J(C,H) = 125.8 Hz; NCHMe₂)

3b: ¹H NMR: δ = 6.57 (tt, 2H; NCH, *cyclo*-C₆H₁₁), 3.75 (s, 2H; HC=CH), 3.58 (m, 8H; OCH₂, THF), 1.97 (m, 4H; *cyclo*-C₆H₁₁), 1.77 (m, 4H; *cyclo*-C₆H₁₁), 1.74 (m, 8H; OCH₂CH₂, THF), 1.62–1.43 (m, 6H; *cyclo*-C₆H₁₁), 1.05–0.81 (m, 6H, *cyclo*-C₆H₁₁); ¹³C NMR: δ = 113.37 (ddd, ¹J(C,H) = 167.5, ²J(C,H) = 10.6, ³J(C,H) = 6.8 Hz; HC=CH), 68.23 (t, ¹J(C,H) = 144.1 Hz; OCH₂, THF), 67.64 (d, ¹J(C,H) = 136.9 Hz; *cyclo*-C₆H₁₁), 35.33 (t, ¹J(C,H) = 126.4 Hz; *cyclo*-C₆H₁₁), 27.04 (t, ¹J(C,H) = 126.4 Hz; *cyclo*-C₆H₁₁), 26.67 (t, ¹J(C,H) = 126.0 Hz; *cyclo*-C₆H₁₁), 26.29 (t, ¹J(C,H) = 131.6 Hz; OCH₂CH₂, THF)

4a: ¹H NMR (25 °C): δ = 5.46 (br. s, 2H; HC=CH), 5.31 (sept., ³J(H,H) = 6.6 Hz, 2H; NCHMe₂), 3.62 (m, 4H; OCH₂, THF), 1.77 (m, 4H; OCH₂CH₂, THF), 1.13 (d, ³J(H,H) = 6.6 Hz, 4H; NCHMe₂); ¹H NMR (–80 °C): δ = 5.50 (m, 2H; NCHMe₂), 5.08 (s, 2H; HC=CH), 3.62 (m, 4H; OCH₂, THF), 1.77 (m, 4H; OCH₂CH₂, THF), 1.13 (d, ³J(H,H) = 5.7 Hz, 6H; NCHMe₂), 1.02 (d, ³J(H,H) = 5.9 Hz, 6H; NCHMe₂); ¹³C NMR: δ = 115.83 (d, ¹J(C,H) = 180.7 Hz; HC=CH), 68.26 (t; OCH₂, THF), 61.05 (d, ¹J(C,H) = 142.7 Hz; NCHMe₂), 26.27 (t; OCH₂CH₂, THF), 22.62 (q, ¹J(C,H) = 127.1 Hz; NCHMe₂)

4b: ¹H NMR (25 °C): δ = 5.56 (s, 2H; HC=CH), 4.88 (tt, 2H; NCH, *cyclo*-C₆H₁₁), 3.62 (m, 4H; OCH₂, THF), 1.96 (m, 4H; *cyclo*-C₆H₁₁), 1.78 (m, 4H; OCH₂CH₂, THF), 1.77 (m, 4H; *cyclo*-C₆H₁₁), 1.61 (m, 2H; *cyclo*-C₆H₁₁), 1.40–1.05 (m, 10H; *cyclo*-C₆H₁₁); ¹H NMR (–80 °C): δ = 5.14 (s, 2H; HC=CH), 5.09 (m, 2H; NCH, *cyclo*-C₆H₁₁), 3.62 (m, 4H; OCH₂, THF), 1.80 (m, 4H; OCH₂CH₂, THF), 1.90–0.85 (m, 20H; *cyclo*-C₆H₁₁); ¹³C NMR: δ = 114.40 (d, ¹J(C,H) = 180.0 Hz; HC=CH), 69.03 (d, ¹J(C,H) = 141.0 Hz; *cyclo*-C₆H₁₁), 68.20 (t; OCH₂, THF), 33.59 (t, ¹J(C,H) = 132.2 Hz; *cyclo*-C₆H₁₁), 26.46 (t; *cyclo*-C₆H₁₁), 26.31 (t; *cyclo*-C₆H₁₁), 26.25 (t; OCH₂CH₂, THF)

[a] The NMR spectra were recorded at 25 °C, and for **4a,b** additionally at –80 °C, in [D₈]THF at 300.075 (¹H) and 75.462 MHz (¹³C) on a Varian-Gemini-300-BB spectrometer. Correct elemental analysis were obtained for all compounds.

1.939 Å^[13] and even exceed the sum of the covalent radii (Ti–N 2.024 Å).^[14] Thus, a π -bonding contribution can be ruled out for these bonds. It is even more surprising that the two nitrogen atoms are nevertheless trigonal planar surrounded and that the five-membered ring Ti(N1–C1=C2–N2), in contrast to those in **5** and **6**, is not folded (Ti, N1, N2, C1, and C2 lie in the mirror plane). As in many enamines the sp²-hybridization of the nitrogen atoms in **2b** evidently results from an interaction of the N electron pairs with the p _{π} orbitals of the C1=C2 bond.^[15] This charge distribution helps to account for why the affected azomethine hydrogen atoms H1 and H2 are so strongly shielded and their ¹H NMR signal is

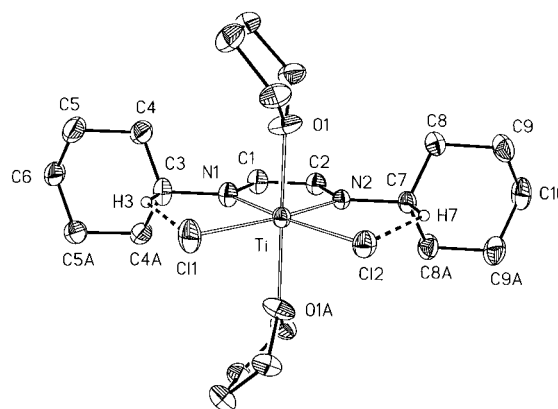


Figure 1. Structure of **2b** in the crystal (ellipsoids are drawn at 40% probability level). Selected bond lengths [Å] and angles [°]: Ti–Cl1 2.399(1), Ti–Cl2 2.386(1), Ti–N1 2.034(4), Ti–N2 2.037(3), Ti–O1 2.102(2), Ti–O1a 2.102(2), N1–C1 1.363(5), N2–C2 1.364(6), C1–C2 1.374(6), H3–C11 2.59(4), H7–C12 2.59(4); N1–Ti–N2 78.0(1), C11–Ti–Cl2 95.56(5), O1–Ti–O2 173.8(1), Ti–Cl1–H3 77(3), Ti–Cl2–H7 78(3), C3–H3–C11 137(3), C7–H7–C12 131(3); sum of angles at N1 and N2 360° (mirror plane).

shifted to high field. A decrease in the charge density at the titanium atom is associated with the extension of the Ti–N bonds, particularly since the Ti–Cl bonds (2.398(2) and 2.387(2) Å) are also relatively long because of the C–H...Cl bonds.^[16] This charge deficit is compensated by two THF ligands, and thus, in contrast to the titanium atoms in **5** and **6**, the titanium atom in **2b** is six-coordinate.

The metal atom is also six-coordinate in the niobium compounds **4a** and **4b**; however, only one THF molecule is required to achieve the octahedral geometry. From the structure of **4a** is clear that this THF molecule, unlike that in the bis(*tert*-butyl)glyoxaldimine-niobium complex **7**^[10b] is coordinated in a *trans* position to a chlorine atom at the niobium atom (Figure 2).^[11b, 17] This

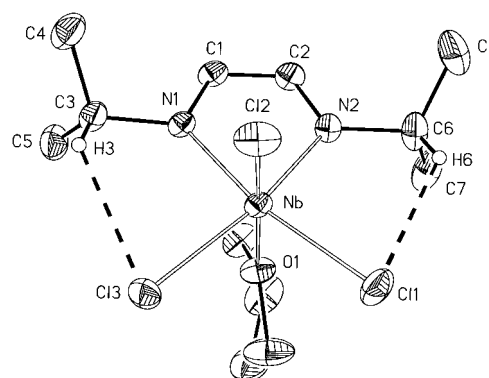
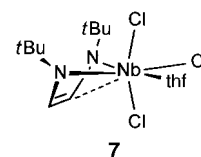


Figure 2. Structure of **4a** in the crystal (ellipsoids are drawn at 40% probability level). Selected bond lengths [Å] and angles [°]: Nb–Cl1 2.379(8), Nb–Cl2 2.387(8), Nb–Cl3 2.3955(8), Nb–N1 2.048(2), Nb–N2 2.057(2), Nb–O 2.188(2), N1–C1 1.366(3), N2–C2 1.369(3), C1–C2 1.351(4), Cl3–H3 2.69(4), C11–H6 2.68(4); N1–Nb–N2 74.88(8), C11–Nb–Cl2 90.90(3), C11–Nb–Cl3 101.64(3), Cl2–Nb–Cl3 91.52(3), O–Nb–Cl2 171.90(5), Nb–Cl1–H6 77(3), Nb–Cl3–H3 74(3), C3–H3–Cl3 125(3), C6–H6–Cl1 126(3); sum of angles at N1 359.9(2), at N2 359.6(2)°; fold angle (Nb,N1,N2)–(N1,C1,C2,N2) θ = 6.3(2)°.

arrangement of ligands is therefore preferred because in this way, as in **2b**, two chlorine atoms are found in the plane of the 1,4-diaza-1,3-diene and can form C–H...Cl hydrogen bonds (H–Cl 2.68(4) and 2.69(4) Å; C–H–Cl 125(3) and 126(3)°) with the methine hydrogen atoms of the isopropyl groups. All other characteristic structural features of **4a**, which are attributed to these C–H...Cl bonds, correspond to those of the titanium complex. However, on account of the differing influence of the ligands chlorine and THF at the axial octahedral positions, the Nb(N1–C1=C2–N2) five-membered ring is slightly folded along the N1–N2 axis ($\theta = 6.3(2)^\circ$).^[18]

The surprising occurrence of intramolecular C–H...halogen hydrogen bonds in the isopropyl- and cyclohexyl-substituted 1,4-diaza-1,3-diene complexes **2**, **3**, and **4** is in agreement with the results obtained by Taylor and Kennard, according to which C–H units frequently occur as H-bond donors, if they are located in the α -position to a nitrogen atom.^[2a] Whether other structural prerequisites are generally required for the occurrence of a C–H...halogen hydrogen bond, such as the additional support through a resonance-stabilized ligand system, and to what extent these intramolecular C–H...halogen hydrogen bonds can be varied with respect to the complex geometry and the choice of the halogen atom^[19] are currently under investigation.

Experimental Section

All work was carried out under argon with carefully dried, degassed solvents. The ¹H and ¹³C NMR data of the new compounds are given in Table 1.

2a: A solution of **1a** (12.20 mmol), prepared from *i*PrN=CHCH=N*i*Pr (1.71 g, 12.20 mmol) and lithium (0.169 g, 24.40 mmol) in THF (50 mL), was added dropwise at –78 °C to a solution of TiCl₄·2THF (4.07 g, 12.20 mmol) in THF (150 mL). The reaction mixture was allowed to warm to room temperature and stirred for 24 h. Subsequently the solvent was removed under vacuum and the residue was extracted with diethyl ether (100 mL). Red crystals of **2a** (3.84 g, 78 %) precipitated from the extract at –20 °C.

2b: Compound **2b** was obtained as described for **2a** by the reaction of **1b** (21.46 mmol), prepared from (cyclo-C₆H₁₁)N=CHCH=N(cyclo-C₆H₁₁) (4.73 g, 21.46 mmol) and lithium (0.298 g, 42.92 mmol), with TiCl₄·2THF (7.17 g, 21.47 mmol) in 67 % yield (6.95 g). Crystals suitable for the crystal structure analysis were obtained from diethyl ether/THF.

3a: TiBr₄ (4.58 g, 12.46 mmol) was dissolved in THF (150 mL) at –78 °C and treated dropwise at this temperature with a solution of **1a** (12.46 mmol), prepared from *i*PrN=CHCH=N*i*Pr (1.75 g, 12.46 mmol) and lithium (0.173 g, 24.92 mmol) in THF (50 mL). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Subsequently the solvent was removed under vacuum and the residue was extracted with diethyl ether (100 mL). Red crystals of **3a** (4.97 g, 81 %) precipitated from the extract at –5 °C.

3b: Compound **3b** was obtained as described for **3a** by the reaction of **1b** (9.55 mmol), prepared from (cyclo-C₆H₁₁)N=CHCH=N(cyclo-C₆H₁₁) (2.10 g, 9.55 mmol) and lithium (0.133 g, 19.10 mmol), with TiBr₄ (3.51 g, 9.55 mmol) in 70 % yield (3.83 g).

4a: A solution of **1a** (10.42 mmol), prepared from *i*PrN=CHCH=N*i*Pr (1.46 g, 10.42 mmol) and lithium (0.145 g, 20.84 mmol) in THF (100 mL), was added dropwise to a solution of NbCl₅ (2.82 g, 10.42 mmol) in THF (150 mL) at –78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. Subsequently the solvent was removed under vacuum until 50 mL of the solution remained. Diethyl ether (100 mL) was added to this reaction mixture. This led to the precipitation of nearly all the lithium chloride, which was separated from the solution by repeated filtration. The filtrate was kept for several days at –20 °C, during

this time **4a** precipitated as an other, microcrystalline solid. Yellow-brown, analytically pure crystals of **4a** (2.49 g, 58 %) were obtained by recrystallization from THF.

4b: Compound **4b** was obtained as described for **4a** by the reaction of **1b** (9.65 mmol), prepared from (cyclo-C₆H₁₁)N=CHCH=N(cyclo-C₆H₁₁) (2.13 g, 9.65 mmol) and lithium (1.34 g, 19.30 mmol), with NbCl₅ (2.61 g, 9.65 mmol) in 55 % yield (2.61 g). Parallelepiped-shaped amber crystals, which were suitable for an X-ray crystal structure analysis were obtained after recrystallization from THF.

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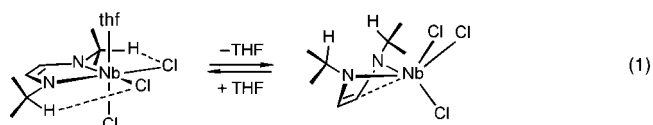
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Keywords: heterodienes • hydrogen bonds • niobium • N ligands • titanium

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- NCHMe₂); b) *N,N'*-bis(cyclohexyl)glyoxaldiimine: ¹H NMR ([D₈]THF, 20 °C): δ = 7.85 (s, 2H; N=CH), 3.14 (m, 2H; NCH, cyclo-C₆H₁₁), 1.83–1.78 (m, 20H; cyclo-C₆H₁₁); ¹³C NMR ([D₈]THF, 25 °C): δ = 160.87 (ddd, ¹J(C,H) = 161.6, ²J(C,H) = 11.3, ³J(C,H) = 8.7 Hz; N=CH), 70.13 (d, ¹J(C,H) = 130.1 Hz; cyclo-C₆H₁₁), 34.91 (t, ¹J(C,H) = 127.9 Hz; cyclo-C₆H₁₁), 26.52, 25.16 (t; cyclo-C₆H₁₁).
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complexes. This indicates a rapid exchange process in which the THF is reversibly cleaved from the complex. We assume that an increase in the C–H···Cl distances is associated with this change in the complex geometry, which leads to the breakage of the hydrogen bonds. At the same time the Nb(N1–Cl=C2–N2) ring is also more strongly folded [Eq. (1)]. This molecular dynamic is supported by the low-temper-



ature ¹H NMR spectra: At -80 °C the equilibrium of this exchange process evidently shifts to the side of the THF complex with a six-coordinate niobium and intact C–H···Cl bonds, since the signals of the methine protons of the isopropyl or cyclohexyl groups move to lower field and the signals of the azomethine protons move to higher field.

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Formation of a Novel Amidinium-Bridged Polyhedral Borane Ion by Incorporation of an Acetonitrile Solvent Molecule**

Fangbiao Li, Kenneth Shelly, Carolyn B. Knobler, and M. Frederick Hawthorne*

The derivative chemistry of the polyhedral borane ion [B₂₀H₁₈]²⁻^[1] has been of considerable interest for a number of years. Recently, we showed that oxidation of the oxygen-substituted derivatives *ae*-[B₂₀H₁₇OR]⁴⁻ produced polyhedral borane anions [*μ*-B₂₀H₁₈OR]²⁻,^[2] which contained both hydrogen and oxygen bridges. This observation, together with the availability of amine-substituted species suitable as candidate target species for boron neutron capture therapy (BNCT) of cancer,^[3] prompted us to extend these studies to the oxidation of *ae*-[B₂₀H₁₇NH₃]³⁻ (**1**, Scheme 1).^[3, 4] The ion **1** and related amine derivatives exhibit excellent tumor uptake and selectivity when delivered by liposomes in vivo.^[3, 4] This has been attributed to the facile intracellular oxidation of the

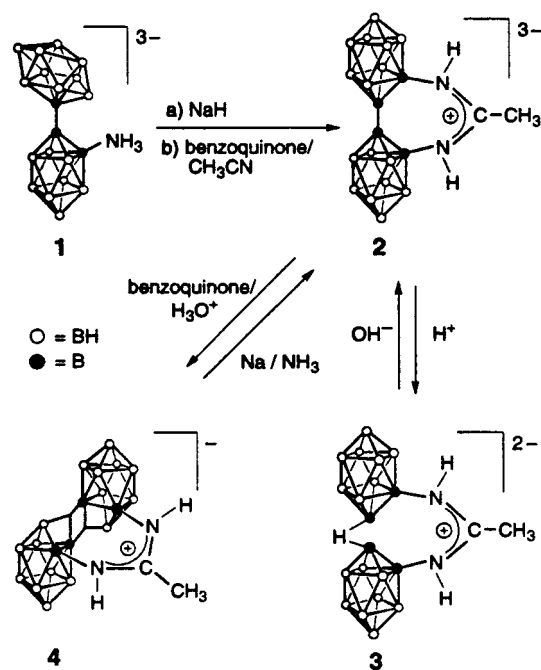
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[**] This work was supported by the U.S. Department of Energy (DE-FG02-95ER61975). The following prefixes are used as isomer designations: *ae* = apical–equatorial isomers of [B₂₀H₁₈]⁴⁻ derivatives ([1-(2-B₁₀H₉)-B₁₀H₉]⁴⁻); *a²* = apical–apical isomers of [B₂₀H₁₈]⁴⁻ derivatives ([1-(1-B₁₀H₉)-B₁₀H₉]⁴⁻); *e²* = equatorial–equatorial isomers of [B₂₀H₁₈]⁴⁻ derivatives ([2-(2-B₁₀H₉)-B₁₀H₉]⁴⁻).

$[\text{B}_{20}\text{H}_{17}\text{NH}_2\text{R}]^{3-}$ ion to a $[\text{B}_{20}\text{H}_{17}\text{NH}_2\text{R}]^-$ species thought to be responsible for bonding with intracellular protein. The isolation and reactivity of an oxidized product of *ae*- $[\text{B}_{20}\text{H}_{17}\text{NH}_3]^{3-}$ would support the proposed mechanism of tumor retention.

During the investigation of the oxidation of **1**, a method was sought for this procedure in nonaqueous media. Benzoquinone and tetrachlorobenzoquinone in acetonitrile are effective reagents for the oxidation of $[\text{B}_{10}\text{H}_{10}]^{2-}$ or $[\text{B}_{20}\text{H}_{18}]^{4-}$ to the $[\text{B}_{20}\text{H}_{18}]^{2-}$ ion.^[5] However, when the oxidation of **1** was attempted with benzoquinone in acetonitrile, an unusual product was observed due to the unexpected participation of the solvent. The novel $a^2-[\mu\text{-CH}_3\text{C}(\text{NH})_2]\text{B}_{20}\text{H}_{16}]^{3-}$ ion (**2**, Scheme 1), with an amidinium-bridged structure, was formed. Further oxidation with additional benzoquinone under acidic aqueous conditions produced the $[\mu\text{-CH}_3\text{C}(\text{NH})_2]\text{B}_{20}\text{H}_{16}]^-$ ion (**4**, Scheme 1). Both **2** and **4** contain an amidinium group that bridges the two B_{10} cage fragments. In the formation of **2**, the bridging amidinium group results from the incorporation of an acetonitrile molecule in the presence of the oxidant benzoquinone. We report here the synthesis, structural analysis, and reactions of **4**.

Following the treatment of $[(\text{Me}_3\text{NH})_3][\textbf{1}]$ with NaH in dry acetonitrile (no reaction was observed unless the ammonio ligand was deprotonated), addition of benzoquinone resulted in the formation of the ion **2** (Scheme 1). Acidification of



Scheme 1. Oxidation of **1**.

an aqueous solution of **2** produced the $[(\mu\text{-H})\{\mu\text{-CH}_3\text{C}(\text{NH})_2\}\text{B}_{20}\text{H}_{16}]^{2-}$ ion (**3**, Scheme 1), which was isolated in 12 % yield as the tetramethylammonium salt. Both **2** and **3** were characterized by ^{11}B NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS). The structure of $[(\text{Me}_4\text{N})_2][\textbf{3}]$ has been confirmed by X-ray crystallographic analysis.^[6]

Further oxidation of **2** at room temperature by benzoquinone in acidic aqueous solution produced the ion **4**, which was isolated in 25 % yield as the corresponding tetramethylammonium salt (Scheme 1). The product was characterized by ESI-MS and ^1H , ^{13}C , and ^{11}B NMR spectroscopy. The structure of $[\text{Me}_4\text{N}][\textbf{4}]$ was determined by single-crystal X-ray diffraction studies.^[7]

An ORTEP drawing of the structure of **4** is presented in Figure 1.^[7] The polyhedral borane anion **4** consists of two

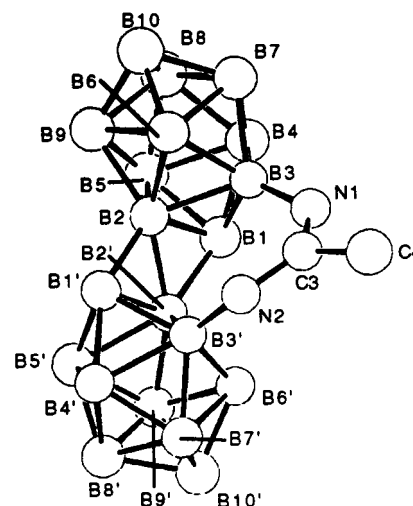
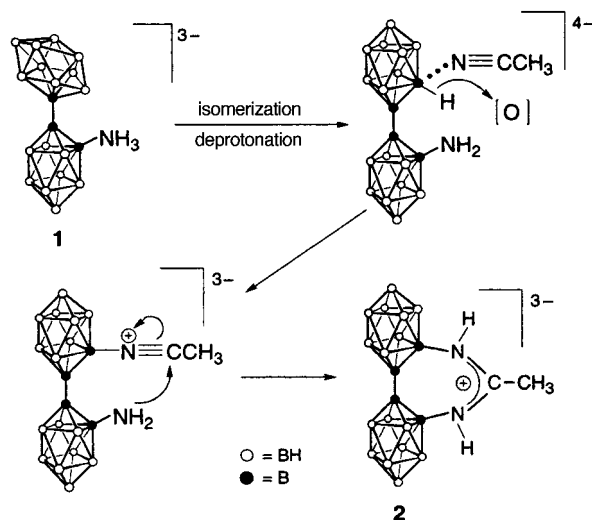


Figure 1. ORTEP representation of the structure of the anion **4**, and the numbering scheme. For clarity, the terminal B–H hydrogen atoms have been omitted. Selected interatomic distances [Å] and angles [°] (estimated standard deviations in parentheses): B3–N1 1.502(9), B3'–N2 1.521(9), N1–H1(N1) 0.95(8), N2–H2(N2) 1.03(8), N1–C3 1.319(8), N2–C3 1.335(8), C3–C4 1.533(10); B3–N1–C3 128.8(6), B3–N1–H1(N1) 124(5), C3–N1–H1(N1) 106(5), N1–C3–N2 125.8(6), N1–C3–C4 117.9(6), C4–C3–N2 116.4(6), C3–N2–H2(N2) 116(4), C3–N2–B3' 126.4(5), B3'–N2–H2(N2) 115(4).

intact decaborate cages joined together by a bridging amidinium group and two three-center, two-electron (3c–2e) bonds. The bonding distances within the two decaborate cages are normal and similar to those found in other structures derived from $[\text{B}_{10}\text{H}_{10}]^{2-}$. Similar 3c–2e bonds were first structurally characterized in the polyhedral borane anion $[\text{B}_{20}\text{H}_{18}]^{2-}$.^[8]

To our knowledge, **4** is the first amidinium derivative of a polyhedral borane to be crystallographically characterized. The delocalization of the positive charge of the amidinium group is clearly indicated by the geometrical parameters of the structure. The three covalent bonds around C3 (C3–N2, C3–N1, and C3–C4) are coplanar, and the sum of the bond angles about C3 is $360.1(6)^\circ$. The C3–C4 bond length is 1.533(10) Å, which is in the normal range for a C–C single bond. However, the C–N bonds are much shorter than expected for a normal C–N single bond, indicating considerable double-bond character. The C3–N1 and C3–N2 bond lengths are 1.319(8) and 1.335(8) Å, respectively. As a result of the sp^2 character of the nitrogen atoms, the three bonds around these centers are also coplanar. The sum of the three bond angles surrounding N1 and N2 are $357.4(6)^\circ$ and $358.8(5)^\circ$, respectively.

A possible mechanism for the formation of **2** is shown in Scheme 2. Initially, the anion undergoes a facile rearrangement to the a^2 isomer,^[3] and the ammonio group is deprotonated.



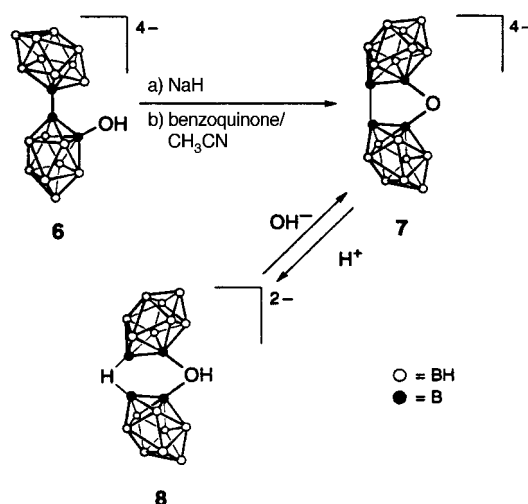
Scheme 2. Proposed mechanism for the formation of **2**. [O] = oxidant (benzoquinone)

nated by NaH. The oxidant (benzoquinone) could subsequently remove a hydride ion from the borane cage to produce a transient, positively charged boron vertex with an empty orbital. This reactive boron vertex could then react with an acetonitrile molecule from the solvent. The nitrogen atom of the amino group would attack the activated nitrile carbon atom of the acetonitrile ligand. The formation of **2** represents a new route for the preparation of disubstituted polyhedral boranes derived from the $[B_{20}H_{18}]^{2-}$ and $[B_{20}H_{18}]^{4-}$ skeletal structures.

The bridging hydrogen atom in **3** is acidic and can be titrated by an aqueous base (Scheme 1). Deprotonation results in the formation of **2**, which can be easily distinguished from **3** in the ^{11}B NMR spectrum. The estimated pK_a of the bridging hydrogen atom of the dianion **3** is 3.5,^[9] which is, as expected, more acidic than for a^2 - $[B_{20}H_{19}]^{3-}$ ($pK_a = 7.3$), a hydrogen-bridged species that does not contain the bridging amidinium group of **3**.

The ion **4** is relatively unstable in aqueous solution. The hydrolysis of $[Me_4N][4]$ in boiling water produces the known $[2-B_{10}H_9NH_3]^-$ ion (**5**),^[10] which was identified by its ^{11}B NMR and ESI mass spectra. The anion **4** could be reduced by sodium metal in liquid ammonia to regenerate **2**, identified by ^{11}B NMR spectroscopy and ESI mass spectrometry (Scheme 1). When a solution of **2** produced in this manner was acidified, $[(Me_4N)_2][3]$ was generated and isolated in 29% yield.

In addition, it was found that ae - $[B_{20}H_{17}OH]^{4-}$ (**6**) could be oxidized by benzoquinone in acetonitrile to produce the oxygen-bridged polyhedral borane anion $[\mu-B_{20}H_{16}O]^{4-}$ (**7**, Scheme 3). Acidification of an aqueous solution of **7** produced the $[\mu-B_{20}H_{17}OH]^{2-}$ anion (**8**), which isolated as the tetramethylammonium salt in approximately 72% yield. The anion **8**



Scheme 3. Oxidation of **6**.

was previously reported to arise from the hydrolysis of $[\mu-B_{20}H_{17}OR]^{2-}$.^[2]

Oxidation of other polyhedral borane anions by benzoquinone in nonaqueous media could also lead to a variety of new species with potential utility in BNCT.

Experimental Section

Reactions were performed under an atmosphere of dry nitrogen using Schlenk techniques. Acetonitrile was dried over CaH_2 and distilled prior to use. Silica gel (230–400 mesh) was used for chromatography. The ^{11}B NMR spectra were obtained with a Bruker AM-500 spectrometer at 160 MHz. ^{11}B NMR chemical shifts were externally referenced to $BF_3 \cdot Et_2O$ in C_6D_6 ; peaks upfield of the reference are designated as negative. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer and referenced to tetramethylsilane as the external reference. ESI mass spectra were recorded by injecting samples dissolved in CH_3CN /water (50/50) into an ionspray source. The mass spectrometer was operated in the negative-ion mode, with signals of the multiply charged ion series from a separate introduction of polypropylene glycol.

2: Dry $[(Me_3NH)_3][1]^{3,4}$ (2.00 g, 4.6 mmol) was added to a stirred suspension of NaH (0.50 g, 20.8 mmol) in CH_3CN (100 mL); hydrogen gas was evolved. The mixture was stirred for 1 h and filtered, and then CH_3CN and Me_3N were removed from the filtrate in vacuo. The residue was dissolved in dry CH_3CN (100 mL). Benzoquinone (1.50 g, 14.1 mmol) was added, and the solution was stirred for 3 h and filtered. The crude product $Na_3[2]$ was obtained by removal of the solvent in vacuo. $^{11}B\{^1H\}$ NMR (H_2O): $\delta = 6.7$ (2 B, B–B); -5.4 (2 B, apical B–H); -13.7 (2 B, B–N); -22.1 , -24.3 , -27.3 , and -29.7 (total of 14 B, equatorial B–H); ESI-MS: m/z : 291.1 $[[H_2CH_3C(NH)_2B_{20}H_{16}]^-]$, 313.1 $[[Na(H)CH_3C(NH)_2B_{20}H_{16}]^-]$.

3: The crude product $Na_3[2]$ obtained above was dissolved in aqueous Me_4NCl (50 mL, 1 N solution). The addition of excess HCl (1 N) solution resulted in a brown precipitate of crude $[(Me_4N)_2][3]$. The precipitate was isolated by filtration and dissolved in $CH_3CN/CHCl_3$ (50 mL, 1/1), and the resulting solution was passed through a silica gel column (3 $\times$ 45 cm, elution with the same solvent mixture). The yellow eluent was collected, and the solvent was removed in vacuo. The residue was dissolved in H_2O (20 mL), and aqueous Me_4NCl (5 mL, 1 N) was added to precipitate $[(Me_4N)_2][3]$. The product was collected by filtration and purified by recrystallization from CH_3CN /isopropanol. It was dried in vacuo to yield $(Me_4N)_2[3]$ (0.25 g, 12%) as a white powder. $^{11}B\{^1H\}$ NMR (H_2O): $\delta = 9.3$ (2 B, apical B–H); -11.8 (2 B, B–B); -14.0 (2 B, B–N); -18.1 , -22.9 , and -25.2 (total of 14 B, equatorial B–H); ESI-MS: m/z : 291.3 $[[H](CH_3C(NH)_2B_{20}H_{17})^-]$, 365.3 $[[Me_4N](CH_3C(NH)_2B_{20}H_{17})^-]$; ^1H NMR (CD_3CN): $\delta = 5.7$ (s, NH); 1.7 (s, CH_3); ^{13}C NMR (CD_3CN): $\delta = 163.5$ (CCH_3), 26.1 (CH_3).

4: Crude $\text{Na}_3[2]$ was prepared from $(\text{Me}_3\text{NH})_3[1]$ (2.00 g, 4.64 mmol) as described above. The crude $\text{Na}_3[2]$ was dissolved in water (50 mL), and the solution was acidified to pH 2 with HCl (2N). The mixture was stirred for 5 min and filtered. Aqueous Me_4NCl (5N) was added until precipitation was complete. The brown precipitate was collected by filtration, the solid dissolved in acetone/chloroform (40 mL, 1/1), and the resulting solution passed through silica gel column (3×45 cm, elution with the same solvent mixture). The yellow solution was collected, and the solvent was removed in vacuo. The residue was dissolved in H_2O (20 mL), and aqueous Me_4NCl (5 mL, 1N) was added to precipitate crude $(\text{Me}_4\text{N})_2[4]$. The product was purified by recrystallization from acetone/ether and dried in vacuo to yield $(\text{Me}_4\text{N})[4]$ (0.42 g, 25 %) as bright yellow crystals. $^{11}\text{B}\{^1\text{H}\}$ NMR (H_2O): $\delta = 31.3$ (2B, apical B–H); 15.6 (2B, B–B); –0.5 (2B, B–N); –4.4, –12.5, –16.7, –19.0 (total of 12B, equatorial B–H); –29.1 (2B, apical B–H); ESI-MS: m/z : 289.3 $[(\text{CH}_3\text{C}(\text{NH})_2\text{B}_{20}\text{H}_{16})^-]$; ^1H NMR (CD_3CN): $\delta = 5.9$ (s, NH); 1.7 (s, CH_3); ^{13}C NMR (CD_3CN): $\delta = 169.1$ (CCH_3), 24.2 (CH_3).

5: Dry $(\text{Me}_4\text{N})[4]$ (1.00 g, 2.75 mmol) was refluxed in water (30 mL) for 2 h. An aqueous solution of $[\text{Ph}_3\text{PMe}]\text{Br}$ was added until precipitation was complete. The white powder was filtered and purified by recrystallization from $\text{CH}_3\text{CN}/\text{ether}$. The resulting solid was dried in vacuo to yield $[\text{Ph}_3\text{PMe}][5]$ (0.37 g, 33 %) as a white powder. The product was identified by its $^{11}\text{B}\{^1\text{H}\}$ NMR^[10] and ESI mass spectra (m/z : 136.4 $[(\text{B}_{10}\text{H}_9\text{NH}_3)^-]$).

7: Dry $[(\text{Me}_3\text{NH})_4][6]^{[11]}$ (2.00 g, 4.08 mmol) was added to a stirred suspension of NaH (0.50 g, 20.8 mmol) in dry CH_3CN ; hydrogen gas was evolved. The mixture was stirred at room temperature for 1 h and filtered, and then the CH_3CN was removed in vacuo. The residue was dissolved in dry CH_3CN (100 mL). Benzoquinone (1.50 g, 14.1 mmol) was added, and the solution was stirred for 3 h. The solution was filtered, and CH_3CN was removed in vacuo. The residue was dissolved in water (50 mL), and the solution was filtered again. The ion **7** in the solution was identified from its $^{11}\text{B}\{^1\text{H}\}$ NMR spectrum.^[2]

8: The solution of ion **7** obtained above was acidified with HCl (1N) to pH 3, stirred for 5 min, and filtered. Aqueous Me_4NCl (1N) was added until precipitation was complete. The resulting white solid was collected by filtration and purified by recrystallization from $\text{CH}_3\text{CN}/\text{EtOH}$. It was dried in vacuo to yield $[(\text{Me}_4\text{N})][8]$ (1.17 g, 72 %). The product was identified by its $^{11}\text{B}\{^1\text{H}\}$ NMR and ESI mass spectra.^[2]

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- [7] Crystal structure analysis of $[(\text{Me}_4\text{N})][4]$. Yellow crystals obtained by recrystallization from acetone/ether: $\text{B}_{20}\text{C}_6\text{H}_{33}\text{N}_3$, $M_r = 363.6$, crystal dimensions $0.15 \times 0.4 \times 0.4$ mm³, Syntex $P1$ diffractometer, $\text{Cu}_{K\alpha}$ radiation, $\lambda = 1.5418$ Å, 298 K; θ – 2θ scan mode to $2\theta_{\text{max}} = 115^\circ$. The unit-cell parameters were determined from 51 accurately centered reflections ($17.4^\circ < 2\theta < 40.3^\circ$): orthorhombic, space group $P2_12_12_1$, $a = 15.404(8)$, $b = 9.544(5)$, $c = 19.647(10)$ Å, $V = 2889$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.01$ g cm^{–3}, $\mu = 3.36$ cm^{–1}. Of the 2131 unique reflections measured ($+h$, $+k$, $\pm l$), 1620 were considered observed ($I > 3\sigma(I)$), and the structure was solved by direct methods; 212 refined parameters, maximum residual electron density 0.1 e Å^{–3}, least-square refinement against $|F^2|$, $R = 0.075$ for the observed reflections, $R_w = 0.092$. 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-101300. Copies of the data can be obtained free of charge on application to: CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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A New Isomer of the $[\text{B}_{20}\text{H}_{18}]^{2-}$ Ion: Synthesis, Structure, and Reactivity of *cis*- $[\text{B}_{20}\text{H}_{18}]^{2-}$ and *cis*- $[\text{B}_{20}\text{H}_{17}\text{NH}_3]^{-*}$

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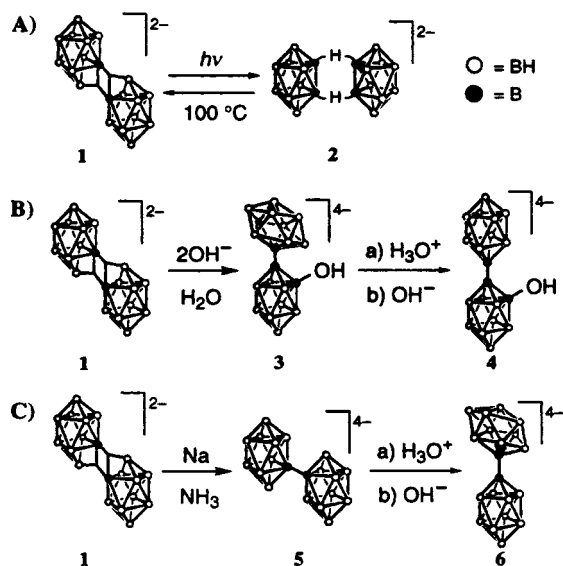
Dedicated to Professor Heinrich Nöth
on the occasion of his 70th birthday

The well-known polyhedral borane anion $[\text{B}_{20}\text{H}_{18}]^{2-}$ (**1**),^[1] hereafter referred to as *trans*- $[\text{B}_{20}\text{H}_{18}]^{2-}$, and its photoisomer *iso*- $[\text{B}_{20}\text{H}_{18}]^{2-}$ (**2**)^[2] were first synthesized in the 1960s, soon after the genesis of polyhedral borane chemistry. The electrophilic polyhedral boranes **1** and **2** (Scheme 1A) have great potential as precursors in reductive substitution reactions which lead to new derivatives for possible employment in boron neutron capture therapy (BNCT).^[3] The two $[\text{B}_{10}\text{H}_9]^-$ cage fragments in **1** are connected by a pair of three-center two-electron (3c–2e) bonds, while the two $[\text{B}_{10}\text{H}_9]^-$ cages in **2** are linked by a pair of B–H–B bridges. These bonds are electron deficient and are therefore susceptible to reactions with nucleophiles. In the facile reaction of **1** with hydroxide ion, the initially formed product is *ae*- $[\text{B}_{20}\text{H}_{17}\text{OH}]^{4-}$ (**3**), which is stable under basic conditions. In neutral aqueous media, **3** slowly isomerizes to *a*²- $[\text{B}_{20}\text{H}_{17}\text{OH}]^{4-}$ (**4**, Scheme 1B).^[4] Although other isomers of $[\text{B}_{20}\text{H}_{18}]^{2-}$ have been proposed,^[5] none have been detected other than the photoisomer **2**.^[2]

The reduction of **1** with sodium in liquid ammonia produced a kinetically controlled product, the *e*²- $[\text{B}_{20}\text{H}_{18}]^{4-}$ ion (**5**), which could be isomerized to the *ae*- $[\text{B}_{20}\text{H}_{18}]^{4-}$ ion (**6**, Scheme 1C).^[1] Oxidation of **5** with iron(III) ions under aqueous, acidic conditions at high temperature regenerates **1**.^[1] However, recent studies of the low-temperature oxidation

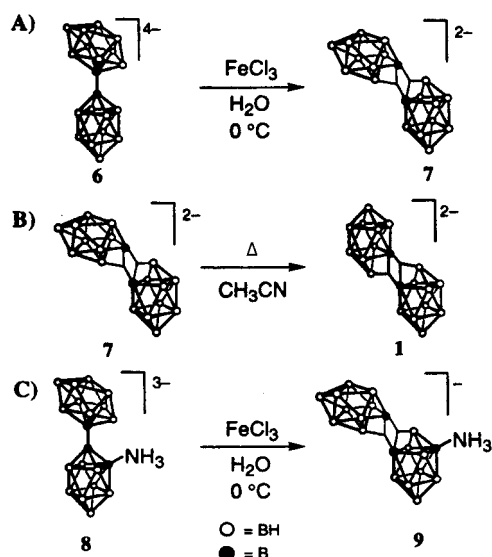
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[**] This work was supported by the U.S. Department of Energy (DE-FG02-95ER61975). The following prefixes are used as isomer designations: *ae* = apical–equatorial isomers of $[\text{B}_{20}\text{H}_{18}]^{4-}$ derivatives ($[(1-(2-\text{B}_{10}\text{H}_9)-\text{B}_{10}\text{H}_9)]^{4-}$), *a*² = apical–apical isomers of $[\text{B}_{20}\text{H}_{18}]^{4-}$ derivatives ($[(1-(1-\text{B}_{10}\text{H}_9)-\text{B}_{10}\text{H}_9)]^{4-}$), *e*² = equatorial–equatorial isomers of $[\text{B}_{20}\text{H}_{18}]^{4-}$ derivatives ($[(2-(2-\text{B}_{10}\text{H}_9)-\text{B}_{10}\text{H}_9)]^{4-}$).



Scheme 1. Reactions of **1**. A) Photoisomerization to **2**. B) Reaction with OH^- ions to **3** and the isomerization of **3** to **4**. C) Reduction to **5** and the isomerization of **5** to **6**.

of **6** did not result in the expected $\text{trans-}[B_{20}H_{18}]^{2-}$ ion (**1**). Instead, the product obtained was the unprecedented polyhedral borane anion **7** (designated $\text{cis-}[B_{20}H_{18}]^{2-}$, Scheme 2 A) which is a new isomer of **1**. The two $[B_{10}H_9]^-$ fragments in **7** are arranged in a cisoid configuration, in contrast to the transoid configuration of **1**. With a similar synthetic strategy we also produced the novel anion **9** (designated here as $\text{cis-}[B_{20}H_{17}NH_3]^-$), which is the ammonio derivative of **7**. We report here the syntheses, structures, and reactions of **7** and **9**.



Scheme 2. A) Synthesis of **7** by oxidation of **6** at low temperature. B) Thermal isomerization of **7** to **1**. C) Oxidation of **8** to **9**.

The addition of an aqueous FeCl_3 solution to an aqueous solution of $\text{K}_4[\text{6}]$ at $0\text{ }^{\circ}\text{C}$ resulted in the rapid formation of **7** in high yield (Scheme 2 A). The product was immediately precipitated as $[\text{Me}_4\text{N}]_2[\text{7}]$ to prevent further reaction or

rearrangement. It was characterized by ^{11}B NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS). The structure of $[\text{Me}_4\text{N}]_2[\text{7}]$ was determined by single-crystal X-ray diffraction.^[6]

An ORTEP drawing of the structure of **7** is shown in Figure 1.^[6] The polyhedral borane anion consists of two intact

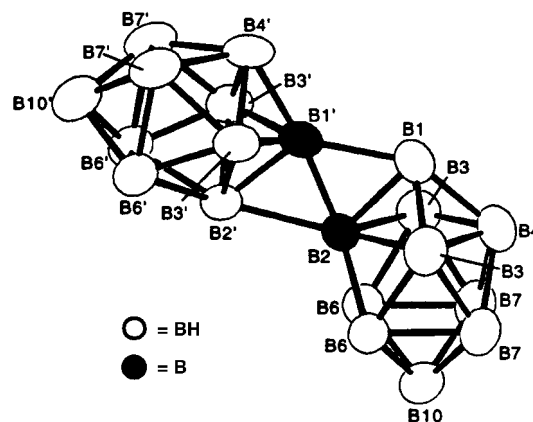


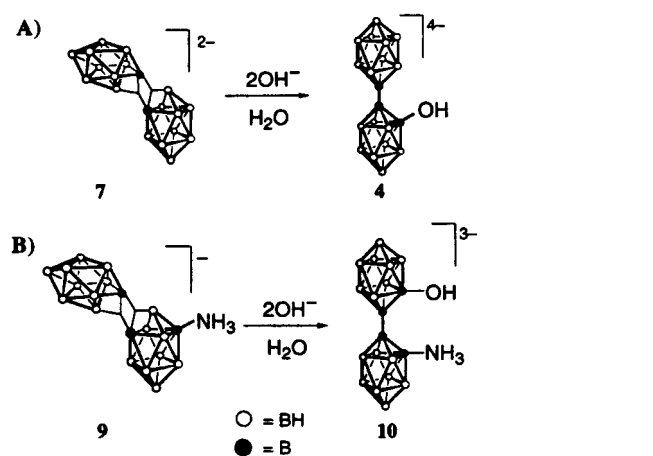
Figure 1. ORTEP representation of the structure of anion **7**, and the atom numbering scheme. For clarity the terminal B–H hydrogen atoms have been omitted. Selected bond lengths [$\text{\AA}$] and angles [$^{\circ}$] (estimated standard deviations in parentheses): $\text{B1}'\text{--B2}'$ 1.670(7), $\text{B1}'\text{--B1}$ 1.853(8), B1--B2 1.683(7), $\text{B2--B2}'$ 1.974(7), $\text{B1}'\text{--B2}$ 1.692(7); $\text{B10}'\text{--B1}'\text{--B1}$ 178.9(2), $\text{B2}'\text{--B1}'\text{--B1}$ 128.4(3), $\text{B1}'\text{--B2}'\text{--B2}$ 54.6(2), $\text{B1}'\text{--B1}\text{--B2}$ 56.9(2), $\text{B1--B2--B2}'$ 120.1(2).

$[B_{10}H_9]^-$ cages linked by two $3c-2e$ bonds. The bond lengths within the two decaborate cages are normal and similar to those found in other structures derived from $[B_{10}H_{10}]^{2-}$. The three apical boron atoms $\text{B10}'$, $\text{B1}'$, and B1 exhibit essentially linear geometry, with a $\text{B10}'\text{--B1}'\text{--B1}$ angle of 178.9° . Similar $3c-2e$ bonds were first structurally characterized in **1**,^[7] whose structure differs markedly from that of **7**. The two $[B_{10}H_9]^-$ cages in **1** are equivalent and arranged in a transoid configuration, while those in **7** are nonequivalent and cisoid.

Solutions of **7** in acetonitrile are unstable even at room temperature, and slowly rearrange to the more stable ion **1**. When a solution of $[\text{Me}_4\text{N}]_2[\text{7}]$ in acetonitrile is heated for 1 h, almost complete conversion of **7** into **1** is observed in the ^{11}B NMR spectra (Scheme 2 B). When **1** was subjected to the same conditions, **7** was not observed, demonstrating that the rearrangement is irreversible.

The UV spectrum of anion **7** in acetonitrile displays two electronic transitions in the near-UV region ($\lambda_{\text{max}} = 277\text{ nm}$, $\epsilon = 1.44 \times 10^4$; $\lambda_{\text{max}} = 229\text{ nm}$, $\epsilon = 3.29 \times 10^4$), which are similar to those the UV spectrum of **1** in the same solvent ($\lambda_{\text{max}} = 292\text{ nm}$, $\epsilon = 1.08 \times 10^4$; $\lambda_{\text{max}} = 232\text{ nm}$, $\epsilon = 2.38 \times 10^4$).^[5] The similarity of the UV spectra of **7** and **1** presumably results from the similarity of the intercage bonding of these two species.

As in the case of **1**, the two $3c-2e$ bonds of **7** are electron deficient and susceptible to nucleophilic attack. The reaction of **7** with an aqueous solution of sodium hydroxide at room temperature led to the direct formation of the stable ion **4** in 77% yield (Scheme 3 A). The anion **4** was previously reported to arise from the isomerization of **3**.^[4] The reductive substitution of **7** represents a new method for the direct synthesis of stable $a^2\text{-}[B_{20}H_{18}]^{4-}$ derivatives.^[2]



Scheme 3. A) Reaction of **7** with OH^- ions to **4**. B) Reaction of **9** with OH^- ions to **10**.

As in the synthesis of **7**, the oxidation of **8**^[3] (the ammonio derivative of **6**) with iron(III) ions in aqueous solution at 0 °C afforded **9** (designated as *cis*- $[B_{20}H_{17}NH_3]^-$, Scheme 2C), which was isolated in 61 % yield as the trimethylammonium salt. $[Me_3NH][9]$ was characterized by ^{11}B NMR spectroscopy and ESI mass spectrometry.

The structure of the anion **9** was determined by single-crystal X-ray structure analysis.^[8] An ORTEP drawing is shown in Figure 2. The structure of **9** exhibits the same borane cage configuration as in **7**. The bond lengths within the two $[B_{10}H_9]^-$ cages are normal and similar to those in **7**.

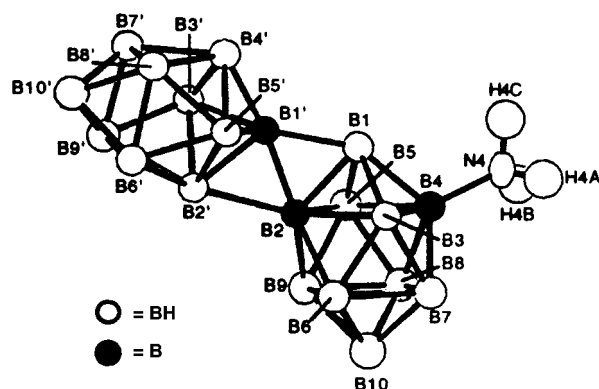


Figure 2. ORTEP representation of the structure of anion **9**, and the atom numbering scheme. For clarity the terminal B-H hydrogen atoms have been omitted. Selected bond lengths [Å] and angles [°] (estimated standard deviations in parentheses): B1-B2 1.716(8), B1-B1' 1.814(8), B1'-B2' 1.680(8), B2'-B2 1.952(8), B1'-B2 1.688(7), B4-N4 1.537(7); B10'-B1'-B1 176.8(3), B2-B1-B1' 57.1(3), B1-B2-B2' 118.5(4), B1-B1'-B2' 129.0(4), B2-B2'-B1' 54.8(3).

Owing to the reduced negative charge of anion **9** compared to ion **7**, **9** is much more reactive with nucleophiles than **1** or **7**, and it will react with weak nucleophiles (such as water) even at room temperature. While solutions of **9** in acetonitrile are relatively stable at room temperature, rearrangement to another as yet unidentified isomer is observed upon heating.

When $[Me_3NH][9]$ was treated with an aqueous solution of sodium hydroxide at room temperature (Scheme 3B), the disubstituted anion a^2 - $[B_{20}H_{16}(OH)NH_3]^{3-}$ (**10**, Scheme 3B) was isolated in 89 % yield. The structure of the ion **10** was established by its ^{11}B NMR and ESI mass spectra although the mechanism leading to **10** is not yet entirely clear. However, the ^{11}B and 2D-COSY NMR spectra of **10** clearly establish that it is a disubstituted $[B_{20}H_{18}]^{4-}$ derivative with a different substituent on each $[B_{10}H_9]^-$ cage. This reaction provides a convenient route to disubstituted derivatives of a^2 - $[B_{20}H_{18}]^{4-}$ and may easily afford other disubstituted derivatives suitable for BNCT.

The synthesis of the anion **7** has not only revealed the existence of a new isomer of $[B_{20}H_{18}]^{2-}$, but has also provided a simple and direct route to stable a^2 derivatives of the polyhedral borane anion $[B_{20}H_{18}]^{4-}$. The new anion *cis*- $[B_{20}H_{17}NH_3]^-$ (**9**) may also have considerable potential in the synthesis of disubstituted derivatives of these polyhedral borane anions.

Experimental Section

7: An aqueous solution of iron(III) chloride (0.5 N, 30 mL, 15 mmol) was added to a solution of $K_4[6]$ ^[4] (2.00 g, 5.1 mmol) in water (100 mL) at 0 °C. An aqueous solution of Me_4NCl was immediately added to precipitate $[Me_4N]_2[7]$. The precipitate was isolated by filtration. The solid was dissolved in CH_3CN (50 mL), and the resulting solution was passed through a small plug of silica gel. The bright yellow solution was collected, and the solvent was removed under reduced pressure. The residue was stirred with water (20 mL), aqueous Me_4NCl solution (5 mL, 1 N) was added, and the mixture was cooled to 0 °C to produce a yellow precipitate. The precipitate was isolated by filtration and dried under vacuum to yield $[Me_4N]_2[7]$ (1.33 g, 3.5 mmol, 69 %). $^{11}B\{^1H\}$ NMR (160 MHz, H_2O): δ = 26.9 (2B, apical B-H), -11.7 and -19.9 (total of 18B); ESI-MS: (m/z): 117.0 $[(B_{20}H_{18})^{2-}]$, 235.0 $[(B_{20}H_{18}+H)^-]$.

9: An aqueous solution of iron(III) chloride (0.5 N, 30 mL, 15 mmol) was added to a solution of $[Me_3NH]_3[8]$ ^[9] (2.00 g, 4.6 mmol) in water (100 mL) at 0 °C to produce a precipitate immediately. The reaction mixture was stirred for 1 h. The precipitate was collected by filtration, the solid was dissolved in CH_3CN (50 mL), and the resulting solution was passed through a small plug of silica gel. The bright yellow solution was collected, and the solvent was removed under reduced pressure. The residue was dissolved in water (20 mL), aqueous $[Me_3NH]Cl$ (5 mL, 1 N) was added, and the mixture was cooled to 0 °C to produce a bright yellow solid. The solid was separated by filtration and dried under vacuum to yield $[Me_3NH][9]$ (0.87 g, 2.8 mmol, 61 %). $^{11}B\{^1H\}$ NMR (H_2O): δ = 26.8 (2B, apical B-H), -1.5 (1B, B-N), -13.2, -17.2, -20.8, and -22.2 (total of 17B); ESI-MS: (m/z): 250.7 $[(B_{20}H_{17}NH_3)^-]$.

4: Dry $[Me_4N]_2[7]$ (0.50 g, 1.3 mmol) was added to a solution of sodium hydroxide (0.50 g, 12.5 mmol) in water (10 mL) at room temperature. The solution was stirred for 4 h. A saturated solution of Me_4NCl in EtOH was added until the solution became turbid. Upon cooling of the solution to 0 °C, a fine white powder separated. The solid was collected by filtration, washed with ethanol, and dried in vacuo to yield $[Me_4N]_3[4]$ (0.55 g, 1.0 mmol, 77 %). The product was identified by $^{11}B\{^1H\}$ NMR spectroscopy.^[4] ESI-MS: (m/z): 253.0 $[(B_{20}H_{17}OH+3H)^-]$, 326.1 $[(Me_4N)(B_{20}H_{17}OH+2H)^-]$.

10: Dry $[Me_3NH][9]$ (1.00 g, 3.3 mmol) was added to a solution of sodium hydroxide (1.00 g, 25.0 mmol) in water (10 mL) at room temperature. The solution was stirred for 4 h. A saturated solution of Me_4NCl in EtOH was added until the solution became turbid. Upon cooling of the solution to 0 °C, a fine white powder separated. The solid was collected by filtration, washed with ethanol, and dried in vacuo to yield $[Me_4N]_3[10]$ (1.40 g, 2.9 mmol, 89 %). The product was identified by ^{11}B NMR spectroscopy. $^{11}B\{^1H\}$ NMR (H_2O): δ = 8.3 (2B, B-B), -2.5 (1B, B-O), -6.2 (1B, apical B-H), -7.4 (1B, apical B-H), -14.1 (1B, B-N), -23.5, -24.9,

–26.3, –29.3, –31.4 and –34.8 (total of 14B); ESI-MS: (m/z): 268.3 [(B₂₀H₁₆(OH)(NH₃))+2H]⁺].

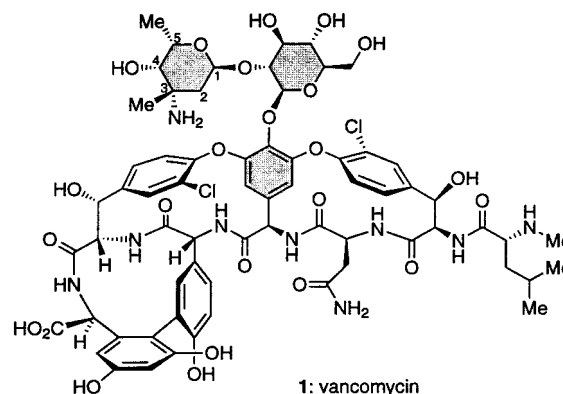
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Expeditious Routes to Evernitrore and Vancosamine Derivatives and Synthesis of a Model Vancomycin Aryl Glycoside**

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The antibiotics vancomycin^[1] (**1**) and everninomicin 13,384-1^[2] (for the structure, see following contribution)^[3] include in their structures C3-branched 2,6-dideoxy-L-sugars containing



an amino^[4] or a nitro group,^[5] respectively. Our interest in the total synthesis of vancomycin^[6] and everninomicin 13,384-1^[7] dictated new synthetic routes to these unique sugars and methods for their attachment onto their respective target molecules. Here we report the successful attainment of both goals, culminating in the construction of key intermediates **11** and **16** (see Scheme 1) and the assembly of vancomycin disaccharide **22** (see Scheme 2). In the following communication^[3] we describe the synthesis of an advanced everninomicin 13,384-1 segment incorporating the nitrosugar.

A key objective of our strategy toward the nitrogen-containing sugar units of these antibiotics was the construction of an intermediate (**7**), from which both compounds **11** and **16** could be generated (Scheme 1). Towards this goal, we envisioned a stereocontrolled *anti* addition^[8] of an acyl anion equivalent to an aldehyde derived from L-lactic acid as a means to install the C4 stereocenter (the numbering is based on the final carbohydrate), where the functionality at C3 was projected to arise by nucleophilic chain extension of an

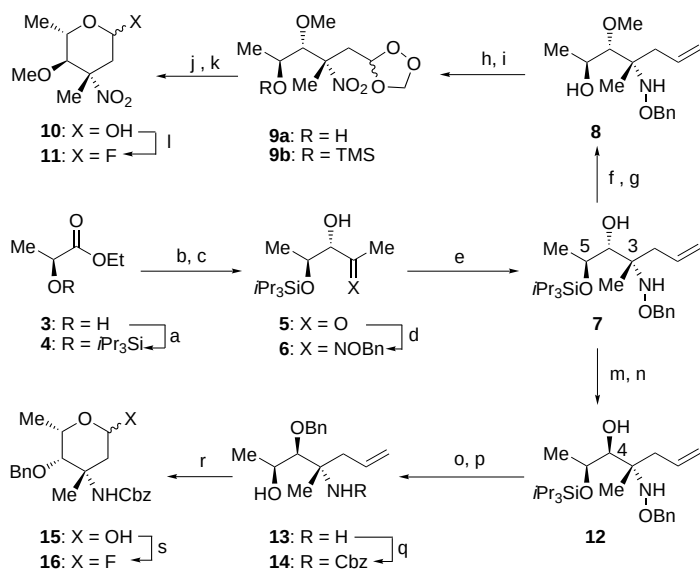
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- [6] a) Crystal structure analysis of [Me₄N]₂[**7**]: colorless crystals from ethanol/acetonitrile: C₈H₄₂B₂₀N₂, *M_r* = 382.7; crystal dimensions 0.18 × 0.38 × 0.5 mm³; Syntex P1 diffractometer, CuK α radiation, λ = 1.5418 Å, 298 K; θ – 2θ scan mode to $2\theta_{\text{max}}$ = 120°. The unit-cell parameters were determined from 25 accurately centered reflections ($18.9^\circ < 2\theta < 26.6^\circ$): orthorhombic, space group *Pnam* (no. 62), *a* = 10.279(2), *b* = 34.000(5), *c* = 8.310(2) Å, *V* = 2904 Å³, *Z* = 4, ρ_{calcd} = 0.97 g cm^{–3}, μ = 2.94 cm^{–1}. Of the 2330 unique reflections measured ($+h$, $+k$, $+l$), 1680 were considered observed ($I > 2\sigma(I)$), and the structure was solved by direct methods; 239 refined parameters, maximum residual electron density 0.13 e Å^{–3}, least-square refinement against $|F^2|$; *R* = 0.078 for the observed reflections, *R_w* = 0.113. 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-101302. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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- [8] Crystal structure analysis of [Me₃NH][**9**]: colorless crystals from an aqueous solution, C₃H₃₀B₂₀N₂, *M_r* = 310.5, crystal dimensions 0.48 × 0.05 × 0.55 mm³, Syntex P1 diffractometer, CuK α radiation, λ = 1.5418 Å, 298 K; θ – 2θ scan mode to $2\theta_{\text{max}}$ = 115°. The unit-cell parameters were determined from 41 accurately centered reflections ($19.7^\circ < 2\theta < 40.1^\circ$): orthorhombic, space group *P2₁2₁2₁*, *a* = 10.334(7), *b* = 10.873(8), *c* = 17.523(12) Å, *V* = 1969 Å³, *Z* = 4, ρ_{calcd} = 1.05 g cm^{–3}, μ = 2.79 cm^{–1}. Of the 1519 unique reflections measured ($+h$, $+k$, $+l$), 1318 were considered observed ($I > 2\sigma(I)$), and the structure was solved by direct methods; 156 refined parameters, maximum residual electron density 0.1 e Å^{–3}, least-square refinement against $|F^2|$; *R* = 0.064 for the observed reflections, *R_w* = 0.082.^[6b]
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Scheme 1. Synthesis of carbohydrate donors **11** and **16**. a) $i\text{Pr}_3\text{SiCl}$ (1.1 equiv), imidazole (2.0 equiv), DMF, 10 h, 99%; b) DIBAL (1.3 equiv), CH_2Cl_2 , -78°C , 45 min; c) EVE-Li (1.3 equiv), THF, -100°C ; then 1N HCl (aq), THF/ H_2O (80/20), 63% over three steps, $de=85\%$; d) $\text{BnONH}_2\cdot\text{HCl}$ (1.1 equiv), py, $0\rightarrow 25^\circ\text{C}$, 97% ($E:Z\approx 4:1$); e) $\text{C}_3\text{H}_5\text{MgBr}$ (2.5 equiv), Et_2O , -35°C , 95% based on 50% conversion; f) NaH (1.1 equiv), MeI (1.3 equiv), DMF, $0\rightarrow 25^\circ\text{C}$, 96%; g) $n\text{Bu}_4\text{NF}$ (1.1 equiv), THF, 92%; h) $(\text{Me}_3\text{Si})_3\text{NH}$ (5.0 equiv), Me_3SiCl (0.05 equiv), CH_3CN ; i) O_3 , $\text{CCl}_4/i\text{C}_8\text{H}_{18}$ (2/1), $-78\rightarrow -25^\circ\text{C}$; j) TFA (2.0 equiv), 5 min; k) Ph_3P (2.0 equiv), 30 min, 82% over four steps; or i) O_3 , CH_2Cl_2 , -78°C ; k) Ph_3P (2.0 equiv), 30 min (**8** $\rightarrow$ **10**), 62% over two steps; l) DAST (1.4 equiv), CH_2Cl_2 , 0°C , 30 min, 83%; m) $(\text{COCl})_2$ (2.0 equiv), DMSO (2.5 equiv), Et_3N (4.0 equiv), $-78\rightarrow 0^\circ\text{C}$, 91%; n) NaBH_4 (3.0 equiv), $\text{Et}_2\text{O}/\text{MeOH}$ (5/1), 0°C , 2 h, 90%, $de=92\%$; o) NaH (1.1 equiv), BnBr (1.2 equiv), $n\text{Bu}_4\text{NI}$ (0.2 equiv), DMF, $0\rightarrow 25^\circ\text{C}$, 2 h, 96%; p) LAH (1.6 equiv), Et_2O , 25°C , 24 h; q) CbzCl (3.0 equiv), Na_2CO_3 (10.0 equiv), $\text{H}_2\text{O}/\text{THF}$ (5/1), $0\rightarrow 25^\circ\text{C}$, 30 min, 78% over two steps; r) 1. O_3 , CH_2Cl_2 , -78°C , 1 h; 2. Ph_3P (2.0 equiv), $-78\rightarrow -25^\circ\text{C}$, 3 h, 95%; s) DAST (1.4 equiv), CH_2Cl_2 , 1 h, 85%. Bn = benzyl, Cbz = benzyloxycarbonyl, DAST = $\text{Et}_3\text{N}\cdot\text{SF}_5$, DIBAL = diisobutylaluminum hydride, EVE-Li = $\text{CH}_2\text{C}(\text{OEt})\text{Li}$, LAH = lithium aluminum hydride, py = pyridine, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

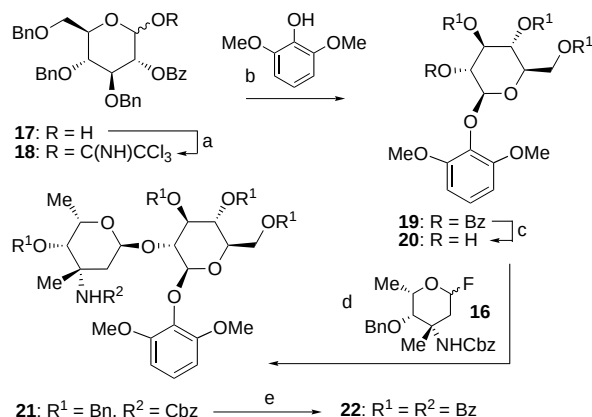
oxime.^[9] Thus, ethyl L-lactate (**3**, Scheme 1) was protected with the bulky $i\text{Pr}_3\text{Si}$ group to give **4** in high yield. Sequential reduction with DIBAL and addition of EVE-Li^[10] at -100°C followed by acidic workup afforded hydroxy ketone **5** as a mixture of diastereoisomers (85% de , 63% overall yield from **3**). After separation from its *syn* epimer by chromatography on silica gel, the *anti* isomer **5** was condensed with *O*-benzylhydroxylamine to afford the readily separable oxime ethers **6** (97%, $E:Z=4:1$).^[11] Gratifyingly, chain extension of the *E* isomer of **6** with allylmagnesium bromide at -35°C afforded hydroxylamine **7** as the sole detectable diastereoisomer (95% based on 50% conversion).^[12] Further elaboration of **7** to everninomicin carbohydrate **10** involved methylation of the free hydroxyl group (96%) followed by desilylation to afford **8** (92%). It was anticipated that exposure of **8** to ozone would generate simultaneously the required aldehyde and nitro groups.^[13] However, ozonolysis of **8** (CH_2Cl_2 , -78°C) followed by workup with Me_2S and chromatography on silica gel afforded, instead of lactol **10**, the remarkably stable ozonide **9a** as a mixture of diastereoisom-

ers (ca. 1:1). In contrast, workup with Ph_3P led smoothly to nitrosugar **10** (63% overall yield from **8**). The yield of the latter transformation was significantly improved by carrying out the ozonolysis in a 2:1 mixture of isooctane and CCl_4 . Although the apolar nature of this solvent system dictated two additional steps (formation of the TMS ether prior to ozonolysis and removal of TMS prior to treatment with Ph_3P), the targeted nitrosugar **10** was obtained in 82% overall yield from **8**. Finally, exposure to DAST led to rapid conversion of **10** into a mixture of glycosyl fluorides **11** (83%).

Intermediate **7** also served as a convenient precursor of the vancomycin derivative **16**. Alcohol **7** carries the correct configurations at C3 and C5 and is readily converted into its C4 epimer **12** by Swern oxidation followed by chelation-controlled NaBH_4 reduction (90% yield, 92% de ; Scheme 1). After purification of **12**, benzylation (96%) and exposure to LAH resulted in the formation of amino alcohol **13** by removal of both the benzyloxy and silyl groups.^[14] The latter compound was converted into its Cbz-protected derivative **14** under standard conditions (78% over two steps). Finally, cleavage of the terminal olefin by ozonolysis followed by treatment with Ph_3P afforded a approximately 1:1 mixture of lactols **15** in 95% yield. As in the case of **11**, conversion of **15** into the glycosyl donor **16** was smoothly effected with DAST (85%).

With multigram quantities of L-vancosamine and L-evernitro donors **16** and **11** at hand, strategies for attachment to their respective natural products were investigated. The stereoselective construction of a vancomycin disaccharide model system is shown in Scheme 2, whereas the introduction of evernitro into its everninomicin segment is reported in the following communication.^[3]

From the reported techniques for forming β -linked aryl glycosides,^[15-17] the trichloroacetimidate method^[18] was found to be the most suitable for our purpose. Thus, conversion of glucose derivative **17** into its trichloroacetimidate **18** followed by coupling with 2,6-dimethoxyphenol in the presence of



Scheme 2. Synthesis of the vancomycin model disaccharide. a) Cl_3CCN (5.0 equiv), DBU (cat.), CH_2Cl_2 , 0°C , 15 min, 100%; b) $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.6 equiv), CH_2Cl_2 , 4-Å molecular sieves, $-30\rightarrow -25^\circ\text{C}$, 24 h, 95%, $\beta:\alpha\approx 13:1$; c) 1% aq NaOH, MeOH, 25°C , 3 h, 90%; d) **16** (1.6 equiv), $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.3 equiv), Me_3SiOTf (0.3 equiv), CH_2Cl_2 , 4-Å molecular sieves, $-30\rightarrow -25^\circ\text{C}$, 72 h, 89% based on 90% conversion, $\alpha:\beta\approx 10:1$; e) 1. H_2 , Pd/C, EtOAc; 2. BzCl (7.0 equiv), py, 85% over two steps. Bz = benzoyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Tf = trifluoromethylsulfonyl.

$\text{BF}_3 \cdot \text{Et}_2\text{O}$ afforded the desired aryl glycoside **19** in excellent yield (95%) and with high stereoselectivity ($\beta:\alpha \approx 13:1$). Debenzoylation gave direct access to glycosyl acceptor **20**, setting the stage for coupling with glycosyl fluoride **16**. A combination of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and Me_3SiOTf was found to be highly effective for activation of **16**, furnishing, upon coupling with **20**, the desired α -glycoside **21** in 89% yield (based on 90% conversion) and with a stereoselectivity of about 10:1 (Table 1). Finally, hydrogenation and benzoylation of **21** gave the protected disaccharide **22** (85% over two steps). The configuration of the newly formed glycosidic bond was confirmed by NMR spectroscopy on **21** ($J_{1,2\text{ax}} = 4.5 \text{ Hz}$)^[16, 19] and **22**. The latter compound was also synthesized through glucal chemistry by Danishefsky and co-workers.^[16]

In summary, we have synthesized vancosamine derivative **15** (11 steps from **3**, ca. 25% overall yield) and evernitrose (**10**, 9 steps from **3**, ca. 30% overall yield) from a common chiral

intermediate derived from L-lactic acid. The described chemistry also provides a plausible scenario for the incorporation of the carbohydrate domain of vancomycin into its parent compound.^[20]

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Table 1. Selected physical properties of compounds **10**, **15**, and **21**.

10: $R_f = 0.25$ (silica gel, 70% Et_2O in hexanes); $[\alpha]_D^{25} = -31.5$ ($c = 1.0$ in CHCl_3); IR (thin film): $\tilde{\nu}_{\text{max}} = 3381, 2987, 2942, 2842, 1548, 1455, 1393, 1354, 1285, 1183, 1155, 1102, 1046, 988, 942, 913, 876, 857 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 5.32$ (bd, $J = 4.0 \text{ Hz}$, 1H, $\alpha\text{-H1}$), 4.88 (dd, $J = 8.0, 4.0 \text{ Hz}$, 1H, $\beta\text{-H1}$), 3.91 (dq, $J = 10.0, 6.0 \text{ Hz}$, 1H, $\alpha\text{-H5}$), 3.84 (bs, 1H, OH), 3.76 (d, $J = 10.0 \text{ Hz}$, 1H, $\alpha\text{-H4}$), 3.74 (d, $J = 10.0 \text{ Hz}$, 1H, $\beta\text{-H4}$), 3.46 (dq, $J = 10.0, 6.0 \text{ Hz}$, 1H, $\beta\text{-H5}$), 3.41 (s, 3H, $\alpha\text{-OCH}_3$), 3.39 (s, 3H, $\beta\text{-OCH}_3$), 3.15 (bs, 1H, OH), 2.41 (dd, $J = 13.5, 4.5 \text{ Hz}$, 1H, $\alpha\text{-H2}_{\text{eq}}$), 2.23 (m, 2H, $\beta\text{-H2}_{\text{eq,ax}}$), 2.17 (dd, $J = 13.5, 1.5 \text{ Hz}$, 1H, $\alpha\text{-H2}_{\text{ax}}$), 1.81 (s, 3H, $\alpha\text{-H3}$), 1.66 (s, 3H, $\beta\text{-H3}$), 1.36 (d, $J = 6.5 \text{ Hz}$, 3H, $\alpha\text{-H6}$), 1.31 (d, $J = 6.0 \text{ Hz}$, 3H, $\beta\text{-H3}$); ^{13}C NMR (125 MHz, CDCl_3) $\delta = 92.4, 90.6, 90.1, 89.6, 84.5, 84.2, 71.2, 66.1, 66.0, 66.0, 60.8, 60.8, 44.2, 40.8, 18.5, 18.4, 18.3, 16.6$; HR-MS (FAB) calcd for $\text{C}_8\text{H}_{15}\text{O}_5\text{NNa}$ [$M + \text{Na}^+$]: 228.0848, found: 228.0848.

15: $R_f = 0.12$ (silica gel, 60% Et_2O in hexanes); $[\alpha]_D^{25} = -56.8$ ($c = 0.5$ in CHCl_3); IR (thin film): $\tilde{\nu}_{\text{max}} = 3410, 3064, 3032, 2930, 1713, 1517, 1453, 1380, 1350, 1280, 1240, 1208, 1160, 1068, 962, 885, 821, 753, 699, 585, 552, 486 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3 , mixture of anomers, ca. 1.8:1): $\delta = 7.32\text{--}7.27$ (m, 10H, ArH), 5.34 (bs, 0.4H, $\alpha\text{-H1}$), 5.03 and 4.99 (AB, $J = 12.5 \text{ Hz}$, 2H, CH_2Ar), 4.92 (bs, 1H, NH), 4.87 (m, 2.5H, $\beta\text{-H1}$, NH, CH_2Ar), 4.64 and 4.54 (AB, $J = 11.0 \text{ Hz}$, 0.8H, CH_2Ar), 4.62 and 4.50 (AB, $J = 11.0 \text{ Hz}$, 1.2H, CH_2Ar), 4.29 (bq, $J = 6.5 \text{ Hz}$, 0.4H, $\alpha\text{-H5}$), 3.82 (bq, $J = 6.5 \text{ Hz}$, 0.6H, $\beta\text{-H5}$), 3.56 (bs, 0.4H, $\alpha\text{-H4}$), 3.52 (bs, 0.6H, $\beta\text{-H4}$), 3.15 (d, $J = 8.0 \text{ Hz}$, 0.6H, $\beta\text{-OH}$), 2.61 (dd, $J = 8.0, 1.5 \text{ Hz}$, 0.4H, $\beta\text{-H2}_{\text{ax}}$), 1.96 (dd, $J = 13.0, 4.5 \text{ Hz}$, 0.6H, $\alpha\text{-H2}_{\text{eq}}$), 1.81 (bd, $J = 11.0 \text{ Hz}$, 0.4H, $\beta\text{-H2}_{\text{ax}}$), 1.78 (bd, $J = 13.5 \text{ Hz}$, 0.6H, $\alpha\text{-H2}_{\text{ax}}$), 1.73 (s, 1.2H, $\alpha\text{-H3}$), 1.55 (s, 1.8H, $\beta\text{-H3}$), 1.30 (d, $J = 6.5 \text{ Hz}$, 0.8H, $\alpha\text{-H6}$), 1.30 (d, $J = 6.5 \text{ Hz}$, 1.2H, $\beta\text{-H6}$); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 154.8, 154.8, 137.9, 136.6, 136.4, 128.5, 128.4, 128.2, 128.2, 128.1, 128.1, 127.8, 92.7, 91.4, 80.1, 78.8, 75.8, 75.6, 70.1, 66.3, 66.2, 64.8, 55.3, 53.6, 40.5, 36.3, 29.7, 24.0, 22.0, 17.7, 17.5$; HR-MS (FAB) calcd for $\text{C}_{22}\text{H}_{27}\text{O}_5\text{NNa}$ [$M + \text{Na}^+$]: 408.1787, found: 408.1780.

21: $R_f = 0.18$ (silica gel, 50% Et_2O in hexanes); $[\alpha]_D^{25} = -43.8$ ($c = 0.24$ in CHCl_3); IR (thin film): $\tilde{\nu}_{\text{max}} = 3409, 3031, 2931, 1723, 1599, 1497, 1478, 1455, 1363, 1297, 1256, 1215, 1111, 1062, 735, 699 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.31\text{--}7.18$ (m, 25H, ArH), 7.02 (t, $J = 8.5 \text{ Hz}$, 2H, phenol-H), 6.57 (d, $J = 8.5 \text{ Hz}$, 2H, phenol-H), 5.32 (bd, $J = 4.5 \text{ Hz}$, 1H, $\text{H1}'$), 5.08 (d, $J = 7.5 \text{ Hz}$, 1H, H1), 4.98 (AB, $J = 11.0 \text{ Hz}$, 2H, CH_2Ar), 4.90 (s, 1H, NH), 4.83 (AB, $J = 11.0 \text{ Hz}$, 2H, CH_2Ar), 4.68 (AB, $J = 11.0 \text{ Hz}$, 2H, CH_2Ar), 4.55 (AB, $J = 11.5 \text{ Hz}$, 2H, CH_2Ar), 4.50 (m, 1H, $\text{H5}'$), 4.45 (AB, $J = 12.0 \text{ Hz}$, 2H, CH_2Ar), 3.94 (t, $J = 8.0 \text{ Hz}$, 1H, H3), 3.77 (s, 6H, OCH_3), 3.72–3.65 (m, 3H, H2 , H4 , H6a), 3.61 (dd, $J = 12.0, 5.5 \text{ Hz}$, 1H, H6b), 3.41 (s, 1H, $\text{H4}'$), 3.37 (m, 1H, H5), 1.84 (s, 3H, $\text{H3}'$), 1.83 (d, $J = 13.0 \text{ Hz}$, 1H, $\text{H2}'_{\text{eq}}$), 1.78 (dd, $J = 13.0, 4.5 \text{ Hz}$, 1H, $\text{H2}'_{\text{ax}}$), 1.09 (d, $J = 6.5 \text{ Hz}$, 3H, $\text{H6}'$); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 154.9, 153.9, 138.6, 138.4, 138.1, 136.6, 134.0, 130.0, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 124.0, 105.5, 100.7, 97.7, 86.0, 80.9, 78.2, 75.8, 75.8, 75.7, 75.3, 74.7, 73.6, 68.8, 66.0, 64.3, 56.1, 53.7, 36.6, 29.7, 23.4, 17.4$; HRMS (FAB) calcd for $\text{C}_{57}\text{H}_{63}\text{O}_{12}\text{NCs}$ [$M + \text{Cs}^+$]: 1086.3405, found: 1086.3450.

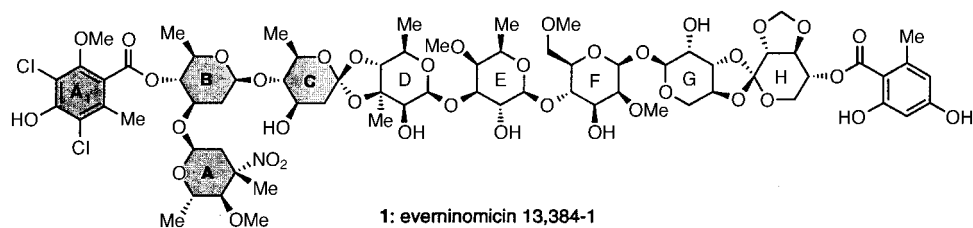
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Stereocontrolled Synthesis of the Everninomicin A₁B(A)C Ring Framework**

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Helen J. Mitchell, and Floris L. van Delft

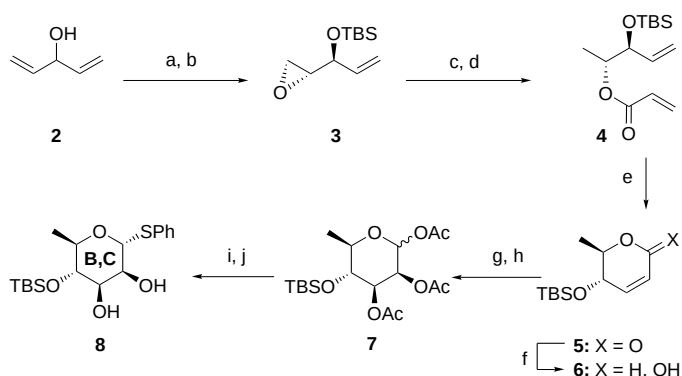
Everninomicin^[1] (13,384-1, **1**), a highly effective antibiotic against drug-resistant bacterial strains, is a member of the



orthosomycin family of compounds. Its novel and challenging structure encompasses, among other structural elements, the nitrosugar **A** and the fully substituted aromatic ring **A₁**, and has stimulated a number of synthetic studies.^[2] Notable

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Scheme 1. Synthesis of **8**. a) L-(+)-diisopropyl tartrate (0.09 equiv), Ti(OiPr)₄ (0.072 equiv), *t*BuOOH (2.0 equiv), CH₂Cl₂, –15 °C, 9 d; b) TBSCl (1.2 equiv), imidazole (1.5 equiv), CH₂Cl₂, 0 → 25 °C, 85 % over two steps; c) LiEt₃BH (1.0 M in THF, 1.1 equiv), CH₂Cl₂, –40 °C, 1 h, 91 %; d) CH₂=CHC(O)Cl (1.1 equiv), Et₃N (1.2 equiv), CH₂Cl₂, 0 → 25 °C, 1 h, 90 %; e) (PCy₃)₂Ru(=CHPh)Cl₂ (0.15 equiv), CH₂Cl₂, 40 °C, 72 h, 90 %; f) DIBAL (2.2 equiv), CH₂Cl₂, –78 °C, 1 h, 98 %; g) OsO₄ (0.03 equiv), NMO (1.5 equiv), acetone/H₂O (20/1), 25 °C, 24 h, 97 %; h) Ac₂O (4.0 equiv), Et₃N (6.0 equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, 0 → 25 °C, 2 h, 98 %; i) PhSH (1.3 equiv), Me₃SiOTf (0.03 equiv), CH₂Cl₂, 0 → 25 °C, 3 h, 69 %; j) K₂CO₃ (0.2 equiv), MeOH, 25 °C, 3 h, 100 %. Cy = cyclohexyl, DIBAL = diisobutylaluminum hydride, 4-DMAP = 4-dimethylaminopyridine, NMO = 4-methylmorpholine *N*-oxide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethylsulfonyl.

among these are the formation of **A₁B(A)** and **A₁BC** systems by Scharf et al.^[2h, k–m] and approaches to 2-deoxy-β-glycosides by Sinay et al.^[2i–j] In the preceding contribution^[3] we described

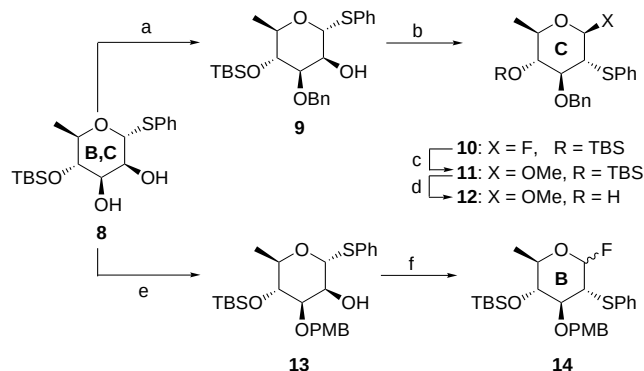
a stereoselective synthesis of evernitrore (ring **A**) in its activated form (**26**, see Scheme 5). Here we report efficient constructions of rings **B**, **C**, and **A₁** as well as their assembly to the **A₁B(A)C** ring system (**28**, see Scheme 5) of everninomicin (**1**). The reported chemistry features a number of interesting strategies including a) an approach based on ring-closing olefin metathesis^[4] to the common precursor **8** for carbohydrate systems **B** and **C** (see Scheme 1), b) control of the stereochemistry of the 2-deoxy-β-anomeric by a 1,2-migration and a sulfur-directed glycosidation,^[5] and c) use of an acyl fluoride to effect formation of the sterically demanding ester bond between rings **A₁** and **B**.

An asymmetric synthesis of the common precursor to rings **B** and **C** is shown in Scheme 1. Sharpless epoxidation of prochiral divinylmethanol (**2**)^[6] followed by silylation (TBSCl, imidazole, 85 % over two steps)^[7] furnished epoxide **3**. Regioselective ring opening of **3** with LiEt₃BH (“super hydride”) followed by esterification with acryloyl chloride under basic conditions (Et₃N) provided diolefin **4** (90 %). Ring-closing metathesis induced by (PCy₃)₂Ru(=CHPh)Cl₂ as catalyst afforded lactone **5** (90 %).^[8] Contrary to expectations, dihydroxylation of **5** under a variety of conditions led to the wrong diastereomer, with the oxygen atoms *cis* to the bulky TBS group. Fortunately, reduction of lactone **5** with DIBAL, followed by OsO₄-catalyzed dihydroxylation of the resulting

among these are the formation of **A₁B(A)** and **A₁BC** systems by Scharf et al.^[2h, k–m] and approaches to 2-deoxy-β-glycosides by Sinay et al.^[2i–j] In the preceding contribution^[3] we described a stereoselective synthesis of evernitrore (ring **A**) in its activated form (**26**, see Scheme 5). Here we report efficient constructions of rings **B**, **C**, and **A₁** as well as their assembly to the **A₁B(A)C** ring system (**28**, see Scheme 5) of everninomicin (**1**). The reported chemistry features a number of interesting strategies including a) an approach based on ring-closing olefin metathesis^[4] to the common precursor **8** for carbohydrate systems **B** and **C** (see Scheme 1), b) control of the stereochemistry of the 2-deoxy-β-anomeric by a 1,2-migration and a sulfur-directed glycosidation,^[5] and c) use of an acyl fluoride to effect formation of the sterically demanding ester bond between rings **A₁** and **B**.

lactol **6** (mixture of anomers), led to the exclusive and quantitative formation of the desired 2,3-diol, which was peracetylated to afford triacetate **7** (98 %, mixture of anomers). Exposure of **7** to PhSH and TMSOTf followed by deacetylation gave dihydroxy- α -thioglycoside **8** as the sole product (69 % over two steps).

Scheme 2 summarizes the selective conversion of thioglycoside **8** into both glycosyl acceptor **12** and glycosyl donor **14**; the 1,2-migration technique previously developed in our

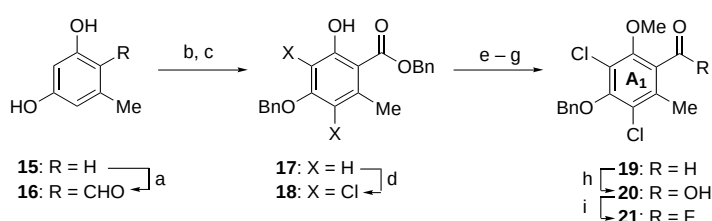


Scheme 2. Synthesis of the **B** and **C** rings. a) 1. $n\text{Bu}_2\text{SnO}$ (1.3 equiv), PhH, 80 °C, 12 h; 2. BnBr (1.5 equiv), $n\text{Bu}_4\text{NI}$ (1.0 equiv), 80 °C, 2 h, 80 %; b) DAST (1.3 equiv), CH_2Cl_2 , 0 °C; c) MeOH (2.0 equiv), SnCl_2 (1.8 equiv), 4-Å molecular sieves, Et_2O , -15 °C, 100 % over two steps, $\alpha/\beta \approx 1:10$; d) $n\text{Bu}_4\text{NF}$ (1.5 equiv), THF, 25 °C, 2 h, 95 %; e) 1. $n\text{Bu}_2\text{SnO}$ (1.3 equiv), PhH, 80 °C, 12 h; 2. PMBCl (1.5 equiv), $n\text{Bu}_4\text{NI}$ (1.0 equiv), 80 °C, 2 h, 92 %; f) DAST (1.3 equiv), CH_2Cl_2 , 0 °C, 100 %. Bn = benzyl, DAST = Et_2NSF_3 , PMB = *p*-methoxybenzyl.

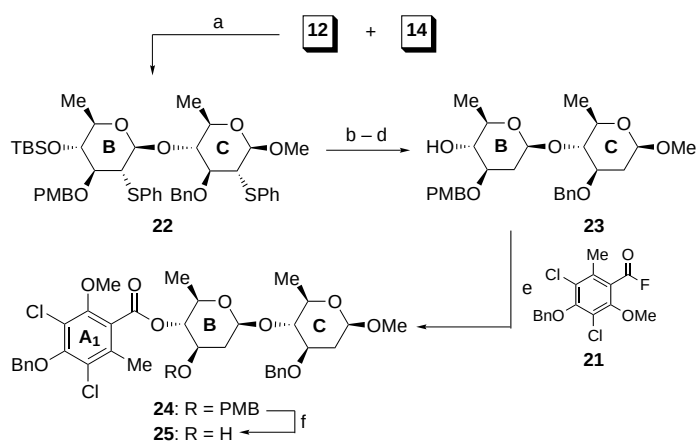
laboratories was employed.^[5] Thus, regioselective protection of position 3 of **8** was effected with $n\text{Bu}_2\text{SnO}$ /BnBr for ring **C** ($\rightarrow$ **9**, 80 %) and with $n\text{Bu}_2\text{SnO}$ /PMBCl for ring **B** ($\rightarrow$ **13**, 92 %). Thioglycosides **9** and **13** underwent smooth 1,2-migration on exposure to DAST to furnish glycosyl fluorides **10** (mixture of β and α anomers, ca. 17:1) and **14** (mixture of β and α anomers, ca. 14:1), respectively, in quantitative yields. As expected, glycosidation of **10** with MeOH and SnCl_2 in Et_2O was directed by the PhS group at C2 to give predominantly the β anomer **11** (91 %, ca. 10:1). Desilylation of **11** gave compound **12** (95 %).

The anticipated difficulties^[2h, k-m] in forming the ester bond between rings **A**₁ and **B** led us to evaluate the use of fluoride **21** (Scheme 3). Its synthesis began with Gatterman formylation of resorcinol **15** ($\rightarrow$ **16**, 92 %). Oxidation of aldehyde **16** to the carboxylic acid (NaClO_2 , 80 %) followed by exposure to benzyl alcohol under Mitsunobu conditions led to the phenol derivative **17** (100 % based on 75 % conversion). Chlorination of **17** (Cl_2 , buffered conditions,^[2e] 70 %) followed by methylation of the phenolic group (CH_2N_2 ,^[2e] 100 %), DIBAL reduction (90 %), and PDC oxidation gave the aldehyde **19** (90 %). Further oxidation of **19** with NaClO_2 and treatment with $[(\text{Me}_2\text{N})_2\text{CF}]\text{PF}_6$ ^[9] then led to the targeted acyl fluoride **21** (97 %), which cleanly withstood chromatographic purification.

The assembly of the **A**₁**BC** ring system **25** from its monocyclic building blocks **12**, **14**, and **21** is shown in Scheme 4. Thus, β -glycosidic coupling,^[5] directed by the PhS



Scheme 3. Synthesis of dichloroisoverninic acyl fluoride (**21**). a) 1. $\text{Zn}(\text{CN})_2$ (1.5 equiv), AlCl_3 (2.4 equiv), HCl (g), 0 °C, 3 h; 2. H_2O , 0 $\rightarrow$ 100 °C, 30 min, 92 %; b) NaClO_2 (2.4 equiv), NaH_2PO_4 (2.5 equiv), DMSO, 0 °C, 12 h, 80 %; c) BnOH (2.0 equiv), DIAD (2.0 equiv), Ph_3P (2.0 equiv), THF, 0 °C, 4 h, 100 % based on 75 % conversion; d) Cl_2 (1.0 M in AcOH, 3.0 equiv), NaOAc (2.25 equiv), AcOH, -50 $\rightarrow$ 0 °C, 70 %; e) CH_2N_2 (excess), Et_2O , dark, 0 °C, 12 h, 100 %; f) DIBAL (1.2 equiv), CH_2Cl_2 , -78 °C, 1 h, 90 %; g) PDC (3.0 equiv), 3-Å molecular sieves, CH_2Cl_2 , 25 °C, 3 h, 90 %; h) NaClO_2 (3.0 equiv), NaH_2PO_4 (3.0 equiv), 2-methyl-2-butene (2.0 M in THF, 4.0 equiv), $t\text{BuOH}$, H_2O , 25 °C, 3 h, 95 %; i) $[(\text{Me}_2\text{N})_2\text{CF}]\text{PF}_6$ (1.5 equiv), $i\text{Pr}_2\text{NEt}$ (2.0 equiv), CH_2Cl_2 , 0 $\rightarrow$ 25 °C, 12 h, 97 %. DIAD = diisopropylazodicarboxylate, PDC = pyridinium dichromate.



Scheme 4. Assembly of the **A**₁**BC** ring system **25**. a) **12** (1.0 equiv), **14** (1.5 equiv), SnCl_2 (1.0 equiv), Et_2O , 4-Å molecular sieves, -15 °C, 12 h, 78 %; b) Raney Ni (excess), MeOH, 65 °C, 2 h; c) BnBr (2.0 equiv), NaH (2.2 equiv), $n\text{Bu}_4\text{NI}$ (0.2 equiv), DMF, 0 °C, 1 h; d) $n\text{Bu}_4\text{NF}$ (1.3 equiv), THF, 25 °C, 2 h, 78 % over three steps; e) 1. **23** (1.0 equiv), 4-Å molecular sieves, THF, 2 h; 2. $n\text{BuLi}$ (1.6 M in hexanes, 2.0 equiv), 25 °C, 1 h; 3. **21** (3.0 equiv), THF, 24 h, 80 %; f) DDQ (2.0 equiv), $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (15/2), 25 °C, 2 h, 80 %. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

group at C2, of **12** with **14** was promoted by SnCl_2 in Et_2O to afford disaccharide **22** in 78 % yield. Desulfurization of **22** with Raney Ni, followed by rebenzylation of the partially deprotected hydroxyl group at C3 of ring **C** and desilylation, furnished disaccharide **23** (78 % over three steps). Activation of **23** with $n\text{BuLi}$ facilitated its coupling with fluoride **21** ($\rightarrow$ **24**, 80 %). Finally, selective removal of the PMB group from **24** was achieved with DDQ to furnish **25** (80 %).

The coupling of tricyclic system **25** with glycosyl fluoride **26**^[3] in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ proceeded stereoselectively to afford the desired α -glycoside **27** (95 %, Scheme 5), from which the benzyl groups were selectively removed by hydrogenolysis to afford the targeted **A**₁**B(A)****C** ring segment **28** of everninomicin (**1**) in 95 % yield.

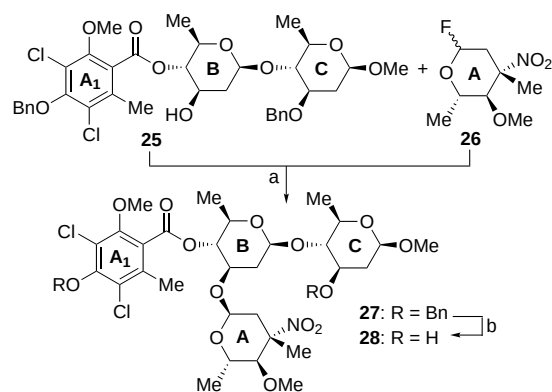
The described chemistry demonstrates a number of novel synthetic strategies for the asymmetric synthesis of carbohydrate units corresponding to everninomicin and for their

Table 1. Selected physical properties of compounds **22**, **25**, and **28**.

22: R_f = 0.42 (silica gel, 30% Et₂O in hexanes); $[\alpha]_D^{25}$ = -45.3 (c = 0.97 in CHCl₃); IR (thin film): $\tilde{\nu}_{\max}$ = 2930, 2855, 1514, 1472, 1438, 1248, 1102, 1024, 871, 837 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.51–7.22 (m, 17H, ArH), 6.79 (d, J = 8.5 Hz, 2H, ArH), 4.92 and 4.72 (AB, J = 10.0 Hz, 2H, CH₂Ar), 4.85 and 4.67 (AB, J = 10.0 Hz, 2H, CH₂Ar), 4.68 (d, J = 9.0 Hz, 1H, H1'), 4.07 (d, J = 8.5 Hz, 1H, H1), 3.77 (s, 3H, *p*-CH₃OAr), 3.56 (dd, J = 9.5, 9.0 Hz, 1H, H4), 3.44 (s, 3H, OCH₃), 3.29 (m, 4H, H3, H3', H4', H5 or H5'), 3.10 (dd, J = 10.5, 8.5 Hz, 1H, H2), 3.05 (dd, J = 9.5, 6.0 Hz, 1H, H5' or H5), 3.00 (dd, J = 11.0, 9.0 Hz, 1H, H2'), 1.45 (d, J = 6.5 Hz, 3H, H6 or H6'), 1.12 (d, J = 6.0 Hz, 3H, H6' or H6), 0.92 (s, 9H, *t*BuSi), 0.06 (s, 3H, CH₃Si), 0.05 (s, 3H, CH₃Si); ¹³C NMR (125 MHz, CDCl₃): δ = 138.8, 136.8, 134.5, 133.0, 130.6, 129.1, 128.5, 127.9, 127.4, 127.1, 126.2, 113.5, 103.9, 102.9, 82.9, 81.7, 80.8, 76.8, 75.7, 75.1, 72.5, 71.1, 57.6, 56.9, 55.6, 55.2, 26.0, 18.7, 18.3, 18.0, -3.4, -3.9; HR-MS (FAB) calcd for C₄₆H₆₀O₈S₂SiCs [M + Cs⁺]: 965.2553, found: 965.2521.

25: R_f = 0.29 (silica gel, 60% Et₂O in hexanes); $[\alpha]_D^{25}$ = -6.43 (c = 0.53 in CHCl₃); IR (thin film): $\tilde{\nu}_{\max}$ = 3500, 2925, 1736, 1651, 1558, 1456, 1392, 1258, 1095, 1068, 1034 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.60 (bd, J = 8.0 Hz, 2H, ArH), 7.44–7.32 (m, 8H, ArH), 5.03 (s, 2H, A₁-CH₂Ar), 4.82 (dd, J = 9.0, 8.5 Hz, 1H, H4'), 4.80 (bd, J = 9.0 Hz, 1H, H1'), 4.71 and 4.67 (AB, J = 11.5 Hz, 2H, CH₂Ar), 4.34 (dd, J = 10.0, 2.0 Hz, 1H, H1), 3.88 (s, 3H, A₁-OCH₃), 3.79 (bddd, J = 9.5, 9.0, 4.0 Hz, 1H, H3'), 3.59 (ddd, J = 11.5, 8.5, 5.5 Hz, H3), 3.48 (s, 3H, OCH₃), 3.38 (m, 2H, H5 and H5'), 3.29 (dd, J = 9.5, 8.5 Hz, 1H, H4), 2.68 (d, J = 4.0 Hz, 1H, OH), 2.36 (s, 3H, A₁-CH₃), 2.36 (m, 1H, H2'_{eq}), 2.3 (ddd, J = 12.5, 5.5, 2.0 Hz, 1H, H2'_{eq}), 1.74 (ddd, J = 12.5, 9.5, 9.0 Hz, 1H, H2'_{ax}), 1.59 (ddd, J = 12.5, 11.5, 10.0 Hz, 1H, H2'_{ax}), 1.34 (d, J = 5.5 Hz, 1H, H6'), 1.30 (d, J = 6.0 Hz, 1H, H6); ¹³C NMR (125 MHz, CDCl₃): δ = 166.4, 153.0, 151.9, 138.6, 135.9, 133.2, 128.6, 128.5, 127.5, 127.4, 127.0, 125.5, 121.4, 100.5, 100.4, 83.2, 79.9, 77.6, 74.9, 71.8, 70.9, 69.7, 62.4, 56.5, 39.4, 37.0, 30.3, 18.2, 17.7, 17.4; HRMS (FAB) calcd for C₃₆H₄₂O₁₀Cl₂Na [M + Na⁺]: 727.2053, found: 727.2029.

28: R_f = 0.3 (silica gel, 50% Et₂O in hexanes); $[\alpha]_D^{25}$ = -45.2 (c = 0.54 in CHCl₃); IR (thin film): $\tilde{\nu}_{\max}$ = 3456, 2926, 2854, 1725, 1544, 1449, 1389, 1299, 1250, 1127, 1037 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 6.98 (s, 1H, A₁-OH), 4.98 (dd, J = 4.5, 1.5 Hz, 1H, H1''), 4.94 (dd, J = 9.0, 9.0 Hz, 1H, H4'), 4.53 (dd, J = 9.5, 1.5 Hz, 1H, H1'), 4.40 (dd, J = 9.5, 1.5 Hz, 1H, H1), 4.21 (ddd, J = 11.5, 9.5, 5.5 Hz, 1H, H3'), 3.92 (dq, J = 9.0, 6.5 Hz, 1H, H5'), 3.88 (s, 3H, A₁-OCH₃), 3.65 (d, J = 9.0 Hz, 1H, H4''), 3.62 (dq, J = 9.0, 6.5 Hz, 1H, H5''), 3.63 (m, 1H, H3), 3.49 (s, 3H, 1-OCH₃), 3.39 (m, 1H, H5''), 3.35 (s, 3H, 4''-OCH₃), 2.99 (dd, J = 9.0, 8.5 Hz, 1H, H4), 2.47 (dd, J = 14.0, 5.0 Hz, 1H, H2'_{ax}), 2.38 (s, 3H, A₁-CH₃), 2.37–2.28 (m, 2H, H2'_{eq} and H2'_{eq}), 2.03 (dd, J = 14.0, 2.0 Hz, 1H, H2'_{eq}), 1.76–1.58 (m, 2H, H2'_{ax} and H2'_{ax}), 1.67 (s, 3H, 3''-CH₃), 1.44 (d, J = 6.5 Hz, 3H, H6 or H6'), 1.29 (d, J = 6.0 Hz, 3H, H6 or H6'), 0.86 (d, J = 6.0 Hz, 3H, H6''); ¹³C NMR (125 MHz, CDCl₃): δ = 165.5, 153.5, 150.2, 134.7, 125.5, 121.6, 117.6, 100.7, 92.5, 89.9, 89.0, 84.3, 82.8, 75.5, 72.0, 70.2, 69.5, 66.4, 62.1, 60.8, 56.7, 40.0, 38.1, 36.0, 34.3, 29.7, 19.5, 18.1, 17.8, 17.7; HRMS (FAB) calcd for C₃₀H₄₃Cl₂NO₁₄Na [M + Na⁺]: 734.1958, found: 734.1938.



Scheme 5. Construction of the A₁B(A)C ring system. a) **26** (1.8 equiv), BF₃·Et₂O (1.3 equiv), CH₂Cl₂, 4-Å molecular sieves, -30 → 25 °C, 36 h, 95%; b) H₂, Pd/C, *t*BuOMe, 25 °C, 2 h, 95%.

stereocontrolled assembly into a polycyclic framework corresponding to the A₁B(A)C region of the target molecule **1**. The total synthesis of **1** and designed analogues for chemical biology studies should be forthcoming.

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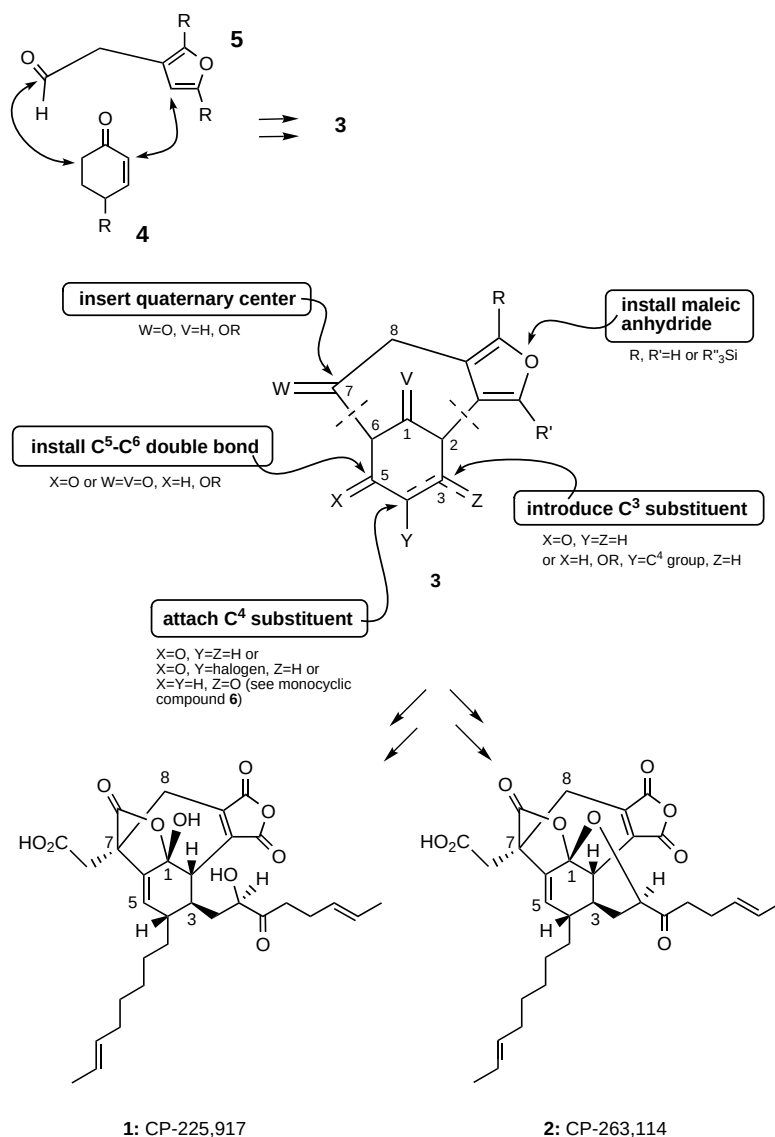
Total Syntheses of CP-225,917 and CP-263,114: Creation of a Matrix Structure By Sequential Aldol Condensation and Intramolecular Heck Ring Closure**

Ohyun Kwon, Dai-Shi Su, Dongfang Meng, Wei Deng, Derin C. D'Amico, and Samuel J. Danishefsky*

Recently Kaneko and co-workers at the Charles Pfizer laboratories described the isolation and structure elucidation of compounds **1** and **2** (see Scheme 1).^[1, 2] Apart from the curiosity provoked by their novel structures, these metabolites warrant additional attention as they are potent inhibitors of squalene synthase and farnesyl transferase. The potentialities of modulating the pathways regulated by these enzymes are of great interest to the pharmaceutical industry, though no agents operating through such mechanisms are in current usage.^[3] Our notice of the Pfizer compounds arose from the inherent summons their syntheses pose to the ingenuity and capacities of organic chemistry.

Given the multifaceted problems which would have to be surmounted to complete such a goal in the case of **1** and **2**, it seems unlikely that achieving a total synthesis would impact on the availability of these natural products for detailed evaluation, let alone clinical application. However, since the structure–activity profiles of such compounds are not known, it is not inconceivable that useful biological function could be realized from rather simpler structures which might, in fact, be available in acceptable amounts through purely synthetic means. An exploration of the total syntheses of **1** and **2** might provide a valuable perspective to study these issues.

Several early and interesting initiatives directed to the synthesis of **1** and **2** have been reported by Nicolaou,^[4] Davies,^[5] Clive,^[6] and Armstrong.^[7] These previous thrusts directly addressed the introduction of the C5–C6 bridgehead double bond, which is present in both compounds. Progress toward this end was accomplished through bond-reorganiza-



Scheme 1. Strategies for a matrix structure **3** in the total synthesis of **1** and **2**.

tion strategies (cycloadditions^[8] or sigmatropic rearrangements).

The route we are exploring herein reflects a different view of the problem. Its main focus is on gaining rapid access to a 5,6-dihydro ring system, with provisions (albeit in less than mature form) for the introduction of all the functional groups needed to obtain **1** and **2**. The scheme provides for properly placed carbonyl groups and double bonds to serve these ends. Central to the plan is the presence of a furan moiety that contributes two carbon atoms to the four-carbon spanning element of coupling agent **5** (Scheme 1). The furan ring provides an annulation handle (see below) and, furthermore, is a locus of reasonable stability in the resultant cyclization product. Moreover, appropriate oxidation of the furan would lead to the maleic anhydride.^[9] The optimal timing of this event would be ascertained as matters unfold. As for the introduction of the C5–C6 bridgehead double bond, we envisioned reliance on functionalities derivable from one or more keto groups at C7 and C1, where C5 is equipped with a leaving group.

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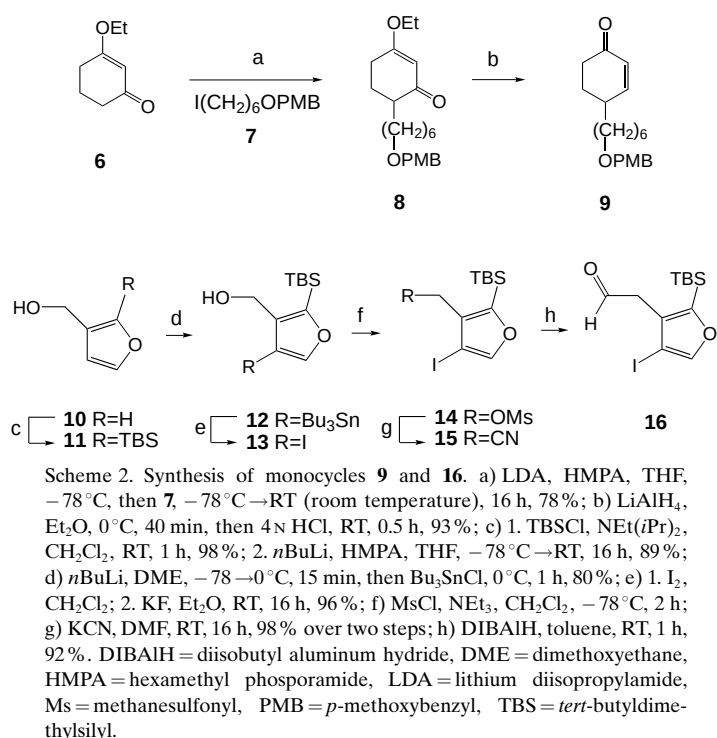
Our general thought process is summarized in formula **3** (Scheme 1). We emphasize that this picture is not intended to represent a specific compound. Rather, it conveys a perspective by which required functional groups are introduced through potential implementation sites in a matrix system. Left unaddressed in such a presentation are important subtleties of timing and orchestration.

Seeking proof of principle, we studied the feasibility of melding systems of types **4** and **5** as a route to the matrix entity **3**. In the particular variation we report here, the future substituent at C4 in **3** is introduced already in the monocyclic precursor **4**. In other constructions, we have introduced this substituent after formation of **3**.

The alkylation of **6** with **7** afforded **8** in 78% yield (Scheme 2).^[10] Reduction of the vinylogous ester **8** and acidic

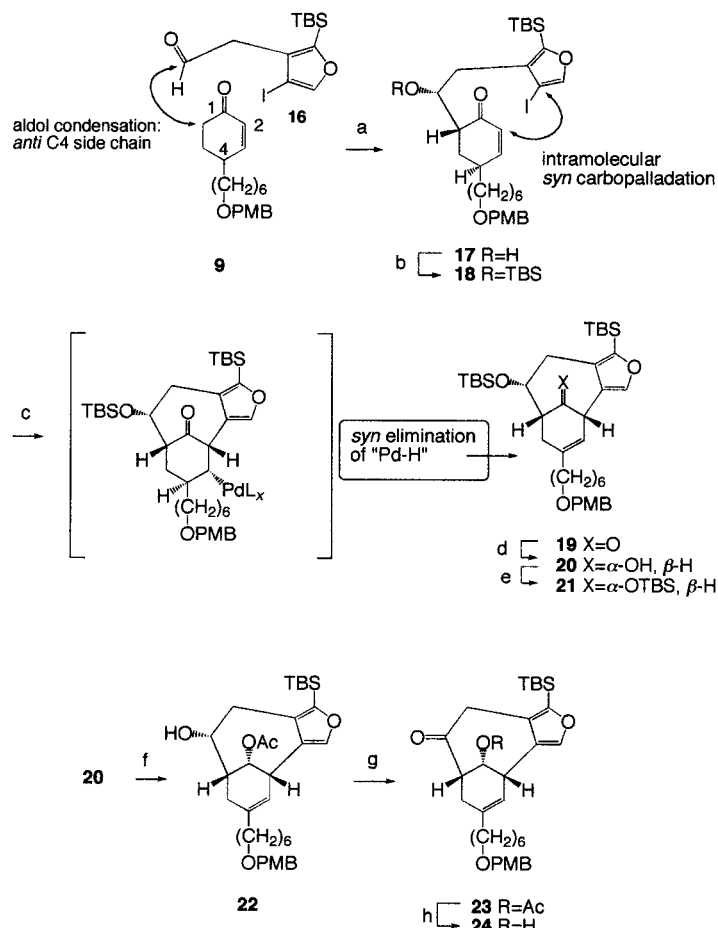
by an intramolecular Heck vinylation reaction.^[14, 15] Aldol reaction of the α' -enolate^[16] derived from **9** with aldehyde **16** afforded with high stereoselectivity^[17] **17** in 91% yield. At this point, it was prudent to protect the C7 alcohol in the form of its TBS derivative **18**.^[18] The stage was now set for the critical intramolecular Heck reaction. In practice, cyclization occurred smoothly to afford **19**. Thus, a credible matrix compound for the projected synthesis is assembled in a remarkably straightforward way. The key to the successful Heck reaction on a side chain at C4 of cyclohexenone is that the aldol reaction at C6 occurs *anti* to the side chain. Thus, following protection and *syn* carbopalladation, *syn* elimination of palladium hydride is possible, which is central to the success of the enterprise.

Once we had compound **19**, we began to explore some possible functional-group modifications which could be helpful in reaching structures **1** or **2**. We found that reduction of **19** with diisobutyl aluminum hydride provides a single alcohol, **20** (Scheme 3). Silylation of **20** gives rise to **21**. Alternatively,



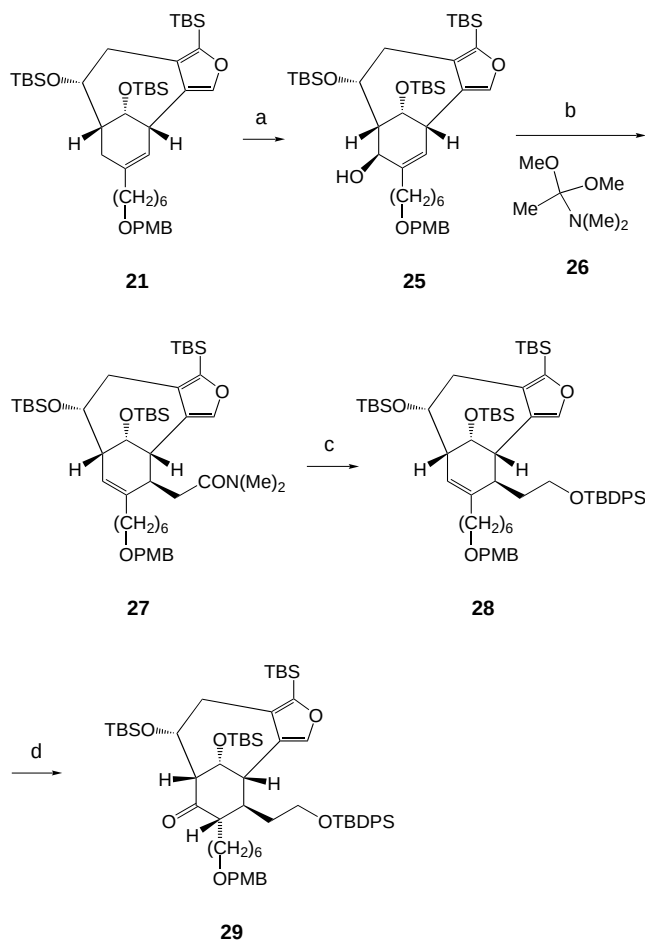
hydrolysis led, as anticipated,^[11] to enone **9**, a specific example of the monocyclic precursor **4**. The synthesis of a furan of type **5** commenced with the commercially available **10**, which was converted into the corresponding *tert*-butyldimethylsilyl ether. Silyloxy-directed metalation at C2 followed by $\text{O} \rightarrow \text{C}$ migration of the silyl group afforded **11**. Next, we made use of hydroxyl-directed metalation at C3 to introduce a stannyl group (**12**). Destannylation iodination in the *ipso* sense provided **13**,^[12,13] which was homologated (via mesylate **14**) to the furanylacetonitrile derivative **15**. Finally, controlled reduction of the nitrile functionality and careful hydrolysis afforded the somewhat labile aldehyde **16**.

With both coupling components in hand, we directed our attention to construction of a prototype corresponding to **3**. The plan involved an initial merger of the two components at the future C6–C7 bond through an aldol condensation. Formation of the bridging carbon–carbon bond would occur



acetylation of **20** followed by cleavage of the C7 silyl group led to **22**, which upon oxidation provided ketone **23**. The latter can be deprotected at C1 (**24**).

Another milestone was reached, albeit in a manner that currently^[19] lacks tight regiochemical control,^[20] through the action of selenium dioxide on **21**. This process produced **25** as well as a somewhat smaller amount of side chain oxidation products (Scheme 4). Reaction of **25** with **26** gave, upon [3,3] sigmatropic rearrangement, the γ,δ unsaturated amide **27**.²¹ Reduction of the amide linkage and protection of the resulting primary alcohol led to **28**, which on hydroboration and oxidation provided **29**.^[22]



Scheme 4. Synthesis of **29**. a) SeO_2 , pyridine, 70°C , 20 min, 31 % (+21 % side chain oxidation product); b) **26**, xylenes, 150°C , 18 h, 91 %; c) 1. LiEt_3BH , THF, $0^\circ\text{C} \rightarrow \text{RT}$, 2 h, then 1N NaOH, H_2O_2 , RT, 1.75 h, 91 %; 2. TBDPSCl, imidazole, DMAP, THF, RT, 2 h, 91 %; d) 1. $\text{BH}_3 \cdot \text{THF}$, $0^\circ\text{C} \rightarrow \text{RT}$, 16 h, then 1N NaOH, H_2O_2 , RT, 1 h, 68 %; 2. Dess–Martin periodinane, CH_2Cl_2 , RT, 2 h, 92 %. TBDPS = *tert*-butyldiphenylsilyl.

In principle, several compounds in this series contain promising functionality implements required to reach CP-225,917 and CP-263,114. This theme will be amplified in the following contribution.^[23]

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(m, 1 H), 1.50 (m, 4 H), 1.18 (m, 8 H), 0.90 (s, 9 H), 0.86 (s, 9 H), 0.79 (s, 9 H), 0.64 (s, 9 H), 0.16 (2s, 6 H), -0.03 (s, 3 H), -0.07 (s, 3 H), -0.09 (s, 3 H), -0.13 (s, 3 H); FT-IR (neat): $\nu=1714, 1512, 1470, 1250, 1104\text{ cm}^{-1}$; MS: calcd for $\text{C}_{62}\text{H}_{98}\text{O}_7\text{Si}_4\text{Na}$: 1089.6, found: 1089.6 [$M+\text{Na}$].

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A Stereospecific Geminal Alkylation Scheme En Route To CP-225, 917 and CP-263,114**

Ohyun Kwon, Dai-Shi Su, Dongfang Meng, Wei Deng, Derin C. D'Amico, and Samuel J. Danishefsky*

Dedicated to Professor Barry M. Trost

In the previous contribution^[1] we outlined a conceptual framework and encouraging results for assembling the ring systems of CP-225,917 (**1**) and CP-263,114 (**2**)^[2, 3] (Figure 1).

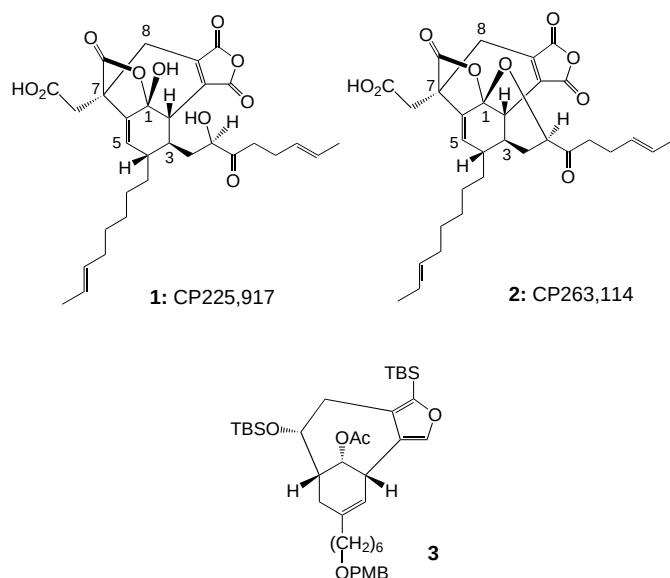


Figure 1. Structures of **1** and **2** as well as the central starting material **3**.

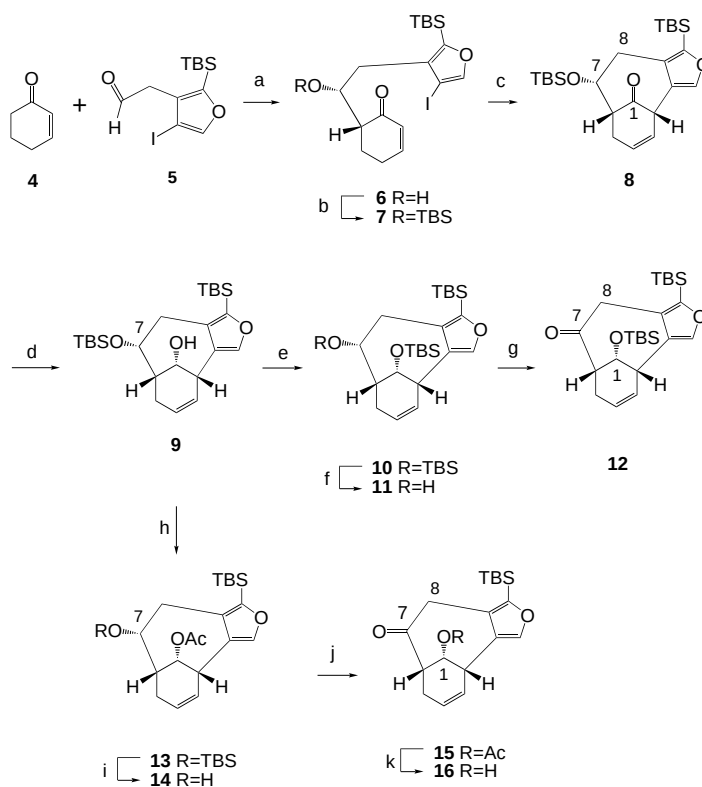
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The key element of our synthetic program is the rapid construction of an intermediate lacking the C5–C6 bridgehead double bond (**3**) through the proper sequencing of aldol and intramolecular Heck-type bond formations using a 2,3,4-trisubstituted furan as a connecting device. We demonstrated how the resultant product of this sequence provides implementation sites through which the requisite functionality for the six-membered ring can be emplaced.^[1]

Herein, we turn our attention to the more complex functionality found in the seven-membered ring of **1** and **2**. To explore our ideas concerning this sector of the natural products, we utilized the previously described **3**^[1] as well as compound **8**, which lacks the substituent of C4 of the cyclohexenone ring (Scheme 1). Compound **8** was assembled through aldol condensation of cyclohexenone **4** with aldehyde **5**, which was also described in the previous article.^[1] In this case, the stereospecificity was somewhat diminished relative to that encountered en route to **3**. The reaction provided **6** in 79% yield (as well an apparent diastereoisomer in 10% yield).^[4] Protection of the secondary alcohol group gave rise to **7**. Intramolecular Heck vinylation, as earlier,^[1] provided **8** in 92% yield.



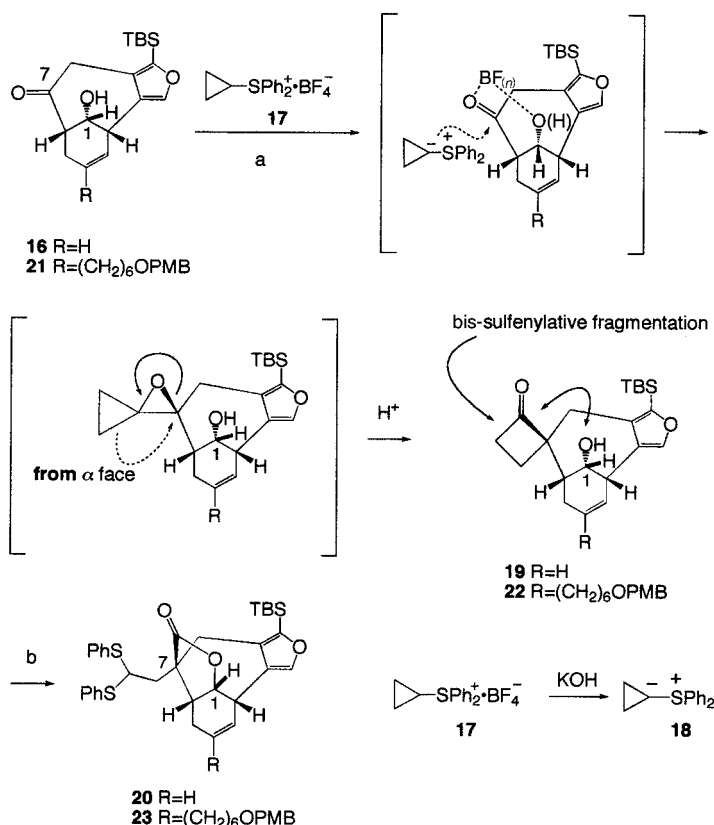
Scheme 1. Synthesis of ketones **12** and **16**. a) **4**, LDA, THF, -78°C , 1 h, then **5**, THF, -78°C , 2 h, 79% plus 10% diastereomer; b) TBSOTf, 2,6-lutidine, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{RT}$ (room temperature), 1 h, 85%; c) $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$, NEt_3 , THF, Δ , 4 d, 92%; d) DIBALH, CH_2Cl_2 , $-78 \rightarrow -30^\circ\text{C}$; e) TBSOTf, 2,6-lutidine, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{RT}$, 16 h, 61% over two steps; f) $\text{EtOH}/10\% \text{H}_2\text{SO}_4$ (10/1), RT, 31 h; g) Dess–Martin periodinane, CH_2Cl_2 , RT, 0.5 h, 85% over two steps; h) Ac_2O , pyridine, DMAP; i) TBAF, AcOH, THF, RT; j) Dess–Martin periodinane, CH_2Cl_2 , 93% over three steps; k) K_2CO_3 , MeOH, RT, 88%. DIBALH = diisobutylaluminum hydride, DMAP = 4-(dimethylamino)pyridine, LDA = lithium diisopropylamide, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

We next sought to generate a unique ketone group at C7 so that we could pursue some interesting possibilities for the installation of the quaternary center. Toward this end, compound **8** was reduced with diisobutylaluminum hydride, and the resultant carbinol **9** was silylated to give **10**. Selective desilylation at C7 ($\rightarrow$ **11**) could be achieved because, in fact, the C1 silyloxy group proved to be difficult to cleave. Oxidation of **11** provided ketone **12**.^[5] In a parallel series of reactions, **9** was acetylated, giving rise to **13**. Desilylation of the latter led to **14**. Oxidation provided **15**, and, following deacetylation, keto alcohol **16** was then in hand. Many attempts were made to deliver various carbon-based nucleophiles to the C7 ketone group of **12**.^[6] Only marginal success was realized toward this goal. It seemed that a significant complicating feature was enolization of the ketone by deprotonation at C8.

It was from this perspective that we turned to the use of the Trost sulfonium salt **17**.^[7, 8] The hope was that the derived ylide **18**, being relatively nonbasic, would provide more favorable possibilities for C–C bond formation at C7 relative to enolization at C8 (Scheme 2). In practice, ketone **12** proved

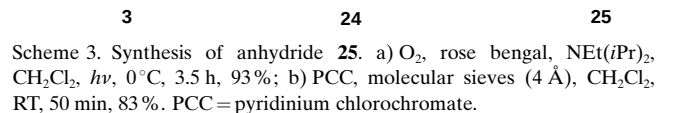
stereoselective fashion to provide, after acidic treatment, a spirocyclobutanone. From close analysis of the NMR spectrum, it seemed likely that **18** already had the stereochemistry indicated in **19**, wherein the spiroketone is on the β -face (i.e., *syn* to the C1 bridge). Such an outcome would be expected if formation of the carbon–carbon bond in the Trost reaction between **16** and **18** had occurred in the expected α sense (perhaps as a consequence of an emerging salt bridge between the oxido functions at C1 and C7). This surmise concerning the stereostructure of **19** was confirmed in a manner which itself augurs well for the synthesis of **1** and **2**: Under the Trost conditions^[9] for bis-sulfonylation of the cyclobutanone, we obtained a cyclobutanone cleavage product in the form of lactone **20** in 62 % yield.^[10] In a similar way, **3** was converted into hydroxyketone **21**,^[11] whose reaction with **18** and afforded **22** after workup with acid. Once again, under the conditions of bis-sulfonylation fragmentation of the cyclobutanone, compound **23** was obtained.

We next turned to validate the hypothesis concerning the use of the silylfuran as an entry to the maleic anhydride moiety. Encouragement toward this hope was secured upon photooxidation of **3** under the conditions shown in Scheme 3.



Scheme 2. Synthesis of lactones **20** and **23**. a) **17**, KOH, DMSO, RT, 2.5 h, then aq HBF₄, Et₂O, RT, 56 % for **19**, 46 % for **22**; b) PhSSPh, NaOMe, MeOH, Δ , 5 d for **20**, 65 h for **23**, 81 % for **20** based on 23 % recovery of **19**, 35 % for **23**. PMB = *p*-methoxybenzyl.

to be quite resistant to attack of **18** (generated from **17** through the action of potassium hydroxide).^[8] We wondered about the possibility that the C7 ketone group of the hydroxyketone **16** might provide a more reactive electrophilic site. Treatment of **16** with **18** occurred in a highly



Scheme 3. Synthesis of anhydride **25**. a) O₂, rose bengal, NEt(*i*Pr)₂, CH₂Cl₂, *h* ν , 0 °C, 3.5 h, 93 %; b) PCC, molecular sieves (4 Å), CH₂Cl₂, RT, 50 min, 83 %. PCC = pyridinium chlorochromate.

This treatment gave rise to compound **24** as a mixture of diastereomers.^[11, 12] Further oxidation with PCC afforded the anhydride **25**.^[13]

Several problems await solution for the challenge of total syntheses of **1** and **2** to be surmounted. Foremost among these is the timing for introduction of the C5–C6 bridgehead double bond.^[14] Nonetheless, the achievements accomplished, thus far in relatively few steps, encourage continued efforts directed at this goal.

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- [14] The construction of the C5–C6 bridgehead double bond has been accomplished recently: D. Meng, Columbia University, unpublished results.

Direct Observation of Fluid Mass Transfer Resistance in Porous Media by NMR Spectroscopy**

Ulrich Tallarek, Dagmar van Dusschoten, Henk Van As, Georges Guiochon, and Ernst Bayer*

In memory of John Calvin Giddings

The transport of solutes by dispersion, a combination of convection and hindered diffusion, through heterogeneous porous media is of fundamental importance in many areas such as liquid chromatography,^[1,2] catalysis,^[3] the migration of pollutants in groundwater,^[4] and petroleum recovery.^[5] Most porous media exhibit bi- or multimodal pore-size distributions, which can result, for example, from the intraparticle and interparticle pores in beds of porous particles, as are used in chromatographic columns.^[1,6] Although the kinetics of mass transfer between the fluid percolating through the system and the stagnant fluid in the diffusional pores is known to be the rate-limiting step in numerous dynamic processes (e.g., the efficiency of chromatographic columns^[2] or the amount of oil that can be economically recovered from a reservoir), no direct, quantitative measurement of these kinetics has been provided so far. Here we show how the pulsed field gradient (PFG) NMR method^[7] allows the determination of these kinetics. A single series of measurements permits the identification of the stagnant fluid fraction, of the fractional volume exchanged as a function of time, and of the porosity and tortuosity of the porous medium.

Figure 1 illustrates the structure of a bed of porous particles as used in column chromatography or in heterogeneous catalysis. Permeable rocks have a more complex porous structure, with a multimodal pore-size distribution and interconnection of the pores.^[8] However, water and oil bypass regions containing networks of finer pores by flowing through cracks. The fluid pools inside zones with fine pores are only accessible by diffusion. In chromatography, axial dispersion of a band arises from axial diffusion along the streamlines, eddy diffusion (resulting from the anastomosis of the porous space and the differences in the average velocity along streamlines), and the kinetics of mass transfer into and out of the particles.^[2]

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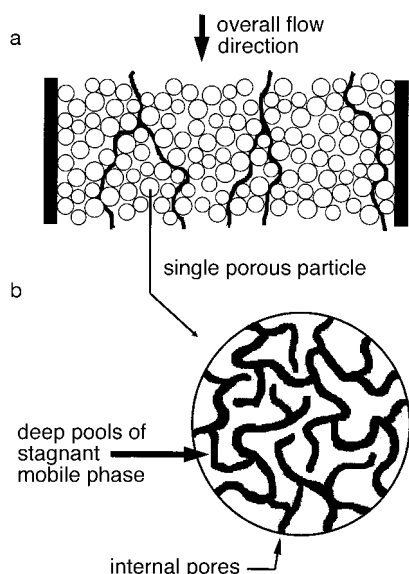


Figure 1. Schematic representation of the structure of a bed of porous particles and distribution of a fluid phase. a) Tortuous streamlines followed by the fluid percolating through the coarse pores between and around particles. b) Stagnant fluid in the fine pores of the particles. Exchange with the interparticulate fluid stream occurs by diffusion only.

Since these phenomena proceed on different dynamic time scales, their contributions to band dispersion can be determined independently and quantitatively by the PFG-NMR method. In these studies a single pure liquid phase continuously flows through the bed, which avoids extracolumn band broadening and problems with NMR detection limits that could arise if a tracer molecule were introduced.^[9]

The PFG-NMR method utilizes the motion-encoding capability of a linear magnetic field gradient superimposed for a short time on the main, static magnetic field.^[7] A second, identical gradient pulse, separated from the first pulse by an adjustable observation time Δ , exactly compensates the position-dependent phase shift induced by the first gradient if the molecule carrying the nuclear spin ($^1\text{H}_2\text{O}$) has remained static with respect to the direction of this gradient. Thus, the distribution of the residual net phase shifts results directly from the dynamics of the fluid molecules over this time Δ . In an ideal PFG-NMR experiment,^[10] the normalized signal amplitude $E(q, \Delta)$ is given by Equation (1).

$$E(q, \Delta) = \int \bar{P}(\mathbf{R}, \Delta) \exp(i2\pi \mathbf{q} \cdot \mathbf{R}) d\mathbf{R} \quad (1)$$

In this equation, the gradient integral defines a wave-vector,^[11] $\mathbf{q} = (2\pi)^{-1} \gamma \delta \mathbf{g}$, which is the space reciprocal of the dynamic displacement $\mathbf{R}$; $\mathbf{g}$ is the amplitude and direction of the pulsed field gradient, δ its duration ($\delta \ll \Delta$), and γ the magnetogyric ratio of the observed nucleus (here ^1H). The quantity $\bar{P}(\mathbf{R}, \Delta)$, which exhibits a direct Fourier relationship with the measured NMR signal, is the displacement probability distribution of the fluid molecules and is known as the averaged propagator.^[12] Hence, the distribution of net (i.e., dynamic) displacements of the fluid molecules can be derived from the measured signal by Fourier transformation of $E(q, \Delta)$ with respect to $\mathbf{q}$. Adjusting the observation time and the flow velocity of the fluid phase allows a detailed investigation of

the mass transfer kinetics between the stagnant and the mobile volume fractions of the fluid.

For classical convective fluid dispersion in a packed bed of nonporous particles, the distribution of migration distances $\mathbf{R}$ is Gaussian^[13] and the averaged propagator $\bar{P}(\mathbf{R}, \Delta)$ along the net flow direction is given by Equation (2).

$$\bar{P}(\mathbf{R}, \Delta) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left[-\frac{(\mathbf{R} - \bar{\mathbf{u}}\Delta)^2}{2\sigma^2}\right] \quad (2)$$

Here, $\bar{\mathbf{u}}$ is the cross-sectional average of the fluid phase linear velocity, and $\sigma^2 = 2D_{\text{ap}}\Delta$ the distribution variance. Thus, for a bed of nonporous particles, the apparent dispersion coefficient of the fluid in the gradient direction D_{ap} and the velocity of the mobile phase $\bar{\mathbf{u}}$ can be derived from the standard deviation σ and the center position of the maximum ($\bar{\mathbf{u}}\Delta$) of this Gaussian distribution, respectively.

With porous particles, by contrast, the spectrum of fluid displacements contains two Gaussian distributions if the exchange between the inter- and intraparticle fluids is incomplete (Figures 2 and 3). The first Gaussian distribution corresponds to molecules that migrate with the fluid stream which percolates through the bed. The second Gaussian distribution is centered at $\mathbf{R} = 0$ and corresponds to diffusion of the molecules of stagnant fluid in the pores of the particles (Figure 1). The ratio of the areas under these two curves provides an estimate of the fraction of molecules in the stagnant fluid that did not undergo exchange with molecules of the stream during the time interval Δ . This fraction decreases with increasing observation (exchange) time. For a given observation time, this fraction is higher for 50- μm particles than for 15- μm particles (Figures 2 and 3). Figure 2

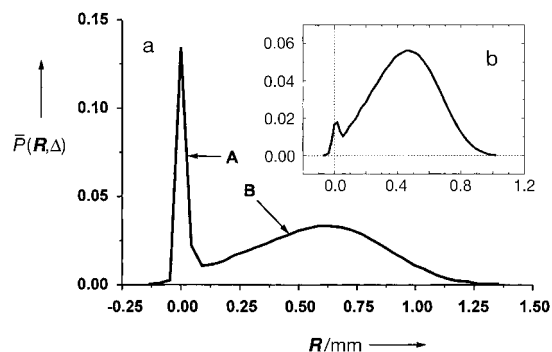


Figure 2. Probability distribution of the displacement of water molecules in two columns packed with spherical, totally porous, C_{18} -functionalized silica particles (YMC Europe, Schermbach, Germany). Intraparticle pore-size distribution: $13 \pm 1.5 \text{ nm}$; flow rate $F_v = 8.8 \text{ mL min}^{-1}$; observation time $\Delta = 30 \text{ ms}$ ($\delta = 4.0 \text{ ms}$); fluid phase: pure, degassed water. The columns ($4.4 \times 150 \text{ mm}$) were slurry-packed according to conventional practice.^[1] PFG-NMR measurements were performed with a 0.5-T NMR spectrometer consisting of an SMIS console (Surrey Medical Imaging Systems, Guildford, UK), an iron-core magnet (Bruker, Karlsruhe, Germany), and an actively shielded gradient and RF probe (Doty Scientific, Columbia, OH, USA). a) Average particle diameter $d_p = 50 \mu\text{m}$. The first Gaussian curve (A, stagnant fluid fraction, 21%) is centered at zero net displacement, and the second Gaussian curve (B, flowing fluid fraction, 79%) at a dynamic displacement of $\bar{\mathbf{u}}\Delta = 0.638 \text{ mm}$ with a standard deviation of $\sigma_1 = 0.365 \text{ mm}$. b) $d_p = 15 \mu\text{m}$. The stagnant fluid fraction at the same observation time is only 2.5%. The maximum of the Gaussian curve that describes the flowing fluid is located at $\bar{\mathbf{u}}\Delta = 0.463 \text{ mm}$ ($\sigma_1 = 0.215 \text{ mm}$).

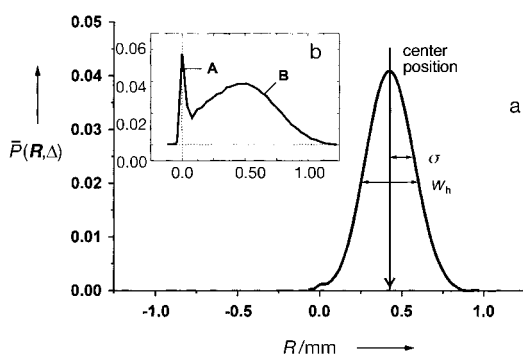


Figure 3. As in Figure 2, but with $F_v = 2.2 \text{ mL min}^{-1}$ and $\Delta = 120 \text{ ms}$. a) $d_p = 15 \text{ }\mu\text{m}$. The stagnant fluid fraction is almost completely exchanged (residual fraction $< 1\%$). The center of the Gaussian distribution is at $\bar{u}\Delta = 0.445 \text{ mm}$ ($\sigma_1 = 0.145 \text{ mm}$). b) $d_p = 50 \text{ }\mu\text{m}$. Stagnant fluid fraction: 8.5% (A); flowing fluid fraction: 91.5% (B). The first Gaussian distribution is centered at the origin, and the second at a net displacement $\bar{u}\Delta = 0.482 \text{ mm}$ and has a standard deviation of $\sigma_1 = 0.276 \text{ mm}$.

shows that at the shortest observation time ($\Delta = 30 \text{ ms}$), 21% of the fluid is stagnant in the column with the larger particles, and only 2.5% in the column with the smaller particles.

After 120 ms practically all the fluid contained in the 15- μm particles was exchanged (Figure 3a), while 8.5% of the stagnant fluid remained unexchanged in the 50- μm particles (Figure 3b). The widths at half height of the two Gaussian distributions can be used to determine the apparent dispersion coefficients of the fluid in the respective pore spaces relative to their porosities and tortuosities. From the averaged propagator distributions shown in Figure 3b, an apparent axial dispersion coefficient of $D_{\text{ap},1} = \sigma_1^2/2\Delta = 3.18 \times 10^{-3} \text{ cm}^2 \text{ s}^{-1}$ in the extraparticle space and a diffusion coefficient of $D_{\text{ap},2} = 1.05 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ in the intraparticle space were calculated. The molecular diffusivity of pure water (unhindered diffusion) was determined by PFG-NMR to be $D_m = 2.15 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ at 23°C . Therefore, the tortuosity factor of the intraparticle pore network is $D_{\text{ap},2}/D_m = 0.51$, a reasonable value for a complicated pore network.^[3] This geometrical parameter is an important characteristic of the pore interconnectivity in porous media. So far, its direct determination was extremely difficult and inaccurate.

When exchange between the two fluid fractions is complete, a single Gaussian distribution is observed. It includes the whole contribution to axial dispersion of the resistance to mass transfer between stagnant and mobile fluid phases (Figure 3). Then, the column or total bed porosity ε_T is easily derived from the average velocity $|\bar{u}\Delta| = 4F_v/\varepsilon_T\pi d_c^2$ (d_c = column diameter, F_v = volumetric flow rate), which itself is derived from the position of the maximum of the Gaussian curve (at $\bar{u}\Delta$). Values of 0.67 and 0.65 were obtained for the 50- and 15- μm particles, respectively, in excellent agreement with data obtained from independent chromatographic determinations.^[14]

In Figure 4 the stagnant fluid fraction f_{st} is plotted versus the Fick number ($2D_m\Delta/d_p^2$). The use of the Fick number normalizes the data with respect to the particle diameter and provides an estimate of the time required for equilibration of the compositions of the stagnant fluid and of the fluid percolating through the bed. The coincidence between the

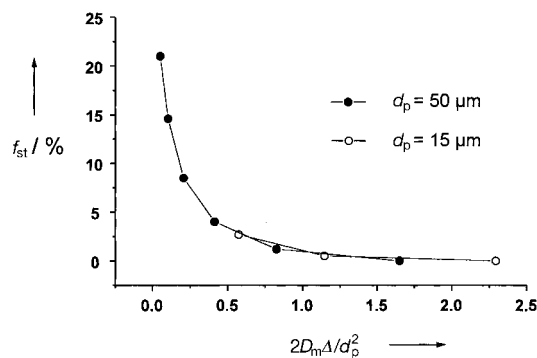


Figure 4. Plot of the stagnant fluid fraction f_{st} that remained unexchanged after time Δ versus the Fick number ($2D_m\Delta/d_p^2$). The observation time was increased stepwise from 30 to 960 ms for the 50- μm particles, and from 30 to 120 ms for the 15- μm particles.

data obtained for the two materials studied was expected since they have the same origin. This result demonstrates the redundant nature of fluid mass transfer resistance in similar pore networks and provides a useful basis for a comparison between different pore spaces.

The use of columns made of poly(aryl ether ether ketone) (PEEK) was critical for obtaining meaningful results. This polymer has high tensile strength and thus permits the packing and operation of columns under conditions realistic for chromatographic applications (up to 350 bar) and the recording of NMR data which are relevant to problems encountered in the study of the properties of consolidated beds of particles.^[15] The implementation is straightforward and is an improvement over the loose, centrifuged arrays of particles that are obtained in conventional NMR tubes and through which solvent percolation is not possible.^[16]

The great potential and broad application of these PFG-NMR studies lies in the ability to determine a variety of important parameters that characterize the fluid dynamics in porous media in a single measurement, performed in less than 15 min. Such mass transfer studies can be performed on any type of porous material in which a fluid is exchanged within and between a microporous and macroporous pore networks. Such situations are found in groundwater transport, in the transport of water between soil and plants, in fermentors, and in the various packed beds used in chemical engineering.

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C-Terminal Peptide Amidation Catalyzed by Orange Flavedo Peptide Amidase**

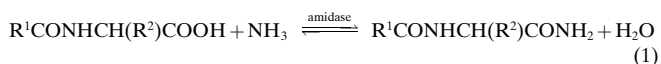
Václav Čerovský* and Maria-Regina Kula*

The presence of a C-terminal α -amido group on the peptide chain is essential for the biological activity of many peptide hormones.^[1] Amidated peptides are usually prepared by solid-phase synthesis on benzhydrylamine resins or by the ammonolysis of C-terminal peptide esters, which can be prepared by conventional peptide synthesis. Recombinant DNA technology allows the production of longer peptides by fermentation, but these products lack the C-terminal amido group. The combination of rDNA technology with chemical modification of the C-terminus requires the laborious protection of the functional groups in the side chains. Therefore, an enzymatic method for the introduction of an α -amido group is highly desirable.

Enzymatic amidation of peptides with ammonia as nucleophile has rarely been described.^[2] Short model peptides and amino acid derivatives were amidated by protease-catalyzed ammonolysis of the corresponding esters.^[3,4] In spite of the advantages of enzymatic methods in peptide synthesis,^[5] the application of proteases for peptide amidation is limited, mainly by the risk of undesired proteolysis. In 1990 we isolated an unusual enzyme which can hydrolyze peptide

amides at the C terminus without cleavage of peptide bonds or amido groups in the side chain.^[6] The enzyme was isolated from the flavedo of oranges and characterized as a peptide amidase.^[7] The broad substrate specificity of the enzyme makes it universally applicable for the deprotection of α -carboxy groups in enzymatic peptide synthesis.^[5]

Our aim was to use the peptide amidase to catalyze the reverse reaction, that is, the C-terminal amidation of peptides [Eq. (1); R^1 = amino acid residue or peptide residue; R^2 = side chain of an amino acid), which has not been described



up to now. In protease-catalyzed peptide synthesis,^[5] the “kinetic approach” is generally considered more effective than the reverse of peptide hydrolysis (“thermodynamic approach”).^[5] Owing to the lack of esterase activity of the peptide amidase, only a thermodynamic approach was possible. In aqueous solutions the equilibrium of the amidase-catalyzed reaction lies far to the side of the hydrolysis products. Initial attempts to detect the reverse reaction with an excess of ammonium acetate in water-miscible solvents were unsuccessful.

Here we report on a more systematic study of amidation reactions with the dipeptide Z-Gly-Phe-OH (Z = benzyloxy-carbonyl) as the acyl component and ammonium hydrogencarbonate as the ammonium source. When the reaction was carried out in acetonitrile in the presence of small amounts of water,^[8] the peptide amide could be detected. The optimal dipeptide concentration was 0.05 M. Increasing the concentration to 0.1 M resulted in a viscous reaction mixture owing to the precipitation of the ammonium salt of the dipeptide, which excludes the substrate from the reaction. As shown in Figure 1, the optimal ratio of acyl component to ammonium hydrogencarbonate was 1:1.4. The slight excess of the ammonium salt maintains slightly alkaline conditions for

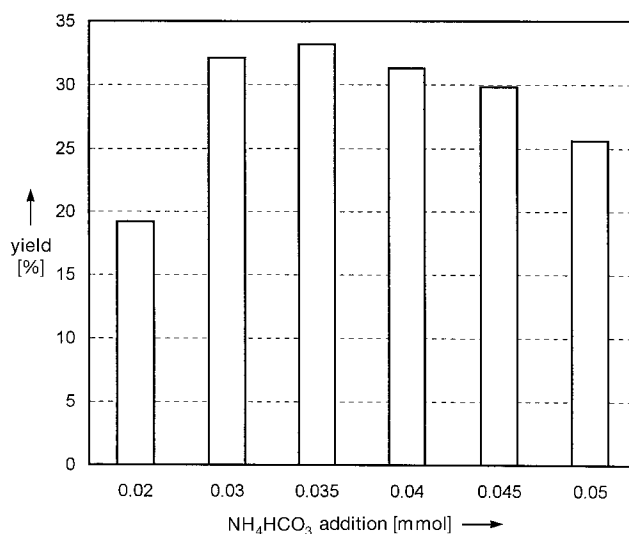


Figure 1. Influence of the ammonium concentration on the product yield in the peptide amidase catalyzed synthesis of Z-Gly-Phe-NH₂ in acetonitrile in the presence of 5 % water. Conditions: 0.025 mmol of Z-Gly-Phe-OH, 2 mg of amidase, 0.5 mL total volume, 48 h, 40 °C.

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the amidase-catalyzed reaction and minimizes the risk of precipitation of ammonium salts.

With the exception of diammonium hydrogenphosphate, very low amide yields were obtained with ammonium salts of strong inorganic and organic acids as the ammonium source (Table 1). In the presence of these salts, the reaction medium

Table 1. Peptide amidase catalyzed amidation of Z-Gly-Phe-OH by various ammonium salts in acetonitrile containing 5% of water at various temperatures.^[a]

Ammonium salt	<i>T</i> [°C]	Yield [%]
ammonium hydrogencarbonate	25	20.0
	30	26.0
	35	29.0
	40	31.5
	45	30.5
ammonium sulfate	40	0.5
diammonium hydrogenphosphate	40	32.0
ammonium acetate	40	5.0
diammonium tartrate	40	8.5
ammonium carbamate	40	4.0 ^[b]
	40	24.5 ^[c]
	40	31.0 ^[d]

[a] 0.025 mmol of Z-Gly-Phe-OH, 0.04 mmol of ammonium salt, 2 mg of amidase, 0.50 mL total volume, 48 h. [b, c, d] With 0.04, 0.025, and 0.015 mmol of ammonium carbamate, respectively, as donor.

does not attain the basicity required for optimal enzyme activity,^[7] as indicated by measurement of the apparent pH value. The use of a stronger base such as ammonium carbamate resulted in negligible amidation under standard conditions. The yield was considerably improved by decreasing the ammonium carbamate concentration in the reaction mixture (Table 1). Clearly, the reaction requires a slightly alkaline "pH value", which is controlled by the concentration of the nucleophile.

The dependence of the amide synthesis on the water concentration is shown in Figure 2. The best results were

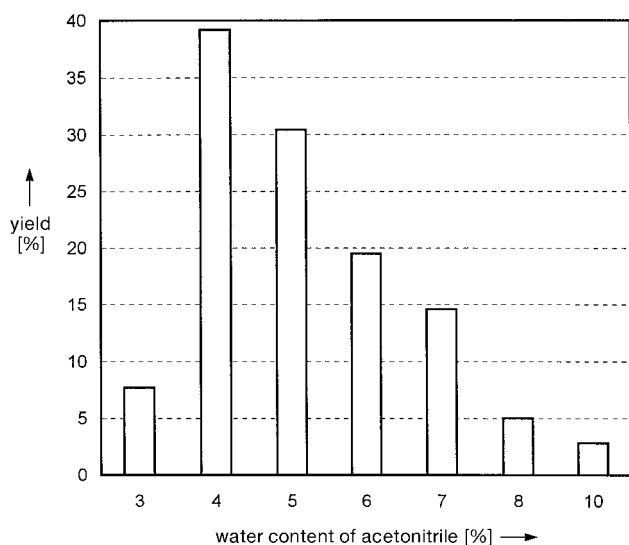


Figure 2. Influence of the water concentration on the product yield in the peptide amidase catalyzed synthesis of Z-Gly-Phe-NH₂ in acetonitrile. Conditions: 0.025 mmol of Z-Gly-Phe-OH, 0.04 mmol of NH₄HCO₃, 2 mg of amidase, 0.5 mL total volume, 72 h, 40 °C.

obtained in acetonitrile with a water content of 5%. Decreasing the water content to 4% had a positive effect on the amidation, but under these conditions the ammonium salt of the dipeptide tends to precipitate. The immediate precipitation of the ammonium salt is presumably responsible for the dramatic drop in the amide yield for a water content of 3%. No amidation was detected in other water-miscible organic solvents, such as 2-propanol, 1,4-butanediol, tetrahydrofuran, diisopropyl ether, or ethyl acetate, in the presence of 5% water.

The optimum reaction temperature was 40 °C (Table 1).

Figure 3 shows the course of the enzymatic amidation of Z-Gly-Phe-OH with time. The maximum product yield at

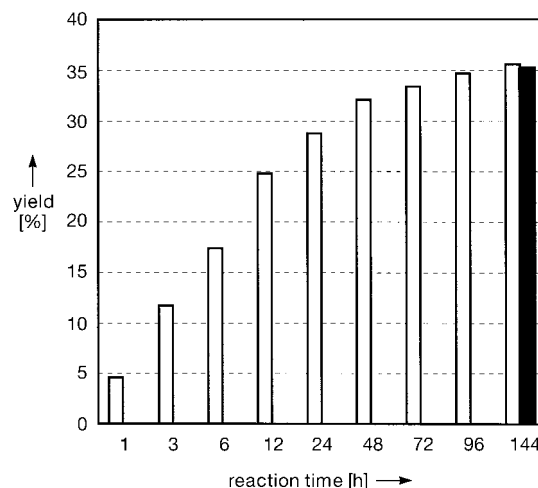


Figure 3. Course of the peptide amidase catalyzed amidation of Z-Gly-Phe-OH in acetonitrile containing 5% water with time. Conditions: 0.025 mmol of Z-Gly-Phe-OH, 0.035 mmol of NH₄HCO₃, 2 mg of amidase, 0.5 mL total volume, 40 °C. Open bars: yield of Z-Gly-Phe-NH₂; solid bars: a second portion of enzyme (2 mg) was added after 72 h of incubation.

equilibrium was reached after two days and remained nearly unchanged for a further four days. The addition of fresh enzyme after 72 h did not influence the amide yield over a further period of 72 h.

In the hydrolysis reaction, the enzyme was nonspecific with respect to the amino acid side chains of the peptide.^[7] The yield of the enzymatic peptide amidation in acetonitrile seems to be dependent on the structure of the peptide substrate (Table 2). Poor yields were obtained in mixtures that led to the formation of insoluble ammonium salts. The dramatic decrease in yield for Z-Gly-Tyr-NH₂ as compared to Z-Gly-Phe-NH₂ cannot be explained at present.

The limitations of the enzymatic amidation of peptides result mainly from solubility parameters. Precipitation of peptide substrates as ammonium salts under reaction conditions must be avoided. The first prerequisite for the successful application of peptide amidase for amidation is to find an optimal solvent mixture with regard to the solubility of the substrate. The excess of nucleophile required for the reaction is surprisingly low. The ammonium donor should be chosen so as to maintain a suitable pH. These requirements must be fulfilled individually for each peptide. Our results demonstrate that enzymatic amidation of unactivated α -carboxy

Table 2. Peptide amidase catalyzed amidation of peptides in acetonitrile containing 5 % of water.^[a]

Peptide	Yield [%] of amide	Precipitation of ammonium salt	t_{ret} [min] amide	t_{ret} [min] peptide
Z-Gly-Phe-OH	33.5	no	6.73	8.84
Z-Gly-Leu-OH	27.5	yes ^[b]	5.83	7.89
Z-Gly-Tyr-OH	1.0	yes	3.96	4.71
Z-Ala-Phe-OH	8.0	yes ^[c]	8.08	11.04
Z-Leu-Phe-OH	23.0	no	19.84	26.83
Z-Pro-Phe-OH	21.5	no	11.58	14.57
Z-Phe-Ala-OH	33.0	yes ^[b]	8.10	9.90
Z-Ala-Pro-Leu-OH	24.0	no	8.75	10.75

[a] 0.025 mmol of peptide, 0.035 mmol of NH_4HCO_3 , 2 mg of amidase, 0.50 mL total volume, 72 h, 40 °C. [b] Precipitation after 40 h. [c] Immediate precipitation.

groups in peptides is possible. The necessary enzyme can be isolated from orange peel, a waste product of the juice industry, by a simple two-stage extraction procedure that yields 300–500 U per kilogram of peel.^[9] Since the unchanged peptide can be easily recycled, enzymatic amidation could be economically feasible after further optimization.

Experimental Section

Typical procedure for the amidase-catalyzed amidation of peptides: The reactions were carried out in 2-mL plastic tubes with screw caps, which were incubated in a rotatory shaker at 1000 rpm and various temperatures. The benzyloxycarbonyl dipeptide (0.025 mmol) was dissolved in acetonitrile (475 μL). The required water and ammonium concentrations were adjusted by the addition of water and 2 M NH_4HCO_3 to give the final calculated volume of 500 μL . After the addition of lyophilized amidase (2 mg), the suspension was shaken at 40 °C for several days. Before the termination of the reaction, the apparent pH value of the mixture was checked with indicator paper. The reactions were terminated by diluting the mixture with 50 % aqueous methanol (1.5 mL) containing 1 % trifluoroacetic acid (TFA). The product yield was estimated by HPLC on an RP-18 column (Merck, WP-300, 5 μm , 25 $\times$ 0.4 cm) operated isocratically with a mixture of methanol and 0.1 % TFA (45/55) at 1 mL min⁻¹. Detection was carried out at 254 nm. The newly formed peak corresponded to the peptide amide and had a retention time identical to that of a standard sample. To follow the course of the amidase-catalyzed amidation of Z-Gly-Phe-OH with time, reactions were performed in several test tubes and terminated after a given time interval.

Synthesis of Z-Gly-Phe-NH₂: Z-Gly-Phe-OH (357 mg, 1 mmol) was dissolved in a mixture of acetonitrile (19 mL) and water (0.3 mL). After a solution of NH_4HCO_3 (0.7 mL, 2 M) and amidase (80 mg) was added, the mixture was shaken in a sealed vessel at 35 °C for 4 d. According to HPLC analysis the yield of Z-Gly-Phe-NH₂ was 31 %. The neutral product was isolated by cation- and anion-exchange chromatography and crystallized from ethyl acetate/petroleum ether to give 82 mg of dipeptide amide (23 % yield, pure according to TLC and HPLC analysis). The m.p. of 133–134 °C corresponds to that of standard sample. Amino acid analysis: Gly 1.00, Phe 0.99; FAB-MS: 356.1 [$M+H$]⁺.

The peptide amidase was isolated according to the literature procedure.^[7,9] The lyophilized enzyme had an activity of 0.2 U mg⁻¹ with Z-Gly-Tyr-NH₂ as substrate. The peptides were purchased from Bachem (Germany), and ammonium salts were obtained from Fluka (Switzerland).

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Secondary Bonding between Chalcogens or Pnictogens and Halogens**

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The more crystal structures we know, the clearer it becomes that in the solid state there are many contacts in the range between a bond and a van der Waals interaction. N. W. Alcock introduced the useful term “secondary bonding” for these, and formulated a set of rules for their occurrence and directionality.^[1]

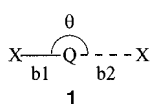
For electron-rich main-group systems there are two popular ways to address in a qualitative way the electronic structure of secondary bonded species—either as a manifestation of hypervalence (electron-rich three-center or multicenter bonding^[2]) or as directional donor–acceptor bonding.^[3] We feel these approaches are in fact equivalent, though we doubt that the number of energetic electrons expended on the demerits of one or the other chemical views is exhausted.

In recent work we have used the concept of donor–acceptor interactions to interpret calculations on hypervalent bonding in the trihalides and hydrogen bihalides,^[4] intermolecular interactions in R_2QX_2 (Q = Se, Te; X = I, Br, Cl),^[5] and the secondary bonding in dimers of Ph_2IX and XF_3 (X = I, Br, Cl).^[6] These studies, and the importance of directionality in secondary bonding,^[7] have led us to look more broadly at the nature of secondary interactions. In this work searches of the Cambridge Structural Database^[8] (CSD) have been used to determine the prevalence and geometries of secondary bonding in crystals containing chalcogens or Group 15

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elements (pnictogens) as one interacting group and halides as the other.^[9] The arrangement of atoms used in our search of the CSD is sketched in **1**. The restrictions we imposed are that *b1* be indexed as a bond (of any type) in the database, *b2* is any kind of contact (bonded or “nonbonded”, inter- or intramolecular) less than 4.5 Å in length, and θ has a value between 150 and 180° (one of Alcock’s rules points to the approximate colinearity of primary and secondary bonds; actually the multitudinous polyiodide structures known to us show that colinearity is not essential—it is the overlap of donor and acceptor functions that is determinative). To maintain as much generality as possible, no restrictions were placed upon either the oxidation state or coordination numbers of the atoms involved in the bonds.

All CSD searches were carried out using the Quest software provided with the database. The total data set obtained was of nontrivial size (almost 3000 entries). The data were post-processed with “custom” software to ensure that *b1* is less than or equal to *b2* (by switching the two values if necessary), to calculate bond asymmetry parameters, and to remove duplicate entries.

While CSD searches were carried out for all possible combinations of *Q* = As, Sb, Bi, Se, Te; *X* = F, Cl, Br, I, for reasons of brevity, and because the data sets show similar features, only two sets of results will be discussed here: the full *X* series for *Q* = Sb and Te.

Figure 1 shows the scatter plots of *b1* and *b2* for the *Q* = Sb, Te; *X* = F, Cl, Br, I systems. Some features are immediately apparent: First, for *Q* = Sb, the bond pairs observed appear to be grouped into two distinct sets. The first, lying close to the line *b1* = *b2*, connects to the second set at large values of *b1*. The graph for Set 2 curves upward sharply as *b1* gets shorter. In order to show the data as compactly as possible the scales for the *b1* and *b2* distances are different. The presence of two sets of bond-pair types in the scatter plots of Figure 1, in contrast to the single set (corresponding to Set 2) observed in earlier structural database studies,^[9a,9c] is due to the generality of the search criteria used. The restrictions on oxidation state

and coordination number or both used in earlier work rule out the appearance of Set 1, which is composed almost exclusively of Sb⁵⁺ compounds.

The plots for *Q* = Sb with *X* ≠ F all show similar curved regions, but the plots for *Q* = Te, *X* ≠ F are shaped differently. These latter plots also seem to be divided into two clear sets, however, the region where *b1* and *b2* are approximately equal is now at a large value of *b1*. Figure 2 shows a schematic view of the two sets of data points for both *Q* = Sb and *Q* = Te.

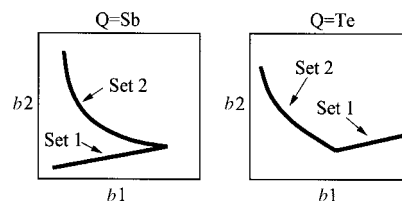


Figure 2. Schematic diagrams of the data sets for *Q* = Sb and *Q* = Te.

Fluorine is different, as usual. For *Q* = Sb there is a very sharply increasing region with only a few points when *b1* has a value between 1.9 and 2.0 Å. This region may correspond to Set 2. However, in general, it seems that intermolecular contacts between pnictogens or chalcogens and fluorine mostly occur at large values of *b2*; these contacts are more like van der Waals interactions than secondary bonds.^[10]

In Figure 3 we plot the bond angle (θ) versus the bond-length asymmetry parameter, *asym* (*asym* = (*b2* − *b1*)/*b1*). These plots share similarities: dense groupings of points with small *asym* and θ close to 180° (these are the members of Set 2). In general, as *asym* increases, the deviations from θ = 180° also increase. Another trend which can be seen in Figure 3 is a general narrowing of the distribution of points along the *asym* axis upon moving from Cl → Br → I.^[11]

Scatter plots (not shown here) constructed for *Q* = As, Bi, and Se, although containing varying numbers of bond pairs, show similar features. The general trend of a narrowing of the distribution of bond asymmetries is also seen as *Q* moves down a column of the periodic table; that is the distribution for *Q* = Bi is narrower than that for *Q* = As.

The regularities in the large crystallographic data set are intriguing. To get a feeling for what is happening, we examine a selection of structures from the *Q* = Sb, *X* = Cl data set. We start at the short (low *b1*) end of Set 1. The [SbCl₆][−] ion is well known—a CSD search turns up more than 200 distinct [SbCl₆][−] units. For instance, the geometry of [SbCl₆][−] when it is a counterion for the meth-

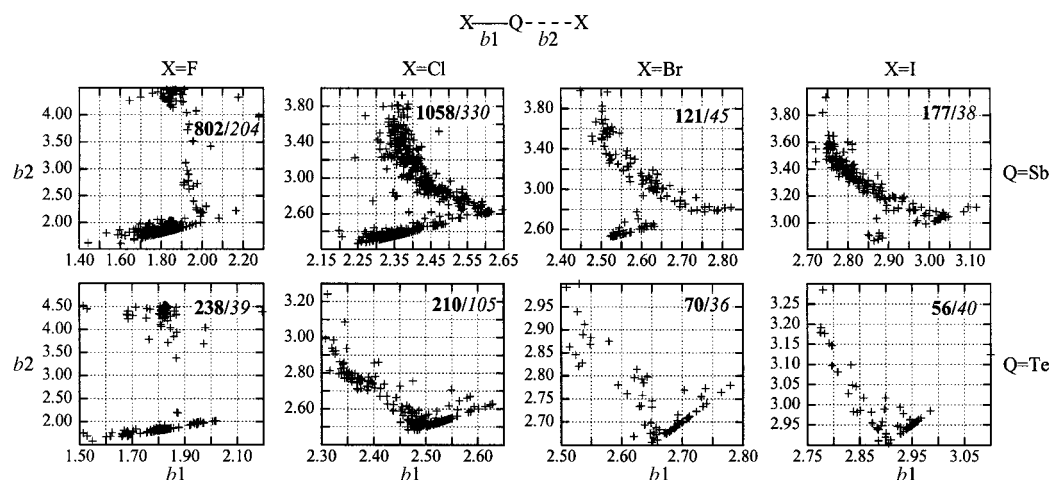


Figure 1. Scatter plots of the bond lengths *b2* and *b1* for the antimony- and tellurium-halide systems. The number in italics in each plot is the number of structures found in the database. The number in boldface is the number of distinct *b1* – *b2* pairs.

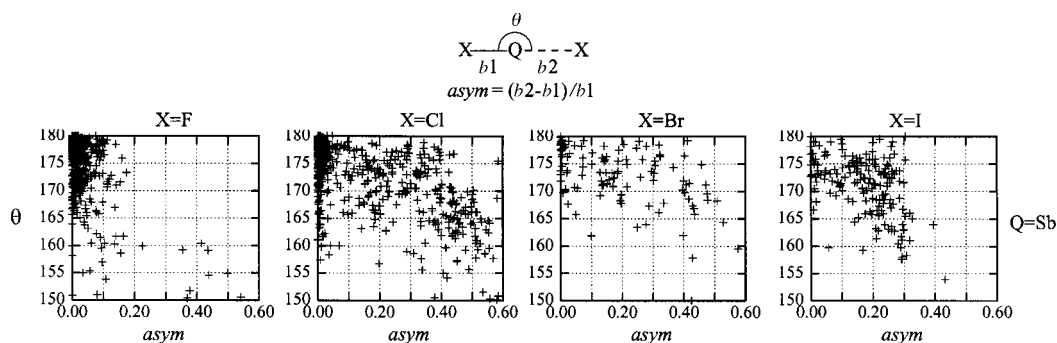
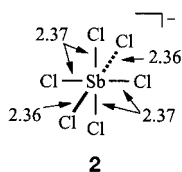


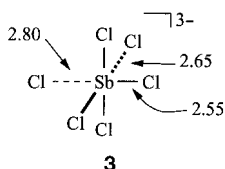
Figure 3. Scatter plots of the bond asymmetry parameter (*asym*) and angle θ for the antimony-halide systems.

ylloxocarbenium ion is shown in **2**.^[12] $[\text{SbCl}_6]^-$, isoelectronic to the familiar SF_6 , is a hypervalent molecule with electron-rich three-center bonds.^[13] The potential energy surfaces for distortions of these bonds are quite flat (more about this below), so we would expect the geometry of $[\text{SbCl}_6]^-$ to be sensitive to its environment in the crystal. Such effects can easily give rise to the 0.01 Å differences in bond lengths observed in **2**.^[14, 15]



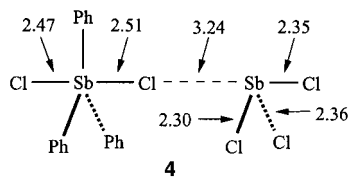
The Sb-Cl distances need not be so short, even if $b_1 = b_2$. An example is SbPh_3Cl_2 .^[16] This trigonal bipyramid structure has Sb-Cl distances of 2.46 and 2.47 Å. The surface for symmetrical hypervalent bonding must therefore be soft.

From the "long side" of the linear region of the Sb-Cl graph, past the point where Sets 1 and 2 merge, comes the $[\text{SbCl}_6]^{3-}$ ion found in tetrakis(dimethylammonium)hexachloroantimony chloride (**3**).^[17] This interesting species is roughly isoelectronic to XeF_6 and exhibits both very long (2.65 Å) symmetrical Sb-Cl contacts and an asymmetrical (*asym* = 0.10) secondary bond. The antimony center here is in the +3 oxidation state and has a lone pair of electrons that should occupy the sixth site of an octahedron. The geometry of the



secondary bond here violates one of Alcock's rules: the secondary bond should not lie in the same direction as a lone pair on the central atom.^[1]

The bonding in these molecules can be described as being not very different from the many, and well-understood, triiodides.^[4] The symmetrical I_3^- , $[\text{SbCl}_6]^-$, and $[\text{SbCl}_6]^{3-}$ ions are classic cases of electron-rich three-center bonding.^[13] In the same way, the unsymmetrical cases can also be viewed as perturbed three-center systems. Alternatively, they may be seen as donor-acceptor complexes: the donor is a halide lone pair of electrons, the acceptor the only remaining σ^* orbital of the I_2 molecule, or the Sb-Cl bond. Alcock's rules are often not followed.



Another species that has Sb-Cl interactions falling into both Sets 1 and 2 is $\text{SbPh}_3\text{Cl}_2 \cdot \text{SbCl}_3$ (**4**).^[18] The Cl-Sb-Cl system within the

SbPh_3Cl_2 molecule here is quite similar to that in $[\text{SbPh}_3\text{Cl}_2]$ itself. The secondary contact (indicated with a thin dashed line) is both long and very asymmetric (*asym* = 0.38), but still shorter than an Sb-Cl van der Waals contact (≈ 4.0 Å).^[19] The geometry of the secondary contact is somewhat unusual, because it is not immediately clear from the geometry which molecule is acting as a donor and which is the acceptor. Both molecules have donor capabilities (SbPh_3Cl_2 through the lone pairs on the Cl atoms and SbCl_3 through the lone pair on the Sb^{3+} ion) and both have σ^* levels which can act as acceptors. The secondary bond is parallel to the σ^* orbitals of both the SbPh_3Cl_2 and SbCl_3 molecules. It seems there is no clear division in this intermolecular complex between the donor and the acceptor species. The Sb-Cl bond of 2.36 Å in the SbCl_3 molecule is also opposite a SbPh_3Cl_2 molecule (not shown in **4**). The shorter Sb-Cl contact (2.30 Å) on SbCl_3 is not involved in intermolecular interactions.

In the Te-Cl data set the bond pairs which are found in Set 1 are also clearly hypervalent: many of the bond pairs are from $[\text{TeCl}_6]^{2-}$ ions (isoelectronic to both XeF_6 and the $[\text{SbCl}_6]^{3-}$ species discussed above). The members of Set 2 are, once again, primarily intermolecular contacts.

Just from this small sampling of structures, the two sets found in the plots of Figure 1 can be interpreted. The systems which lie in Set 1 (with low asymmetry parameters and angles close to 180°) are best described as intramolecular electron-rich three-center bonds. Set 2 consists mainly of intermolecular and long intramolecular contacts: these are secondary bonds, best thought of as donor-acceptor interactions.^[20] These conclusions can be extended to the other members of the pnictogen-halide and chalcogen-halide series.

The potential energy surfaces for distortions of a $[\text{SbCl}_6]^-$ octahedron were systematically explored by using density functional calculations. Three distortions, corresponding to the symmetric stretch in an octahedron, a symmetrical stretch of the axial bonds alone, and an asymmetric stretch of just one bond, were studied. The energy curves computed, *per bond distorted*, are nearly identical. In every case, the energy required to stretch an individual Sb-Cl bond by 0.15 Å is on the order of only 2 kcal mol⁻¹. Similar results are obtained for the isoelectronic species TeCl_6 and $[\text{ICl}_6]^+$. The surface for the distortion of $[\text{ICl}_6]^-$, isoelectronic to $[\text{SbCl}_6]^{3-}$ and XeCl_6 , is even softer: a distortion of the I-Cl bond by 0.15 Å costs less than 1 kcal mol⁻¹. The surfaces for distorting these electron-rich three-center bonds are really flat.

There are still some questions left unanswered about the plots of Figures 1 and 2. For example, why is it that the incidence of secondary bonding seems to decrease as Q or X move upwards in the periodic table^[1] (Figure 1)? Why does the width of the distribution of the asymmetry parameter (*asym*) decrease as X changes from Cl → Br → I or as Q moves down a column of the periodic table? These two questions are intimately related and can be answered simultaneously, we believe.

If we focus on the members of Set 2 in Figure 1 (recall that these are the secondary contacts), there is a clear inverse correlation between secondary (*b2*) and primary (*b1*) bond lengths: as *b2* becomes shorter, *b1* gets longer. So, forming the secondary bond weakens the primary bond; an effect that an inorganic chemist would call a “*trans* influence”. This is what we would predict based upon our donor–acceptor view of these interactions; increased secondary bond strength indicates increased donation into the antibonding orbitals (and thus weakening) of the primary bond.

Towards the top of the periodic table bonds tend be stronger—this effect is well known for primary bonds and presumably holds for secondary bonds as well. The delicate balance between two effects—bond strengthening and the competition between primary and secondary bonds—may change as we move up the periodic table, affecting in turn the nature of the secondary bonds observed. For example, as we pointed out above, the distribution of the bond asymmetry parameter for secondary systems changes with position in the periodic table. As either Q or X is moved up in the table, the width of the distribution of *asym* gets broader; a consequence of the secondary bonds getting longer relative to the primary bonds. Since bonds *b1* and *b2* are both of the same type (between the same types of atoms), the secondary bonds must be getting weaker relative to the primary bonds. Note that these comments are about general trends; it is possible to delve into the data sets and find specific counter-examples.

Finally, we would like to point out that there is no clear dividing line between secondary and hypervalent bonding in the systems that we have examined. For example, the curve of Set 2 in the Sb–Cl system (Figure 1) runs smoothly, without breaks, between *b2* = *b1* = 2.65 Å (this hypervalent contact is shown in 3) and the higher regions where *b2* is approximately 4.0 Å. There just is no logical place to divide the data that connect these two extremes.

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Insertion of an Osmium Nitride into Boron–Carbon Bonds**

Thomas J. Crevier and James M. Mayer*

The activation and functionalization of C–X bonds has long been a focus of transition metal chemistry. In most cases, either the carbon atom or the X group bonds directly to the metal. Here we report novel reactions that cleave aryl–boron bonds, where both the aryl and boryl groups are added to a nitrido ligand. They can formally be considered as insertions of the nitrido ligand into B–C bonds. Nitrido complexes typically react to add single electrophiles or nucleophiles to the nitrogen atom.^[1] Electrophilic reactions include the alkylation of [Os(N)R₄][–] to [Os(NMe)R₄] by MeI,^[2a] and the reversible addition of BF₃·Et₂O to [CpOs(N)R₂] to form [CpOs(NBF₃)R₂] (R = CH₂SiMe₃).^[2b] The addition of PPh₃ is a typical nucleophilic process, as in the conversion of [Os(N)(tpy)Cl₂]Cl into [Os(NPPh₃)(tpy)Cl₂]Cl (tpy = 2,2':6'2''-terpyridine).^[2c]

Reaction of the nitrido complex [TpOs(N)Cl₂] (**1**; Tp = HB(pz)₃, hydrotris(pyrazolyl)borate)^[3,4] with one equivalent of BPh₃ rapidly gives the borylanilido compound [TpOs{N(Ph)BPh₂}Cl₂] (**2**) in excellent yield (Scheme 1). A similar product, [TpOs{N(Ph)B(Ph)OBPh₂}Cl₂] (**3**), is formed from the reaction of Ph₂BOBPh₂. Compound **2** reacts rapidly with atmospheric moisture in solution or in the solid state, while **3** can be handled briefly in the air. Reactions with water cleave the boron–nitrogen bond to give the known osmium(IV)

anilide [TpOs(NHPh)Cl₂] (**4**).^[4] Hydrolysis of **2** also yields Ph₂BOBPh₂ (1/2 equiv). PhBCl₂ and B(C₆F₅)₃ appear to form similar borylanilido complexes quantitatively (as shown by ¹H and ¹⁹F NMR spectroscopy), which are also converted by traces of moisture into **4** or [TpOs{NH-(C₆F₅)Cl₂}] (¹H, ¹⁹F NMR). BPh₃, PhBCl₂, and B(C₆F₅)₃ react rapidly with **1**, while Ph₂BOBPh₂ reacts substantially slower. Addition of **1** (1/3 equiv) to a 1:1 mixture of BPh₃ and B(C₆F₅)₃ leads to the exclusive and quantitative formation of **2** (¹H and ¹⁹F NMR), and aerobic workup gives **4** in good yield.

The X-ray crystal structures of **2** and **3** (Figures 1 and 2) show isolated molecules with roughly octahedral osmium

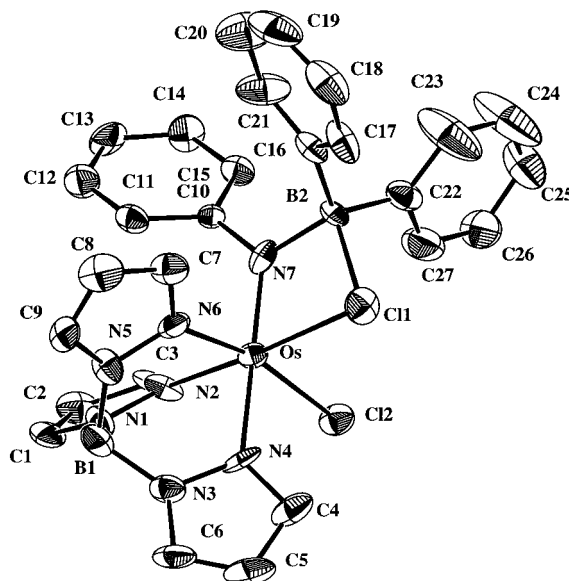
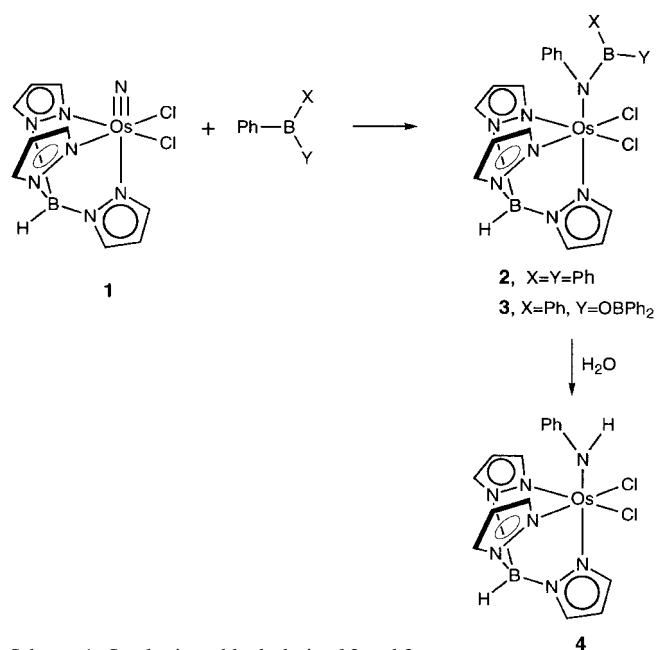


Figure 1. ORTEP diagram of the structure of **2**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Os–N7 1.884(10), Os–Cl1 2.404(3), Os–Cl2 2.354(3), N7–B2 1.600(20), B2–Cl1 2.078(14); Os–N7–B2 112.1(7).



Scheme 1. Synthesis and hydrolysis of **2** and **3**.

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centers. The borylamido nitrogen atom is planar in both structures (sum of the angles at N = 359.2°, 359.9°). The B2–N7 distance of 1.60(2) Å in **2** corresponds to a long single bond (av B–N 1.52 Å^[5]), while the Os–N7 bond is short (1.884(10) Å), indicative of multiple-bond character. In **3**, the B2–N7 distance is shorter (1.509(13) Å), and the Os–N7 distance is longer (1.937(7) Å), implying more delocalized π bonding. Consistent with the lack of B–N π bonding in **2**, the boron makes a weak fourth bond with a chloride ligand and has a roughly tetrahedral geometry. The B–Cl distance (2.078(14) Å) is the longest reported so far (av 1.822 ± 0.049 Å^[6]). Complex **3** lacks a B–Cl interaction because π donation from the N and O atoms reduces the Lewis acidity of the boron atom. The structures of **2** and **3** contrast with those of other structurally characterized transition metal borylamido complexes, which involve 3d metal centers and exhibit short B–N multiple bonds and little M–N π bonding.^[7]

Compounds **2** and **3** can be viewed as basic [TpCl₂Os^{IV}=NPh][–] fragments stabilized by Lewis acidic boryl moieties. The imido fragment can be formed independently from **1** and PhMgBr or LiPh (and also yields **4** on exposure to

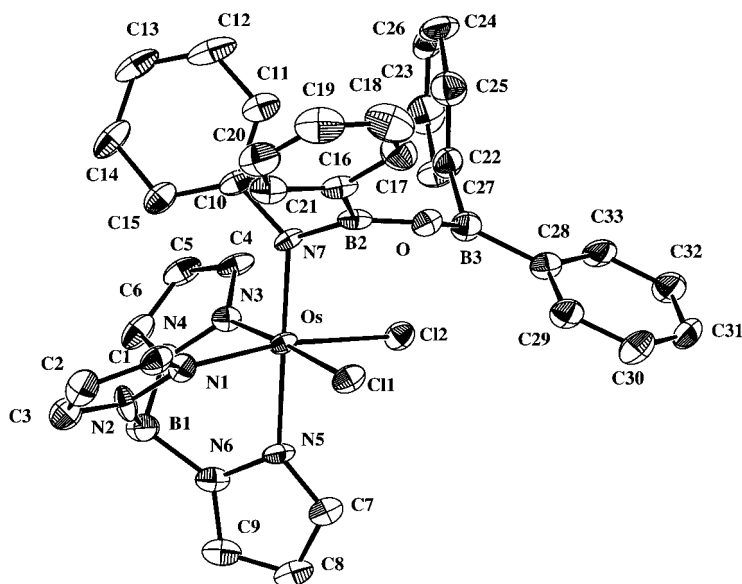


Figure 2. ORTEP diagram of the structure of **3**. The CH_2Cl_2 solvent molecules and hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Os–N7 1.937(7), Os–Cl1 2.362(2), Os–Cl2 2.372(2), N7–B2 1.509(13); Os–N7–B2 115.6(6).

moisture).^[4] The reactions involve reduction of the osmium center from +VI to +IV with concomitant oxidation of a phenyl group, from formally Ph^- in BPh_3 to Ph^+ in the borylamido product. Assignment of the oxidation state Os^{IV} to the osmium centers in **2** and **3** is supported by their narrow, paramagnetically shifted ^1H NMR spectra, characteristic of d^4 octahedral Os^{IV} and Re^{III} complexes.^[8] The spectra show C_s symmetry (down to -45°C for **2**), which indicates either that the B–Cl interaction in **2** is not maintained in solution or that it is cleaving rapidly on the NMR time scale.

The only previously reported reaction of a metal nitrido complex with an organoborane is the formation of the Lewis acid/base adduct $[\text{Re}(\text{NBPh}_3)(\text{Et}_2\text{dtc})_2(\text{PMePh}_2)]$ from BPh_3 and $[\text{Re}(\text{N})(\text{Et}_2\text{dtc})_2(\text{PMe}_2\text{Ph})]$ (Et_2dtc = diethyldithiocarbamate).^[9] The transfer of aryl and alkyl groups from boron to nitrogen centers has previously been observed on treatment of boranes with azides or chloramines.^[10] These reactions are proposed to proceed by initial adduct formation ($\text{N}:\rightarrow\text{B}$) followed by carbon migration to a low-lying empty orbital on the nitrogen oxidant (similar to Baeyer–Villiger oxidations).^[11] A similar mechanism is possible for the reactions of **1**, although the nitrido ligand has very low basicity. It is unreactive with respect to $\text{BF}_3\cdot\text{Et}_2\text{O}$, $\text{MeOSO}_2\text{CF}_3$, and $\text{Ph}_3\text{C}^+\text{BF}_4^-$, the latter being isoelectronic and much more Lewis acidic than BPh_3 . Instead, the nitrido nitrogen atom acts as an electrophile and forms adducts with PPh_3 and a N–Ph bond with the Ph^- group from PhMgBr , as noted above.^[4] The observation that **1** reacts preferentially with BPh_3 rather than the much more acidic $\text{B}(\text{C}_6\text{F}_5)_3$ indicates that the reaction is not dominated by the Lewis acidity of the borane but rather also involves the nucleophilicity of the aryl group. Rate-limiting aryl transfer could occur by direct attack of the nitrido, either at the *ipso* carbon atom or at the B–C bond, or by migration in a weak borane–nitrido adduct.

Experimental Section

Manipulations were carried out under N_2 with dry degassed reagents.

2: A mixture of **1** (180.0 mg, 0.368 mmol), BPh_3 (108.0 mg, 0.446 mmol, 1.21 equiv), and benzene (10 mL) was stirred for 5 min. The solution was filtered through a glass frit, layered with hexane (60 mL), and allowed to stand overnight to yield dark orange crystals of **2** (138 mg, 52%). ^1H NMR (CDCl_3): δ = 6.29 (t, 2 H, 1 H, pz), 6.94 (d, 2 H, 1 H, pz), 7.47 (d, 2 H, 1 H, pz), 6.12 (t, 2 H, 2 H, pz'), 6.05 (d, 2 H, 2 H, pz'), 7.00 (d, 2 H, 2 H, pz'), 4.50 (d, 7 Hz, 2 H, *ortho*-NPh), 7.26 (t, 7 Hz, 2 H, *meta*-NPh), 6.90 (t, 7 Hz, 1 H, *para*-NPh), 7.63 (d, 7 Hz, 4 H, *ortho*-BPh₂), 7.32 (t, 7 Hz, 4 H, *meta*-BPh₂), 7.43 (t, 7 Hz, 2 H, *para*-BPh₂); elemental analysis calcd for $\text{OsC}_{27}\text{H}_{25}\text{N}_7\text{B}_2\text{Cl}_2$ (found): C 44.40 (44.03), H 3.45 (3.42), N 13.43 (13.42).

3: Prepared as above for **2** except that the mixture was stirred overnight; yield of isolated product 34%. ^1H NMR (CDCl_3): δ = 5.96 (t, 2 H, 1 H, pz), 5.73 (d, 2 H, 1 H, pz), 4.72 (d, 2 H, 1 H, pz), 6.69 (t, 2 H, 2 H, pz'), 6.96 (d, 2 H, 2 H, pz'), 4.12 (d, 2 H, 2 H, pz'), 9.20 (t, 7 Hz, 2 H, Ph), 7.70 (d, 7 Hz, 4 H, *ortho*-BPh₂), 7.47 (t, 7 Hz, 1 H, *para*-Ph), 4.10 (t, 7 Hz, 2 H, Ph), 1.91 (t, 7 Hz, 1 H, *para*-Ph), 1.27 (overlapping, 4 H, d), 0.89 (t, 7 Hz, 2 H, Ph), –4.10 (t, 7 Hz, 4 H, *meta*-BPh₂); EI-MS: m/z : 834 (v weak, M^+), 799 (v weak, $M - \text{Cl}$), 722 (weak, $M - \text{Ph} - \text{Cl}$), 567 (major, $M^+ - \text{PhBOBPh}_2$), 531 (major, $M^+ - \text{PhBOBPh}_2 - \text{Cl}$).

Structure analysis of **2** and **3**: Crystals were obtained by slow evaporation of solutions in $\text{CH}_2\text{Cl}_2/\text{Me}_3\text{SiOSiMe}_3$, and were immersed in oil and mounted under a stream of N_2 . Data were collected on an Enraf-Nonius CAD4 diffractometer at 187 K with $\text{MoK}\alpha$ radiation (λ = 0.71073 Å). Full-matrix least-squares refinement was carried out with SHELXL-93.^[12] Semi-empirical absorption corrections were made with ψ scans. **2**: $\text{OsC}_{27}\text{H}_{25}\text{N}_7\text{B}_2\text{Cl}_2$, monoclinic, space group $C2/c$, a = 21.268(4), b = 9.739(2), c = 28.269(5) Å, β = 108.88°, V = 5540(1) Å³, Z = 8, ρ_{calcd} = 1.751 g cm^{–3}, 4258 reflections, 3629 unique, 352 parameters, R = 0.0389, $R_w(\text{on } F^2)$ = 0.0924, GOF = 0.945. **3**· CH_2Cl_2 : $\text{OsC}_{34}\text{H}_{32}\text{N}_7\text{OB}_2\text{Cl}_4$, triclinic, space group $P\bar{1}$, a = 11.578(3), b = 12.343(5), c = 15.482(5) Å, α = 91.31(2), β = 110.59(2), γ = 115.35(2)°, V = 1832.0(11) Å³, Z = 2, ρ_{calcd} = 1.666 g cm^{–3}, 6404 reflections, 5986 unique, 445 parameters, R = 0.0591, $R_w(\text{on } F^2)$ = 0.1452, GOF = 1.093. 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-100925. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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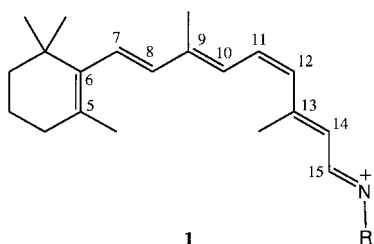
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Absolute Sense of Twist of the C12–C13 Bond of the Retinal Chromophore in Rhodopsin—Semiempirical and Nonempirical Calculations of Chiroptical Data**

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The protonated Schiff base of 11-*cis*-retinal, 11-*cis*-retinal PSB (**1**), is the light-sensitive chromophore of rhodopsin, the



photoreceptor that is responsible for dim-light vision of vertebrates. Photochemical isomerization of **1** to the all-*trans* isomer triggers the visual transduction process, which eventually results in the excitation of the visual nerve and the liberation of all-*trans*-retinal from the protein.^[1] To understand this process on a molecular basis, the conformation of the retinal chromophore and its interaction with neighboring groups inside the protein-binding pocket have been studied by a variety of methods, mostly spectroscopic and including circular dichroism (CD) spectroscopy.^[2]

All retinals are chiral (point group C_1), a consequence of the distorted geometry about the C6–C7 bond of the β -ionone ring. In addition, steric hindrance from the C13 methyl group may cause the C13–N16 fragment in **1** to rotate about

the C12–C13 bond into a more stable geometry. In the absence of other sources of chirality, retinal conformations in which the dihedral angles are twisted in the opposite direction are enantiomers and cannot be distinguished. In the chiral environment of the protein pocket, discrimination between the enantiomers takes place and the chromophore becomes optically active, leading to two well-resolved positive CD absorptions in the visible (480 nm) and near-UV (340 nm) region. These absorptions are called the α and the β band, respectively.^[3] It has long been assumed, on the basis of spectroscopic studies of conformationally locked retinal analogues,^[4] that the α - and β -bands derive their rotatory strengths from the twist about the C12–C13 and the C6–C7 bonds, respectively.

Recently, in a study of artificial pigments formed from bovin opsin with several 11,12-dihydroretinal derivatives, the absolute sense of twist of the C12–C13 bond was derived from CD exciton chirality theory,^[5] a method that cannot be applied to the native chromophores with their through-conjugated π systems. In view of the importance of the absolute configuration of the retinal chromophore for modeling the binding site in rhodopsin, we computed the chiroptical properties of 11-*cis*-12-*s-trans*-retinal PSB directly with the best methodologies available. The results prove that a positive long-wavelength CD absorption of this compound corresponds to a positive twist about the C12–C13 *s-trans* bond.

The starting point for every calculation of chiroptical properties is a reliable three-dimensional molecular structure. The only known crystal structure of a retinal PSB has an all-*trans*-configured chromophore, including *trans* C11–C12 and C6–C7 bonds.^[6] This configuration corresponds to the dark-adapted state of bacteriorhodopsin^[7] but not to rhodopsin, in which the conformation is twisted 6-*s-cis*-11-*cis*-12-*s-trans*. The crystal structure of 11-*cis*-retinal is of no use either as the chromophore is twisted from 12-*s-cis*.^[8] Computational resources are now sufficient to treat molecules as large as retinal in a rigorous manner. We have recently reported the completely optimized geometry of *N*-methyl-11-*cis*-12-*s-trans*-retinal PSB (**1**, R = Me) employing *ab initio* (RHF/6-31G**) and density functional theory (DFT) methodologies (B3LYP/6-31G**).^[9] According to these calculations the whole chromophore is planar except for the C6–C7 dihedral angle. This structure agrees with results of other calculations of comparable sophistication,^[10] and with the exception of the rotation about the C12–C13 bond, is our basis for the calculation of chiroptical properties.

From resonance Raman spectroscopy^[11] it is known that the C12–C13 bond is twisted significantly from *s-trans* as a consequence of steric and/or electronic interactions with the protein environment, a factor that we have not taken into account in our calculations. We arbitrarily assigned values of $+160^\circ$ and -160° to this dihedral angle (180° corresponds to a planar *s-trans* conformation) and have combined each of these with the two possible orientations of the cyclohexene ring. Calculations of the excited states of these geometries were performed with three different theoretical models: CNDO/S including configuration interaction of 100 singly excited states (model 1); the nonempirical method CIS from the GAUSSIAN 94 package^[12] using the same basis set as for the

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geometry optimization augmented by diffuse functions, that is 6-31 + G**, (model 2); and the nonempirical method CASSCF/CASPT2 from the MOLCAS-4 package^[13] (model 3). This last set of calculations was too demanding on computational resources, and so the saturated residue of the cyclohexene ring (C1 to C4) was substituted by two hydrogen atoms. The basis set of density matrix averaged atomic natural orbitals (ANO-L^[14]) consisted of 3s2p functions for the heavy elements and 2s for the hydrogen atoms. The active space chosen contained 12 electrons in 11 orbitals, all of local π symmetry. The results of the calculations are summarized in Table 1.

All three methods identify the excited state of lowest energy as the strongly allowed ^1B_u state (approximate

Table 1. The calculated wavelength λ , oscillator strength f , and rotatory strength R of the lowest excited state of **1** as determined by three different methods for four different combinations of dihedral angles θ_{6-7} and θ_{12-13} .

θ_{6-7}	θ_{12-13}	Method ^[a]	λ [nm]	f	R [$D\mu_B$]
-60°	160°	1	440	1.4	0.4
		2	351	1.96	2.6
		3	483	2.35	1.1
58°	-160°	1	443	1.5	-0.43
		2	354	1.97	-2.3
		3 ^[b]	-	-	-
-60°	-160°	1	439	1.5	-0.98
		2	351	1.98	-1.79
		3	483	2.35	-1.06
58°	160°	1	443	1.5	0.98
		2	354	1.99	2.0
		3 ^[b]	-	-	-

[a] 1: CNDO/S; 2: GAUSSIAN94/CIS; 3: MOLCAS4/CASPT2. [b] Not calculated because of close enantiomeric relationship to conformation above.

symmetry label according to the C_{2h} point group of an all-*trans*-configured polyene) consisting mainly of the HOMO–LUMO excitation of the conjugated π system. This excited state is polarized approximately along the long axis of the molecule and has high oscillator strength. The energies of this state differ considerably between the models. Of the two nonempirical methods used, the results of perturbational calculations are closest to the experimental wavelength at 480 nm for the α band. This agreement is at least partly accidental since all the factors assumed to be responsible for the special long-wavelength shift that the chromophore undergoes in the protein pocket (the opsin shift) are not considered in these calculations. The CIS calculations deviate by more than 130 nm from the experimental value, no doubt a consequence of the very limited configuration interactions, which considers only singly excited states. The parametrized semi-empirical method is intermediate in its accuracy. The origin of the β band is more difficult to ascertain. So far our calculations have not yielded converging results for the higher excited states of **1**.

Regardless of these differences all three models yield positive rotatory strengths R for the lowest excited state independent of the orientation of the β -ionone ring (the sign of θ_{6-7}), provided the dihedral angle at the C12–C13 bond is

positive. The calculated rotatory strength is negative when this angle is negative. The absolute value of R depends, like the oscillator strength, on the method of calculation; the magnitude is, however, in the range of the experimentally observed value of about $0.5 D\mu_B$.^[3]

There is a simple physical picture which supports the correlation between the sign of θ_{12-13} and the sign of the α band. Figure 1 shows 11-*cis*-12-*s-trans*-retinal PSB with a

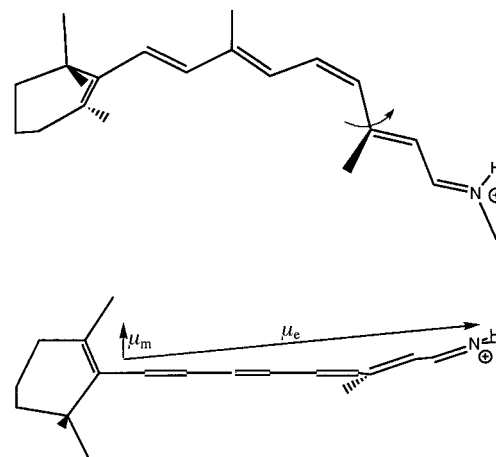


Figure 1. Side view (top) and plan view (bottom) of the twisted conformer of **1**. The geometry corresponds to that of the first entry of Table 1. For an explanation of the electric and magnetic transition moments, μ_e and μ_m , respectively, see the text.

negative dihedral angle θ_{6-7} and a positive dihedral angle θ_{12-13} . The electric transition moment μ_e that is directed along the chromophore lies in the plane of the central fragment but has a small, though critical, perpendicular component in the direction of the twisted C13–N16 fragment. The magnetic transition moment μ_m is caused mainly by the circular charge movement along the chromophore and is almost perpendicular to the central chromophore fragment, but also in the direction of the C–N⁺ fragment. The resulting rotatory strengths computed as the scalar product of the two is thus positive (the angle between the two moments is 87.9° according to CNDO/S and 87.7° according to CIS calculations). Changing the sign of θ_{12-13} inverts the perpendicular component of the electric transition moment but leaves the magnetic moment unchanged, with the result that the rotatory strength changes sign.

Is there a flaw in our treatment in that we started with a chromophore that was calculated to be planar except for the twisted C6–C7 bond? We believe not. In principle, torsion about any bond of the chromophore could be the origin of the observed CD spectrum. We have concentrated on the C12–C13 bond for two reasons. Firstly, the location of the bond close to the center of the chromophore is crucial. Our calculations show (and intuition suggests) that terminal torsion, for example about the C6–C7 bond, results only in minor perturbation of the long-wavelength absorption. Secondly, the C12–C13 bond is especially prone to distortion because of steric hindrance between the C13 methyl group and the C10 hydrogen atom. The planar minimum-energy geometry is realized only in the protonated species where the

system can gain maximal benefit from resonance stabilization. In the deprotonated species, the system relaxes into a geometry which is twisted in this region, albeit slightly.^[9] In rhodopsin, the chromophore is certainly not deprotonated. However, according to two photon spectroscopic measurements the binding site of rhodopsin is neutral;^[15] that is the charge balanced by a negatively charged counter ion, most probably the carboxylate group of glu113, which interacts with the chromophore in the C12–C13 region^[16] and may cause not only partial fixation of the double bond but also additional steric distortion.

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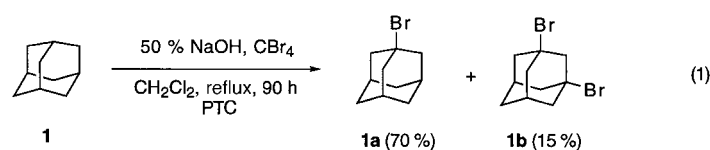
Selective C–H Activation of Aliphatic Hydrocarbons under Phase-Transfer Conditions**

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Dedicated to Professor Paul von Ragué Schleyer

The selective activation of aliphatic hydrocarbons,^[1] is mostly achieved with electronically unsaturated transition metal complexes,^[2–6] superacids,^[32] or enzymatic processes.^[7, 8] In this paper we present a highly unusual C–H activation of aliphatic hydrocarbons by phase-transfer catalysis (PTC) in mixed aqueous/organic solvents.

When treated with tetrabromomethane and sodium hydroxide under standard PTC conditions (catalyst: triethylbenzylammonium chloride), adamantane **1**^[9] gives 1-bromo- (**1a**) and 1,3-dibromoadamantane (**1b**) in 85 % conversion and 70 % yield [Eq. (1); Table 1]. The dibromide **1b** can also



be obtained from **1a** under the same conditions but with longer reaction times, which indicates a stepwise incorporation of bromine into the adamantane core. Although the synthesis of polybromoadamantanes^[10] is straightforward,^[11–15] we have chosen **1** as a model for studying tertiary C–H bond activations.^[1]

We arrived at these reaction conditions in the course of derivatizing adamantane **1** to its bridgehead substituted analogues^[9, 10] by dibromocarbene (from HCCl_3 /50 % $\text{NaOH}/\text{CH}_2\text{Cl}_2$ /PTC, 16 h, reflux) insertion into the bridgehead C–H bond. Apart from the desired dibromomethyladamantane (**1c**, 33 %),^[16] we also found **1a** (41 %), **1b** (16 %), and traces of 2-bromoadamantane (**1d**) (2 %). Since isolated **1c** does not form **1a** or **1b** under the same reaction conditions, we surmised that it is not the reaction of :CBr_2 with **1** that yields the bromoadamantanes. Rather, we reasoned that the halogen may be transferred from CBr_4 . This compound is known to equilibrate with HCCl_3 under the reaction conditions used.^[17, 18]

The transformation is highly regiospecific for the bridgehead position of **1** (the methyl groups of methyladamantanes

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Table 1. Bromination of some aliphatic hydrocarbons with 50 % NaOH/CBr₄ in CH₂Cl₂ under phase-transfer conditions (*T* = 40 °C, unless indicated; catalyst: triethylbenzylammonium chloride). Product yields [%] (preparative yield in parentheses) according to GC/MS and NMR analysis.

Entry	Substrate	<i>t</i> [h]	Product 1	Yield [%]	Product 2	Yield [%]
1	1	4	1a	31 (26)	1b	traces
2	1	16	1a	46 (40)	1b	5
3	1	90	1a	70 (61)	1b	15 (11)
4	1 ^[a]	16	1a	71 (61)	1b	11 (8)
5	1a ^[a]	90	1b	40 (35)	–	–
6		3 16		3a 35 (29)		3b 3
7		3 40		3a 38 (30)		3b 4
8		3 64		3a 38 (31)		3b 5
9		4 16		4a 24		4b traces
10		4 40		4a 38 (31)		4b 3
11		4 64		4a 44 (35)		4b 5
12		5 40		5a 43 (34)	–	–
13		5 64		5a 46 (37)	–	–
14		6 ^[b-d] 16		6a 37	–	–
15		7 ^[b,c] 16		7a 44	–	–
16		7 ^[b,c] 90		7a 70	–	–
17		8 90		8a 45 (41)	–	–

[a] Subsequent addition of two equivalents of CBr₄. [b] Substrate + 5 mL CH₂Cl₂ used as solvent. [c] Yield determined relative to amount of CBr₄ used. [d] At 25 °C.

3–5 remain intact, Table 1, entries 6–13) but it is not limited to the functionalization of adamantanes. Even acyclic hydrocarbons like **6** can be converted into the corresponding bromides selectively; only the tertiary C–H bond is activated. In the absence of tertiary C–H bonds, secondary C–H bonds can also be functionalized: cyclohexane (**7**) gives cyclohexyl bromide (**7a**) in 70 % yield (90 h, Table 1, entry 16)!

Although this paper presents a new synthetic method, we wish to communicate some preliminary findings concerning the reaction mechanism, which is complicated because of the two-phase system.^[18] Electrophilic catalysis by traces of impurities, as suggested for classical bromination reactions, is rather unlikely under these reaction conditions.^[12] For instance, electrophilic activation (with Br₂/Al₂Br₆) of 2-oxaadamantane (**8**) only gives 4-bromo-2-oxaadamantane in low yields.^[19] Here, however, we exclusively find 5-bromo-2-oxaadamantane (**8a**) in moderate yields (45 %, Table 1, entry 17).

A plausible mechanism is the formation of carbanions through deprotonation with “highly activated” OH[–].^[20, 21] While the hydroxide ion is able to deprotonate even allyl benzene (p*K*_a = 34)^[22, 23] and other weak C–H acids^[24, 25] under similar phase-transfer conditions, we did not find H/D

exchange^[24] in **1** in NaOD/D₂O under otherwise identical reaction conditions. No alkyl bromides were detected in the reaction with HOBr (from NaOH + Br₂), which should also transfer a bromonium ion onto an intermediate carbanion. While it is common that the phase-transfer agent is used up in carbanion reactions, we were able to recover most of the catalyst unchanged.^[18, 24, 25] Hence, though it cannot yet be entirely excluded, the formation of carbanions is rather unlikely.

Although the rate of the reaction is only very slightly reduced in the dark under N₂ atmosphere, a radical^[26] or single-electron transfer (SET) process^[17, 27–30] is indicated. This is supported by the fact that no alkyl bromides were detected in the presence of TEMPO (tetramethylpiperidyl *N*-oxide), an efficient radical trapping agent. The reaction mixtures turn dark after a short while due to polymer formation;^[17] CBr₄ is used up, and the transformation comes to a standstill after long reaction times. Addition of a second equivalent of CBr₄ restarts the conversion and increases the yields significantly (Table 1, entry 4). While lower NaOH concentrations decrease the yields considerably, the absence of the phase-transfer catalyst can in part be compensated by thorough mixing (high stirring speeds). The latter finding and the

observation that the reaction practically stops when not stirred hints at an interphasic PTC rather than an extraction mechanism.^[18]

Hence, we propose that the reaction is initiated by single-electron oxidation of OH[−] by CBr₄ [Eq. (2)]. This is likely to be a thermodynamically inefficient process in solution where the equilibrium lies to the far left. Similar equilibria were postulated for the reactions of carbanions with CBr₄.^[30] This mechanistic picture is supported by the findings that the reaction is rather slow and that no conversion occurs at much lower NaOH concentrations. The ·CBr₃ radical, possibly formed from CBr₄[−] [Eq. (3)], can then start the chain reaction [Eqs. (4) and (5)]. This mechanism may, at least in part, also



explain the observed selectivities for **1**. Although the 1- and 2-adamantyl radicals have similar thermodynamic stabilities ($\Delta H_f^\circ = 14.8$ and 12.3 kcal mol^{−1}, respectively),^[33] 2-adamantyl products only form in trace amounts.^[31] This last observation is likely to be due to the larger steric demands of the 2-adamantyl radical in both the hydrogen abstraction [Eq. (4)] and the radical substitution step [Eq. (5)]. It is important to emphasize the unusually high selectivity of tertiary over secondary C–H bonds and the monobromination in **6–8**. In stark contrast, free radical bromination of **1** with CBr₄/AIBN in CH₂Cl₂ under reflux afforded a mixture of **1a** and **1d** (2:1) in only 5% yield after 30 h.

In conclusion, we have found a new, highly selective method for the direct bromination of aliphatic hydrocarbons under phase-transfer conditions. The reaction is likely to proceed by single-electron-transfer initiation followed by a radical substitution with unusually high selectivity. A detailed elucidation of the reaction mechanism and the extension of this synthetic approach are well underway in our laboratories.

Experimental Section

General procedure: To a stirred solution of tetrabromomethane (1.33 g, 4.0 mmol), CH₂Cl₂ (15 mL), triethylbenzylammonium chloride (60 mg, 0.26 mmol), and substrate (4.0 mmol) was added 50% aqueous NaOH (10 mL). The solution was heated to 40°C (25°C for **6**) and stirred for various lengths of time (*t*[h]; see Table 1). The organic phase was separated off and the aqueous phase extracted with CH₂Cl₂ (4 × 10 mL). Excess reagents and solvents were removed by vacuum distillation. The residues were separated by column chromatography (silica gel, petroleum ether). All products were analyzed and identified by GC, MS, and NMR analysis. Preparative yields (Table 1, in parentheses) were determined for the reactions of **1–5** (entries 1–13) and **8** (entry 17).

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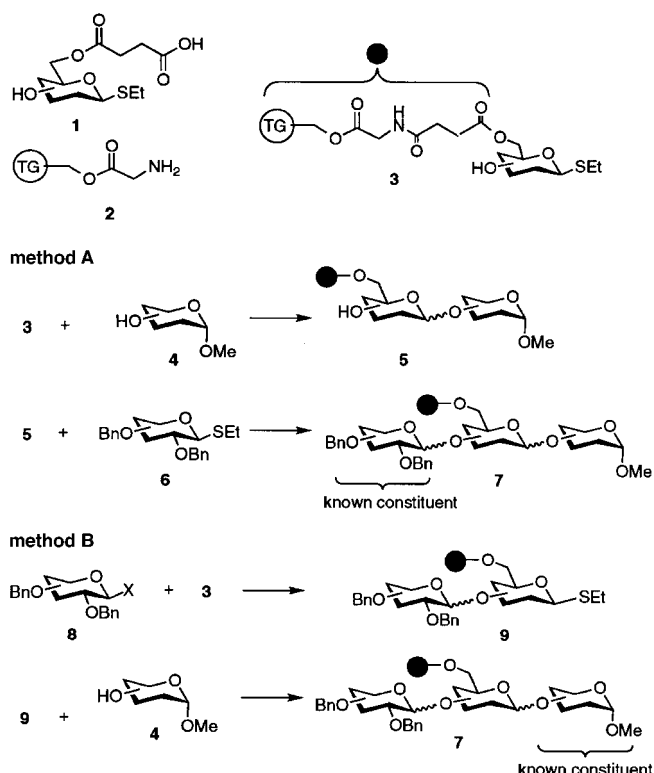
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A Two-Directional Approach for the Solid-Phase Synthesis of Trisaccharide Libraries

Tong Zhu and Geert-Jan Boons*

In recent years the search for novel pharmacological agents has focused on the preparation of "chemical libraries" as potential sources of new lead compounds for drug discovery.^[1] Combinatorial chemistry has been developed mainly for the preparation of peptide and nucleic acid libraries and some small molecules, but only very few reports deal with combinatorial carbohydrate chemistry.^[2] We report here the synthesis of a combinatorial saccharide library on a solid support whereby all glycosidic linkages are intentionally synthesized as mixtures of anomers. This approach addresses problems associated with classical oligosaccharide solid-phase synthesis.^[3] In addition, a novel two-directional approach^[4] for the assembly of the oligosaccharides on the solid support is used in which each immobilized saccharides can act as a glycosyl donor as well as an acceptor.

The strategic considerations for the preparation of trisaccharide libraries are summarized in Scheme 1. The thioglycosyl building blocks **1** are immobilized onto a solid support through the formation of an amide linkage between the carboxylic acid of a succinic acid moiety and the amine group

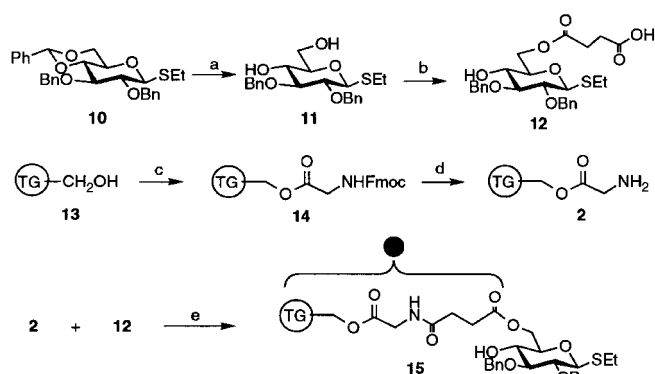


Scheme 1. A two-directional strategy for the syntheses of trisaccharide libraries.

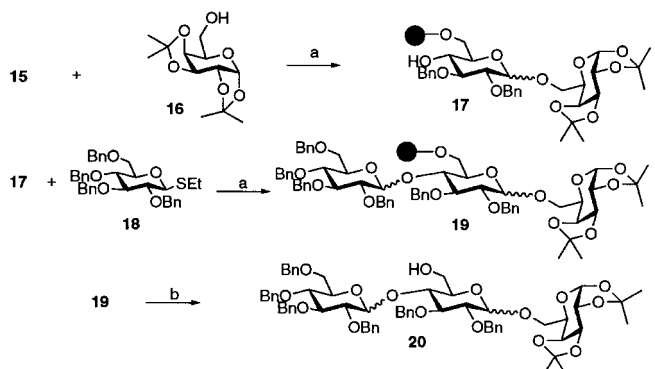
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of a glycine-derivatized polymer. This amide bond formation should offer a very reliable approach for immobilization. However, a product can simply be removed from the solid support by base-mediated cleavage of the ester linkage between the carbohydrate and the succinimide residue. Glycine-derivatized TentaGel hydroxyl resin (**2**; TG = TentaGel) was selected as the solid support so that the high flexibility and mobility of its polyethylene glycol moieties could be utilized, thus ensuring high reactivities of the immobilized compounds.^[5] A resin-bound saccharide **3** can first act as a glycosyl donor, and on reaction with a glycosyl acceptor **4** in solution will give a disaccharide **5**. It is hoped that oligomerization will be prevented by site isolation of the immobilized substrates. The resulting disaccharide can immediately be used in the next step as a glycosyl acceptor. When coupled with a thioglycoside **6** that is in solution, **5** will give a resin-bound trisaccharide **7**. A library of trisaccharides can be prepared by a mix-and-split approach. Thus, **3** can be coupled in individual glycosylation reactions to a range of acceptors, and the products can be mixed and split before each pool of resin-bound acceptors are glycosylated with a range of donors. After cleavage of the resin and deprotection, a library with a known residue at the nonreducing end is generated (method A). Alternatively, compound **3** can act as an acceptor and on coupling with donor **8** (X = F, SPh, or OCNHCCl₃) will give a resin-bound glycosyl donor **9**, which in a subsequent step can be coupled with an acceptor **4** to give a trisaccharide. A mix-and-split approach will thus give a trisaccharide library with a known residue at the reducing end of the saccharides (method B). A key principle will be that each glycosylation will be performed under conditions that give a mixture of anomers. Recently, we established^[6] that glycosylations^[7] of thioglycosides mediated by *N*-iodosuccinimide/trimethylsilyl trifluoromethanesulfonate (NIS/TMSOTf) in dichloromethane at room temperature consistently give mixtures of anomers.

Treatment of the dibutyltin acetal of diol **11** with succinic anhydride afforded **12** in an excellent yield of 85% (Scheme 2).^[8] Attachment of a Fmoc-protected glycine (Fmoc = fluorenyloxycarbonyl) to the TentaGel hydroxyl resin **13** (0.37 mmol g⁻¹ resin) under standard conditions^[9a] and subsequent removal of the Fmoc group by treatment with piperidine gave polymer **2**. Compound **12** was immobilized by amide bond formation with **2** in the presence of benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) to give the polymer bound monosaccharide **15** (Scheme 2).^[9b] Compound **15** was coupled with **16** in the presence of NIS/TMSOTf to give the desired disaccharide **17**, which after washing was used as an acceptor. Glycosylation with the perbenzylated thioglycosyl donor **18** gave the trisaccharide **19** (Scheme 3). This latter coupling was repeated due to an incomplete reaction (the 4'-OH group of **17** has a low reactivity). Completion of each reaction step was ascertained by thin-layer chromatography and matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) of the crude product after cleavage of a small amount of beads (3–5 mg) by treatment with base. Finally, treatment of **19** with MeONa/MeOH in 1,4-dioxane gave trisaccharide **20** (≈ 65% overall yield based on the resin



Scheme 2. Synthesis of the polymer-bound thioglycoside **15**. a) Trifluoroacetic acid (TFA), CH_2Cl_2 , 95 %; b) $\text{Bu}_2\text{Sn}(\text{OMe})_2$, benzene, Dean–Stark conditions then succinic anhydride, pyridine, 85 %; c) N,N' -diisopropylcarbodiimide (DIC), 4-dimethylaminopyridine (DMAP), Fmoc-GlyOH, DMF; d) piperidine (20 % in DMF), >90 % overall yield; e) PyBOP, diisopropylethylamine (DIPEA), DMF.



Scheme 3. Synthesis of trisaccharide **20** (method A). a) NIS/TMSOTf, CH_2Cl_2 , 4-Å molecular sieves; b) MeONa, MeOH, 1,4-dioxane then DOWEX50 (H^+) ion-exchange resin.

loading; Scheme 3). Analysis by NMR spectroscopy and mass spectrometry showed that no oligomerization had occurred and that all glycosidic linkages were formed as mixtures of anomers (Glc(1-4)Glc: $\alpha/\beta \approx 2/1$ and Glc(1-6)Gal: $\alpha/\beta \approx 1/1$). Thus, the NIS/TMSOTf-mediated glycosylation of thioglycosides in dichloromethane is highly compatible with the solid support and linker system employed. It is noteworthy that the glycosylation rates are significantly decreased (4 h) compared to those for similar reactions in solution (5–10 min). However, this feature does not affect the reliability of the glycosylation approach.

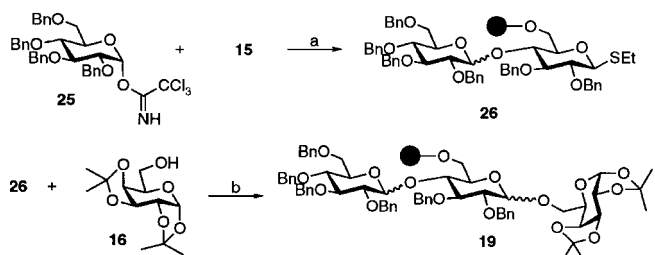
Encouraged by these results, we turned to the glycosyl acceptor **22** that has an unreactive 4-hydroxyl group. Unfortunately, coupling of **15** with **22** in the presence of NIS/TMSOTf gave a small amount of oligomeric products (5–10 %) in addition to the required product **23** (Scheme 4). A



Scheme 4. Synthesis of polymer-bound disaccharide **23**. a) NIS/TMSOTf, CH_2Cl_2 , 4-Å molecular sieves; b) DHP, PPTS; c) AcOH, THF, H_2O .

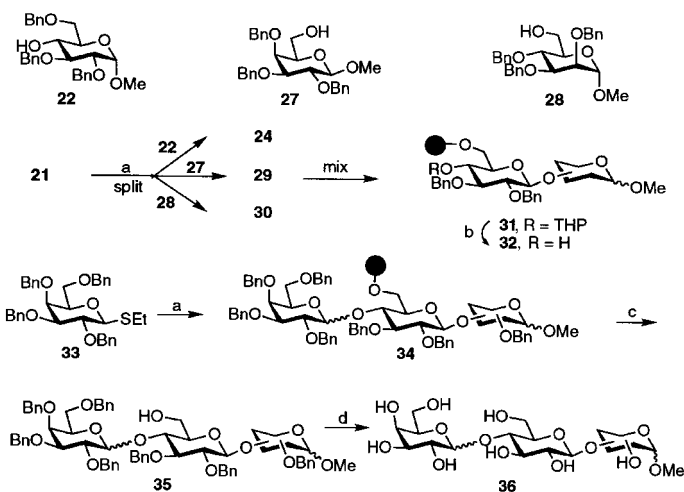
similar result was obtained when the more rigid Merrifield resin (1 % cross-linked) was employed as the solid support. The hydroxyl group of **15** was therefore protected as a tetrahydropyranyl (THP) ether to avoid oligomerization. Thus, treatment of **15** with 3,4-dihydro-2-pyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS)^[10] gave **21** in virtually quantitative yield. This product was successfully coupled with **22** to give the disaccharide **24**. The THP group of **24** was easily removed by treatment with acetic acid/water to yield **23**.

Immobilized **12** also proved to be a good glycosyl acceptor when coupled with a perbenzylated trichloroacetimidate donor. Thus, the TMSOTf-mediated coupling of **15** with an excess of **25** gave resin-bound **26**. This product was further coupled with acceptor **16** to give trisaccharide **19** (60 % overall yield based on the resin loading) (Scheme 5).



Scheme 5. Synthesis of polymer-bound trisaccharide **19** (method B). a) TMSOTf, CH_2Cl_2 , 4-Å molecular sieves; b) NIS/TMSOTf, CH_2Cl_2 , 4-Å molecular sieves.

To verify the proposed strategy, a relatively small library of 12 trisaccharides was prepared (Scheme 6). Three different glycosyl acceptors **22**, **27**, and **28** were coupled in individual



Scheme 6. Synthesis of the trisaccharide library **36**. a) NIS/TMSOTf, CH_2Cl_2 , 4-Å molecular sieves; b) HOAc/THF/ H_2O , 4/2/1, 50 °C; c) MeONa, MeOH, 1,4-dioxane then DOWEX50 (H^+) ion-exchange resin; d) $\text{Pd}(\text{OAc})_2$, H_2 , EtOH.

reactions with **21**, with NIS/TMSOTf as the promoter, to give three different disaccharides (**24**, **29**, and **30**, respectively) as mixtures of anomers. The beads were combined, the THP group removed by treatment with HOAc/THF/ H_2O (4/2/1),^[11]

and the mixture of disaccharide acceptors coupled with the glycosyl donor **33**, again with NIS/TMSOTf as the promoter. The trisaccharide library was released from the polymer after thin-layer chromatography and MALDI-TOF MS had shown that all the disaccharides had been consumed. The library was purified by size-exclusion column chromatography (LH-20; CH₂Cl₂/MeOH, 1/1), and the benzyl groups removed by hydrogenation over Pd(OAc)₂ to give the deprotected library **36** (55% overall yield based on the resin loading).^[12]

To further examine the quality of this library, a monosaccharide compositional analysis was performed. A portion of the trisaccharide library was treated with aqueous trifluoroacetic acid (2M) at 100°C for 4 h. Analysis of the resulting mixture of monosaccharides by HPLC (Dionex with a PA1 column and pulsed amperometric detection) showed that galactose, glucose, and mannose were present in approximately the required ratio.^[13]

In conclusion, a highly efficient approach for the synthesis of oligosaccharide and saccharide libraries on a solid-support has been described. Saccharides can be reliably immobilized by amide bond formation between a succinimide linker and a glycine-derivatized TentaGel resin. The products can be analyzed after each reaction step by MALDI-TOF MS and thin-layer chromatography by cleavage of the base-labile ester linker from a small amount of resin. The glycosylation strategy is two-directional: The immobilized thioglycoside acts first as a donor, and the product bearing a free hydroxyl group is used in subsequent glycosylation as an acceptor and glycosylated with a thioglycosyl donor. A mix-and-split approach gave a library with a known monosaccharide residue at the nonreducing end. Immobilized **12** can also act first as a glycosyl acceptor and the resulting disaccharides can be used as a glycosyl donor.

Experimental Section

General procedure for NIS/TMSOTf-mediated glycosylation on a solid support: The polymer-bound thioglycosyl donor (0.1 mmol) was placed in a round-bottom flask just covered with dichloromethane and allowed to swell for 15 min. Glycosyl acceptor (0.5 mmol) in dichloromethane (4 mL) and 4-Å molecular sieves (200 mg, beads) were added, and the suspension was shaken at room temperature for 15 min. NIS (0.5 mmol) and TMSOTf (0.05 mmol) were then added, and the mixture was shaken at room temperature for 2–4 h. After removal of the molecular sieves by decanting, the resin was washed successively with DMF (3 × 20 mL), dichloromethane (3 × 20 mL), and methanol (3 × 20 mL), and dried in vacuo over P₂O₅ for 24 hours.

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NO_x Abatement in Exhaust from Lean-Burn Combustion Engines by Reduction of NO₂ over Silver-Containing Zeolite Catalysts**

Johan A. Martens,* Anne Cauvel, Agna Francis, Chris Hermans, François Jayat, Marc Remy, Michael Keung, Jan Lievens, and Pierre A. Jacobs

Lean-burn gasoline and diesel engines operated with excess air offer the most efficient power source for transportation known today,^[1] but their nitrogen oxide (NO_x = NO + NO₂) emissions remain unacceptably high.^[2] Although selective catalytic reduction of NO_x with hydrocarbons from the exhaust or the fuel under oxidizing conditions (lean DeNO_x) has been extensively studied,^[3–7] a breakthrough of this technology is hindered by the low activity, narrow temperature window, and insufficient durability of the catalysts.^[8] Here we report that silver/proton-exchanged zeolites represent a unique redox system that outperforms the known catalysts for reduction of NO₂ and is devoid of their disadvantages. In the presence of an excess of oxygen, silver is the only transition metal ion that does not segregate from the zeolite;^[9] hence, the stability of the catalyst depends entirely upon the steam stability of the H zeolite. The zeolite framework, its Brønsted acidity, and the specific redox behavior of silver in association with the zeolite are the three key catalyst functions that cooperate to form nitrogen from NO₂ via intermediate nitro, amino, and diazonium compounds.

Below 400 °C, silver catalysts are rather inactive for reducing NO in lean-burn exhaust, unless oxygenated hydrocarbons are added as reducing agents.^[10] For the reduction of NO with hydrocarbons, silver zeolites do not have any advantages over copper or cobalt zeolites.^[11] We used a synthetic gas mixture that mimicks the exhaust composition of a lean-burn engine with NO₂ as the NO_x component. The gas mixture was passed over a fixed bed of catalyst at high gas velocity. Curves for the reduction of NO_x to N₂ at different reaction temperatures over ferrierite (FER) and mordenite (MOR) zeolites loaded with transition metal ions are shown in Figure 1. The silver zeolites are highly active at all temperatures. In particular, the Ag/H-FER catalyst transforms more than 60% of the NO_x into N₂ between 250 and 450 °C.

When used as lean DeNO_x catalysts, many transition metal exchanged zeolites, of which Cu-ZSM-5^[2, 3, 7] and Co-ZSM-5^[5, 6] are representative examples, are deactivated in the presence of water vapor due to segregation of the metal oxide from the zeolite phase.^[12] The Ag/H-FER catalyst does not

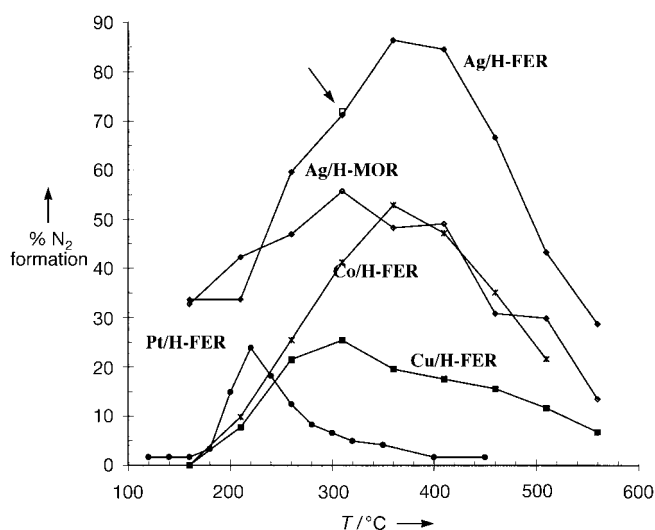
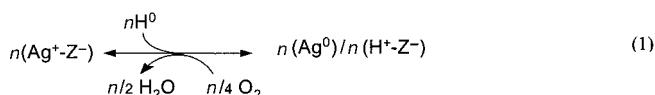


Figure 1. Nitrogen formation over H-MOR and H-FER zeolites with a loading of 5 wt% of silver, copper, or cobalt ions, or 1 wt% of platinum ions as a function of reaction temperature. The arrow on the curve for Ag/H-FER indicates a sample that was subjected to fast ageing (24 h at 560 °C under normal reaction conditions).

show any deactivation below 600 °C (Figure 1) and retains 80% of its original activity after 16 h of continuous operation at 660 °C; the limiting factor is the hydrothermal stability of the Brønsted acid sites of the zeolite. The excellent lean DeNO_x performance of the Ag/H zeolites even remained unaffected by the presence of 150 ppm of sulfur dioxide. Under reaction conditions, the silver is not converted into nitrate species, and no nitrogen deficiency was observed in the mass balance or detected by in situ IR spectroscopy (absence in all instances of a peak at 1385 cm⁻¹). Since silver cations in zeolites have a low tendency to undergo hydrolysis and silver oxide particles are thermally unstable, this remarkable catalytic stability is a unique feature of Ag zeolites. Irrespective of the position or degree of sintering of the metallic silver clusters formed by reduction, the zeolite can be restored to its original form by oxidation^[9] [Eq. (1)].



The mechanism of the lean DeNO_x reaction was investigated with several organic compounds as reducing agents. At 250 °C, the rate of NO₂ reduction over Ag/H-MOR decreases in the following order: propene (55%) > nitropropane, cyclopentanone, octane (45%) >> propane, acetic acid, carbon monoxide (5%). The more active reducing agents have a higher tendency to undergo radical oxidation by O₂.^[13] Pronounced activity peaks occur when the catalyst temperature is increased in steps (Figure 2). These activity peaks are not due to the spontaneous reaction of NO_x that has accumulated in the catalyst (storage effect) since the independently determined NO_x conversion and N₂ formation were in agreement. This behavior was also exhibited by other zeolitic catalyst carriers (MOR, ZSM-5, FER) with NO₂-containing exhaust, irrespective of the nature of the charge-

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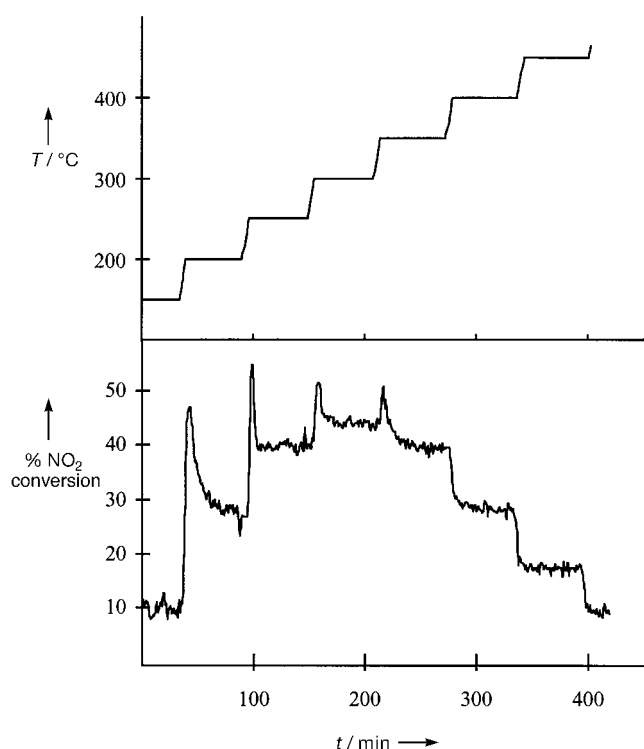
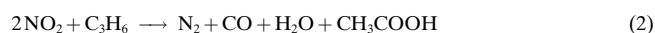


Figure 2. Nitrogen formation over Ag/H-MOR with stepwise increase of the reaction temperature ($8^{\circ}\text{Cmin}^{-1}$).

compensating metal ion (Cu, Co, Pt, Ce, Na) in the zeolite or of the hydrocarbon reducing agent. This indicates that a zeolite-induced radical reaction takes place. Below 300°C NO_2 does not react in the absence of propene, and vice versa; this suggests that the two compounds react with one another.

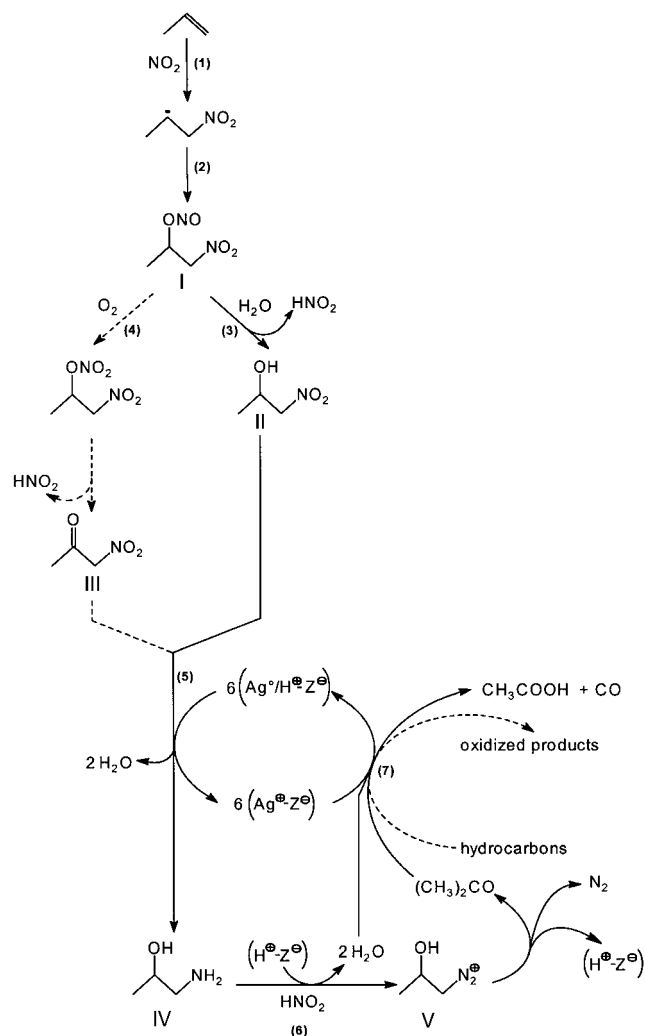
Below 270°C in the absence of organic compounds, prerduced Ag/H-MOR does not catalyze the conversion of the exhaust gas. Upon injection of propene, the conversion passes through a peak value before reaching a steady state. This shows that metallic silver, although involved in the mechanism, is unable to reduce NO_2 in the absence of alkene, and suggests that the pairing of N atoms in the DeNOx reaction occurs via an organic nitrogen species rather than by disproportionation^[14] of NO on the metal ions. Experiments performed at 220°C gave further clues as to the nature of these intermediates: 1) the lower reactivity of H-MOR is enhanced to the level of Ag/H-MOR when nitropropane is replaced by, for example, propylamine as reducing agent; 2) a MOR zeolite exchanged with ammonium ions has excellent DeNOx activity until all ammonium ions are consumed.

Optimization of the exhaust gas composition allowed product stoichiometries at low reaction temperatures (below 200°C) to be determined. One CO molecule is obtained per N_2 molecule formed, and two NO_2 molecules can be reduced with one molecule of propene. Almost equimolar amounts of acetic acid, nitrogen, and carbon monoxide were detected together with traces of acetone. Consequently, the overall stoichiometry of the NO_2 reduction with propene corresponds to Equation (2). At higher reaction temperatures, all inter-



mediates undergo complete oxidation. The catalyst is active in the absence of water, dioxygen, or both, but is most active in the presence of the typical concentrations of these compounds.

A mechanism for the reduction of NO_2 with propene that is consistent with all of these experimental observations is presented in Scheme 1. The initial step (1, 2; first catalyst



Scheme 1. Reaction mechanism of NO_2 reduction with propene on Ag/H zeolites.

function) is a zeolite-catalyzed radical nitro–nitrosooxy addition^[16] of two NO_2 molecules to the olefin,^[17] a reaction already invoked for Ce-ZSM-5.^[18] β -Nitropropyl nitrate (**I**) can react with water (3) to give β -hydroxynitropropane (**II**) and nitrous acid.^[19] The nitro group is subsequently reduced (5) by the reduced catalyst (second catalyst function) to β -hydroxypropylamine (**IV**). On zeolitic Brønsted acid sites, amines react with nitrous acid (6, third catalyst function) to form unstable diazonium salts (**V**),^[20] which decompose rapidly to nitrogen, carbon monoxide, and acetic acid (7), the typical autoxidation product of acetone. Acidic zeolites presumably operate according to the same mechanism, whereby the catalytic function of silver is performed less efficiently by carbonaceous deposits. This reaction scheme is

also valid for saturated hydrocarbons with labile hydrogen atoms.

As exhaust from lean-burn engines contains NO as the main NO_x component, the present knowledge could be technically implemented as a dual-catalyst system.^[21] On an oxidation catalyst such as Pt-ZSM-5, NO_x from a lean-burn exhaust stream can be converted into NO₂, which in turn is converted over an Ag/H zeolite catalyst. Injection of sufficient reducing agent between the two catalysts is required.

Experimental Section

In the experiment of Figure 1, the synthetic exhaust gas was composed of 400 ppm NO₂, 350 ppm propene, 350 ppm CO, 10% CO₂, 10% O₂, and 12% H₂O, balance helium. The volumetric hourly space velocity (VHSV) and the weight hourly space velocity (WHSV) were 160 000 h⁻¹ and 320 000 h⁻¹, respectively. NO, N₂O, and NO₂ were monitored by chemiluminescence and IR detectors. N₂ was monitored by gas chromatography.

In the experiment of Figure 2, the synthetic exhaust gas was composed of 450 ppm NO₂, 50 ppm NO, 175 ppm propene, 175 ppm propane, 350 ppm CO, 10% CO₂, 6% O₂, 12% water, balance helium. The VHSV was 60 000 h⁻¹.

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Determination of the Orientation of a Distant Bond Vector in a Molecular Reference Frame by Cross-Correlated Relaxation of Nuclear Spins**

Bernd Reif, Henning Steinhagen, Bernd Junker, Michael Reggelin, and Christian Griesinger*

Dedicated to Professor Richard R. Ernst on the occasion of his 65th birthday

Recently, a new class of structural restraints has been introduced that allows the measurement of projection angles between internuclear vectors from relaxation rates of double-quantum (DQ) and zero-quantum (ZQ) coherences.^[1] This relaxation mechanism is induced by cross-correlation of two individual dipolar coupling tensors. Angular restraints can also be obtained by the measurement of relaxation rates of DQ and ZQ coherences that are induced by the cross-correlation of one dipolar coupling and a chemical shift tensor.^[2,3] So far applications have addressed only the measurement of such rates in fully ¹³C/¹⁵N-labeled biomacromolecules. We show here by comparison with a crystal structure that angles between H–H and C–H bond vectors that are separated in space by 7 Å in a small organic molecule can be determined with an accuracy of a few degrees. It is further shown that by measuring two such relaxation rates it is possible to determine the orientation of one vector in the frame of reference of the two other vectors. For sensitivity reasons we had to introduce ¹³C labeling in part of the molecule. The accuracy and precision of the measurement established in this publication will be used in a forthcoming paper to derive long-range structural information for a catalytic intermediate that cannot be crystallized.

In two pairs of nuclei (A¹–A² and B¹–B²) cross-correlated relaxation rates Γ_{A¹A²B¹B²} of DQ and ZQ coherences between nuclei A¹ and B¹ can be measured provided the DQ and ZQ coherence between these nuclei can be excited, the scalar coupling between A¹ and A² as well as between B¹ and B² is resolved, and the main relaxation source for A¹ (B¹) is the dipolar coupling to A² (B²). If we identify the nuclei A¹, A², B¹, and B² according to Table 1 and Figure 1 with (A¹,A²) = (H²⁶,H²⁵) or (H²³,H²⁴) and (B¹,B²) = (C³,H³) all the above requirements are fulfilled by the η³-allylpalladium complex **1**.

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Table 1. Comparison of the angle determined by NMR experiment and crystal structure analysis.

	A ¹	A ²	B ¹	B ²	$\Gamma_{A^1A^2,B^1B^2}^c$	$\theta_{A^1A^2,B^1B^2}^{\text{NMR}}$	$\theta_{A^1A^2,B^1B^2}^{\text{X-ray}}$
DQ/ZQ ₁ ^[a]	H ²⁶	H ²⁵	C ³	H ³	(+0.33 ± 0.30) Hz	$\theta_1 = 52^\circ, 128^\circ, 3^\circ$ ^[b]	54 ^{°[c]}
DQ/ZQ ₂ ^[a]	H ²³	H ²⁴	C ³	H ³	(+1.60 ± 0.10) Hz	$\theta_2 = 41^\circ, 139^\circ, 1^\circ$ ^[b]	140 ^{°[c]}
SQ ^[d]	H ²⁶	H ²⁵	H ²⁶	C ²⁶	(−0.60 ± 0.05) Hz	–	60 ^{°[c]}

[a] Nuclear assemblies for the DQ and ZQ coherences and the SQ coherence described in the text. [b] The angles were determined from the measured relaxation rates according to Equation (3). [c] The projection angles were taken from the crystal structure. [d] The determined rates.

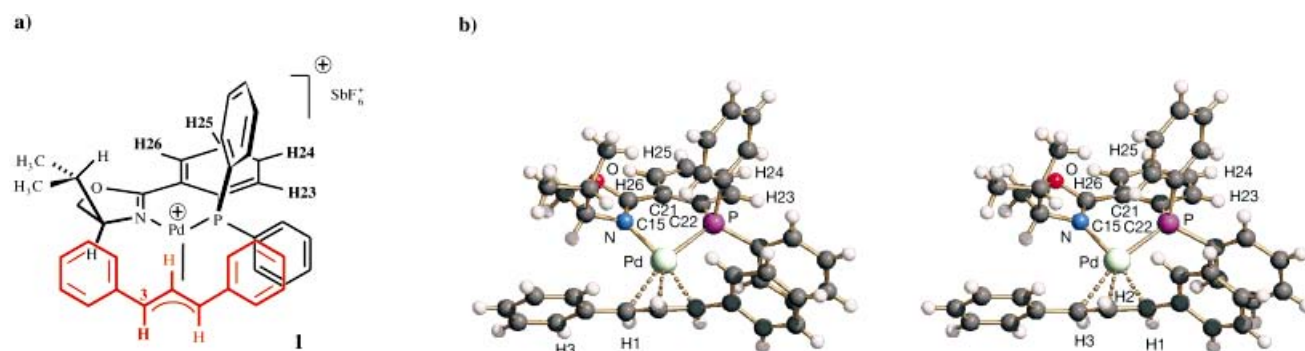


Figure 1. a) Structural formula and b) stereoview of the crystal structure of the η^3 - π -allylpalladium complex cation **1**. 1,3-Diphenyl[¹³C₃]propenol was prepared from [¹³C₁]benzaldehyde, benzene, and [¹³C_{1,2}]-acetylchloride^[8] and was converted into 1,3-diphenyl[¹³C₃]propenylpalladium chloride according to the literature procedure.^[9] Reaction with the corresponding phosphanyloxazoline ligand yields **1**.^[9]

This complex constitutes the catalytic resting state of the allylic substitution that is catalyzed by palladium complexes with chiral phosphanyloxazoline ligands.^[4, 5]

One of the aforementioned cross-correlated relaxation rates is $\Gamma_{H^{26}H^{25},C^3H^3}^c$ and originates from the cross-correlation of the C³–H³ and the H²⁵–H²⁶ dipolar couplings. This relaxation rate is measured on the DQ or ZQ coherence of C³ and H²⁶ and contains structural information according to Equation (1).

$$\Gamma_{H^{26}H^{25},C^3H^3}^c = \frac{\gamma_H\gamma_{13C}}{(r_{C^3,H^3})^3} \frac{\gamma_H\gamma_{1H}}{(r_{H^{26},H^{25}})^3} \left(\frac{\hbar\mu_0}{4\pi} \right)^2 P_2(\cos\theta_{H^{26}H^{25},C^3H^3}) J(0) \quad (1)$$

$$\text{with } J(\omega) = \frac{2}{5} \frac{\tau_c}{1 + (\omega\tau_c)^2} \text{ and } P_2(x) = (3\cos^2 x - 1)/2$$

Here, γ_X denotes the gyromagnetic ratio of nucleus x , and $r_{X,Y}$ is the distance between the nuclei (X,Y). $\theta_{H^{26}H^{25},C^3H^3}^c$ (θ_1) is the projection angle of the C³–H³ and the H²⁵–H²⁶ vectors. The formula for the cross-correlated relaxation between the C³–H³ and the H²⁴–H²³ vectors is analogous. Both projection angles θ_1 and $\theta_{H^{23}H^{24},C^3H^3}^c$ (θ_2) can be used to define the orientation of the allylic moiety with respect to the aromatic ring (C²¹–C²⁶) despite the large intervector distance of approximately 7 Å (Figure 1).

The excitation of the DQ and ZQ coherences between H²⁶ (DQ/ZQ₁, Table 1) or H²³ and C³ (DQ/ZQ₂, Table 1) is achieved by relayed coherence transfer from the protons H²⁶ and H²³, respectively, through the ³¹P atom to the C³ carbon atom (Figure 2). The respective coupling constants are $^4J(H^{26},P) \approx 4$ Hz, $^3J(H^{23},P) = 7.0$ Hz, and $^3J(C^3,P) = 27$ Hz. The H²⁶–C³ DQ and ZQ coherences show a doublet of

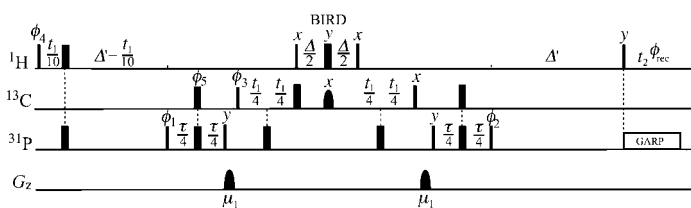


Figure 2. Real-time DQ/ZQ-HPC correlation experiment. Coherence transfer is accomplished by H,P-transfer in a HMQC-type fashion and P,C-transfer in a HSQC-type fashion. The DQ and ZQ coherences are recorded simultaneously and obtained by subtracting spectra acquired with $\phi_3 = \phi_4 = 0^\circ, 180^\circ$ and adding the spectra acquired with $\phi_3 = \phi_4 = 90^\circ, 270^\circ$. Quadrature detection for both DQ and ZQ evolution time is achieved by States TPPI on ϕ_3 and ϕ_5 . $t_1^{\text{max}} = 140$ ms. Decoupling of the proton in the position *meta* to H²⁶ or H²³ is achieved by continuous-wave irradiation with a field strength of $\gamma B_1/2\pi = 6$ Hz. The selective ¹³C BIRD pulse (0.45 ms) serves to refocus all couplings to C³ during the evolution time. The total duration between the first excitation pulse and the detection is $1/3J(H,H) = 128.2$ ms. $\Delta' = 40.5$ ms. In the experiment for H²³ (H²⁶): number of scans = 16 (128), number of t_1 experiments = 320 (142), spectral width in $\omega_1/2\pi = 1000$ Hz (500 Hz). The total duration of the experiment was 4.3 h (15.2 h).

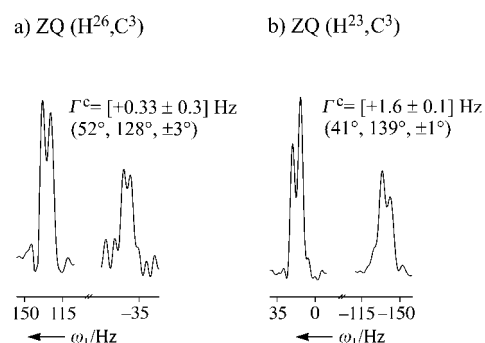


Figure 3. ω_1 traces from the ZQ spectrum of the DQ/ZQ-HPC experiment (Figure 2) applied to **1** (approximately 88 mM) at -60°C in [^D₈]THF. Slices taken at a) H²⁶ and b) H²³ are derived from the H²⁶,C³ and H²³,C³ ZQ coherences. The two doublets from the $^1J(C^3,H^3)$ and the $^3J(H^{26},H^{25})$ coupling for H²⁶ (a) and the $^3J(H^{23},H^{24})$ coupling for H²³ (b) are plotted separately. The cross-correlated relaxation rates and derived angles are also given.

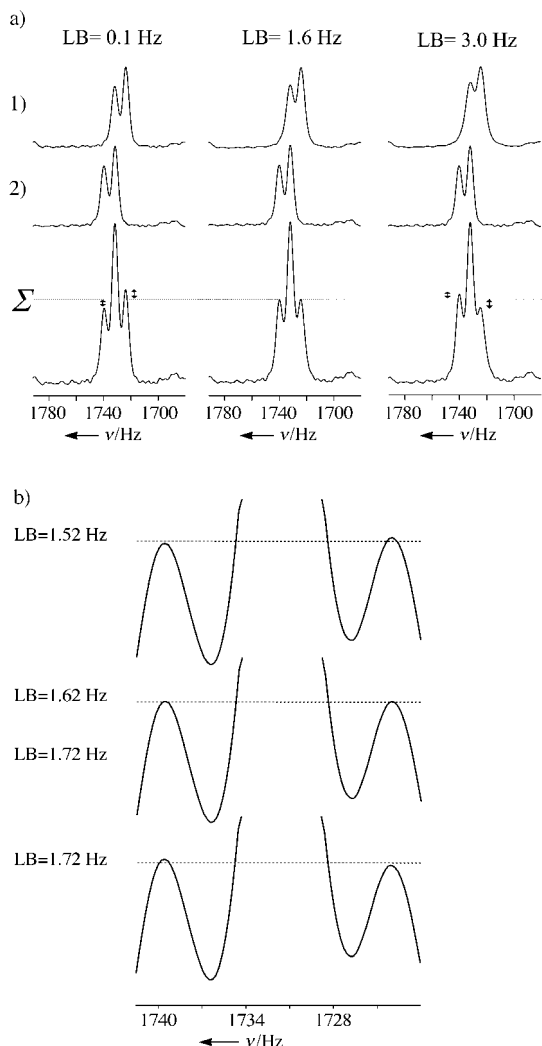


Figure 4. a) Extraction routine for the cross-correlated relaxation on the example of the high-field component of the SQ spectrum of H^{26} (see Figure 5b). The two components in the doublet, which we call $\alpha\alpha$ for the low-field line and $\alpha\beta$ for the high-field line, have a frequency difference of J and reflect the same line shape $\mathcal{F}(\omega)$ except for the Lorentzian contribution:

$$\mathcal{L}(\omega, \Gamma_{\alpha\alpha} - \Gamma_{\alpha\beta}) = \frac{(\Gamma_{\alpha\alpha} - \Gamma_{\alpha\beta})^{-1}}{1 + (\omega / (\Gamma_{\alpha\alpha} - \Gamma_{\alpha\beta}))^2}$$

The ($\alpha\alpha$) line is broader than the ($\alpha\beta$) line. By duplicating the doublet, shifting the duplicate to the low-field side (1) by J , convoluting it with a trial Lorentzian line with linewidth LB , and adding the result to the second doublet at higher field (2) a triplet (Σ) is formed that has identical outer multiplet components if $LB = (\Gamma_{\alpha\alpha} - \Gamma_{\alpha\beta})$. b) The same example shows that the precision is better than 0.1 Hz. The error for Γ has been determined by adding 20 different noise sections from the same trace on top of the multiplets and applying the extraction procedure. The standard deviation of the mean value of $\Gamma_{\alpha\alpha} - \Gamma_{\alpha\beta}$ then defines the errors of the cross-correlated relaxation rate.

doublets due to the homonuclear coupling $^3J(H^{25}, H^{26}) = 7.8$ Hz and the heteronuclear coupling $^1J(H^3, C^3)$ of 154 Hz (Figure 3a). The H^{23}, C^3 DQ and ZQ coherences show an analogous multiplet structure (Figure 3b). The four lines of the doublets of doublets represent the spin states $\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, and $\beta\beta$ of the passive spins A^2 and B^2 . The desired cross-correlated relaxation rate $\Gamma_{A^1 A^2, B^1 B^2}^c$ is then given by Equation (2).^[1,6]

$$\Gamma_{A^1 A^2, B^1 B^2}^c = \frac{1}{4}(\Gamma_{\alpha\alpha} - \Gamma_{\alpha\beta} - \Gamma_{\beta\alpha} + \Gamma_{\beta\beta}) \quad (2)$$

The experiment depicted in Figure 2 is a real-time experiment with a total duration increasing with t_1 incrementation. In contrast to a constant-time experiment the cross-correlated relaxation rates have to be extracted from the different linewidths of the multiplet. These differences in linewidths can be determined by fitting the $\alpha\alpha$ line to the $\alpha\beta$ line by convolution of the $\alpha\alpha$ line with a Lorentzian line of variable linewidth (Figure 4). The extracted cross-correlated relaxation rates together with the extracted errors are summarized in Table 1.

The size of the cross-correlated relaxation of the DQ and ZQ coherences was calibrated by measuring the cross-correlated relaxation rate of the H^{26} single quantum coherence (SQ_1 , Table 1), which is determined by a dipolar coupling of the single bonded H^{26}, C^{26} and of the *ortho* H^{26}, H^{25} pair (Figure 5). The corresponding cross-correlated relaxation rate $\Gamma_{H^{26} C^{26}, H^{26} H^{25}}^c$ is given by Equation (3).

$$\Gamma_{H^{26} C^{26}, H^{26} H^{25}}^c = \frac{\gamma_H \gamma_C}{(r_{H^{26} C^{26}})^3} \frac{\gamma_H \gamma_H}{(r_{H^{26} H^{25}})^3} \left(\frac{\hbar \mu_0}{4\pi} \right)^2 P_2(\cos \theta_{H^{26} C^{26}, H^{26} H^{25}}) [J(0) + \frac{3}{4} J(\omega_H)] \quad (3)$$

For a correlation time τ_c of 1.8 ns as found at 600 MHz and -60°C for the 88 mm solution of **1** in $[D_8]\text{THF}$, $J(0) + 3/4 J(\omega_H) = 1.06 J(0)$.

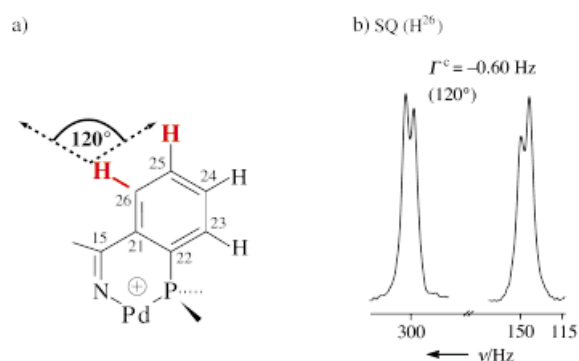


Figure 5. a) The $C^{26}-H^{26}-H^{25}$ moiety for which the cross-correlated relaxation between the $C^{26}-H^{26}$ and the $H^{26}-H^{25}$ dipoles is measured. b) The ^{13}C -filtered 1D ^1H spectrum of H^{26} recorded without refocusing and without ^{13}C decoupling showing the expected doublet of doublets from the $^1J(C^{26}, H^{26})$ and the $^3J(H^{26}, H^{25})$ coupling constants. The high-field doublet has been inverted in sign.

To convert the cross-correlated relaxation rates into direction cosines, the ratio of the cross-correlated relaxation rates of the DQ and ZQ coherences is divided by the rate of the SQ coherence. This value of the desired direction cosines assumes isotropic reorientation, no appreciable effects from internal motion, and identical C–H bond distances in the allyl moiety and the aromatic ring. By using Equations (1) and (3) we arrive at a value of the directional cosines [Eq. (4)].

$$\frac{\Gamma_{H^{26} H^{25}, C^3 H^3}^c}{\Gamma_{H^{26} H^{25}, H^{26} C^{26}}^c} = \frac{(r_{H^{26} C^{26}})^3 P_2(\cos \theta_{H^{26} H^{25}, C^3 H^3})}{(r_{C^3 H^3})^3 P_2(\cos \theta_{H^{26} H^{25}, H^{26} C^{26}})} 1.06 \quad (4)$$

A comparison of the calculated values with those derived from the X-ray structure is given in Table 1. The angles are the same within $\pm 3^\circ$. The accuracy is quite remarkable and

indicates the crystal and the solution structure of complex **1** are identical. In addition, the NMR measurement is very precise; the angles derived here are in the order of 45° where the cross-correlated relaxation rates are most sensitive to the angle. The SQ cross-correlated relaxation rate could also be used for the calibration of the absolute cross-correlated relaxation rates.

In the molecular frame of the aromatic ring ($C^{21}-C^{26}$) the two direction cosines of $C^3 \rightarrow H^3$ relative to $H^{25} \rightarrow H^{26}$ and $H^{24} \rightarrow H^{23}$ define two cones whose intersections determine the orientation of the C^3-H^3 vector (Figure 6). The cartesian coordinates of these vectors are given by Equation (5).

$$x = \cos\theta_1, y = \frac{\cos\theta_2 - \cos\theta_0 \cos\theta_1}{\sin\theta_0}, z = \pm \sqrt{1 - (x^2 + y^2)} \text{ with } |y| < 1 \quad (5)$$

Figure 6 shows these vectors in two graphical representations; Figure 6a is a perspective schematic view and Figure 6b

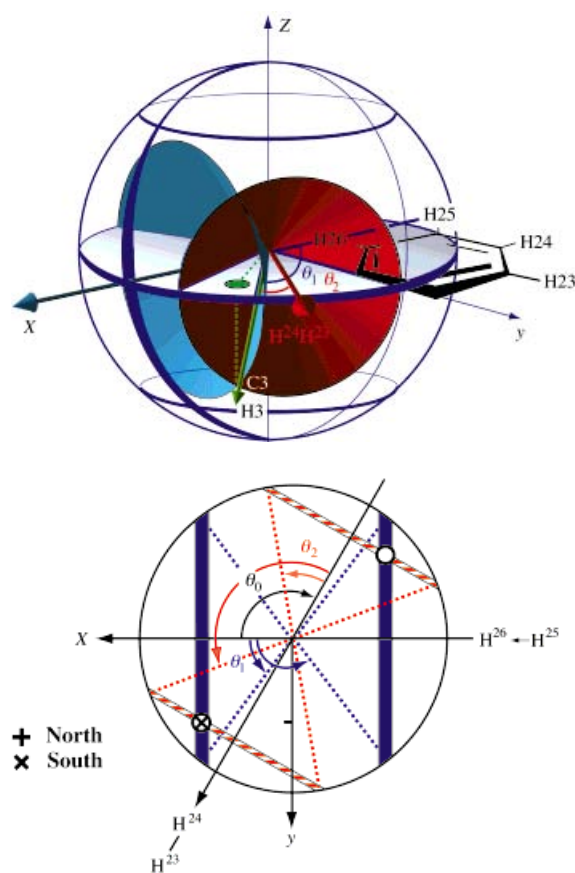


Figure 6. Orientation of the C^3-H^3 vector in the molecular frame of the aromatic ring ($C^{21}-C^{26}$) in a) a 3D representation and b) a polar projection. In both (a) and (b) the two directional cosines from $I_{H^{25}H^{26}, C^3H^3}$ ($\theta_1 = 52, 128, \pm 3^\circ$) and $I_{H^{24}H^{23}, C^3H^3}$ ($\theta_2 = 41, 139, \pm 1^\circ$) define two cones for the $C^3 \rightarrow H^3$ vector along the $H^{25} \rightarrow H^{26}$ bond direction (x axis) and the $H^{24} \rightarrow H^{23}$ bond direction ($+(1/2)x + (\sqrt{3}/2)y$ axis), respectively. The two angles θ_1 and θ_2 are also given. The intersection of the cones define the $C^3 \rightarrow H^3$ vector orientation (only one out of the four possibilities is shown in (a)). b) The intersection of each cone with the sphere shows up in the polar representation as two lines in the north and south hemispheres that are perpendicular to the symmetry axis of the cone and intersecting that symmetry axis at $\pm \cos\theta_1$ and $\pm \cos\theta_2$, respectively. The error in $\cos\theta_{1,2}$ is represented by the width of the lines. The intersections of the cones defines two south and two north orientations of the C^3-H^3 vector ($\odot$). The coordinates are given in the text. The orientation found in the high-resolution crystal structure is marked with an $\otimes$.

a stereographic projection.^[7] For both Figures $H^{25} \rightarrow H^{26}$ is assumed to lie along the x axis and $H^{24} \rightarrow H^{23}$ along the $(+(1/2)x + (\sqrt{3}/2)y)$ axis). The z axis is assumed to be perpendicular to the x and y axes in a right-handed coordinate system. The angle measured from $H^{25} \rightarrow H^{26}$ to $H^{24} \rightarrow H^{23}$ is $\theta_0 = 120^\circ$. The two cones defined from the two direction cosines $|\cos\theta_1|$ and $|\cos\theta_2|$ are illustrated in Figures 6a and 6b. Their intersections define the possible orientations of the $C^3 \rightarrow H^3$ vector. From the fact that there is no information from the NMR data on the sign of the z -component of the $C^3 \rightarrow H^3$ vector and because of the ambiguity of the $3\cos^2\theta - 1$ dependence, four possible coordinates of the $C^3 \rightarrow H^3$ vector are possible: $(x, y, z) = (0.588, 0.545, \pm 0.599)$ and $(-0.588, -0.545, \pm 0.599)$. The one found in the X-ray structure is $(x, y, z) = (0.616, 0.516, -0.595)$ and matches with the second orientation found from NMR measurements.

In conclusion, we have measured the orientation of internuclear vectors in a small organic molecule over a distance that is large by NMR standards. In the favorable case encountered here the accuracy and precision of the measurement is better than 3° , as shown by comparison with a high-resolution crystal structure. The angular information derived from NMR spectroscopy allows the orientation of two molecular moieties to be defined relative to each other. It is apparent that no other structural parameter used in solution-state NMR spectroscopy would have been able to provide this information. Encouraged by the accuracy and precision of the measurement, we are currently working on using this method to derive information on the catalytic intermediate that has been found in the palladium complex catalyzed allylic transfer and which cannot be crystallized.^[4c]

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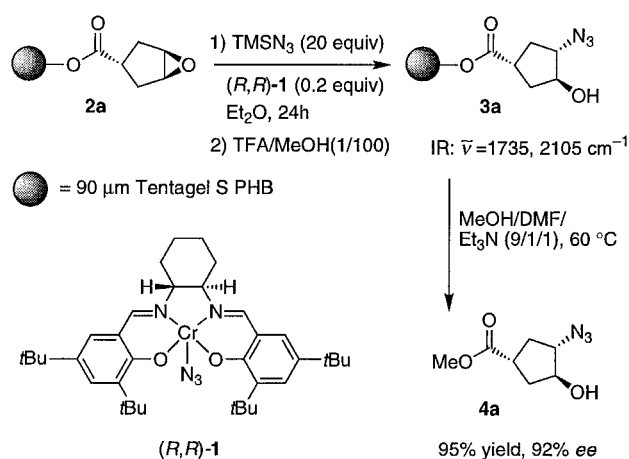
Stereochemistry as a Diversity Element: Solid-Phase Synthesis of Cyclic RGD Peptide Derivatives by Asymmetric Catalysis**

D. Allen Annis, Olivier Helluin, and Eric N. Jacobsen*

The emergence of combinatorial and parallel library synthesis as an important strategy for the generation and optimization of pharmaceutical lead structures has resulted in major and exciting new challenges in the field of synthetic methodology.^[1] The preparation of libraries with significant structural and functional diversity requires synthetic reactions that are not only highly effective, but also generally applicable. Since solid-phase synthesis is the method of choice for the generation of libraries, the development of methods applicable to immobilized substrates adds yet another dimension to the challenge.

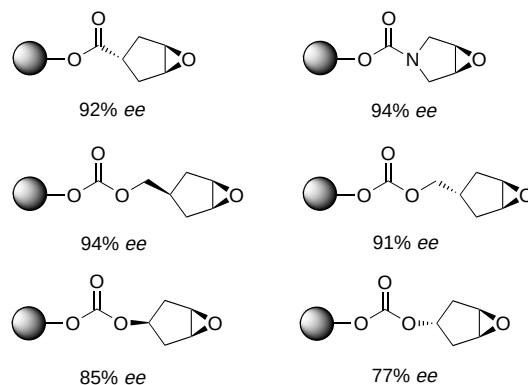
Despite the enormous recent progress in solid-phase synthesis,^[2] stereoselective reactions have played a relatively minor part.^[3, 4] A possible explanation is that absolute stereocontrol is not important in library synthesis. Indeed, if the goal is to generate as many compounds as possible and the screening process allows for the evaluation of mixtures and the deconvolution of individual components, then stereochemical control may not be necessary or even desirable. However, if both specificity and affinity for a target are sought, then evaluation of stereoisomerically pure compounds may be essential. For example, cyclic compounds that contain the amino acid sequence Arg-Gly-Asp (RGD) can switch specificities to different targets as a result of subtle structural and stereochemical variation of the peptide backbone.^[5, 6] With the goal of developing enantioselective methods for solid-phase syntheses and highlighting their possible utility for lead discovery and optimization, we describe here the asymmetric catalytic ring opening of polymer-bound *meso*-epoxides with trimethylsilyl azide (TMSN₃),^[7] and the transformation of the resulting products into stereochemically diverse templates for the synthesis of compounds with RGD pharmacophores.

The reaction of the TentaGel S PHB-immobilized^[8] epoxy ester **2a** with an excess of TMSN₃ in the presence of the [(salen)CrN₃] complex^[9] (*R,R*)-**1** proceeded to completion within 24 h, as monitored by IR spectroscopy (Scheme 1). The



Scheme 1. Asymmetric ring opening of polymer-bound *meso*-epoxides catalyzed by [(salen)CrN₃] (**1**).

product was isolated, excess reagents and catalyst were removed by filtration, and the product was desilylated with a dilute methanolic solution of trifluoroacetic acid to afford resin-bound azido alcohol **3a**. Transesterification with MeOH/DMF/Et₃N (9/1/1) then provided soluble **4a** in greater than 95% yield with 92% ee, as established by ¹H NMR spectroscopy and gas chromatography. The scope of this solid-phase asymmetric reaction was evaluated on a series of other *meso*-epoxides with five-membered rings (Scheme 2). In all cases, epoxide ring opening occurred cleanly to provide the corresponding azido alcohol derivatives with good to excellent enantiomeric excesses.



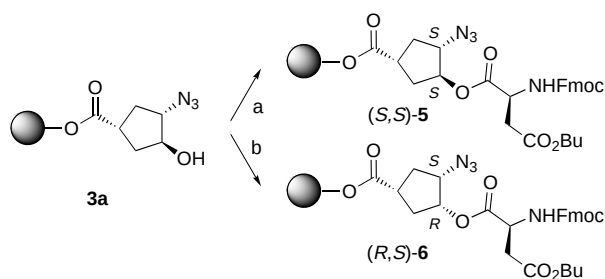
Scheme 2. Enantioselectivities of the asymmetric ring opening of some polymer-bound *meso*-epoxides.

Having established polymer-bound epoxides as viable substrates for the asymmetric ring-opening reaction, we evaluated the optically active azido alcohol products for their utility as conformationally constrained templates for the synthesis of RGD-containing compounds. The synthesis of cyclic compounds (*S,S*)-**9**, (*R,R*)-**9**, (*R,S*)-**12**, and (*S,R*)-**12** is outlined in Schemes 3 and 4. Acylation of the resin-bound azido alcohol (*S,S*)-**3a** with FmocAsp(OtBu) provided the *trans* azido ester (*S,S*)-**5** in quantitative yield. In a transformation that permitted the introduction of additional stereochemical diversity, esterification under Mitsunobu conditions^[10] pro-

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Supporting information for this article (structural coordinates for (*S,S*)-**9**, (*R,R*)-**9**, (*R,S*)-**12**, and (*S,R*)-**12** in PDB format) is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



Scheme 3. Stereochemical control by means of the acylation conditions. a) FmocAsp(OtBu), DIC, DMAP, DMF, 100%; b) premixed FmocAsp(OtBu) and PPh₃/DEAD, THF, 0 °C, 90% (+5% *trans* product). Fmoc = 9-fluorenylmethoxycarbonyl, DIC = *N,N'*-diisopropylcarbodiimide, DMAP = 4-dimethylaminopyridine, DEAD = diethyl azodicarboxylate.

vided the corresponding *cis* azido ester (*R,S*)-6 with greater than 15:1 diastereoselectivity, as determined by HPLC analysis. The synthesis of cyclic peptides containing the RGD sequence from 5 and 6 was completed by using well-established solid-phase methods.^[11] Cleavage from the resin and deprotection of the side chain were accomplished in one step to provide the desired macrocycles (*S,S*)-9 and (*R,R*)-9 with the cyclopentyl ring in the *trans* configuration as colorless solids after preparative HPLC purification (64% and 58% overall yield, respectively). Macrocycles (*R,S*)-12 and (*S,R*)-12, in which the cyclopentyl ring has the *cis* configuration, were obtained in a similar manner in 59% and 48% overall yield.

To assess the influence of backbone configuration on the conformation of the RGD pharmacophore, the structures of the macrocycles in solution were estimated from 2D NOESY spectra in [D₆]DMSO by distance geometry/energy minimization methods.^[12] Centroids of the lowest energy conformational families of the cyclic peptides are shown in Figure 1.

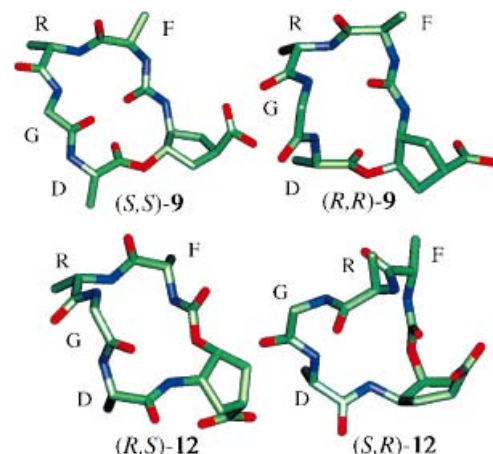
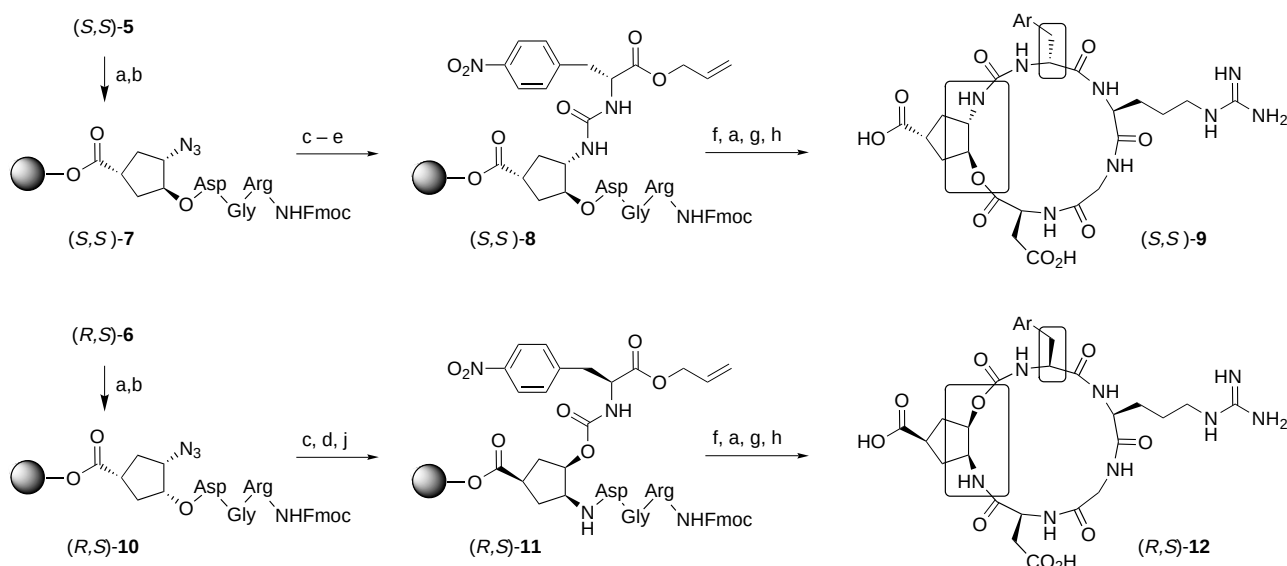


Figure 1. Solution structures of cyclic RGB peptides that were obtained by asymmetric ring opening of polymer-bound epoxides (side chains omitted for clarity).

Compound (*S,S*)-9 adopts a flat structure with a type II' β turn that results from a hydrogen bond between the carbonyl group of urea and the NH group of glycine, and the RGD sequence has an extended conformation. In contrast, (*R,R*)-9, which was constructed on the enantiomeric *trans*-amino alcohol template, adopts a type I β turn, and the RGD sequence is bent in the region of the glycine residue. Thus, enantiomeric templates induce different β turns, resulting in a dramatic change in the conformation of the RGD pharmacophore. Compounds (*R,S*)-12 and (*S,R*)-12, constructed on enantiomeric *cis*-amino alcohol templates, both contain γ turns about the glycine residues; however, the orientations of the γ turns differ with respect to the Asp and Arg side chains because of rotation about the D–G and G–R amide planes. As a result, the RGD conformations in (*R,S*)-12 and (*S,R*)-12 are puckered in opposite directions.



Scheme 4. Synthesis of macrocycles containing the RGD sequence. a) Piperidine/DMF (1/4); b) FmocArg(Pmc)Gly, HBTU, DIPEA, DMF; c) SnCl₂, Et₃N, PhSH, THF; d) 2 M phosgene in PhMe, DIPEA, DMAP, THF, 0 °C; e) D-4-NO₂PhOAll, DIPEA, DMAP, DMF; f) [Pd(PPh₃)₄], CHCl₃/HOAc/morpholine (37/2/1); g) HATU, HOAt, DIPEA, THF; h) TFA/H₂O/Me₂S (90/5/5); j) L-4-NO₂PhOAll, DIPEA, DMAP, DMF. Pmc = 2,2,5,7,8-pentamethylchroman-6-sulfonyl, HBTU = benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, DIPEA = diisopropylethylamine, All = allyl, HATU = *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole, TFA = trifluoroacetic acid.

The significant conformational differences in the stereoisomeric cyclic peptides prompted us to compare their affinity toward the $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ integrins.^[13] Selective inhibitors of $\alpha_v\beta_3$ hold great promise in cancer treatment as suppressors of tumor-induced angiogenesis, while $\alpha_{IIb}\beta_3$ inhibitors are of interest as potential antithrombotic agents.^[6] All compounds displayed affinity for $\alpha_v\beta_3$, but substantial differences were observed in selectivity for the two integrin receptors (Table 1). In the most striking example, (S,R)-**12** binds three

Table 1. Inhibition of integrin binding by cyclic compounds containing the RGD sequence.

Compound	$\alpha_v\beta_3$ ^[a]	$\alpha_{IIb}\beta_3$ ^[b]	$\alpha_v\beta_3$ selectivity ^[c]
(S,S)- 9	0.6	280	470
(R,R)- 9	24	> 10 ⁶	> 40 000
(R,S)- 12	6.0	120	20
(S,R)- 12	1.7	> 10 ⁶	> 500 000

[a] IC₅₀ [μM], platelet adhesion to osteopontin. [b] IC₅₀ [μM], platelet adhesion to fibrinogen. [c] IC₅₀($\alpha_{IIb}\beta_3$)/IC₅₀($\alpha_v\beta_3$).

times more strongly to $\alpha_v\beta_3$ but over four orders of magnitude times less strongly to $\alpha_{IIb}\beta_3$ than its diastereomer (R,S)-**12**.^[14] If **12** had been prepared as a mixture from racemic azido alcohol **3a**, the specificity for the critically important $\alpha_v\beta_3$ target would not have been recognized.

The differences in conformation, affinity, and selectivity of the cyclic peptides prepared in this study emanate from stereochemical alterations in their amino alcohol backbones, and thus illustrate the possible future importance of enantioselective reactions in library synthesis. Product isolation and purification are greatly simplified by performing the enantioselective reaction on polymer-immobilized substrates. More important, substrate immobilization opens the possibility of library synthesis in a split-pool manner, in which simultaneous ring opening of families of polymer-bound epoxides is performed.

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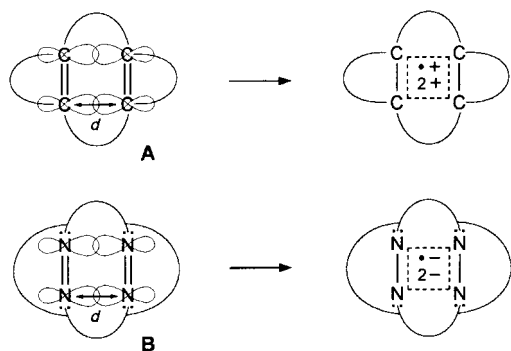
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Do Nonclassical, Cyclically Delocalized 4N/5e Radical Anions and 4N/6e Dianions Exist?—One- and Two-Electron Reduction of Proximate, Synperiplanar Bis-Diazenes**

Kai Exner, Dieter Hunkler, Georg Gescheidt,* and Horst Prinzbach*

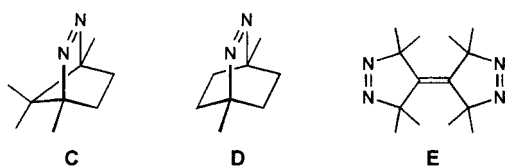
Dedicated to Professor Hans Fritz
on the occasion of his 70th birthday

Rigid, proximate, synperiplanar and “anti-Bredt” protected caged dienes **A** (Scheme 1; $d = 2.8–3.0$ Å) fulfill the prerequisites for one- and two-electron oxidation to nonclassical, theoretically intriguing, and surprisingly stable 4C/3e radical cations and 4C/2e dications (“ σ -bis-homoaromaticity”).^[1] Reduction to the corresponding 4C/5e radical anions and 4C/6e dianions was not possible so far.^[2] Upon oxidation of the comparably proximate bis-diazenes **B** (Scheme 1; $d = 2.8–3.0$ Å),^[3–6] electrons are removed from n_- orbitals,



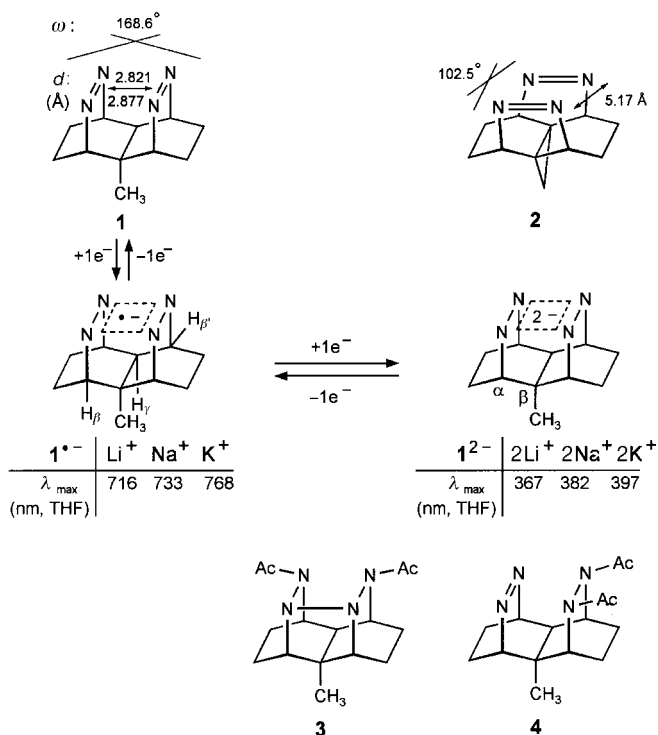
Scheme 1. One- and two-electron oxidation of the caged dienes **A** to 4C/3e radical cations and 4C/2e dications as well as one- and two-electron reductions of similarly proximate bis-diazenes to 4N/5e radical anions **B^{•−}** and 4N/6e dianions **B^{2−}**.

with through-space interaction between the n_- orbitals being not significant (photoelectron spectroscopic analysis).^[3] Here we show that one- and two-electron reductions of such bis-diazenes provides access to previously unknown, nonclassical, cyclically delocalized 4N/5e radical anions **B^{•−}** and 4N/6e



dianions **B^{2−}** of unusual persistence.^[2] Systematic ESR studies of the relatively facile one-electron reduction of cycloaliphatic monodiazenes have been published.^[7, 8] For the ions of type **C^{•−}**, **D^{•−}**, and **E^{•−}**, which are of interest here as references, ¹⁴N hyperfine coupling constants between +0.8 and +1.0 mT have been measured; in **E^{•−}** the unpaired electron is localized in one of the two pyrazoline rings. No mention was made of a significant deepening of the color or of a subsequent reduction step.^[7, 9]

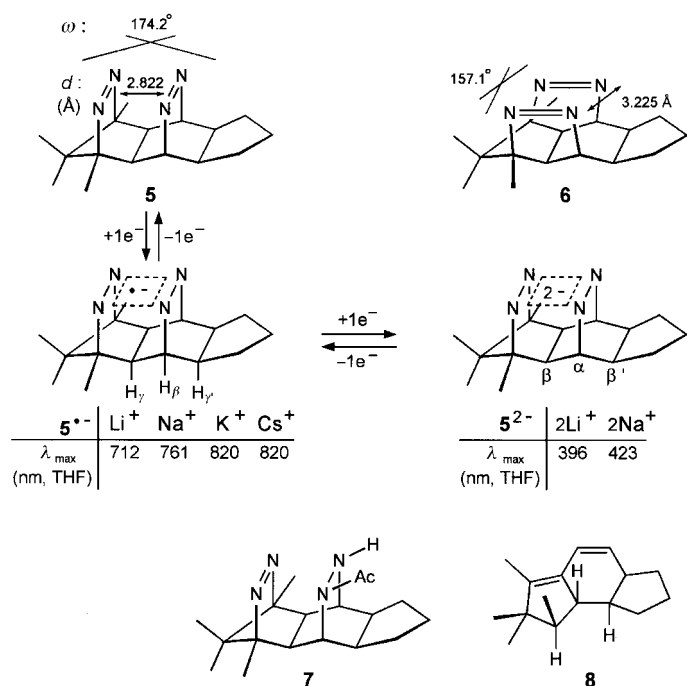
In spite of their favorable d/ω parameters, photoexcitation of the bis-diazenes **1** (Scheme 2) and **5** (Scheme 3), did not lead to $[N_2 + N_2]$ cycloaddition (only N_2 elimination occurred). However, transannular N–N bond formation was observed in the case of their *N*-oxides.^[3, 5] When degassed, dry solutions of **1** and **5** in THF (ca. 4×10^{-2} M) were exposed at room temperature to freshly cut thin lithium sheets,^[7] immediate reduction to the deep green radical anions $Li^+1^{\bullet-}$ and $Li^+5^{\bullet-}$ ($\lambda_{max} = 716$ and 712 nm, respectively) took place. Within minutes the color changed to the red (golden yellow at high dilution) of the dianions $(Li^+)_21^{2-}$ and $(Li^+)_25^{2-}$ ($\lambda_{max} = 367$ and 396 nm, respectively). When exposed to air, the red samples immediately became green and then colorless; neutral **1** and **5** were identified as the residues. After addition of acetic anhydride to $(Li^+)_21^{2-}$ a mixture of **1** (11 %), **3** (37 %), and **4** (52 %) was isolated; reaction of $(Li^+)_25^{2-}$ gave mainly **7** (95 %).^[10] Radical anions and dianions with Na^+ , K^+ , and Cs^+ as counterions were generated with the corresponding metal mirrors. The longest wavelength UV/Vis absorption of the radical anions and dianions (with the exception of



Scheme 2. Reduction of **1** to give the deep green radical anion **1^{•−}** and further reduction to the dianion **1^{2−}**. Addition of acetic anhydride to $(Li^+)_21^{2-}$ gives a mixture of **1** (11 %), **3** (37 %), and **4** (52 %). The longest wavelength UV/Vis absorptions of the radical anion and dianion are significantly dependent on the counterion.

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Scheme 3. Reduction of **5** to give the deep green radical anion in **5 $\bullet^-$** and further reduction to the dianion in **5 $^{2-}$** . Addition of acetic anhydride to $(Li^+)_25^{2-}$ gives **7** (95 %). The longest wavelength UV/Vis absorptions of the radical anion and dianion are significantly dependent on the counterion. At 25 °C $(K^+)_25^{2-}$ decomposes rapidly to **8**, which was isolated in almost quantitative yield.

Na^+5^{2-} ; the spectra are temperature-invariant between -60 and $+25$ °C) depends significantly on the counterions. A bathochromic shift of 108 nm is observed on going from Li^+5^{2-} to K^+5^{2-} , and of 30 nm from $(Li^+)_21^{2-}$ to $(K^+)_21^{2-}$, in agreement with the decreasing ion association. Solutions of the radical anions in THF at room temperature remain unchanged for days, and those of the dianions even survive prolonged heating at 100 °C; only $(K^+)_25^{2-}$ decomposed rapidly at 25 °C to give **8** in almost quantitative yield^[10] and (presumably) N_2 and N_2^{2-} . In solution **1** and $(Li^+)_21^{2-}$ synproportionate to Li^+1^{2-} .

For the formulation of the green radical anions as **1 $\bullet^-$** and **5 $\bullet^-$** , in which five electrons are cyclically delocalized in the plane of the four N atoms (4N/5e), besides the deep colors, the ESR analyses are decisive. Degassed solutions of **1** and **5** at -70 to $+25$ °C were reduced for a short time (Li, Na, K, Cs) and, still free of dianions, used for ESR experiments. The ^1H hyperfine coupling constants were determined by ENDOR and TRIPLE measurements,^[11] and are presented in Table 1 for the well-resolved spectra of K^+1^{2-} and K^+5^{2-} (Figure 1, top). The central criteria for the distinction from localized structures are: the symmetry of the neutral precursors is retained on the time scale of the hyperfine coupling measurements, the ^{14}N hyperfine coupling constants, which were determined by simulation, are pairwise comparable, and with 0.420/0.396 mT for K^+1^{2-} and 0.430/0.340 mT for K^+5^{2-} only roughly half the size of the ones typical for the reference ions C^{2-} – E^{2-} ;^[7] the delocalization of charge and spin is rather uniform over both diazene units. There is excellent agreement

Table 1. Hyperfine coupling constants [mT] and g factors of K^+1^{2-} and K^+5^{2-} .

K^+1^{2-}	K^+5^{2-}
+0.625 (1H _γ)	+0.842 (2H _γ)
+0.420 (2N)	+0.430 (2N)
+0.396 (2N)	+0.340 (2N)
+0.189 (2H)	+0.098
+0.168 (2H)	+0.066
–0.016	–0.021
$g = 2.0042$	$g = 2.0039$

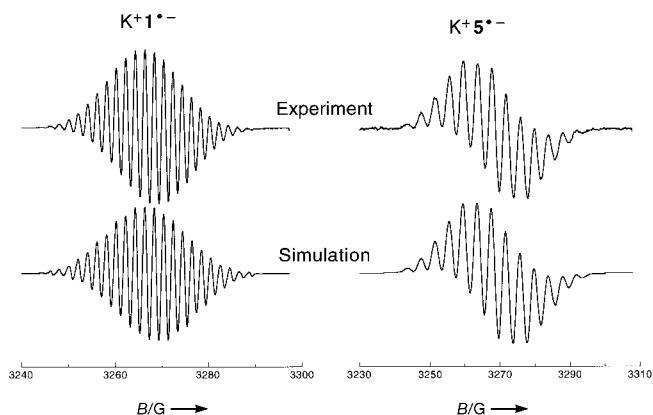


Figure 1. ESR spectra (1,2-dimethoxyethane, -40 °C) of K^+1^{2-} and K^+5^{2-} (top), and the calculated spin-density distribution for 5^{2-} (bottom).

with calculations at the B3LYP/6-31G* level,^[12, 13] which give ^{14}N hyperfine coupling constants of 0.434/0.384 mT for **1 $\bullet^-$** and 0.453/0.346 mT for **5 $\bullet^-$** .^[14] The unusually large hyperfine coupling constants of the γ -protons (0.625 and 0.842 mT) are explained by the calculated spin-density distributions (shown for **5 $\bullet^-$** in Figure 1, bottom), and can be taken as an indication of a relatively large spin density between the diazene units.^[7d, 9]

Compounds **1** and **5** were exhaustively reduced over Li in $[D_8]THF$ (ca. 4×10^{-2} M), and the resulting red solutions were used to record high-resolution ^1H and ^{13}C NMR spectra at room temperature. The assignments (Figure 2) were confirmed by NOE and selective $^1H/^{13}C$ decoupling experiments. In agreement with the delocalized, C_s -symmetrical electron configurations in $(Li^+)_21^{2-}$ and $(Li^+)_25^{2-}$, the high-field shifts

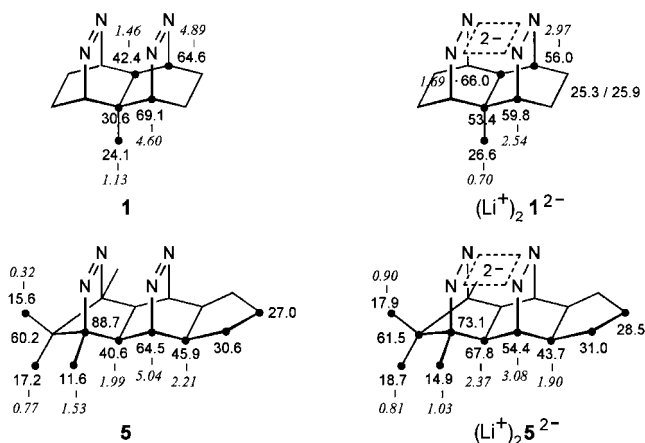


Figure 2. Assignments of ^1H and ^{13}C NMR signals for **1**, **5**, $(\text{Li}^+)_2\mathbf{1}^{2-}$, and $(\text{Li}^+)_2\mathbf{5}^{2-}$ in $[\text{D}_8]\text{THF}$.

of the $\alpha\text{-H}$ ($\alpha\text{-}^{13}\text{C}$) signals are similar [$\Delta\delta = -1.92/-2.06$ ($-8.6/-9.3$) for $(\text{Li}^+)_2\mathbf{1}^{2-}$; $\Delta\delta = -1.96$ ($-10.1/-15.6$) for $\mathbf{6}^{2-}(\text{Li}_2^+)$]; the large low-field shifts of the ^1H and ^{13}C signals of the $\beta\text{-protons}$ ($\beta\text{-C}$ atoms) that are flanked by the two N_2 bridges are also similar [$\Delta\delta = +0.23$ ($+23.6/+22.8$) for $(\text{Li}^+)_2\mathbf{1}^{2-}$; $\Delta\delta = +0.38$ ($+27.2$) for $(\text{Li}^+)_2\mathbf{5}^{2-}$].

The B3LYP/6-31G* calculations on the bis-diazene **5**^[12, 13] reproduce the X-ray data well^[5] and confirm for $\mathbf{5}^{2-}$ and $\mathbf{5}^{2-}$ (free of counterions) the energetic advantage of the cyclic conjugation with plausible lengthening ($+0.063$ ($+0.051$); $+0.132$ ($+0.120$) Å) of the vicinal and shortening (-0.141 ; -0.228 Å) of the transannular N–N distances relative to **5** (Figure 3).

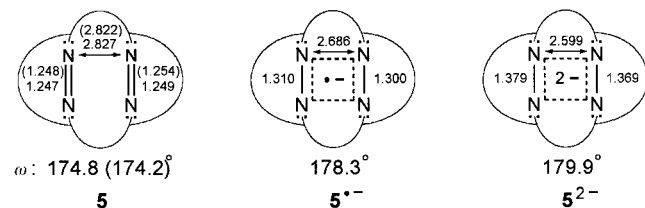


Figure 3. Structural data calculated at the B3LYP/6-31G* level for **5** (X-ray data in parentheses), $\mathbf{5}^{2-}$, and $\mathbf{5}^{2-}$.

The thermodynamic properties of this novel class of $\sigma\text{-bis}$ homoaromatic dianions $\mathbf{B}^{2-}$,^[15] the relationship between cyclic conjugation and structural parameters (d , ω), the structural details in the solid state as a function of the counterions, and the formation of counterion-free ions in the gas phase are central aspects of forthcoming investigations, which will include cyclovoltammetric studies. Initial results^[16] show that reduction of **2**, which is more mobile and far less proximate than **1**, and of **6**, which is the N_2/N_2 metathesis isomer of **5** (from which it differs only slightly), did not lead to formation of deeply colored ions.

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[16] In an ene/diazenes^[17] with a structure very similar to that of the bis-diazene **5** (one N–N double bond is replaced by a C–C double bond), after one-electron reduction the spin density remains more strongly localized in the diazene unit (according to calculations:^[12] $\rho(\text{N}=\text{N}) = 0.765$; $\rho(\text{C}=\text{C}) = 0.168$; ^{14}N hyperfine coupling constant: 0.71/0.77 mT).^[2]

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Self-Assembling Supramolecular Daisy Chains**

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The design and synthesis of supramolecular polymers^[1] is one of the major goals of contemporary supramolecular chemistry.^[2] Hydrophobic bonding, hydrogen bonding, and metal coordination have all been used^[1] successfully to self-assemble^[3] supramolecular polymers in solution and in the solid state. We have devised a self-assembling approach to supramolecular polymer formation (Figure 1) which relies upon the self-complementarity of monomers incorporating a π electron rich macrocyclic "head" and a π electron deficient acyclic "tail" that are unable to interact intramolecularly.^[4] Cyclic and/or linear oligomers, self-assemble spontaneously in solution by the insertion of the tail of one monomer through the cavity within the head of another. The driving forces responsible for this recognition event are [C–H...O] hydrogen bonds augmented by π – π stacking interactions between the complementary π electron deficient and π electron rich recognition sites. Here, we report a) the syntheses of four different self-complementary monomers, b) the spectroscopic evidence for their self-assembly to afford supramolecular

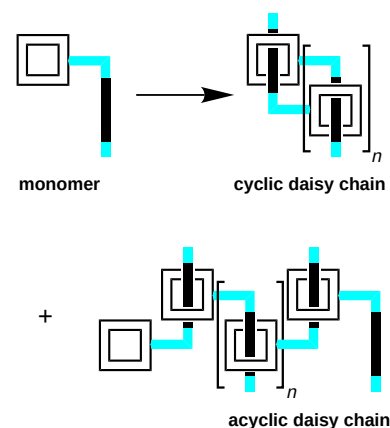


Figure 1. Cyclic and acyclic daisy chains which can be formed by a self-complementary monomer unit.

oligomers in solution, and c) the X-ray crystal structure of a homodimeric cyclic supermolecule formed when one of the monomers crystallizes from solution.

The four monomers **6**·2PF₆–**9**·2PF₆ (Figure 2) were synthesized^[5] as illustrated in Scheme 1. Reaction of *N*-

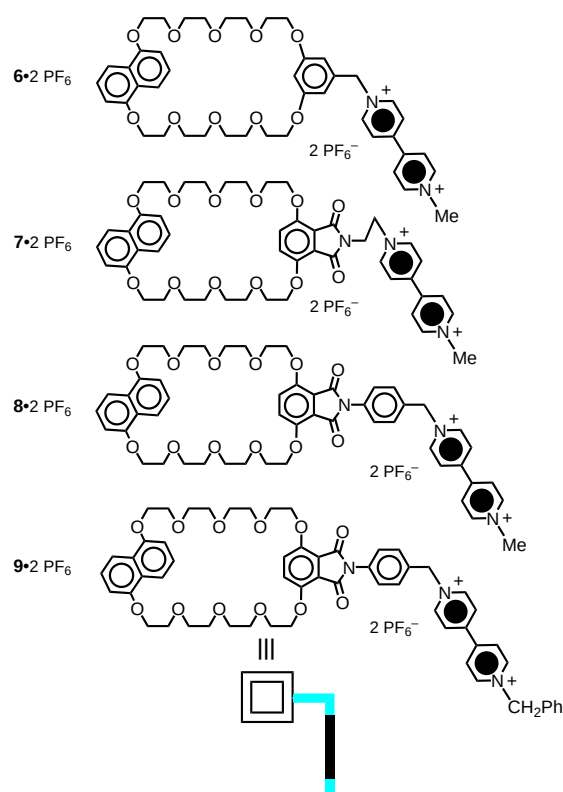


Figure 2. The self-complementary monomers **6**·2PF₆–**9**·2PF₆.

methyl-4,4'-pyridylpyridinium hexafluorophosphate with the macrocyclic polyether **1** gave **6**·2PF₆ in a yield of 14% after counterion exchange. Reaction of 4,4'-bipyridine with the macrocyclic polyethers **2** and **3**, followed by the alkylation of the resulting hexafluorophosphate salts **4**·PF₆ and **5**·PF₆ with methyl iodide or benzyl chloride, gave the self-complemen-

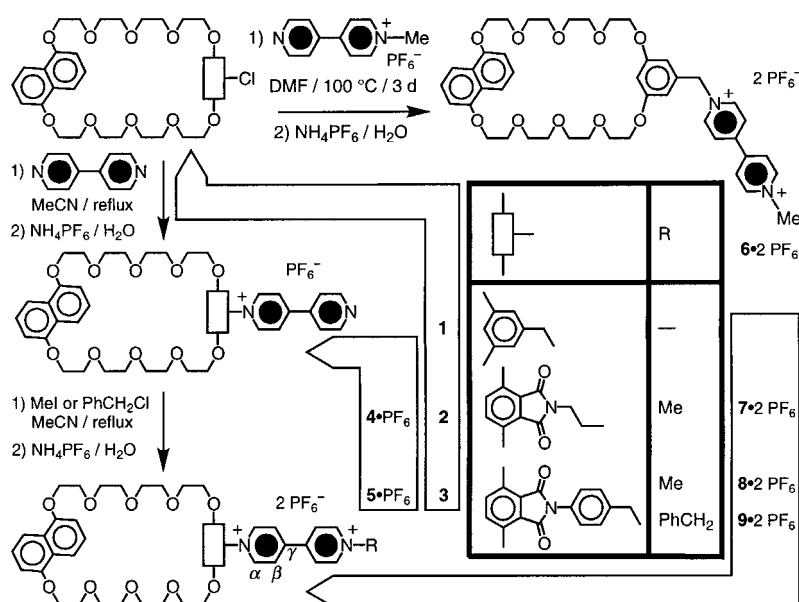
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Scheme 1. Synthesis of the bis(hexafluorophosphate) salts $6 \cdot 2\text{PF}_6$ – $9 \cdot 2\text{PF}_6$.

tary monomers $7 \cdot 2\text{PF}_6$, $8 \cdot 2\text{PF}_6$, and $9 \cdot 2\text{PF}_6$ in yields of 82, 91, and 60%, respectively, after counterion exchange.

The liquid secondary ion (LSI) mass spectra of the bis(hexafluorophosphate) salts $6 \cdot 2\text{PF}_6$ – $9 \cdot 2\text{PF}_6$ revealed the formation of oligomeric supermolecules (Table 1). The LSI mass spectra of $6 \cdot 2\text{PF}_6$ – $9 \cdot 2\text{PF}_6$ show peaks for the tetrameric, trimeric, and dimeric supermolecules corresponding to the loss of one or more hexafluorophosphate counterions. In addition, signals for $[M - \text{PF}_6]^+$ and $[M - 2\text{PF}_6]^+$, corresponding to the loss of one and two hexafluorophosphate counterions, respectively, from the monomers, are also observed. In the case of $6 \cdot 2\text{PF}_6$ and $7 \cdot 2\text{PF}_6$, the LSI mass spectra show peaks for $[5M - 3\text{PF}_6]^+$ corresponding to the loss of three hexafluorophosphate counterions from the pentameric supermolecules.

The ^1H NMR spectra of $6 \cdot 2\text{PF}_6$ – $9 \cdot 2\text{PF}_6$ in CD_3CN at 25°C show time-averaged signals for species with different degrees of aggregation in solution. Significant changes in the chemical shift are observed^[6] upon varying the concentrations from 2.5×10^{-2} to $2.5 \times 10^{-4}\text{M}$. The broad resonances observed at high concentrations shift to lower fields and become sharp and well-resolved upon dilution. The changes in the δ

values are particularly evident (up to $\Delta\delta = +0.5$) for the protons in the β -positions on the bipyridinium units. Shifts to lower field and broadening of most of the resonances are also observed in the ^{13}C NMR spectra of $6 \cdot 2\text{PF}_6$ – $9 \cdot 2\text{PF}_6$ in CD_3CN upon increasing the temperature from 0 to 70°C . The changes in the δ values are particularly evident (up to $\Delta\delta = +10$) for the γ -carbon atoms of the bipyridinium units.

The absorption UV/Vis spectra of $6 \cdot 2\text{PF}_6$ – $9 \cdot 2\text{PF}_6$, recorded in MeCN at 25°C , show strong charge-transfer bands in the visible region ($\lambda_{\text{max}} \approx 470\text{ nm}$) arising from the donor–acceptor interactions between the bipyridinium units and the complementary π electron rich aromatic units. In all cases, the presence of several oligomeric supermolecules in solution led to nonlinear correlations between λ_{max} and the concentration over the range 2.5×10^{-2} to $2.5 \times 10^{-4}\text{M}$.

One of the self-complementary monomers—namely, $6 \cdot 2\text{PF}_6$ —produced orange single crystals from a benzene/MeCN solution. X-Ray structural analysis^[7] on one of these crystals (Figures 3 and 4) reveals that, in the solid state, pairs of 6^{2+} dications interweave with each other to form a C_2 -symmetric homodimeric pair.^[8] The bipyridinium unit appended to the macrocyclic polyether

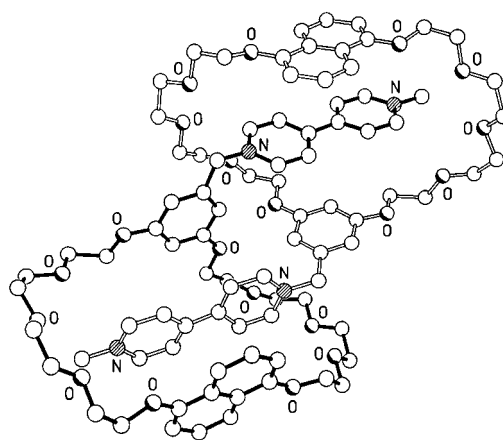


Figure 3. Ball-and-stick representation of the dimeric 6^{2+} complex in the solid state.

Table 1. LSI-MS data for the bis(hexafluorophosphate) salts $6 \cdot 2\text{PF}_6$ – $9 \cdot 2\text{PF}_6$.^[a]

Compound	Pentamer $5M - 3\text{PF}_6$			Tetramer $4M - 3\text{PF}_6$			Trimer $3M - 3\text{PF}_6$			Dimer $2M - 3\text{PF}_6$			Monomer $M - 2\text{PF}_6$	
	PF_6	2PF_6	3PF_6	PF_6	2PF_6	3PF_6	PF_6	2PF_6	3PF_6	PF_6	2PF_6	3PF_6	PF_6	2PF_6
$6 \cdot 2\text{PF}_6$ ^[b]	4868	4098	3953	3807	–	3037	2892	2747	–	1976	1831	1686	915	770
$7 \cdot 2\text{PF}_6$ ^[c]	5285	4430	4284	–	–	3285	3142	–	–	2143	1998	1851	998	853
$8 \cdot 2\text{PF}_6$	–	4679	4534	4388	4242	3473	3328	3183	–	2267	2122	1977	1060	915
$9 \cdot 2\text{PF}_6$	–	4982	4837	4692	4546	3701	3556	3410	3265	2419	2274	2128	1136	991

[a] LSI mass spectra were obtained from a VG Zabspec mass spectrometer equipped with a 35-keV cesium ion gun. Samples were dissolved in either a 3-nitrobenzyl alcohol or 2-nitrophenyloctyl ether matrix previously coated on to a stainless steel probe tip. The m/z values reported correspond to the centroids of the isotopic distributions of monocationic species in all cases. M is the mass of the monomeric bis(hexafluorophosphate) salt. [b] Signals for $[3M + \text{Na}]^+$, $[2M]^+$, $[M + \text{Na}]^+$, and $[M]^+$ at m/z values of 3205, 2122, 1084, and 1061, respectively, were also observed. [c] Signals for $[4M + \text{Na}]^+$, $[3M + \text{Na}]^+$, $[2M + \text{Na}]^+$, and $[M + \text{Na}]^+$ at m/z values of 4597, 3454, 2311, and 1166, respectively, were also observed.

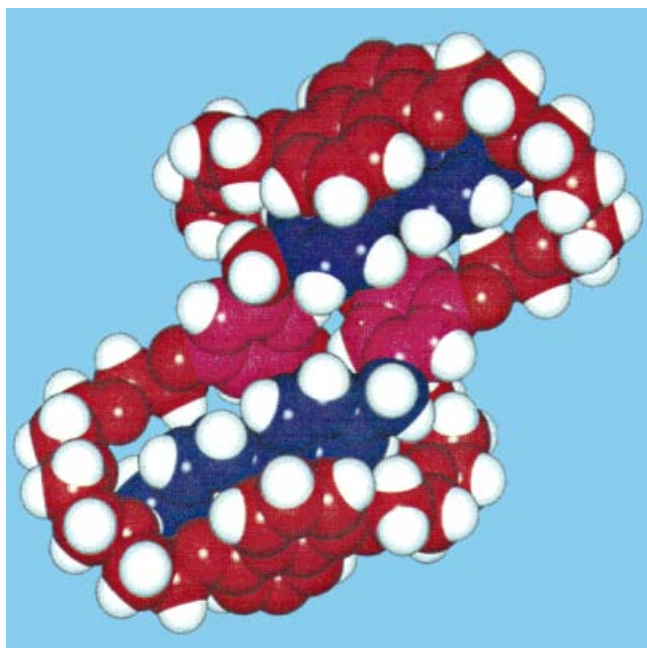


Figure 4. Space-filling representation of the dimeric 6^{2+} complex in the solid state; red: the macrocyclic “head”, blue: the acyclic “tail”, magenta: the resorcinol unit connecting the two.

of one dication is inserted through the center of the macrocyclic polyether of another, and vice versa, and sandwiched between the resorcinol and 1,5-dioxynaphthalene ring systems. One of the pyridinium rings of the dication is oriented orthogonally to the resorcinol ring of the macrocyclic polyether. This “edge-to-face” geometry results in a marked distortion in the external angles at the C-5 position on the resorcinol ring of about $\pm 6^\circ$; a deformation directly analogous to that observed^[9] in diphenyl ethers. Intracomplex stabilization is achieved by π - π stacking between the bipyridinium ring systems and their sandwiching π electron rich aromatic ring systems.^[10] Further complex stabilization is achieved through the cooperative effect of ten [C-H...O] hydrogen bonds. There is an absence of any extended intercomplex interactions, presumably as a result of the inclusion of significant amounts of solvent into the lattice.

Although one of the four plerotropic monomers we have investigated with self-complementary donor-acceptor recognitions sites crystallizes to form [c2]daisy chain^[11] supermolecules, presumably under kinetic control, there is overwhelming evidence, in the case of two of the monomers, for the existence under thermodynamic control of daisy chain supermolecules containing up to at least five repeating units in solution. This observation is encouraging in the face of the challenge to synthesize acyclic $[a_\infty]$ daisy chain supermolecules en route to the preparation of mechanically interlocked polymers in the shape of macromolecular daisy chains.

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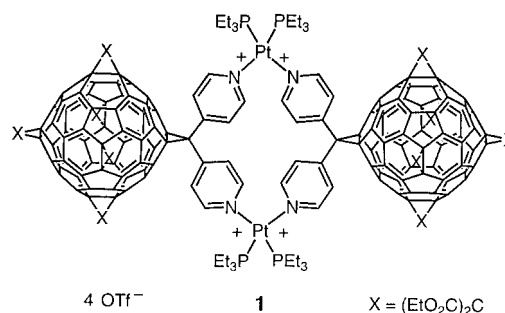
NMR (2.50×10^{-2} M): 8.85 (brs, 2H), 8.69 (brs, 2H), 7.90 (brs, 2H), 7.83 (brs, 2H), 7.69 (br d, $^3J = 7$ Hz, 2H), 7.32–7.50 (m, 4H), 7.11 (brt, $^3J = 7$ Hz, 2H), 6.83 (s, 2H), 6.64 (brd, $^3J = 7$ Hz, 2H), 5.93 (brs, 2H), 4.41 (brs, 3H), 4.05 (brs, 4H), 3.89 (brs, 8H), 3.60–3.80 (m, 20H); ^{13}C NMR (2.50×10^{-2} M): $\delta = 154.9, 150.8, 148.1, 147.2, 146.4, 142.3, 141.6, 134.6, 132.4, 131.5, 129.2, 127.0, 126.6, 126.5, 122.9, 114.9, 106.8, 71.5, 71.2, 70.5, 70.4, 70.2, 69.2, 64.9, 49.6$. **9** · 2 PF₆: yield 60%; m.p. 270 °C (decomp); UV/Vis (1.60×10^{-2} M): λ_{max} (ϵ) = 472 nm (255); HR-MS: calcd for (C₉₈H₆₁F₆N₃O₁₂P) [M – PF₆]⁺: 1136.3897, found: 1136.3885; ^1H NMR: (1.58×10^{-2} M): $\delta = 8.88$ (d, $^3J = 7$ Hz, 2H), 8.60 (d, $^3J = 7$ Hz, 2H), 8.27 (d, $^3J = 7$ Hz, 2H), 7.74 (brd, $^3J = 5$ Hz, 2H), 7.63 (d, $^3J = 8$ Hz, 2H), 7.54 (d, $^3J_{\text{AB}} = 8$ Hz, 2H), 7.50–7.40 (m, 5H), 7.36 (d, $^3J_{\text{AB}} = 8$ Hz, 2H), 7.20 (t, $^3J = 8$ Hz, 2H), 6.95 (s, 2H), 6.75 (d, $^3J = 8$ Hz, 2H), 5.78 (s, 2H), 5.10 (s, 2H), 4.15 (t, $^3J = 4$ Hz, 4H), 4.03 (t, $^3J = 4$ Hz, 4H), 3.90 (t, $^3J = 4$ Hz, 4H), 3.77 (t, $^3J = 4$ Hz, 4H), 3.59–3.72 (m, 16H); ^{13}C NMR (1.58×10^{-2} M): $\delta = 165.5, 155.0, 151.0, 150.0, 146.5, 146.4, 134.7, 133.5, 132.7, 131.2, 131.1, 130.6, 130.4, 129.2, 127.8, 127.2, 126.5, 123.0, 71.4, 70.4, 70.1, 69.1, 65.8, 65.1$.

- [6] For tables listing the chemical shifts of selected resonances observed in the ^1H NMR spectra of **6** · 2 PF₆–**9** · 2 PF₆ at various concentrations, see the supporting information.
- [7] Crystal data for **6** · 2 PF₆: C₄₄H₅₄N₂O₁₀ · 2 PF₆ · 4 PhH · 0.5 MeCN, $M_r = 1393.8$, monoclinic, space group $C2/c$ (no. 15), $a = 22.497(5)$, $b = 17.912(4)$, $c = 34.814(10)$ Å, $\beta = 103.67(2)^\circ$, $V = 13632(6)$ Å³, $Z = 8$, $\rho_{\text{calcd}} = 1.358$ g cm^{−3}, $\mu(\text{Cu}_{\text{K}\alpha}) = 13.8$ cm^{−1}, $F(000) = 5832$, $T = 213$ K. An orange block of dimensions $0.40 \times 0.40 \times 0.27$ mm was used for the data collected, and 3477 independent reflections were measured on a Siemens P4/RA diffractometer with Cu_{Kα} radiation (graphite monochromator) and ω -scans. The structure was solved by direct methods. On account of a shortage of observed data, only the oxygen and nitrogen atoms of the ordered portions of the cyclophane were refined anisotropically—the carbon atoms, and all of the non-hydrogen atoms of the disordered section of one of the polyether arms (for which two partial occupancy orientations were identified), were refined isotropically. The aromatic rings were refined as idealized rigid bodies. The hexafluorophosphate counterions were disordered, and in each case two partial-occupancy orientations were identified with only the atoms of the major-occupancy orientations being refined anisotropically. The included benzene solvent molecules were distributed over a mixture of full- and partial-occupancy sites, and they were refined isotropically as idealized rigid bodies. The 50% occupancy MeCN molecule was refined isotropically. Refinement was by full matrix least-squares based on F^2 to give $R_1 = 0.114$ and $wR_2 = 0.305$ for 2202 independent observed reflections ($|F_o| > 4\sigma(|F_o|)$), $2\theta \leq 106^\circ$) and 496 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-101199. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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- [11] We describe daisy chain arrays and assemblies as being acyclic [a] or cyclic [c] and use these two letters, along with numbers in the conventional manner, to define the nature and repeating unit, respectively, present in a particular supramolecular array or molecular assembly.^[8] Note that only [c]daisy chains experience maximal (recognition) site occupancy (ref. [2b], p. 182–183) and that small [c]daisy chains (supermolecules) are also favored entropically with respect to large [a]daisy chains (supramolecular arrays).

Pt^{II}-Directed Self-Assembly of a Dinuclear Cyclophane Containing Two Fullerenes**

Tilo Habicher, Jean-François Nierengarten, Volker Gramlich, and François Diederich*

In order to develop fullerene-containing supramolecular assemblies and advanced materials,^[1] C₆₀ has been incorporated into multicomponent molecular systems such as rotaxanes,^[2] catenanes,^[3] and oligopyridine Ru^{II} complexes.^[4] The properties of these C₆₀ hybrids are encouraging and have generated our interest in the construction of even more complex two- and three-dimensional systems. To achieve this objective, we wished to take advantage of the self-assembly of multidentate ligand precursors with transition metal centers^[5] which, in the hands of Fujita,^[6] Stang,^[7, 8] and others,^[9] has led to the formation of some spectacular molecular architectures consisting of multinanometer-sized polynuclear molecular squares and three-dimensional molecular objects.^[10] Here, we report the synthesis and X-ray crystal structure of the fullerene-containing rigid dinuclear cyclophane **1** which is obtained by self-assembly of the novel fullerene ligand **2** with Pt^{II} centers.



In the preparation of **1**, dipyrindylchloromethane **5** (obtained in two steps from 4-pyridinecarboxaldehyde **3** through **4**^[11]) was treated under the conditions of the Bingel cyclopropanation method^[12] to afford the fullerene monoadduct **6** (Scheme 1).^[13] Attempts to complex ligand **6** with **7** led to a

[*cis*-Pt(PEt₃)₂(OTf)₂] **7**

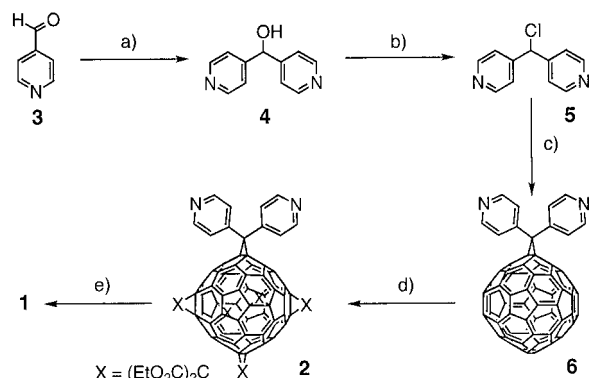
black, completely insoluble precipitate. In order to solubilize the expected complex, we prepared the yellow C_{2v}-symmetrical fullerene hexakis-adduct **2**^[14] (m.p. > 270 °C) using the

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Scheme 1. Preparation of cyclophane **1**. a) 4-Lithiopyridine, Et₂O, –78 °C to 20 °C, 52 %; b) 1. methanesulfonyl chloride, NEt₃, CH₂Cl₂, 2. CaCl₂, Me₂SO, 62 %; c) C₆₀, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), toluene, 20 °C, 32 %; d) diethyl 2-bromomalonate, DBU, 9,10-dimethylantracene, toluene, 35 %; e) **7**, CD₂Cl₂, 20 °C, N₂, 91 %.

DMA-templated addition (DMA = 9,10-dimethylantracene) of diethyl 2-bromomalonate.^[15]

The pseudo-octahedral all-equatorial functional relationship of the addends in the hexakis-adduct **2** was proven by X-ray crystallography (Figure 1).^[16] The unit cell of the crystal structure contains four fullerene molecules in two slightly different conformations, four benzene molecules, and ethyl acetate. The partially resolved ethyl acetate molecules and the flexible malonate esters give rise to some disorder in the structure. Despite this disorder, the dipyridylmethanofullerene core of the structure is well resolved. The C(pyr)–C(pyr) (pyr = pyridine) bond angle at the quaternary C atom of the dipyridylmethano bridge was 113(1)°.

By mixing an equimolar amount of **2** and **7** the tetracationic cyclophane **1** was obtained quantitatively as the tetrakis-triflate salt (triflate = trifluoromethane sulfonate). The multinuclear (¹H, ¹³C, ¹⁹F, ³¹P) NMR spectroscopy data in CD₂Cl₂ were consistent with the formation of a single, highly symmetrical (*D*_{2h}) compound. The presence of triflate counterions is indicated by the typical ¹⁹F NMR signal (δ = –79.1), as well as the characteristic IR absorptions (1027, 1111, 1153 cm^{–1}). The ³¹P NMR spectrum displayed one sharp singlet with appropriate Pt satellites for the equivalent P atoms. This resonance (δ = –4.56) is upfield shifted relative to **7** (δ = 8.95) because of the ligation by **2**. Particularly revealing are the ¹H NMR chemical shifts of the pyridyl and phosphane protons. The resonances of the α and β H atoms on the pyridyl rings in **1** are downfield shifted by $\Delta\delta$ = 0.62 and 0.32, respectively, relative to their positions in **2**. The CH₂P signal is shifted upfield by $\Delta\delta$ = 0.16, relative to its position in **7**. This upfield shift, which contrasts the downfield shifts of the CH₂P resonance

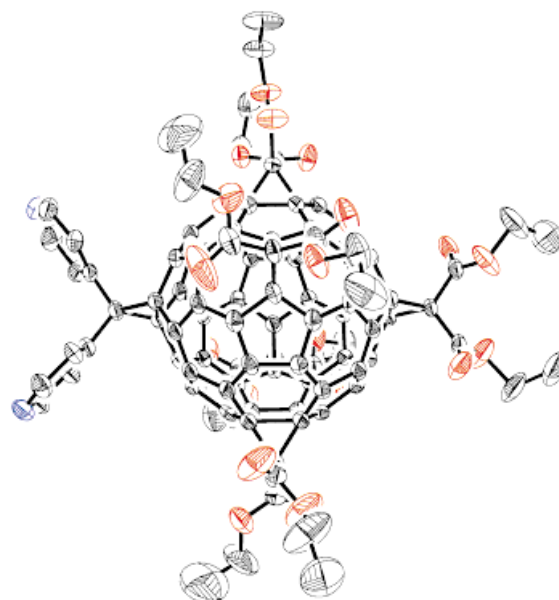


Figure 1. X-ray crystal structure of **2** (displacement ellipsoids are shown at the 30 % probability level). Only one of the two conformers is shown.

reported for other molecular squares,^[8a, b, d, f] can readily be explained by the shielding influence of the benzenoid rings in the neighboring fullerene hexakis-adducts in **1**.^[17]

The X-ray crystal structure analysis unambiguously proved the [2+2] parallelogram-type structure^[7a] of **1** (Figure 2).^[16] Although the resolution of the structure is only moderate in view of 1) the high molecular weight of **1** (C₂₄₀H₁₇₆F₁₂N₄O₅₂P₄Pt₂S₄, *M*_r = 4818), 2) the small crystal size, 3) the disorder in the ethyl moieties of the phosphane and malonate units and in the triflate counterions, and 4) the inclusion of large amounts of unresolved solvent molecules (EtOAc), the identity of the molecule is in no doubt. Specifically, the rigid part of the complex with the fullerenes and the dinuclear cyclophane are well resolved. Several interesting details were revealed. The Pt^{II} coordination is square-planar, but with a significant deviation from the ideal

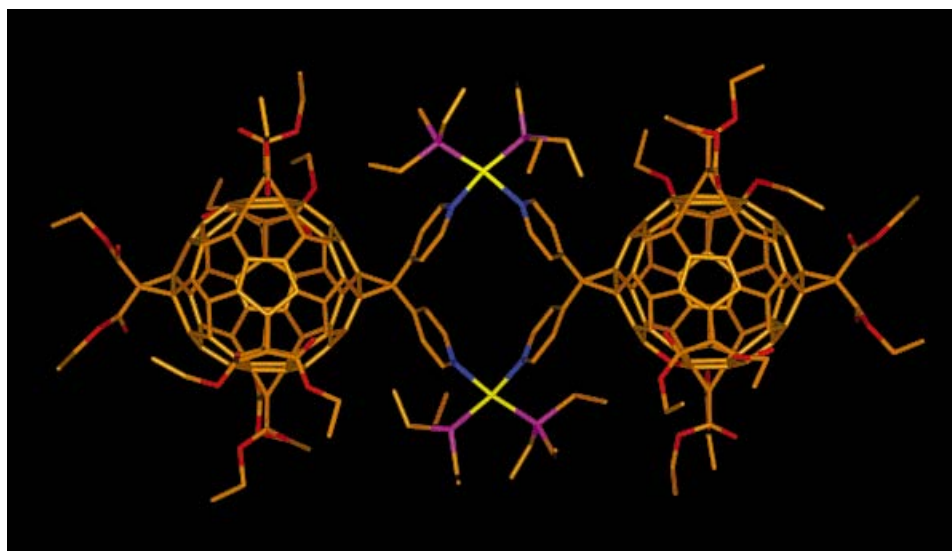


Figure 2. X-ray crystal structure of tetracationic **1**. The counteranions are omitted. C gold, Pt yellow, N blue, and P purple.

90° angles. The N–Pt–N angles are 81.6(3)°, whereas the P–Pt–P angle widens up to 97.2(2)°. The C(pyr)–C–C(pyr) angle of 113(2)° at the quaternary C atoms of the dipyrityldimethano groups in **1** is identical to the angle seen in the X-ray crystal structure of ligand **2**.

The sum of the angles at the vertices of the macrocyclic parallelogram, measured at the two Pt atoms and the two quaternary C atoms of the dipyrityldimethano groups is 390(5)° though 360° is needed for a perfectly planar assembly. In the reported X-ray structures of metal-assembled quadrangles, two situations are well documented: 1) The sum of the vertex angles is lower than the required value and the structures, in order to accommodate these smaller angles, adopt puckered conformations^[8a] and 2) the sum of the angles fits this 360° requirement, and these structures typically show a perfectly planar macrocyclic conformation.^[8b, c] An angular sum much larger than the ideal 360°, as observed for **1**, has, to the best of our knowledge, not been previously reported. In spite of an angular sum of 390(5)°, the assembly reported here is still planar; the maximum deviation of the two Pt^{II} centers, the quaternary C atoms, and the pyridine N and C_γ atoms from the best plane encompassing these centers is only 0.09 Å. The four pyridyl rings are nearly orthogonally oriented with respect to this plane: The maximum deviation of their best planes from perfect orthogonality is only 2°. As a result of the imperfect vertex angle sum, an outward bending of the edges in the parallelogram can be expected and, despite the moderate resolution of the structure, is actually observed. The Pt–P (2.26(1) Å) and the Pt–N (2.10(5) Å) bond lengths are normal. The cavity of the dinuclear cyclophane is small: the Pt–Pt distance is 10.26(3) Å and the distance between the quaternary C atoms only 7.42(6) Å, thus offering at best space for inclusion of an aliphatic chain.

Although the angles are not optimal for the synthesis of the macrocycle only one type of complex is formed, and oligomer formation was not observed at all. This result underlines the potential of this powerful metal-directed self-assembly to construct even more complex supermolecular fullerene arrays selectively: upon replacing further diethyl malonate addends in **2** with dipyrityldimethano groups, larger assemblies such as rods or two- and three-dimensional fullerene networks should become accessible.

Experimental Section

1: To a solution of **2** (11 mg, 6.55×10^{-6} mol) in CD₂Cl₂ (1 mL) under Ar in the dark was added **7** (4.34 mg, 5.96×10^{-6} mol). The resulting mixture was stirred for 5 min until analysis by ¹H NMR spectroscopy showed complete complex formation. Recrystallization from EtOAc/CH₂Cl₂/PhH/Et₂O yielded **1** (13 mg, 91 %): yellow crystals; m.p. > 250 °C; UV/Vis (CH₂Cl₂): λ_{max} (ε) = 271 (191 400), 282 (185 500), 318 (117 200), 337 (99 600), 437 (sh, 2700), 451 (sh, 1600); IR (KBr): ν̄ = 1741 cm⁻¹ (C=O); 1153, 1111, 1027 (triflate); ¹H NMR (CD₂Cl₂, 300 MHz): δ = 1.13–1.42 (m, 96H); 1.78 (br. t, J = 7.3 Hz, 24H); 4.23–4.46 (m, 40H); 8.07 (d, J = 6.6 Hz, 8H); 9.20 (br. d, 8H); ¹³C NMR (75 MHz, CD₂Cl₂): δ = 8.03, 14.26, 14.29, 14.35, 15.6–16.2 (m, CH₂P), 45.69, 46.26, 46.39, 46.81, 63.57, 63.67, 63.91, 69.47, 70.05 (2x), 70.26, 73.14, 131.08, 141.27, 141.82, 141.87, 141.93, 142.18, 143.03, 144.76, 145.93, 146.17, 146.22, 146.28, 146.82, 150.00, 152.29, 163.90, 164.06, 164.13 (2x); ¹⁹F NMR (280 MHz, CD₂Cl₂): δ = –79.06; ³¹P NMR (120 MHz, CD₂Cl₂): δ = –4.56 (J_{Pt–P} = 3134 Hz).

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partially resolved EtOAc molecules ($C_{120.75}H_{64}N_2O_{20}$, $M_r = 1862.74$): Triclinic space group $P\bar{1}$, $Z = 4$, $\rho_{\text{calc}} = 1.368 \text{ g cm}^{-3}$, $a = 14.218(7)$, $b = 25.562(13)$, $c = 25.916(13) \text{ \AA}$, $\alpha = 84.18(3)$, $\beta = 74.84(3)$, $\gamma = 89.81(4)^\circ$, $V = 9042(8) \text{ \AA}^3$. The structure was solved starting with a single fullerene oriented by PATTSEE orientation search and subsequent tangent expansion in PL1. Refinement by full-matrix least-squares analysis (SHELXTL PLUS; heavy atoms anisotropic, H atoms fixed, whereby H positions are based on stereochemical considerations) to give $R(1) = 0.0964$ and $R_w(2) = 0.2564$ for 2554 variables, 756 restraints, and 18545 observed reflections with $I > 2\sigma(I)$ and $1.74 \leq \theta \leq 50.01$. b) X-ray crystal data for **1**:^[16c] Yellow rhomboid crystals ($0.1 \times 0.1 \times 0.015 \text{ mm}$) were obtained by slow diffusion of hexane into a solution of **1** in EtOAc/PhH and contained a large amount of unresolved solvent molecules ($C_{200.5}H_3N_2O_{20}P_2PtS$, $M_r = 3050.16$): Monoclinic space group $P2(1)/c$, $Z = 4$, $\rho_{\text{calc}} = 1.580 \text{ g cm}^{-3}$, $a = 29.17(2)$, $b = 17.986(9)$, $c = 27.37(2) \text{ \AA}$, $\alpha = 90$, $\beta = 116.75(5)$, $\gamma = 90^\circ$, $V = 12821(13) \text{ \AA}^3$. The structure was solved by Patterson methods and refined by full-matrix least-squares analysis (SHELXTL PLUS; heavy atoms isotropic, bond distances and angles of the partially disordered diethyl malonate groups constrained by SHELX-DFIX-instructions) to give $R = 0.109$ and $R_w = 0.092$ (based on F) for 756 variables and 5549 observed reflections with $I > 2\sigma(I)$ and $1.70 \leq \theta \leq 35.10$. c) Data collection at $T = 293 \text{ K}$: Picker–Stoe diffractometer, $Cu_{K\alpha}$ radiation using ω scans, $\lambda = 1.54178 \text{ \AA}$. 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-101112. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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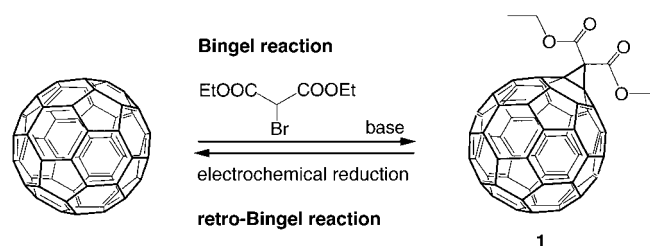
Preparation of Enantiomerically Pure C_{76} with a General Electrochemical Method for the Removal of Di(alkoxycarbonyl)methano Bridges from Methanofullerenes: The Retro-Bingel Reaction**

Roland Kessinger, Jeanne Crassous, Andreas Herrmann, Markus Rüttimann, Luis Echegoyen,* and François Diederich*

Since its discovery in 1993, the Bingel reaction^[1] has been widely used as a mild, versatile method to introduce one or more methano bridges into C_{60} ^[2] and the higher fullerenes.^[3] Cyclopropanation of a fullerene, according to the original

Bingel protocol, occurs by treating the carbon allotrope with 2-bromomalonate esters in the presence of base. Modified procedures allowing in situ formation of the 2-bromo- or 2-iodomalonates have also been reported.^[4, 5] Cyclopropane rings fused to fullerenes are highly stable and cannot be removed thermally or by wet-chemical methods, although mass spectrometric fragmentation occurs rather readily.^[6]

The majority of methanofullerenes are also known to be very stable under the conditions of cyclic (CV) and steady-state voltammetry (SSV).^[7] A notable exception was reported by Haddon, Wudl, and co-workers^[8] for the monoanion of 1,2-methano[60]fullerene-61,61-dinitrile, which was unstable under CV conditions and, based upon voltammetric observations, was reported to revert back to C_{60} .^[9] Also, the electrochemistry group of M. Gross at Strasbourg had noted a decomposition of dianions of specific bis(methano)fullerenes with a *cis*-2 addition pattern during CV and SSV, and this observation provided the impetus for the work reported here.^[7c, 10] In this paper, we describe the retro-Bingel reaction (Scheme 1) as a general, preparative electrochemical method^[11, 12] for the removal of di(alkoxycarbonyl)methano bridges from methanofullerenes and illustrate its power with the preparation of the pure enantiomers of C_{76} .^[13, 14]



Scheme 1. The Bingel and retro-Bingel reactions.

Electrochemical investigations on diethyl 1,2-methano[60]fullerene-61,61-dicarboxylate (**1**) and similar C_{60} monoadducts have shown that the first two reduction steps are electrochemically and chemically reversible on the voltammetric time scale at a scan rate of 100 mV s^{-1} .^[7b, 8] Our CV data are in agreement with these earlier findings (Figure 1). Chemical irreversibility of the second reduction is only evident at very slow scan rates. We reduced **1** electrochemically in CH_2Cl_2 containing $0.1 \text{ M Bu}_4\text{NPF}_6$ at 293 K at controlled potential, initially to its monoanionic state (at -1.2 V versus a Ag wire pseudo reference electrode).^[15] The charge transferred corresponded exactly to one electron per molecule, and the resulting anion was very stable under these conditions, with no apparent decomposition after 30 min. The formation of the dianion (at -1.55 V versus Ag) by controlled potential electrolysis (CPE, Figure 1), on the other hand, was surprising, because the charge transferred corresponded to four electrons per molecule and not just one. Clear changes in the CV indicated that some chemical reaction had taken place. After 30 min of electrolysis, reoxidation of the solution at 0 V (versus Ag), followed by column chromatography (SiO_2 , toluene) yielded pure C_{60} in over 80% yield (Table 1). It must be stressed that the two first reduction steps are perfectly reversible on the CV time scale at a scan rate of

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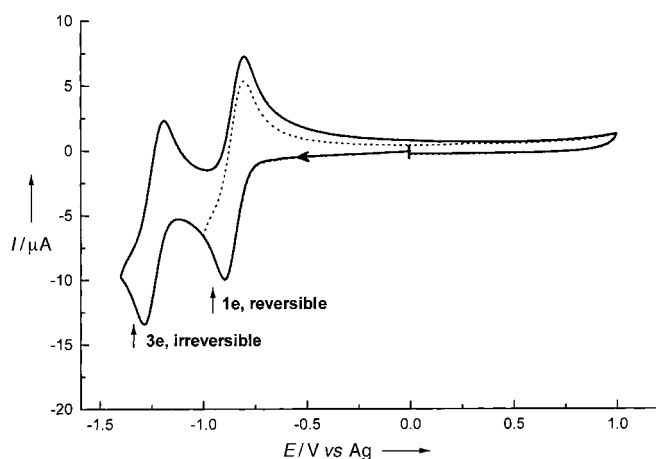


Figure 1. CV of **1** in CH_2Cl_2 containing 0.1M Bu_4NPF_6 , with a scan rate of 100 mV s^{-1} . The working electrode was a glassy carbon mini-electrode. The dotted line corresponds to a scan with a switching potential of -1 V versus the Ag wire pseudo reference electrode, and the solid line to one with a switching potential of -1.4 V . Shown are the potentials applied in the controlled potential coulometry.

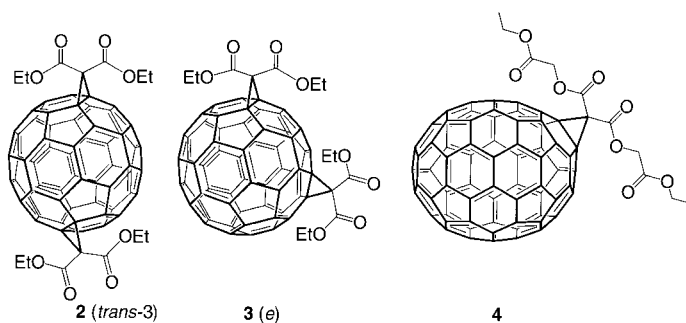
Table 1. Results of the retro-Bingel reaction by CPE in CH_2Cl_2 .

Starting material	Product	Yield[%]
1	C_{60}	82
2	C_{60}	75
3	C_{60}	75
4	C_{70}	70
5	C_{76}	5 ^[a]
6	<i>ent</i> - C_{76}	9 ^[a]

[a] Not optimized.

100 mV s^{-1} (Figure 1). It was thus surprising to see that controlled potential bulk electrolysis at the second reduction potential led to complete chemical irreversibility yielding predominantly C_{60} . The mechanism of this reaction, which we call the retro-Bingel reaction, is not yet fully understood but is under investigation in our laboratory.

The generality of the retro-Bingel reaction was proven by CPE (under the conditions described above) of the bis-Bingel adducts^[2] **2**^[16] and **3**^[7c], which were converted cleanly and in over 75 % yield into C_{60} (Table 1). As in the case of **1**, CPE was conducted at the second reduction potential, but the number of electrons transferred per molecule was approximately six instead of four. The reaction is not limited to C_{60} derivatives and was shown to work also for the C_{70} monoadduct **4**,^[17a] which reacted cleanly to give C_{70} in 70 % yield.



We monitored the retro-Bingel reaction of **4** by CV. The first reduction step is fully reversible (Figure 2a), whereas the second reduction process in this case is electrochemically irreversible (Figure 2b), and, not surprisingly, bulk electrolysis

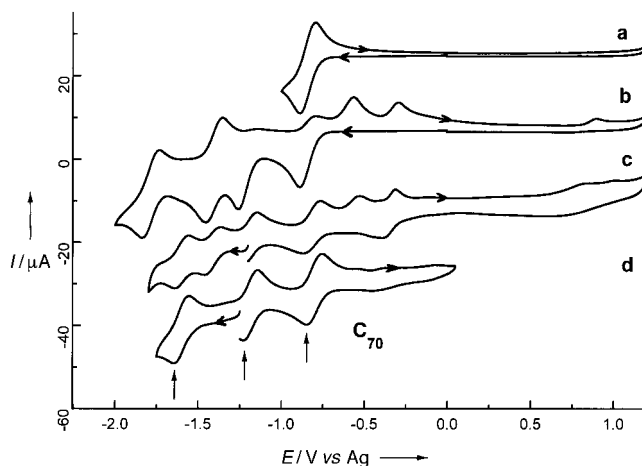
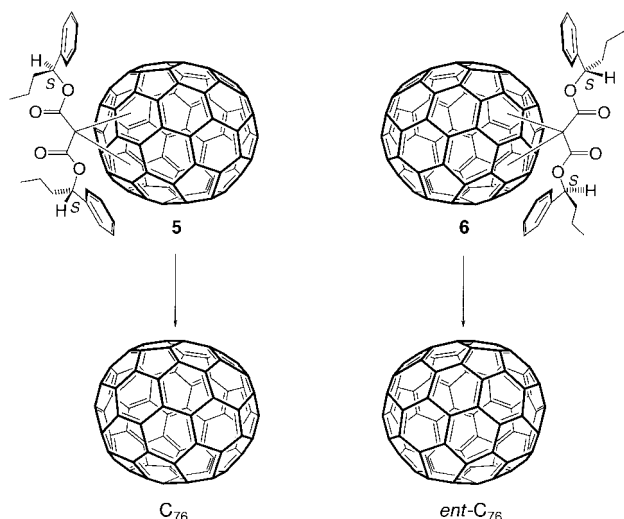


Figure 2. CV data for **4** in CH_2Cl_2 containing 0.1M Bu_4NPF_6 , with a glassy carbon working electrode and a scan rate of 100 mV s^{-1} . a) Initial scan showing the reversibility of the first reduction process. b) Scan with a switching potential of -2 V (versus Ag), clearly showing the irreversibility of subsequent reductions, even the second one. c) Voltammogram recorded after electrolyzing the solution with a net charge corresponding to a four-electron transfer per molecule. The scan was started at the rest potential, around -1.25 V (versus Ag). d) Same as in (c), but after waiting approximately 30 min. Notice the almost exclusive observation of the first three reduction waves of pure C_{70} .

at the potential corresponding to the irreversible second reduction process (-1.3 V versus Ag) led to a net charge transfer of four electrons per molecule, transforming **4** into C_{70} . This conversion occurs stepwise since new waves between 0 and -0.5 V (versus Ag) started appearing during electrolysis (Figure 2c), providing evidence for the formation of intermediates. These intermediates eventually disappeared when the conversion into pure C_{70} was complete (Figure 2d). These intermediate species are under current investigation as possible clues to the mechanism of the retro-Bingel reaction.

Hawkins and Meyer had performed the kinetic optical resolution on a small scale of the inherently chiral fullerene $D_2\text{-C}_{76}$ by employing the asymmetric Sharpless osmylation reaction.^[14a] A comparison of the circular dichroism (CD) spectra reported by Hawkins and Meyer for the C_{76} enantiomers^[14a] to those of a variety of optically active, covalent derivatives of C_{76} prepared by us^[18] had revealed a large, unexpected difference in the magnitude of the Cotton effects. Whereas the covalent C_{76} derivatives displayed bands whose $\Delta\epsilon$ values can be up to $250 \text{ M}^{-1} \text{ cm}^{-1}$, the enantiomers of the pure fullerene displayed bands with $\Delta\epsilon$ -values up to only $32 \text{ M}^{-1} \text{ cm}^{-1}$.^[14a, 19] In order to reinvestigate the chiroptical properties of C_{76} , we applied the retro-Bingel reaction to the preparation of the enantiomerically pure higher fullerene (Scheme 2). When the optically active, diastereoisomerically pure C_{76} monoadducts **5** and **6**, with enantiomeric carbon cores,^[18] were submitted to CPE and subsequent purification by HPLC,^[20] the two enantiomers, C_{76} and (*ent*- C_{76}) were



Scheme 2. Retro-Bingel reaction of the diastereoisomerically pure, optically active C₇₆ monoadducts **5** and **6**. The location of the malonate addend is not exactly known although tentative constitutional assignments have been made. The CD spectra, however, provide unambiguous evidence that the two compounds are associated pairs of diastereoisomers.^[18, 21]

obtained in low yields (about 5–10%) which have not yet been optimized because of the limited availability of the starting materials.

The CD spectra of C₇₆ and ent-C₇₆ displayed the expected mirror image shapes (Figure 3, Table 2) with band positions in full agreement with those reported by Hawkins and Meyer.^[19] In contrast, however, the Cotton effects in our spectra are almost a full magnitude larger than those previously reported. The $\Delta\epsilon$ values can be as large as 210 M⁻¹cm⁻¹ and are therefore much more in agreement with the values measured for optically pure C₇₆ derivatives such as **5** and **6**.^[21] Two possible reasons may account for the noticeably low values reported by Hawkins and Meyer: Either the enantiomeric purity of their samples was not very high or their concentrations were not accurately determined.^[22]

We now intend to apply the retro-Bingel reaction also to the formation of other enantiomerically pure higher fullerenes such as D₃-C₇₈ or D₂-C₈₄, starting from diastereoisomerically pure malonate adducts. Furthermore, the sequence of the Bingel followed by the retro-Bingel reaction also permits the

Table 2. Circular dichroism spectra of C₇₆ ($c = 3.4 \times 10^{-6}$ M in toluene) and ent-C₇₆ ($c = 8.0 \times 10^{-6}$ M in toluene) in the range 290–800 nm. Both compounds were prepared from the retro-Bingel reaction.

C ₇₆		ent-C ₇₆	
λ [nm]	$\Delta\epsilon$ [M ⁻¹ cm ⁻¹]	λ [nm]	$\Delta\epsilon$ [M ⁻¹ cm ⁻¹]
315	-73 ^[a]	316	+80 ^[a]
331	+53.4	331	-52.3
352	-18.8	351	+23.7
391	+186 ^[a]	391	-186 ^[a]
406	+210.4	407	-215.5
463	+74.1	462	-66.0
519	-32 ^[a]	520	+45 ^[a]
541	-55.8	549	+69.5
578	-106.3	578	+117.0
629	-6 ^[a]	629	+6 ^[a]
694	+9.7	700	-9.7

[a] Shoulders; $\Delta\epsilon$ values have greater uncertainties.

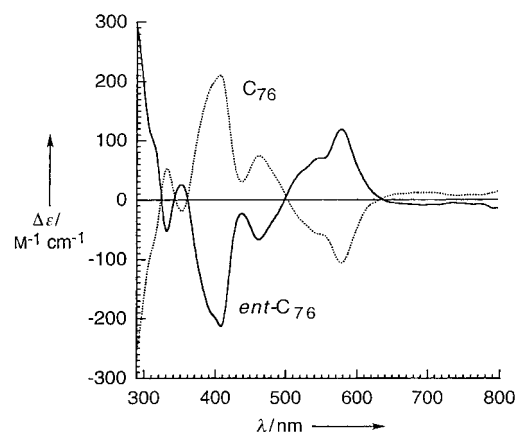


Figure 3. CD Spectra of C₇₆ and ent-C₇₆ in toluene (see Table 2).

introduction of the cyclopropane ring as a new protecting group in fullerene chemistry, which should be selectively removable in the presence of many other addends. With the capability of selectively reversing both fullerene cyclopropanation and, by an indirect method,^[7c, 23] the Diels–Alder addition, our tether-directed remote functionalization,^[2c] which introduces both cyclopropane and cyclohexene rings, should now lead to an even greater diversity of hitherto unknown multiple addition patterns on the fullerene surface that are not available by other methods.

Experimental Section

Fullerene monoadduct **1** (11 mg, 12.5 μmol) and supporting electrolyte Bu₄NPF₆ (0.8 g) were added into a home-built electrochemical cell,^[12b] and the cell was degassed and pumped to 10⁻⁶ Torr before the dried CH₂Cl₂ (17 mL), which had also been degassed and pumped to the same pressure, was vapor-transferred directly into the cell. CPE at 293 K on a Pt mesh working electrode (100 mesh, 6.5 cm²) at -1.55 V versus a Ag wire pseudo reference electrode, separated from the solution by a Vycor tip, was performed for 30 min after which the solution was reoxidized at 0 V versus Ag for the same length of time. The electrolyte was removed by passing the mixture through a short column of SiO₂, and elution with toluene yielded pure C₆₀ (7.4 mg, 82%).

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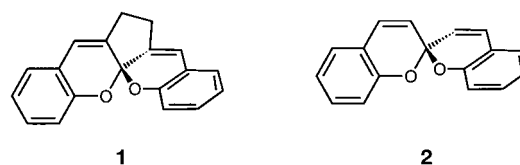
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- [19] CD spectrum of enantiomerically pure C_{76} ($c = 3.8 \times 10^{-5}$ M) in toluene:^[14a] λ [nm] ($\Delta\epsilon$ [$M^{-1}cm^{-1}$]): 315 (–11.7), 330 (+8.9), 354 (–4.2), 394 (+29.4), 405 (+31.6), 460 (+12.6), 541 (–11.1), 573 (–18.2), 639 (+2.5).
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Enantiomeric Enrichment of Stereolabile Chiral Spiro Compounds by Dynamic HPLC on Chiral Stationary Phases**

Klaus Lorenz, Eiji Yashima, and Yoshio Okamoto*

Chromatographic enantioseparation on chiral stationary phases (CSPs)^[1–5] has become a very useful method for the analysis of chiral compounds and the preparative separation of enantiomers because of recent progress in the development of CSPs with high chiral recognition ability. In addition, the newly developed dynamic high-performance liquid chromatography (DHPLC) has received considerable attention as a powerful tool for investigating dynamic processes of interconverting enantiomers;^[6–11] kinetic data and enantiomerization barriers for stereolabile compounds can be obtained from a series of temperature-dependent plateaus and peak shapes by chiral DHPLC. Here, we focus on the influence of CSPs on the equilibrium of interconverting enantiomers which will result in nonracemic mixtures. In the case of interconverting enantiomers, the use of CSPs opens the possibility for combining separation techniques and equilibrium shift in one step. By employing quite simple new chromatographic procedures we may, in principle, obtain one enantiomerically pure enantiomer in 100% yield from a racemate with standard HPLC equipment.

We investigated the racemic spiro compounds **1** and **2** as model compounds. Both enantiomerize thermally and photo-



chemically through an electrocyclic [1,6]-ring opening of the C–O bond next to the spiro center and consecutive ring closure.^[12]

Figure 1a shows a standard HPLC chromatogram for the resolution of **1** on Chiralcel OD.^[13] Compound **1** can be completely resolved at 20 °C without any enantiomerization. However, at higher temperatures (ca. 50 °C), the enantiomerization processes described in Scheme 1 (DHPLC on CSPs)^[14,15] lead to plateau-like elution profiles^[16] (Figure 1b). In the heterogeneous system (CSP/mobile phase) the adsorbed enantiomer showing a longer retention time (B) should be enriched, whereas the eluent may contain a racemic mixture under equilibrium conditions.

According to the kinetic differential equations describing the enantiomerization processes during DHPLC, only race-

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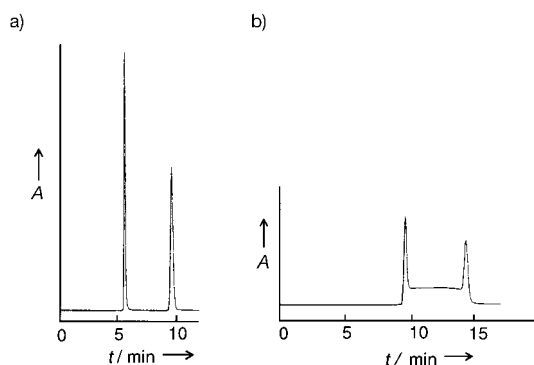
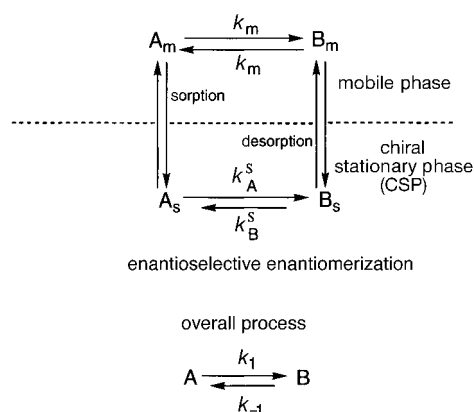


Figure 1. Chromatograms in the resolution of spiro compound **1** on Chiralcel OD with hexane/2-propanol (9/1) as eluent at 20 °C (a) and 50 °C (b). The flow rate was 1.0 mL min⁻¹ (a) and 0.25 mL min⁻¹ (b).



Scheme 1. Processes occurring during DHPLC: vertical sorption/desorption of enantiomers A (first eluted) and B (second eluted), horizontal enantiomerization in the mobile phase and enantioselective enantiomerization^[15] of adsorbed species with respective kinetic rate constants. The indices m and s indicate the enantiomer in the mobile phase and a sorbed enantiomer; the rate constants for the “overall process” k_1 and k_{-1} describe the sum of enantiomerization in the mobile phase and enantioselective enantiomerization, respectively.

mic samples are to be expected on elution under usual conditions (constant temperature and constant flow). Nevertheless, an enantiomeric surplus of the second eluted compound is built up during the time that both enantiomers are on the column; removal of the first eluted enantiomer by elution disturbs the equilibrium and a rather fast back-reaction towards the first eluted enantiomer will take place. Finally, the racemic compound is obtained.

To suppress the back-reaction, the time interval after elution of the first peak until elution of the second ($t_B - t_A$) should be kept as small as possible with respect to t_A . Therefore, experiments were carried out as follows:^[17–19] After injection of the racemic solution into the HPLC apparatus the chromatographic flow (1.5 mL min⁻¹) was stopped after 2 min for equilibration on the CSP. After an appropriate time (1–6 h) the chromatographic flow was restarted, which delivered chromatograms showing an excess of the second eluted enantiomer. The chromatograms usually contained two peaks for the optical antipodes, but in the case of high α values four peaks appeared (Figure 2; $\alpha = \frac{t_B - t_0}{t_A - t_0} = 2.29$). The peaks A and A' as well as B and B' were derived from enantiomers

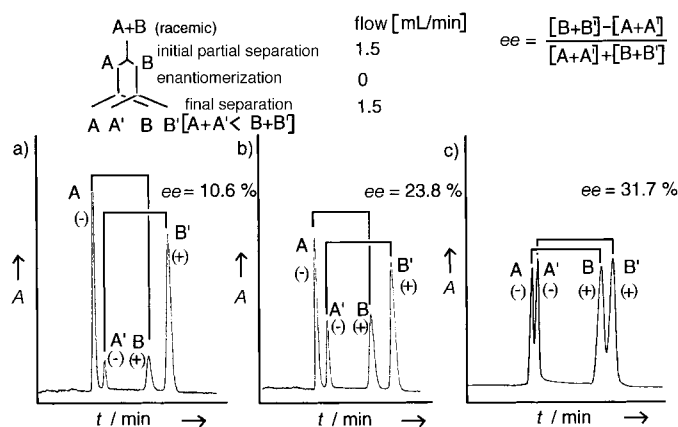


Figure 2. Chromatograms of compound **1** on Chiralcel OD with hexane/2-propanol (99/1) as eluent at 40 °C. After 2 min the flow was stopped for equilibration on the CSP. Equilibration time was 16 min (a), 57 min (b), and 6 h (c). Then flow was then restarted, and the chromatograms were monitored.

already separated during the initial separation. Experimental chromatograms before complete equilibrium (Figure 2a,b) and at equilibrium (Figure 2c) indicate that the third peak (B) is derived from the first (A) and the second peak (A') from the last (B') during the time interval of enantiomerization. Equilibrium rate constants k_1 and k_{-1} can be calculated from these data (see below).

Equations (1)–(3) have been developed in order to find a quantitative relation between retention factors k' and equilibrium concentrations c_A^{eq} and c_B^{eq} on the CSP.; c_A^{eq} and c_B^{eq} are

$$\frac{k_1}{k_{-1}} = \frac{c_B^{\text{eq}}}{c_A^{\text{eq}}} \quad (1)$$

$$\frac{k_1}{k_{-1}} = \frac{1 + k'_B}{1 + k'_A} \quad (2)$$

$$\frac{c_B^{\text{eq}}}{c_A^{\text{eq}}} = \frac{1 + k'_B}{1 + k'_A} \quad (3)$$

defined as overall equilibrium concentrations of A (A + A') and B (B + B') on the CSP. To prove Equation (3) as a combination of Equations (1) and (2)^[20] experimentally, racemic spiro compounds **1** and **2** were equilibrated on various CSPs under the conditions described above. The results are summarized in Table 1. To determine the retention factors, one additional experiment at constant chromatographic flow was necessary. The plot in Figure 3 according to Equation (3) gave a straight line in good agreement with the calculated one. Deviations from the calculated values may be due to errors in retention factors and experimental equilibrium concentrations.

To increase the enantiomeric excess of spiro compounds obtained after DHPLC, only one enantiomer was equilibrated selectively. Two CSPs were employed, as represented in Scheme 2. The basic idea is that enantiomerization occurs on the second CSP at relatively high temperature, whereas thermal interconversion can be suppressed on the first CSP at relatively low temperature.

After the first eluted enantiomer A had left the first column (0 °C) and had been transported to the second column (40 °C), the chromatographic flow was stopped and enantioselective

Table 1. DHPLC of spiro compounds **1** and **2**.^[a]

Entry	Compd	CSP	Eluent	<i>T</i> [°C]	<i>t</i> [min]	<i>k'</i> _A	<i>k'</i> _B	$\frac{1+k'_B}{1+k'_A}$	$\frac{C_B^{eq}}{C_A^{eq}}$
1	1	A	hexane/ <i>i</i> PrOH (99/1)	40	360	2.55	5.85	1.93	1.93
2	1	A	hexane/EtOH (99/1)	32	210	1.36	3.09	1.73	1.80
3	2	B	hexane/ <i>i</i> PrOH (99/1)	45	165	1.66	3.38	1.65	1.62
4	1	A	hexane/ <i>i</i> PrOH (9/1)	40	200	0.78	1.61	1.47	1.50
5	2	A	hexane/ <i>i</i> PrOH (99/1)	45	167	3.08	4.31	1.30	1.30
6	2	C	hexane/ <i>i</i> PrOH (99/1)	45	155	1.00	1.55	1.29	1.22
7	1	B	hexane/ <i>i</i> PrOH (99/1)	32	150	3.13	4.25	1.27	1.22
8	2	A	hexane/EtOH (99/1)	40	170	1.55	2.09	1.20	1.15
9	2	A	hexane/ <i>i</i> PrOH (9/1)	50	67	0.75	1.05	1.17	1.14

[a] *t* is the time for equilibration on the CSPs; the flow rate after equilibration was 1.5 mL min⁻¹; A, B, and C stand for the following CSPs: A: cellulose tris(3,5-dimethylphenylcarbamate) (Chiralcel OD), B: xylan bis(3,5-dimethylphenylcarbamate),^[21] C: cellulose tris(3-fluoro-5-methylphenylcarbamate).^[22]

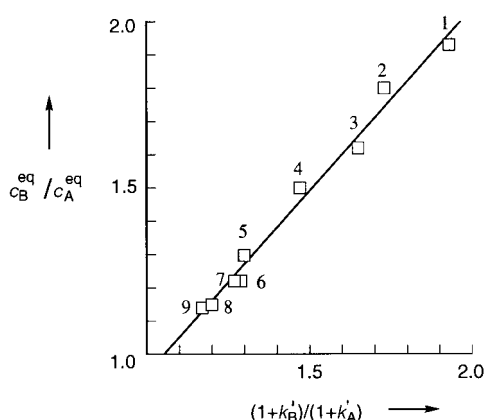
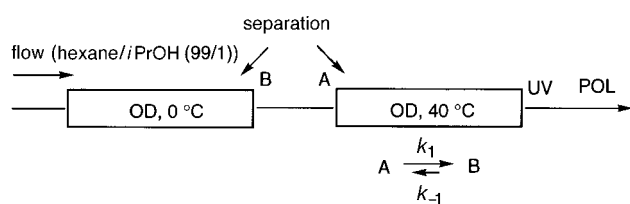


Figure 3. Plot of $(1+k'_B)/(1+k'_A)$ versus the ratio of equilibrium concentrations C_B^{eq}/C_A^{eq} [Eq. (3)], as obtained by DHPLC on various CSPs (Table 1). The numbers represent entry numbers in Table 1.



Scheme 2. Two-column system for selective enantiomerization of one enantiomer. Left: B does not equilibrate at 0 °C. Right: equilibration of the first eluted A (40 °C).

enantiomerization^[15] of A was allowed to proceed for 2 h. On elution three peaks appeared in the chromatogram as expected (Figure 4). The first and second peaks can be assigned to A (ca. 20 mol %) and B (ca. 30 mol %), respectively. Peak B was derived from A on the second CSP by enantiomerization. The equilibrium between A and B was not completely reached after 2 h. The last peak is noninterconverted B (50 mol %). As a result, the enantiomeric excess increased from 31 % (normal equilibrium) to about 60 % in the case of selective enantiomerization of A. If the equi-

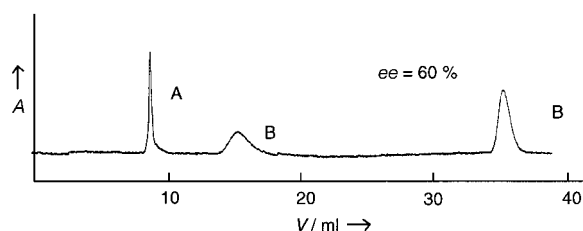


Figure 4. Chromatogram of spiro compound **1** in selective enantiomerization on the CSPs. For details, see Scheme 2.

brium between A and B would have been completely reached, the enantiomeric excess would be even higher (68 %). More cycles of enantioselective equilibration of one enantiomer—for example, by recycling the undesired enantiomer in a chromatographic recycling system (reinjection) and collecting the desired enantiomer—would lead to an enantiomerically pure compound.

The kinetics of enantiomerization on a CSP can be experimentally estimated in the same way as for the thermodynamic equilibrium (Figure 2). The only difference is that the time interval allowed for enantiomerization was shorter and variable. Plots according to Equations (4) and (5)

$$-\ln\left(1 - \frac{B_{(t)}(2 + k'_A + k'_B)}{(A_{(t)} + B_{(t)})(1 + k'_B)}\right) = (k_1 + k_{-1})(t - t_0) \quad (A \rightarrow B) \quad (4)$$

$$-\ln\left(1 - \frac{A'_{(t)}(2 + k'_A + k'_B)}{(A'_{(t)} + B'_{(t)})(1 + k'_A)}\right) = (k_1 + k_{-1})(t - t_0) \quad (B' \rightarrow A') \quad (5)$$

gave straight lines, and the sum of kinetic rate constants k_1 and k_{-1} was determined for both plots to be $3.4 \times 10^{-4} \text{ s}^{-1}$ for **1** on Chiralcel OD as a CSP, with hexane/2-propanol (99/1) as eluent at 40 °C. With Equation (6) k_1 and k_{-1} were finally calculated to be 2.2×10^{-4} and $1.2 \times 10^{-4} \text{ s}^{-1}$, respectively.

$$k_1/k_{-1} = (1 + k'_B)/(1 + k'_A) \quad (6)$$

The compounds presented in this work readily undergo thermal interconversions and are thus of interest as model

compounds. It would be an interesting perspective to replace the CSP at higher temperature by acid or basic catalysts such as ion exchangers, as many other classes of stereolabile compounds—for example, carbonyl compounds bearing a hydrogen-substituted, asymmetric carbon center in the α -position—could be investigated.

The chromatographic procedures summarized under the title “enantiomeric enrichment by HPLC” are a new method to convert an interconvertible racemic mixture into an excess of one enantiomer and to separate the enantiomers at the same time. Especially in cases where only one enantiomer is of interest, this may be a new approach to obtain enantiomerically pure compounds.

Experimental Section

Compounds **1** and **2** were prepared according to literature procedures.^[23,24] For the chromatographic experiments the following equipment was used: pump: JASCO PU 986, degasser: JASCO DC-980-50, UV detector JASCO MD-910 multiwavelength detector and JASCO 875-UV, polarimetric detector: JASCO OR990 and JASCO Shodex OR1.

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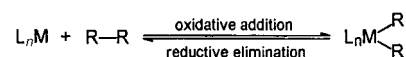
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The First Metathesis of C–C Single Bonds in Homogeneous Solution: Titanocene-Mediated and Photocatalyzed Cleavage and Recombination of Disubstituted Butadiynes**

Siegmar Pulst, Frank G. Kirchbauer, Barbara Heller, Wolfgang Baumann, and Uwe Rosenthal*

Dedicated to Dr. Erhard Kurras
on the occasion of his 70th birthday

The cleavage (oxidative addition) and coupling (reductive elimination) of carbon–carbon bonds (Scheme 1) are elemental steps in many transition metal catalyzed reactions and



Scheme 1.

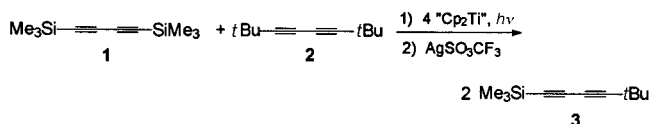
are strongly influenced by the nature of the ligands L, metal centers M, and organic groups R. The copper-catalyzed Glaser coupling reaction (R = alkynyl) has long been known and is a well-established method for preparing 1,4-disubstituted 1,3-butadiynes.^[1] In contrast, examples of the reverse reaction, the activation and cleavage of the central C–C single bond, are rare.^[2]

The cleavage of the C–C single bonds of butadiynes with “Cp₂Ti” and “Cp₂Zr” (Cp = cyclopentadienyl) is influenced by the metal,^[2c] the substituents,^[3] and by the stoichiometry.^[4] So far, all attempts to combine the cleavage reaction with a subsequent coupling reaction of the resulting alkynyl groups have failed, both with homobimetallic Ti and Zr systems and early/late heterobimetallic systems such as Ti/Ni and Zr/Ni.^[2e] The high thermal stability of the intermediate metal complexes and side reactions such as diyne coupling^[4, 5] and ligand cleavage^[6] have until now prevented the controlled metathesis of diynes.^[2c, 4] Recently, we found that the coupling reaction of the alkynyl groups in [Cp₂Ti(C≡CtBu)₂]^[7] is photo-accelerated.^[8] Basset et al.^[9] described the first heterogeneous “metathesis of alkanes” with silica-supported transition metal hydrides as catalysts. Here we report the first metathesis of the C–C single bonds of disubstituted butadiynes in homogeneous solution; the reaction is mediated by titanocene and photocatalyzed.

An equimolar mixture of the symmetrically substituted butadiynes **1** and **2** was irradiated with light of wavelength 390–450 nm in the presence of an excess of the titanocene (“Cp₂Ti”) source [Cp₂Ti(η²-Me₃SiC≡CSiMe₃)]^[10] at 100 °C in toluene. After oxidative workup with AgSO₃CF₃, the diyne starting materials and the unsymmetrically substituted butadiyne **3** were detected by gas chromatography (Scheme 2,

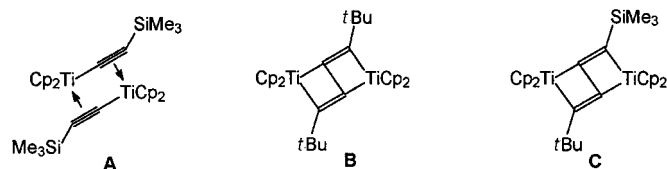
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Scheme 2. “Cp₂Ti”-mediated photocatalytic formation of **3** from **1** and **2**.

Experimental Section). The formation of **3** indicates a C–C single bond metathesis with cleavage of the butadiynes and subsequent recombination of the alkynyl groups. Since the workup was not optimized and is associated with a certain degree of decomposition of the three butadiynes, the yield of isolated **3** was only 4.9% with respect to the diyne starting materials. However, ¹H NMR measurements showed the presence of 71% of the diynes **1–3**, stabilized in the form of the complexes **A** (14%), **B** (36%), and **C** (21%). The reverse reaction, the irradiation of **3** in the presence of “Cp₂Ti”, also leads to a nearly identical mixture of the complexes **A–C** and of the butadiynes **1–3** after workup.



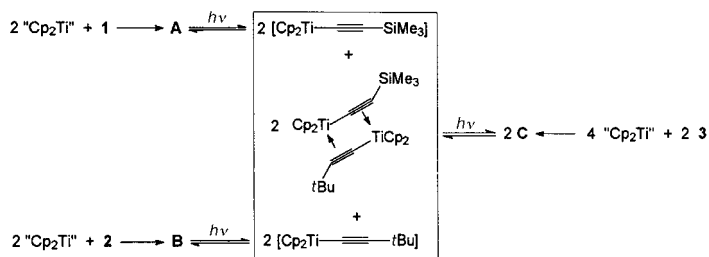
At 100 °C the titanocene source and irradiation are both essential for achieving metathesis of the butadiynes. At 140 °C and in the presence of titanocene the reaction proceeds slowly without irradiation (Table 1). Hence, the titanocene-mediated metathesis is photo-accelerated and can be regarded as a photocatalyzed reaction.^[11]

Table 1. Intensities of the ¹H NMR signals of complexes **A–C** after various reaction times *t*.^[a]

<i>t</i> [h]	A	Ratio of product B	C
0	0.50	0.50	0
20 ^[b]	0.38	0.50	0
7 ^[c]	0.21	0.39	0.17
20 ^[c]	0.14	0.36	0.21
4 ^[d]	0.51	0.26	0
18 ^[d]	0.44	0.21	0.18

[a] In [D₈]toluene with cyclohexane as internal reference for quantification; sealed tube. [b] Without irradiation at 100 °C. [c] With irradiation at 100 °C. [d] Without irradiation at 140 °C.

To understand the course of the reaction, equimolar mixtures of the intermediates **A** and **B** with and without addition of **1** or **2** were irradiated in an NMR tube. In some experiments, decomposition of the silylalkyne compounds **1**, **3**, and **A** occurred. Irradiation of the mixture of complexes **A** and **B** gave the highest yield of the metathesis product **C** (and **3** after workup). Complexes **A** and **B** result from stoichiometric reactions of one equivalent of the butadiynes **1** and **2** with two equivalents of “Cp₂Ti”, and can be regarded as the initially formed intermediates.^[2b, 4] In our proposed mechanism (Scheme 3), the dimeric complexes **A** and **B** (as well as **C** in



Scheme 3. Possible mechanism of the metathesis reaction.

the reverse reaction) decompose on irradiation to afford the monomeric σ-alkynyltitanium(III) complexes [Cp₂Ti–C≡CtBu] and [Cp₂Ti–C≡CSiMe₃]. These monomeric species are unstable,^[12] coordinatively unsaturated 15-electron d¹ systems, and, because an equilibrium exists between the different types of complexes,^[13] they recombine to give a mixture of symmetrical and unsymmetrical dimeric complexes. A similar dissociation of **A–C** also occurs in the mass spectrometer.^[3, 14]

Further results of the ¹H NMR investigations are summarized in Table 2. Thermal excitation or irradiation of mixtures

Table 2. Table 1: Intensities of the ¹H NMR signals of **A–C** and **1–3** after irradiation.

System (1:1)	Products	Ratio
1 + 2 ^[a]	1 , 2	1:1
A + B ^[a]	A–C	1:1.67:1
C ^[a]	A–C	1:1:1
1 + 2 + 4 “Cp ₂ Ti” ^[b]	A–C	3.3:2.3:1
A + 2 ^[b]	no C , no 3	–
B + 1 ^[b]	no C , no 3	–

[a] 2 h irradiation, 140 °C, 1,3,5-trimethylbenzene. [b] 4 h irradiation, 100 °C, toluene.

of **1** and **2** without titanocene complex did not give **3**. The addition of the radical initiator AIBN had no effect;^[15] a mechanism involving organic radicals can therefore be excluded.^[16] The NMR spectra also showed that the bis(σ-alkynyl)titanium(IV) complexes [Cp₂Ti(C≡CSiMe₃)₂]^[7] and [Cp₂Ti(C≡CtBu)₂]^[7] are not formed. Irradiation of the silylalkynyl complex **A** in the presence of **2** or of **B** in the presence of **1** gave no **C** or **3**. Therefore, a direct reaction of the postulated monomeric σ-alkynyltitanium(III) intermediates with the butadiynes in a Ti–C/C–C metathesis reaction can be ruled out.

A very high titanocene concentration is essential for the success of the metathesis. An increasing butadiyne to titanocene ratio favors the formation of titanacyclopentadienes as coupling products.^[4] This may explain why we have so far been unable to carry out a catalytic titanocene-mediated reaction.

Compared to titanocene complexes, the corresponding zirconocene complexes were more reactive with respect to C–C bond cleavage of butadiynes.^[10b] However, the “mixed” butadiyne **3** was not observed after irradiation of mixtures of **1** and **2** in the presence of the “Cp₂Zr” source [Cp₂Zr(py)(η²-Me₃SiC≡CSiMe₃)] (py = pyridine). Apparently, the initially formed dimeric σ-alkynylzirconium(III) complexes are more

stable toward dissociation. The above-mentioned early/late transition metal combinations Ti/Ni and Zr/Ni^[2e] were also inactive.

The sp³ orbitals of aliphatic C–C bonds are not available for interaction with transition metals. The sp orbitals of the central C–C single bond of butadiynes are better suited to this purpose and can be dramatically activated by complexation in titanacyclocumulenes.^[4] Furthermore, some theoretical approaches describe free butadiynes as “dicarbenecumulenes” rather than as dialkynes.^[19] The partial double bond character of the central C–C bond is more pronounced in metallacyclocumulenes and is apparent in some reactions.^[8]

The novel reaction of butadiynes (Scheme 2) is the first metathesis of C–C single bonds in homogeneous solution. It can serve as a model reaction for the degradation of long-chain alkanes and polymers, which is currently of growing interest.^[20] Applications in organic syntheses, analogous to known catalytic metathesis reactions of olefins and alkynes such as ring enlargement of cyclic 1,3-diynes by oligomerization and polymerization and ring-opening metathesis by combination of cyclic and acyclic 1,3-diynes, are currently under investigation.

Experimental Section

Representative experimental procedure: A solution of [Cp₂Ti(η²-Me₃SiC≡CSiMe₃)] (38 mg, 0.108 mmol), **1** (5.4 mg, 0.027 mmol), and **2** (4.5 mg, 0.027 mmol) in toluene (20 mL) under argon was irradiated with light of wavelength 390–430 nm (two 460 W Philips HPM 12 lamps) at 100 °C for 4 h. The solvent was removed at 60 °C under vacuum, and AgSO₃CF₃ (19 mg, 0.076 mmol) and THF (2.5 mL) were added. The mixture was stirred at 50 °C for 2 h and then filtered over silica gel. The yields of the butadiynes were determined by gas chromatography: 18.3 % **1**, 19.5 % **2**, 4.9 % **3**; same procedure, starting with **A** and **B**: 15.4 % **1**, 17.9 % **2** and 5.1 % **3**. Yields without irradiation after 18 h at 140 °C: 10.8 % **1**, 18.7 % **2** and 6.5 % **3**; starting from **A** and **B**: 16.9 % **1**, 15.4 % **2** and 8.5 % **3**.

NMR investigation: A solution of **A** (0.027 mmol) and of **B** (0.027 mmol) in [D₈]toluene (0.5 mL; cyclohexane as reference) was irradiated at 100 °C with light of the wavelength 390–430 nm (two 460 W Philips HPM 12 lamps) for 20 h in a sealed NMR tube (or allowed to react for 30 h in 1,3,5-trimethylbenzene at 140 °C without irradiation). The reaction was monitored by means of the ¹H NMR signals of the Cp and Me groups. Alternatively, the irradiation was carried out in an open tube under argon, the solvents were removed under vacuum, and the residue dissolved in [D₈]toluene (0.8 mL) for recording the ¹H NMR spectra.

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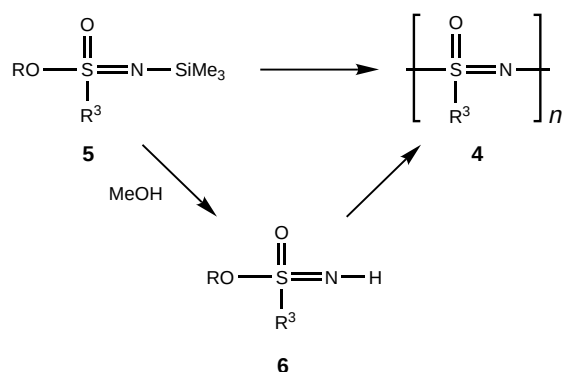
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Thionylphosphazene Monomers and Polymers—The Synthesis of Alternating Copolymers of Phosphazenes and Oxothiazenes**

Vanchat Chunechom, Teresa E. Vidal, Harry Adams, and Michael L. Turner*

Inorganic polymers with a backbone of phosphorus, sulfur, and nitrogen atoms are a recent addition to the growing list of novel inorganic macromolecules.^[1, 2] Polymers with sulfur(IV) centers in the backbone, the polythiophosphazenes, were first reported by Allcock et al. in 1990;^[2a] whereas the more stable S^{VI}-based polymers, the polythionylphosphazenes (**1**), were prepared by Manners et al. in 1991.^[2b] Application of the polythionylphosphazenes in phosphorescent oxygen sensors have recently been demonstrated.^[3] One class of phosphorus–sulfur–nitrogen based polymers that have so far eluded researchers in this field are polymers in which the side groups are bound by P–C or S–C bonds. Herein we report the first synthesis of a polythionylphosphazene in which the substituents at phosphorus and sulfur are either alkyl or aryl groups.

Phosphazene polymers, [P(R¹)(R²)=N]_n **2**, with alkyl or aryl side groups were first prepared in the mid-1980s^[4] by the polymerization of a *N*-silylphosphoranimine, RO–P(R¹)(R²)=N–SiMe₃ (**3**) (R = CH₂CF₃ or Ar; R¹, R² = alkyl or aryl), with elimination of ROSiMe₃.^[4b] Polymers (**2**) of well-defined molecular weight have recently been prepared by a living cationic polymerization.^[5] Analogous sulfur–nitrogen based polymers, the polyoxothiazenes, [S(O)(R³)=N]_n (**4**), can be prepared by the polymerization of an *N*-silylsulfonimide, RO–S(O)(R³)=N–SiMe₃ (**5**), or a sulfonimine, RO–S(O)(R³)=NH (**6**).^[6]



Clearly, the preparation of polythionylphosphazenes with alkyl or aryl side groups can be envisaged by the copolymerization of *N*-silylphosphoranimines (**3**) and *N*-silylsulfonimides (**5**). Unfortunately, heating mixtures of **3** and **5** at over

140 °C produces an inseparable mixture of oligomers of low molecular weight and cyclic compounds. However, if equimolar amounts of **3** and **5** are heated at between 80 and 140 °C, then a regioselective coupling of the two compounds can be accomplished. The reaction of **3b** (R = CH₂CF₃, R¹ = Ph, R² = Me) and **5b** (R = CH₂CF₃, R³ = Ph) has been monitored by ³¹P NMR spectroscopy. The spectra in C₆D₆ are collected in Figure 1 which shows that a slow decrease in the signal at δ = 20 for **3b** is accompanied by the growth of two new singlets at

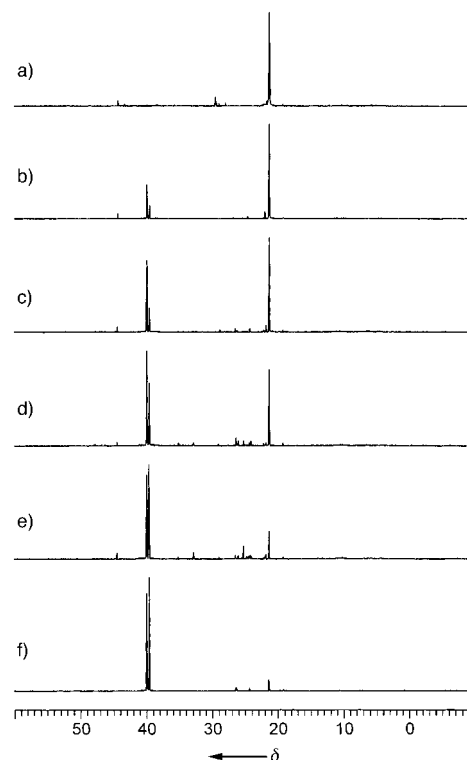


Figure 1. ³¹P NMR spectra (101 MHz, C₆D₆) of the reaction between **3b** and **5b** when heated at 120 °C for a) **3**, b) **9**, c) **12**, d) **18**, and e) **21** days. f) ³¹P NMR spectrum of **7b**, which was isolated by extraction of the reaction mixture with hexane.

δ = 39.6 and 40.0. These peaks can be assigned to the formation of the new thionylphosphazene CF₃CH₂O–P(Me)–(Ph)=N–S(O)(Ph)=N–SiMe₃ (**7b**). The presence of two signals of equal intensity can be attributed to the presence of equimolar amounts of two diastereomers, as **7b** contains both an asymmetric phosphorus and an asymmetric sulfur atom.

A number of examples of these compounds **7a–7d** have been prepared and they are typically isolated by vacuum distillation in moderate yields as colorless liquids or crystalline solids at room temperature. The structures of these compounds have been fully characterized by spectroscopic and analytical techniques, and the solid-state structure of **7c** has been determined by X-ray crystallography (Figure 2).^[7]

The single-crystal X-ray structure analysis of **7c** confirmed that the coupling reaction of **3** and **5** is highly regioselective and that it is the SiMe₃ group of the phosphoranimine and the trifluoroethoxy group of the sulfonimide that is lost upon reaction. The selectivity of this reaction is determined by the greater nucleophilicity of the nitrogen atom of the phosphor-

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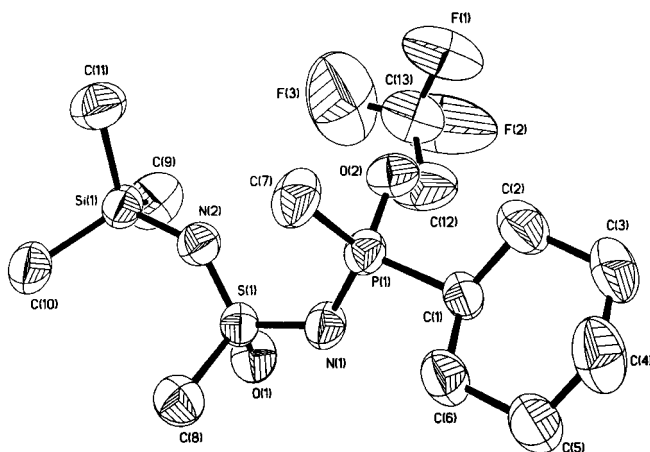
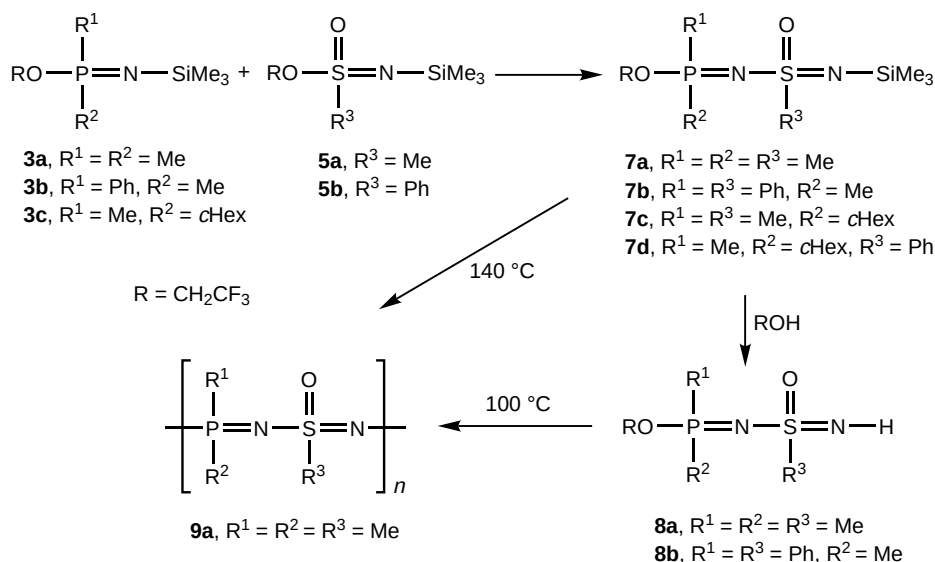


Figure 2. Solid-state structure of **7c**. Selected bond lengths [Å] and angles [°] (estimated standard deviations in parentheses): S(1)–O(1) 1.448(3), S(1)–N(2) 1.499(4), S(1)–N(1) 1.598(3), S(1)–C(8) 1.760(5), Si(1)–N(2) 1.712(4), Si(1)–C(9) 1.848(6), Si(1)–C(11) 1.850(5), Si(1)–C(10) 1.855(5), P(1)–N(1) 1.576(4), P(1)–O(2) 1.591(4), P(1)–C(7) 1.787(4), P(1)–C(1) 1.800(4), O(2)–C(12) 1.404(7), C(1)–C(6) 1.525(6), C(1)–C(2) 1.534(6), C(2)–C(3) 1.519(7), C(3)–C(4) 1.523(8), C(4)–C(5) 1.520(7), C(5)–C(6) 1.511(7); O(1)–S(1)–N(2) 118.8(2), O(1)–S(1)–N(1) 108.3(2), N(2)–S(1)–N(1) 110.4(2), O(1)–S(1)–C(8) 105.0(2), N(2)–S(1)–C(8) 110.5(2), N(1)–S(1)–C(8) 102.4(2), N(2)–Si(1)–C(9) 111.5(2), N(2)–Si(1)–C(11) 105.8(2), C(9)–Si(1)–C(11) 110.6(3), N(2)–Si(1)–C(10) 111.3(2), C(9)–Si(1)–C(10) 109.1(3), C(11)–Si(1)–C(10) 108.5(3), N(1)–P(1)–O(2) 115.4(2), N(1)–P(1)–C(7) 117.6(2), O(2)–P(1)–C(7) 100.1(2), N(1)–P(1)–C(1) 105.8(2), O(2)–P(1)–C(1) 107.4(2), C(7)–P(1)–C(1) 110.2(2), P(1)–N(1)–S(1) 126.8(2), S(1)–N(2)–Si(1) 130.5(2), C(12)–O(2)–P(1) 122.6(3), C(6)–C(1)–C(2) 110.9(4), C(6)–C(1)–P(1) 112.1(3), C(2)–C(1)–P(1) 114.3(3), C(3)–C(2)–C(1) 110.7(4), C(2)–C(3)–C(4) 111.8(4), C(5)–C(4)–C(3) 110.4(4), C(6)–C(5)–C(4) 111.0(5), C(5)–C(6)–C(1) 111.7(4), O(2)–C(12)–C(13) 110.4(5).

animine over that of the nitrogen atom of the sulfonimide. The geometry around sulfur and phosphorus in **7c** is pseudotetrahedral with bond angles varying from 102.4(2) to 118.8(2)° and 100.1(2) to 117.6(2)°, respectively. The N–S–N and P–N–S angles are 110.4(2)° and 126.8(2)°, which are consistent with similar N–S–N and P–N–S angles recorded for cyclic thionylphosphazenes.^[8] The S–N bond lengths of **7c** are 1.499(4) and 1.598(3) Å, the P–N bond length is 1.576(4) Å.

These values lie between those of single and double bonds but are more indicative of double- rather than single-bond character.^[8]

The thionylphosphazenes **7a**–**7d** are highly reactive and were rapidly hydrolyzed on exposure to the atmosphere. Reaction of **7a** or **7b** with trifluoroethanol at room temperature resulted in replacement of the trimethylsilyl group with a proton to give the thionylphosphazenes $\text{CF}_3\text{CH}_2\text{O}-\text{PMe}(\text{R}^1)=\text{N}-\text{S}(\text{O})(\text{R}^3)=\text{N}-\text{H}$ **8a** ($\text{R}^1 = \text{R}^3 = \text{Me}$) or **8b** ($\text{R}^1 = \text{R}^3 = \text{Ph}$), respectively. The functional groups of the thionylphosphazenes **7** and **8** are analogous to those of the oxothiazene monomers **5** and **6**, and as such may undergo polymerization in a similar fashion by elimination of $\text{CF}_3\text{CH}_2\text{OSiMe}_3$ or $\text{CF}_3\text{CH}_2\text{OH}$, respectively.^[6]

Initial polymerization studies on the permethyl-substituted thionylphosphazenes **7a** and **8a** suggest that this is indeed the case. Heating **7a** at 140 °C in a thick-walled evacuated ampoule resulted in an increase in viscosity of the tube contents and the formation of two liquid layers. After one week the tube was opened and a volatile component removed under vacuum. This was identified as $\text{CF}_3\text{CH}_2\text{OSiMe}_3$ by ^1H NMR spectroscopy. The solid contents of the polymerization tube were dissolved in CH_2Cl_2 and precipitated into stirred toluene. A white solid was recovered from the toluene which was redissolved in CH_2Cl_2 and reprecipitated into toluene. This process was repeated at least three times and the resulting white powder was finally dried under high vacuum at 50 °C overnight. The polymeric product was soluble in organic solvents such as CH_2Cl_2 , CHCl_3 , and DMSO, and it was also very soluble in water. The polymer structure was assigned by spectroscopic and analytical techniques as $[\text{PMe}_2=\text{N}-\text{S}(\text{O})\text{Me}=\text{N}]_n$ (**9a**), an alternating copolymer of dimethyl phosphazene and methyloxothiazene units. This is the first polythionylphosphazene with alkyl or aryl side groups and the first inorganic polymer with a repeating unit of one sulfur, one phosphorus, and two nitrogen atoms.

Polymerization of thionylphosphazene **8a** occurred rapidly on heating at 100 °C in a nitrogen-filled flask. The reaction was accelerated by decreasing the pressure to remove the trifluoroethanol produced on condensation. The reaction was complete within three to four hours and the polymer isolated from this reaction was essentially identical to that obtained on polymerization of **7a**. The molecular weight of polymer **9a** was estimated by gel permeation chromatography to be in the low thousands with an average degree of polymerization (DP) of around 30. The low molecular weight of **9a** explained the presence of small peaks in the ^{31}P NMR spectrum at $\delta = 59.2$, 24.2, 22.3, 21.7, 19.1 and 16.3 (Figure 3). These peaks were assigned to the polymer end groups, as analogous signals have been observed in the ^{31}P NMR spectrum of oligomeric $[\text{NPCL}_2]_n$ prepared by a cationic living polymerization.^[5a]

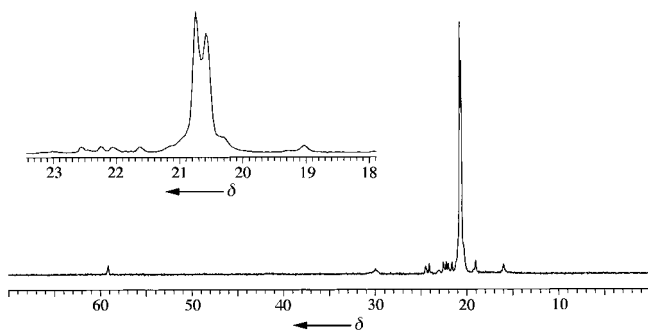


Figure 3. ^{31}P NMR spectra (162 MHz, CDCl_3) of **9a**. Insert: Expansion of the region $18 < \delta < 23$.

Identification of the polymer end groups and confirmation of the backbone structure was obtained by FAB mass spectrometry. Intense ions corresponding to $\text{CF}_3\text{CH}_2\text{O}[\text{P}(\text{Me})_2=\text{N}-\text{S}(\text{O})\text{Me}=\text{N}]_n\text{H}$ were detected up to the detection limit of the instrument (ca. 3800 Da). Integration of the polymer end groups in the ^{31}P and ^1H NMR spectra gave an absolute molecular weight (M_n) for **9a** of 8000 (DP = 53). The backbone structure of **9a** is an exact alternating copolymer of dimethylphosphazene and methyloxothiazene units. The phosphorus atoms are adjacent to sulfur atoms with either isotactic (a *meso* diad) or syndiotactic (a *rac* diad) placement of the two methyl groups. These phosphorus environments are inequivalent as two major peaks are detected in the ^{31}P NMR spectrum (CDCl_3) of **9a** at $\delta = 20.57$ and 20.74 . The intensities of these signals are very similar indicating that the polymer backbone has equal amounts of *meso* and *rac* placements and hence is completely atactic. The atacticity was confirmed by the ^1H and ^{13}C NMR spectra of **9a** which showed three doublets in a 1:2:1 ratio for the methyl groups attached to phosphorus. The intense doublet is assigned to the equivalent methyl groups of the *rac* diad and the less intense doublets to the inequivalent methyl groups of the *meso* diad.^[4b]

In summary, *N*-silylphosphoranimines **3** and *N*-silylsulfonimides **5** can be regioselectively coupled to give *N*-silylthionylphosphazenes **7**. Initial studies show that the methyl-substituted derivatives **7a** and **8a** can be thermally polymerized to give an alternating copolymer of dimethylphosphazene and methyloxothiazene units. This polymer, **9a**, is the first polythionylphosphazene in which the side groups are bound by P–C and S–C bonds and the first inorganic polymer with a repeating unit of one sulfur, one phosphorus, and two nitrogen atoms.

Experimental Section

7: *N*-Silylphosphoranimine **3a** (5.05 g, 20 mmol) and *N*-silylsulfonimide **5a** (5.06 g, 20 mmol) were heated in a round-bottomed flask at 140°C for four days. The volatile products of the reaction were removed under vacuum and characterized by ^1H NMR spectroscopy as $\text{CF}_3\text{CH}_2\text{OSiMe}_3$. The liquid residue was extracted with toluene. The toluene was removed at reduced pressure and the resulting viscous brown oil was distilled (60°C , 0.01 mmHg) to give a colorless liquid (**7a**) in 55% yield (3.63 g, 11 mmol). Positive-ion FAB-MS: m/z (%): 324 (27) [M^+], 309 (100, [$M^+ - \text{Me}$]), 232 (65, [$M^+ - \text{FSiMe}_3$]), 225 (9, [$M^+ - \text{CF}_3\text{CH}_2\text{O}$]); ^{31}P NMR (101 MHz, C_6D_6): $\delta = 52.7$; ^1H NMR (250 MHz, C_6D_6): $\delta = 0.26$ (s, 6H; SiMe_3), 1.21, 1.26 (2d, $J_{\text{PH}} = 11$ Hz, 6H; PMe), 2.80 (d, $J_{\text{PH}} = 3$ Hz, 3H; SMe), 4.02, 4.48 (2ddq, $J_{\text{HH}} = 9$ Hz, $J_{\text{EH}} = 17$ Hz, $J_{\text{PH}} = 4$ Hz, 2H; CH_2CF_3); ^{13}C NMR

(63 MHz, C_6D_6): $\delta = 1.85$ (s, SiMe_3), 13.95, 15.45 (2d, $J_{\text{PC}} = 25$ Hz; PMe), 49.46 (d, $J_{\text{PC}} = 6$ Hz; SMe), 62.58 (dq, $J_{\text{EC}} = 37$ Hz, $J_{\text{PC}} = 6$ Hz; CH_2CF_3), 122.7 (dq, $J_{\text{EC}} = 278$ Hz, $J_{\text{PC}} = 10$ Hz; CH_2CF_3). Compounds **7b–7d** were prepared in a similar fashion and isolated by distillation in 39% (140°C , 0.03 mmHg), 35% (104°C , 0.02 mmHg), and 45% (162°C , 0.01 mmHg) yield.

9a: Thionylphosphazene **7a** (7.08 g, 22 mmol) was sealed in an evacuated glass ampoule and heated to 140°C for 16 days. The tube was opened and the volatile components removed under vacuum. These were identified as $\text{CF}_3\text{CH}_2\text{OSiMe}_3$ by ^1H NMR spectroscopy. The solid contents were dissolved in CH_2Cl_2 and precipitated into stirred toluene. A white solid was recovered from the toluene which was redissolved in CH_2Cl_2 and reprecipitated into toluene. This process was repeated at least three times, and the resulting white powder (1.02 g, 25%) was finally dried under vacuum at 50°C overnight. ^{31}P NMR (162 MHz, CDCl_3): $\delta = 20.57$, 20.74 ; ^1H NMR (400 MHz, CDCl_3): $\delta = 1.68$ (d, $J_{\text{PH}} = 14$ Hz, 3H; *meso*- PMe_2), 1.73 (d, $J_{\text{PH}} = 14$ Hz, 6H; *rac*- PMe_2), 1.77 (d, $J_{\text{PH}} = 14$ Hz, 3H; *meso*- PMe_2), 3.17 (s, 6H; SMe); ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 18.44$ (d, $J_{\text{PC}} = 84$ Hz; *meso*- PMe_2), 18.50 (d, $J_{\text{PC}} = 90$ Hz; *rac*- PMe_2), 18.64 (d, $J_{\text{PC}} = 95$ Hz; *meso*- PMe_2), 48.75 (s, SMe). Elemental analysis: calcd: C 23.68, H 5.92, N 18.42, S 21.05; found: C 23.24, H 6.03, N 16.24, S 21.72. Thionylphosphazene **8a** (6.28 g, 25 mmol) polymerizes on heating at 100°C to give polymer **9a** (2.0 g, 25%), identical to that prepared from **7a**.

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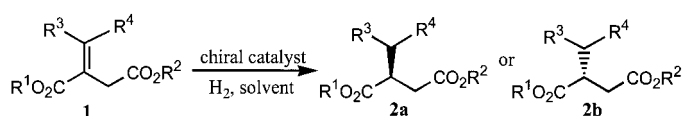
Keywords: main group elements • phosphazenes • phosphorus • polymers • sulfur

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- [7] Crystal data for **7c**: single crystals crystallize from toluene/hexane as colorless blocks; crystal dimensions $0.63 \times 0.44 \times 0.32$ mm, triclinic, space group $P\bar{1}$, $a = 10.224(2)$, $b = 10.371(2)$, $c = 10.739(2)$ Å, $\alpha = 100.51(2)$, $\beta = 100.38(2)$, $\gamma = 107.93(2)^\circ$, $U = 1030.7(3)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.265$ g cm^{−3}. Measuring range $3.5 < 2\theta < 45^\circ$, 3116 reflections measured, 1946 observed with $|F|/\sigma(|F|) > 4.0$. Refinement converged at a final $R = 0.0543$ ($wR_2 = 0.1520$) for all 2565 unique data, 208 parameters. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101046. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Practical Access to 2-Alkylsuccinates through Asymmetric Catalytic Hydrogenation of Stobbe-Derived Itaconates**

Mark J. Burk,* Frank Bienewald, Michael Harris, and Antonio Zanolli-Gerosa

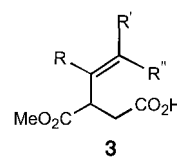
Enantiomerically enriched 2-substituted succinic acid derivatives of general structure **2** have attracted great interest recently because of their utility as chiral building blocks and peptidomimetics in the design of pharmaceuticals, flavors and fragrances, and agrochemicals with improved properties.^[1] Asymmetric catalytic hydrogenation of β -substituted itaconic acid derivatives (**1**) potentially offers one of the most convenient and practical routes to this class of compounds. No such catalyst system has yet been developed for the highly enantioselective synthesis of a diverse range of valuable 2-alkylsuccinates of type **2**.



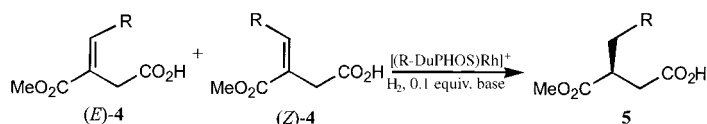
While asymmetric catalytic hydrogenation of the parent itaconates (**1**; $R^3, R^4 = H$) to 2-methylsuccinate derivatives has been accomplished with considerable cogency,^[2] the ability to hydrogenate β -substituted itaconate derivatives with high enantioselectivities has remained challenging. Of the few examples documented thus far only β -phenyl and β -1-naphthylitaconate derivatives have been hydrogenated with reasonably high enantioselectivity, and then only when the substrates **1** were employed as the pure *E*-geometric isomer.^[3] The curtailed effectiveness of known asymmetric hydrogenation catalysts is particularly apparent when R^3 or R^4 , or both, of **1** is an alkyl group. Yet even less success has been reported for asymmetric hydrogenation of β,β -disubstituted itaconate derivatives (**1**; $R^3, R^4 \neq H$), where the highest enantioselectivity recorded to date is 78% *ee*.^[4]

We herein describe a broadly effective catalyst system that permits highly enantioselective hydrogenation of a wide array of β -substituted itaconate derivatives of type **1**. Both β -aryl and β -alkyl substituents are tolerated, and the substrates may be employed as crude *E/Z*-isomeric mixtures. Moreover, a series of β,β -disubstituted itaconate derivatives have been hydrogenated with high enantioselectivities. A practical process has been developed for the production and isolation of enantiomerically pure 2-alkylsuccinates from crude products derived from the Stobbe reaction.

Most convenient access to either β -substituted or β,β -disubstituted itaconate derivatives involves a base-promoted Stobbe condensation reaction between dialkylsuccinates and aldehydes or ketones, respectively.^[5] Unfortunately, the Stobbe condensation reaction typically leads to a mixture of *E* and *Z* isomeric itaconate products, which often are contaminated with varying quantities of deconjugated isomer (for example **3**). The presence of geometric isomers can cause complications since the (*E*)- and (*Z*)-itaconate derivatives are likely to be hydrogenated with vastly different rates and enantioselectivities.^[6,7] Accordingly, separation of the (*Z*)-itaconate derivative from the favored *E* isomer typically is necessary prior to hydrogenation with most current catalysts. Moreover, the presence of isomerized substrate **3** in the mixture is potentially detrimental since any hydrogenation of this material necessarily will afford a racemic succinate product.



We initially surveyed a series of cationic rhodium complexes bearing the DuPHOS and BPE ligands^[8,9] (*R*-DuPHOS and *R*-BPE = 2',5',2'',5''-tetra-*R*-substituted 1,2-bis(phospholanyl)-benzene (*R* = Me, Et) and -ethane (*R* = Me, Et, *i*Pr), respectively) for effectiveness in the asymmetric catalytic hydrogenation of a model substrate **4** (*R* = *i*Pr, *E/Z* ratio 3:1). This substrate was selected for preliminary studies since the highest enantioselectivity achieved thus far in the asymmetric hydrogenation of this itaconate derivative (as the pure *E* isomer) was 76% *ee* with the cationic [(dipamp)Rh]⁺ catalyst (dipamp = 1,2-ethylene bis[(2-methoxyphenyl)phenylphosphane]).^[3e] This screening of the catalysts was performed under a standard set of conditions (MeOH, *c* = 0.5 M, 10% NaOMe, substrate/catalyst ratio S/C = 1000, 20 °C, 5.5 bar H₂, 1 h) and revealed a significant influence of the ligand structure upon the level of enantioselectivity attained in the hydrogenation reaction. The [(Et-DuPHOS)Rh]⁺ catalyst



was found to be manifestly superior for this process in which the minor enantiomer could not be detected by chiral GC methods (Table 1). The addition of catalytic amounts of base such as sodium methoxide or 0.1 equivalents of primary or tertiary amines led to significant rate enhancements in these

Table 1. Ligand effects in the hydrogenation of **4** (*R* = *i*Pr).^[a]

Ligand (L)	<i>ee</i> [%] ^[b] (config.) ^[c]
{(R,R)-(Me-DuPHOS)}	94 (<i>S</i>)
{(S,S)-(Et-DuPHOS)}	> 99 (<i>R</i>)
{(S,S)-(Me-BPE)}	47 (<i>R</i>)
{(R,R)-(Et-BPE)}	80 (<i>S</i>)
{(S,S)-(iPr-BPE)} ^[d]	97 (<i>S</i>)

[a] Catalyst precursor = [(L)Rh(cod)]BF₄ (cod = cycloocta-1,5-diene). [b] Determined by chiral phase GC. [c] Absolute configuration assigned by comparison with reported optical rotation^[3e]. [d] 25% conversion after 3 h.

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reactions, presumably by facilitating coordination of the substrate through the carboxylate group to the catalyst.

On the basis of these auspicious results, we examined the scope of the [(Et-DuPHOS)Rh]⁺ catalyst for asymmetric hydrogenation of a range of β -itaconates **4**. In many cases, the deconjugated isomer **3** (10–25 %) was also present in the substrate mixture but was found unreactive under the conditions employed (see below). The results of these studies are shown in Table 2 and demonstrate the versatility of the [(Et-DuPHOS)Rh]⁺ catalyst for this transformation.

Table 2. Asymmetric hydrogenation of itaconates **4** with [(Et-DuPHOS)Rh] catalyst.^[a]

Entry	R (in 4) ^[b]	S/C	t [h] ^[c]	ee [%] ^[d]
1	H ^[e]	1000	1	97
2	Et	1000	1	99
3	<i>n</i> Bu	1500	2	97
4	CH ₂ CH ₂ Ph	2000	2	99
5	(E)-CHCHPh	1000	20	99 ^[f]
6	<i>i</i> Pr	3000	2	99
7	cyclopropyl	2000	2	99
8	cyclohexyl	1500	3	98
9	<i>t</i> Bu	5000	4	99
10	Ph	3000	12	97
11	1-naphthyl	3000	12	98
12	2-naphthyl	3000	12	97
13	2-thienyl	1000	15	99

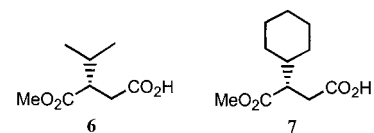
[a] Conditions: catalyst precursor = [(*S,S*)-(Et-DuPHOS)Rh](cod)]BF₄, room temperature, 5.5 bar H₂, MeOH, 10 % NaOMe per mol of **4**. [b] Most substrates **4** employed as crude *E/Z* mixtures ranging from 2/1 to >10/1. [c] Reaction time over which complete conversion was observed. [d] Determined on chiral phase (cyclodextrin) GC columns after conversion of crude product **5** to dimethyl ester. [e] Dimethyl itaconate substrate used. [f] *tert*-Butylammonium salt of substrate employed.

Hydrogenation of crude itaconate derivatives **4**, prepared conveniently and economically by Stobbe condensation reactions, produced a wide variety of 2-alkylsuccinates **5** with very high enantioselectivities. This process directly yields valuable succinate derivatives **5** that possess differentially protected carboxyl functionalities. In all cases examined, the *R,R* catalyst afforded (*S*)-2-alkylsuccinates, while the *S,S* catalyst furnished the *R* isomer. The [(Et-DuPHOS)Rh]⁺ catalysts tolerate many different types of β -substituents on **4**, including linear alkyl, branched alkyl, aromatic, and heteroaromatic groups. In addition to the high enantioselectivity observed, the hydrogenation is highly regioselective: only the itaconate unit is reduced while the aliphatic double bond of a γ,δ -styrenyl function is unaffected (Table 2, entry 5).^[10]

Although this process remains unoptimized, high catalytic efficiency was demonstrated with S/C ratios as high as 5000 and with average turnover frequencies of up to 2000 cycles/h. Itaconate derivatives bearing β -alkyl substituents (*E/Z* = 2/1–5/1) were ostensibly hydrogenated more rapidly than the β -aryl itaconates (predominantly *E* isomers) obtained from the Stobbe condensation reaction.

In addition to β -substituted itaconates, preliminary studies also indicate that the β,β -disubstituted itaconates **1** (R³,R⁴ ≠ H) may be hydrogenated with high enantioselectivities. Given

the sterically encumbered nature of the disubstituted itaconates (tetrasubstituted alkenes), it is not surprising that the most effective catalysts identified were derived from Me-BPE, the least hindered ligand of our bis(phospholane) collection.^[8] As an example, the two succinate derivatives **6** and **7** were prepared from the corresponding itaconate with the cationic [(*S,S*)-(Me-BPE)Rh]⁺ catalyst.



Relative to **4**, hydrogenation of the disubstituted itaconates used higher catalyst loadings (S/C = 500) and higher hydrogen pressures (11 bar H₂) to achieve reasonable rates of conversion (15–20 h). Under otherwise standard conditions, **6** and **7** were obtained in 91 % *ee* and 88 % *ee*, respectively.^[11] Interestingly, hydrogenation of the *tert*-butylammonium salts of these β,β -disubstituted substrates proceeded readily at 0 °C to furnish the products in 96 % *ee*. The enantioselectivities listed are by far the highest ever reported for this challenging class of substrates.^[4]

Our objective was to develop a proficient and practical route to 2-alkylsuccinates **2** through asymmetric hydrogenation of crude Stobbe condensation products. Demonstration that catalysis proceeded smoothly despite the use of unpurified substrates was encouraging. However, as alluded to above, Stobbe condensation reactions involving alkyl aldehydes often afford varying amounts of the deconjugated isomer **3**, which upon hydrogenation would lead to a racemic succinate. Importantly, we have found that the cationic catalysts [(*R*-DuPHOS)Rh]⁺ and [(*R*-BPE)Rh]⁺ specifically hydrogenate the itaconate substrates without affecting **3**. Moreover, we have established that isomer **3** may be removed simply by treatment of the hydrogenation product mixture with basic iodine solution (leading to iodolactonization of **3**) and extraction. Subsequent acidification afforded the pure succinates (for example **5**) in high yield. It is noteworthy that in most cases examined, enantiomerically pure succinates were obtained in 500 g quantities through simple crystallization of the corresponding *tert*-butylammonium salts (see *Experimental Section*).

Overall, we have developed a versatile asymmetric catalytic process for the synthesis of valuable 2-alkylsuccinate derivatives. We have demonstrated that crude isomeric mixtures of itaconate substrates obtained directly from the Stobbe condensation reaction may be hydrogenated with high catalytic efficiencies and high enantioselectivities.

Experimental Section

4 (R = *i*Pr): Potassium *tert*-butoxide (988 g, 8.8 mol) was dissolved in *tert*-butyl alcohol (6 L). A mixture of isobutyraldehyde (577 g, 8 mol) and dimethyl succinate (1.46 kg, 10 mol) in *tert*-butyl alcohol (1 L) was added to this solution over a period of 1 h. The mixture was heated to 50 °C for 2 h, and stirring was continued at room temperature overnight. The solvent was removed under reduced pressure and the residue dissolved in water (5 L) and extracted with ethyl acetate (2 × 1 L). The aqueous phase was acidified (conc. HCl) and the organic layer separated off. The aqueous phase was extracted with ethyl acetate (2 × 2 L). The combined organic phases were

dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure to yield a yellow oil. Treatment of this crude material with pentane (2 L) induced crystallization. The crystals were filtered off, washed twice with 300 mL pentane, and dried in vacuo to afford a light yellow, sticky solid (658 g, 44%). ¹H NMR analysis indicated a mixture of approximately 82% (*E*)-itaconate, 7% (*Z*)-itaconate, and 11% **3**. This material was used in the hydrogenation reaction without further purification.

5 (*R* = *i*Bu): Sodium methoxide (96 g, 172 mol) was added to a solution of the mixture from above (532 g, 2.86 mol) in methanol (4.5 L), and the mixture transferred to a 7 L hydrogenation vessel. After degassing the solution with a nitrogen sparge, the reactor was subjected to five pressurization/release cycles; each pressurization step involved stirring for 5 min under 5.2 bar hydrogen. Subsequently, a solution of [(*R,R*)-(Me-DuPHOS))Rh(COD)]BF₄ (540 mg, 0.89 mmol, S/C = 3200) in degassed methanol (20 mL) was added, and the mixture was allowed to stir under a hydrogen atmosphere (5.2 bar) for 4 h. ¹H NMR analysis revealed that both *E* and *Z* isomers were hydrogenated and the deconjugated methyl 2-isobutenylsuccinate **3** remained unaffected. The enantiomeric excess of the crude methyl 2-isobutylsuccinate was 94% *ee* (see Table 1 and method below). The reaction mixture was concentrated to approximately 1 L, followed by addition of water (500 mL), NaHCO₃ (101 g, 1.2 mol), and iodine (119 g, 0.47 mol), and allowed to stir at room temperature for 16 h. Solid sodium sulfite (slight excess) was added to the mixture to destroy excess iodine. The mixture was concentrated under reduced pressure to a approximately 1 L and extracted with ethyl acetate (3 × 0.5 L). The aqueous phase was acidified (conc. HCl) and again extracted with ethyl acetate (3 × 300 mL). Analysis of aliquots from the latter organic layers showed only the presence of monomethyl 2-isobutylsuccinate with an enantiomeric excess of 94%. ¹H NMR (CDCl₃): δ = 11.05 (s, 1H), 3.70 (s, 3H), 2.96–2.86 (m, 1H), 2.74 (dd, *J* = 16.7, 9.9 Hz, 1H), 2.48 (dd, *J* = 17.2, 4.9 Hz, 1H), 1.66–1.53 (m, 2H), 1.39–1.28 (m, 1H), 0.93 (d, ³*J* = 6.4 Hz, 3H), 0.90 (d, ³*J* = 5.9 Hz, 3H); ¹³C NMR (CDCl₃): δ = 177.8 (s), 175.6 (s), 51.7 (q), 40.9 (t), 38.9 (d), 36.0 (t), 25.6 (d), 22.3 (q), 22.0 (q).

Further purification was accomplished by formation of an ammonium salt as follows: The organic layers from above (about 900 mL) were combined and further diluted with ethyl acetate (1 L). A solution of *tert*-butylamine (219 g, 3 mol) in ethyl acetate (200 mL) was added over 2 h. The ammonium salt rapidly precipitated to form a very thick mixture that was allowed to stir for an additional 2 h at room temperature. The precipitated solid was filtered, washed with ethyl acetate (3 × 2 L), and dried in vacuo to afford 465 g (71% yield from substrate mixture) of the desired product **5** (*R* = *i*Bu) as a colorless powder (> 99% *ee*); [*α*]_D = –12.8° (*c* = 6.07 g dm^{–3}, MeOH, 20 °C); ¹H NMR (CD₃OD): δ = 5.06 (s, 3H), 3.66 (s, 3H), 2.94–2.85 (m, 1H), 2.47 (dd, *J* = 17.2/9.9 Hz, 1H), 2.25 (dd, *J* = 17.2/5.3 Hz, 1H), 1.63–1.46 (m, 2H), 1.36 (s, 9H), 1.37–1.25 (m, 1H), 0.94 (d, ³*J* = 5.3 Hz, 3H), 0.90 (d, ³*J* = 5.3 Hz, 3H); ¹³C NMR (CD₃OD): δ = 179.9 (s), 178.7 (s), 52.2 (s), 51.9 (q), 42.8 (t), 42.3 (d), 41.7 (t), 28.0 (q, 3C), 27.2 (d), 23.3 (q), 22.5 (q). The enantiomeric excess was determined, after conversion of crude **5** to the dimethyl ester by treatment with trimethylsilyldiazomethane, by chiral phase GC; GC parameters: capillary GC column Chirasildex-CB (25 m × 0.25 mm), 80 °C for 35 min then heated to 200 °C at 4 °C min^{–1}, helium 1.4 bar, *t*₁(S) = 39.98 min, *t*₂(R) = 40.31 min).

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- [11] The [(Me-DuPHOS)Rh]⁺ catalyst was found to provide the 2-isopropylsuccinate derivative **6** in only 71% *ee*, compared to 91% *ee* with [(Me-BPE)Rh]⁺ at 20 °C. This result highlights the strong relationship between the steric and conformational constitution of the ligand and the enantioselectivities achieved in these reactions.

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A Tetraphenylporphyrin with Four Fullerene Substituents**

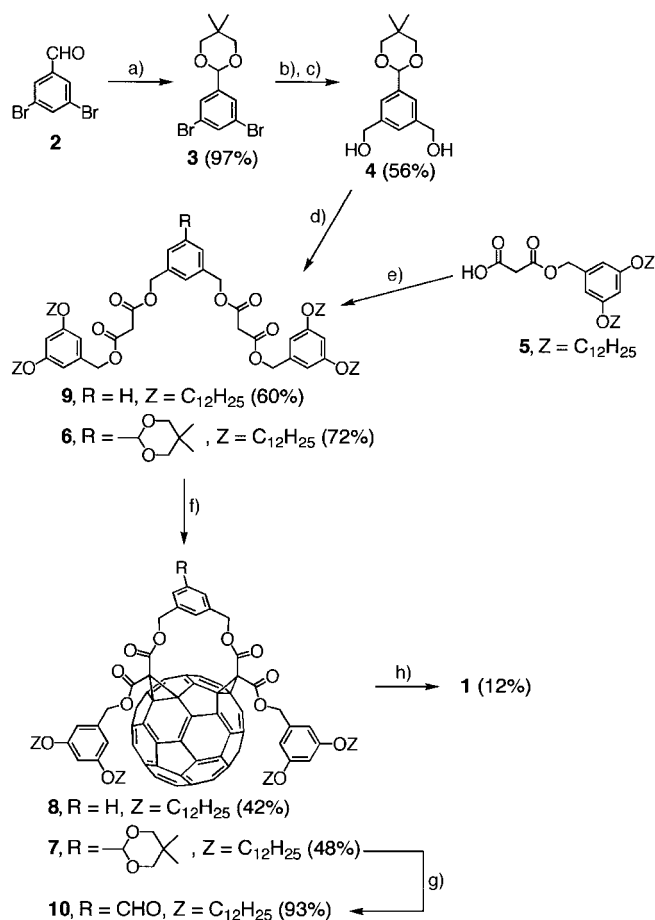
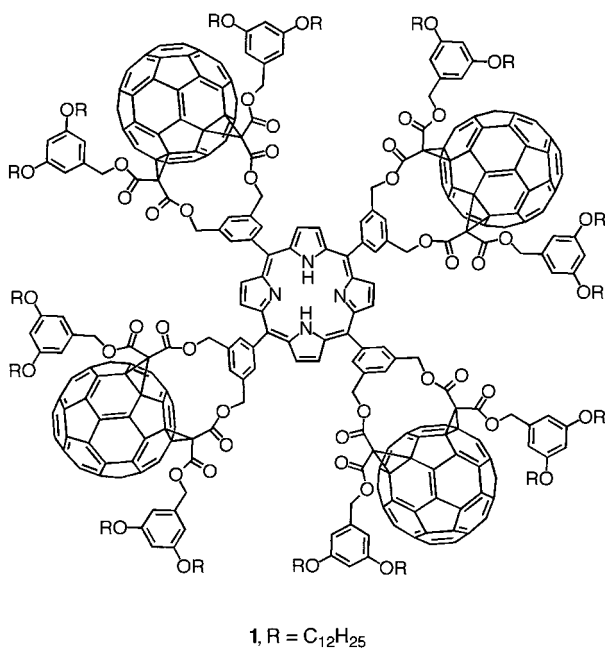
Jean-François Nierengarten,* Corinne Schall, and Jean-François Nicoud

Dedicated to Dr. Arlette Solladié-Cavallo on the occasion of her 60th birthday

In light of their special electrochemical and electronic properties, C_{60} and porphyrins have proven to be interesting building blocks for the construction of new photochemical molecular devices.^[1, 2] Recent progress in the chemistry of C_{60} ^[3] allows the preparation of many fullerene derivatives covalently bound to donor moieties.^[1, 4] Gust and co-workers described the first preparation of a C_{60} -linked porphyrin,^[5] and several other fullerene-porphyrin hybrids have since been reported.^[6, 7] These systems provide entry into intramolecular processes such as electron transfer and energy transfer.^[1, 4–7] The C_{60} group appears to be a particularly interesting electron acceptor in artificial photosynthetic models because of its symmetrical shape, its large size, and the properties of its π -electron system.^[1] All the porphyrin- C_{60} dyads reported to date have been synthesized by reaction of a preconstructed porphyrin derivative with C_{60} itself^[5, 6] or with a C_{60} -acid derivative,^[7] and no porphyrin with more than one fullerene substituent has been described until now. We report here the preparation of the soluble tetraphenylporphyrin **1** with four fullerene substituents by reaction between

a bis-adduct of C_{60} bearing an aldehyde functionality and pyrrole in the presence of an acid catalyst. Electrochemical investigations reveal a strong effect on the redox properties of the porphyrin moiety in **1** owing to the presence of the surrounding fullerene subunits.

Porphyrin **1** was synthesized as depicted in Scheme 1. 3,5-Dibromobenzaldehyde (**2**) was prepared from 1,3,5-tribromobenzene according to the literature procedure^[8] and allowed to react with 2,2-dimethyl-1,3-propanediol in refluxing benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) to give **3** (97% yield). Treatment of **3** with excess *t*BuLi^[9] in THF followed by quenching



Scheme 1. Synthesis of porphyrin **1**. a) 2,2-Dimethyl-1,3-propanediol, C_6H_6 , *p*-TsOH (cat.), Δ , Dean-Stark trap; b) *t*BuLi (4 equiv), THF, $-78 \rightarrow 0^\circ C$, then DMF, $-78 \rightarrow 0^\circ C$, then 2M HCl in H_2O ; c) DIBAL-H, CH_2Cl_2 , $0^\circ C$; d) DCC, DMAP, CH_2Cl_2 , $0^\circ C \rightarrow RT$; e) 3-hydroxymethylbenzyl alcohol, DCC, DMAP, CH_2Cl_2 , $0^\circ C \rightarrow RT$; f) C_{60} , DBU, I_2 , toluene, RT; g) CF_3CO_2H , H_2O , CH_2Cl_2 , RT; h) pyrrole, $BF_3 \cdot Et_2O$, $CHCl_3$ (containing 0.75% EtOH), RT, then *p*-chloranil, Δ .

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with *N,N*-dimethylformamide (DMF) and subsequent reduction of the resulting dialdehyde with diisobutylaluminum hydride (DIBAL-H) produced diol **4** in an overall yield of 56%. Esterification of **4** with the mono-ester **5**^[11] of malonic acid in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC)^[10] yielded bis-malonate **6**. The functionalization of C_{60} was based on the highly regioselective Diederich reaction,^[12] which led to macrocyclic bis-adducts of C_{60} through a

macrocyclization reaction of the carbon sphere with bis-malonate derivatives in a double Bingel addition.^[13] Treatment of C₆₀ with **6**, iodine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at room temperature afforded the C_s-symmetric *cis*-2 bis-adduct **7** in 48 % yield. Model compound **8** was prepared in a similar manner from 3-hydroxymethylbenzyl alcohol by esterification of **5** with DCC followed by treatment of the resulting bis-malonate **9** with C₆₀ in toluene in the presence of DBU and iodine (25 % overall yield). Treatment of **7** with CF₃CO₂H in CH₂Cl₂/H₂O (1/1) afforded the orange-red glassy benzaldehyde **10** in 93 % yield. The preparation is thus easily carried out on a gram scale.

Preparation of porphyrin **1** was first attempted under the classical conditions reported by Lindsey and co-workers.^[14] Reaction of benzaldehyde **10** with pyrrole in CH₂Cl₂ in the presence of CF₃CO₂H as catalyst followed by oxidation with *p*-chloranil (tetrachlorobenzoquinone) yielded mainly **10** and polymers; no trace of **1** could be detected in the reaction mixture. However, **1** could be obtained through use of the reaction conditions developed by Lindsey^[15] for the synthesis of sterically hindered porphyrins such as tetramesitylporphyrin. A key feature of these conditions is BF₃–ethanol cocatalysis. The condensation of **10** with pyrrole was performed in commercial CHCl₃ (which contains 0.75 % ethanol as stabilizer) at room temperature in the presence of BF₃·Et₂O. After a reaction period of five hours *p*-chloranil was added to irreversibly convert the porphyrinogen into a porphyrin. The desired tetraphenylporphyrin **1** was subsequently isolated in 12 % yield after a tedious chromatographic separation. Characterization of **1** was complicated, because there proved to be a mixture of several conformers in slow equilibrium on the NMR time scale at room temperature; nevertheless, all the anticipated signals were present in the spectrum. Force-field calculations with the model compound **8** revealed that the fullerene sphere is located above the phenyl ring of the bridge. In tetraphenylporphyrin **1**, all the fullerene substituents can be situated on one side or the other of the phenyl rings of the bridge. Free rotation of the four phenyl substituents on the porphyrin is therefore necessary to produce an NMR spectrum with sharp, symmetric signals. A study of the temperature dependence of the NMR spectrum (CDCl₂CDCl₂, 400 MHz) demonstrated a perfectly reversible narrowing of all signals at 125 °C, but a sharp spectrum could not be obtained below the maximum measurement temperature. Nevertheless, this NMR study unambiguously documents the existence of a dynamic effect. The UV/Vis spectrum of **1** in CH₂Cl₂ (Figure 1) shows the characteristic porphyrin absorption bands. The Soret band (420 nm) and the four Q bands (513, 547, 587, and 644 nm) are clearly visible, as is the characteristic absorption profile of a fullerene *cis*-2 bis-adduct. Furthermore, the absorption coefficients are consistent with a fullerene-to-porphyrin ratio of 4:1.

The redox potential for the first oxidation of the porphyrin moiety in **1** (Table 1) is significantly more anodic ($\Delta E \approx 175$ mV) than for *meso*-tetrakis(3,5-di-*tert*-butylphenyl)porphyrin^[16] (H₂TBP). This observation could be related to the strong electron-withdrawing effect of the four fullerene substituents, which could substantially destabilize the first oxidized state of the porphyrin moiety. However, solvation

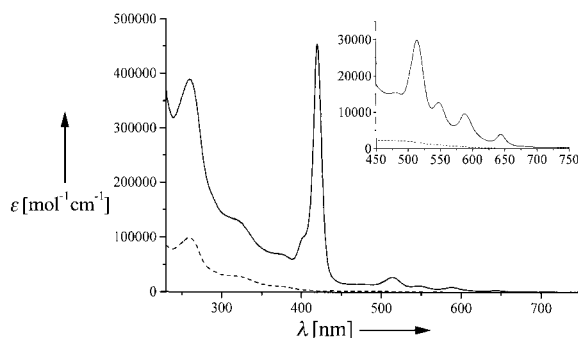


Figure 1. UV/Vis spectrum of **1** (—) and of **8** (---) in CH₂Cl₂.

Table 1. Electrochemical properties of **1**, **8**, and H₂TBP. Values for ($E_{pa} + E_{pc}$)/2 [V] (vs. SCE) and ΔE_{pc} [mV] (in parentheses) are given.^[a]

Compound	E_1	E_2	Reduction E_3	E_4	Oxidation E_1
1	−0.55 (70)	−0.85 (100) ^[b]	−1.16 (85) ^[b]	−1.55 (80) ^[b]	+1.195 (80)
8	−0.55 (85)	−0.86 (100) ^[b]	−1.16 (110) ^[b]	−1.55 (110) ^[b]	
H ₂ TBP	−1.16 (85)	−1.50 (120)			+1.02 (90)

[a] Cyclic voltammetry measurements: platinum electrode, degassed CH₂Cl₂, 0.1 M Bu₄NBF₄, scan rate 0.1 V s^{−1}. [b] Irreversible process.

effects caused by the presence of the surrounding fullerene groups could also be the source of the observed shift in potential. This effect in the case of **1** can be related to recently reported results with a Cu^I-complexed rotaxane that bears two fullerene stoppers.^[4c, 17] In this molecular assembly, the redox potential of the Cu^I/Cu^{II} couple is also significantly more anodic than for similar mononuclear complexes ($\Delta E = 200$ –300 mV). Although the redox properties of the porphyrin moiety in **1** are apparently influenced significantly by the C₆₀ substituents, those of the fullerene subunits seem to remain unchanged by the porphyrin. Compounds **1** and **8** show effectively similar behavior, entirely consistent with previously reported data for fullerene *cis*-2 bis-adducts.^[12c, 18] The third reduction, which occurs at approximately −1.16 V (relative to the standard calomel electrode, SCE), is characteristic of *cis*-2 bis-adducts. Indeed, it has been shown that the second electron transfer in the *cis*-2 derivatives is followed by a chemical reaction, which generates a species reducible at about −1.16 V.^[12c, 18] The porphyrin and fullerene reduction waves for compound **1** could not be clearly distinguished because both constituents are reduced at similar potentials.

Preliminary luminescence measurements indicate that emission from the porphyrin part of **1** is completely quenched at room temperature by the surrounding fullerene subunits. The anodic shift observed by cyclic voltammetry for oxidation of the porphyrin moiety in **1** together with the absence of emission seems to indicate electronic interaction between the molecular components in the ground state as well as in the excited states.

Experimental Section

7: DBU (422 mg, 2.775 mmol) was added under Ar at room temperature to a stirred solution of C₆₀ (400 mg, 0.555 mmol), I₂ (352 mg, 1.387 mmol), and **6** (745 mg, 0.555 mmol) in toluene (700 mL). The mixture was stirred for 12 h and then filtered through a short column of silica gel (toluene, then

CH_2Cl_2). Compound **7** was isolated by column chromatography (SiO_2 ; CH_2Cl_2 /hexane, 8/3; 548 mg, 48%). Orange-red glassy product; UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 259 (117170), 323 (28230), 375 (sh, 12110), 437 (sh, 4510), 467 nm (3760); IR (CHCl_3): $\tilde{\nu}$ = 2927 (s), 2855 (s), 1749 (s), 1598 (s), 1458 (m), 1394 (w), 1294 (m), 1281 (m), 1264 (s), 1235 (s), 1206 (m), 1170 (s), 1107 (s), 1062 cm^{-1} (w); ^1H NMR (200 MHz, CDCl_3): δ = 0.84 (s, 3H), 0.89 (t, J = 6.5 Hz, 12H), 1.27 (m, 72H), 1.31 (s, 3H), 1.73 (m, 8H), 3.75 (AB, J = 11 Hz, 4H), 3.85 (t, J = 6.5 Hz, 8H), 5.09 (d, J = 13 Hz, 2H), 5.24 (d, J = 12 Hz, 2H), 5.33 (d, J = 12 Hz, 2H), 5.46 (s, 1H), 5.84 (d, J = 13 Hz, 2H), 6.36 (t, J = 2 Hz, 2H), 6.47 (d, J = 2 Hz, 4H), 7.42 (brs, 2H), 7.49 (brs, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ = 14.12, 21.82, 22.67, 23.06, 26.07, 29.22, 29.35, 29.41, 29.61, 30.21, 31.90, 49.00, 66.83, 67.17, 68.02, 68.60, 70.55, 77.62, 100.65, 101.57, 107.02, 123.45, 124.04, 134.39, 135.73, 136.08, 136.52, 136.78, 137.81, 139.07, 140.00, 141.00, 141.06, 142.27, 142.68, 143.10, 143.52, 143.68, 143.90, 144.09, 144.28, 144.51, 144.89, 144.95, 145.11, 145.28, 145.53, 145.70, 146.00, 147.25, 147.40, 148.58, 160.33, 162.52; elemental analysis calcd for $\text{C}_{142}\text{H}_{128}\text{O}_{14}$ (2059): C 82.8, H 6.3; found: C 82.9, H 6.3.

1: A 0.8 M solution of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CHCl_3 (0.04 mL) was added under Ar at room temperature to a stirred solution of **10** (601 mg, 0.305 mmol) and pyrrole (20.4 mg, 0.305 mmol) in CHCl_3 that contained 0.75% EtOH (30.5 mL, reagents: 10^{-2}M each, BF_3 : 10^{-3}M). After 5 h *p*-chloranil (100 mg, 0.407 mmol) was added, and the solution was heated under reflux for 1.5 h and then concentrated. Two successive filtrations through short silica gel columns (CH_2Cl_2 /hexane, 5/3–5/2) followed by gel permeation chromatography (Biorads, Biobeads SX-I, toluene) yielded unchanged **10** (89 mg) and crude **1**. Two successive column chromatographic separations (Al_2O_3 , hexane/ CH_2Cl_2 , 3/1–3/2) followed by precipitation from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ led to pure **1** (74 mg, 12%). Red-brown glassy product; UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 259 (390000), 319 (sh, 131400), 378 (sh, 67900), 403 (sh, 101150), 420 (454260), 479 (15500), 513 (29850), 547 (12750), 587 (9650), 644 nm (4030); IR (CHCl_3): $\tilde{\nu}$ = 2965 (s), 2854 (s), 1748 (s), 1597 (s), 1457 (s), 1376 (w), 1345 (w), 1294 (m), 1280 (m), 1235 (s), 1205 (s), 1189 (w), 1171 (s), 1112 (w), 1104 (w), 1060 cm^{-1} (m); ^1H NMR (200 MHz, CDCl_3 , 25°C): δ = –2.78 (brs, 2H), 0.86 (t, J = 6.5 Hz, 48H), 1.26 (m, 288H), 1.66 (m, 32H), 3.82 (brt, 32H), 5.25–5.60 (m, 24H), 6.05–6.20 (m, 8H), 6.33 (brs, 8H), 6.48 (brs, 16H), 7.85–8.05 (m, 4H), 8.10–8.25 (m, 8H), 8.75–9.10 (m, 8H); elemental analysis calcd for $\text{C}_{564}\text{H}_{478}\text{N}_4\text{O}_{48}$ (8080): C 83.8, H 6.0, N 0.7; found: C 83.8, H 6.5, N 0.6.

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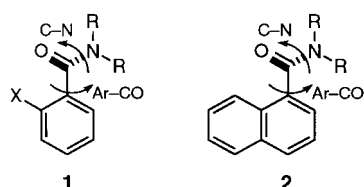
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Concerted Rotation in a Tertiary Aromatic Amide: Towards a Simple Molecular Gear**

Jonathan Clayden* and Jennifer H. Pink

The design of molecular analogues of macroscopic mechanical components is an important part of any attempt to construct devices capable of doing mechanical work^[1] or of storing or transmitting information on a molecular scale.^[2] Recent developments in this field have included the design and synthesis of molecular brakes and switches,^[3–5] ratchets,^[6] turnstiles,^[7] and gears,^[8, 9] and we have shown that a series of conformationally interlocked tertiary amides can act as a device for the transmission of stereochemical information.^[10] Subsequent to the pioneering studies of Mislow and Iwamura,^[8] most investigations into molecular gears have addressed the question of concerted rotation in relatively complex triptycyl-based systems.^[11] We have now studied a much simpler type of molecule as a possible molecular gear, a tertiary aromatic amide, and show here that two dynamic processes—rotation about the C–N and Ar–CO bonds—can be concerted.

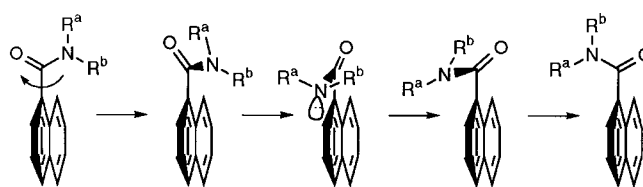
In the ground states of tertiary 2-substituted benzamides **1**^[12] and 1-naphthamides **2**^[13] (Scheme 1) the amido group lies



Scheme 1. Slow bond rotations in the tertiary aromatic amides **1** and **2**.

perpendicular to the aromatic ring, and barriers to rotation about the aryl–CO bonds are typically greater than 65 kJ mol^{–1}.^[14] In common with all amides, **1** and **2** also possess rotationally restricted C–N bonds, with barriers to exchange of the two R groups comparable in magnitude to the Ar–CO barrier.^[15]

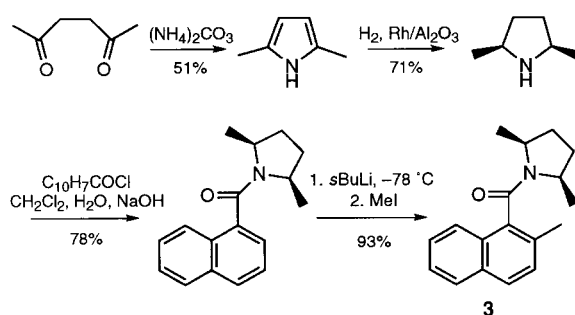
Variable-temperature NMR studies^[16] permitted us to show that the barriers to rotation about both the aryl–CO and C–N bonds of *N,N*-diisopropynaphthamide **2** (R = *i*Pr) are remarkably similar: 75 ± 1 kJ mol^{–1},^[17] which raises the possibility that the two processes might in fact be concerted. Scheme 2 shows a mechanism for concerted Ar–CO and C–N rotation. At the transition state the carbonyl group loses conjugation with the lone electron pair on nitrogen, but this is compensated to some extent by increased conjugation with the aromatic ring.^[18] Amide conjugation is regained most smoothly when motion of the alkyl substituents R^a and R^b is



Scheme 2. Concerted rotation in **2**.

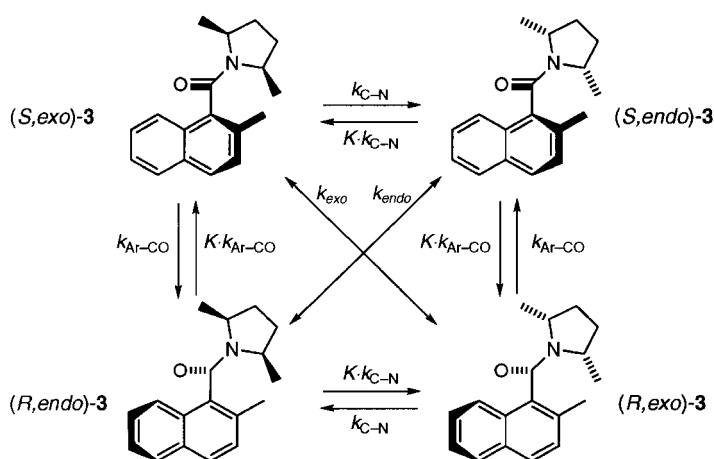
interlocked with rotation around the Ar–CO bond. Concerted rotation would imply correlation between two processes: isomerization of **2** to its enantiomer and exchange of the two groups carried by the nitrogen atom; indeed, such a correlation has been hinted at by one previous study.^[19, 20]

The assignment problem associated with the individual methyl groups of **2** led us to design **3** as a better substrate for investigating concerted rotation; our synthesis of **3** is shown in Scheme 3. Amide **3** has a number of important features. It can



Scheme 3. Synthesis of **3**.

exist in two diastereoisomeric conformations, *endo*-**3** and *exo*-**3**, which can interconvert by rotation about either the C–N bond or the Ar–CO bond (Scheme 4). Each diastereoisomer



Scheme 4. Stereoisomers of **3** and their interconversion.

mers is chiral, and enantiomerization requires both Ar–CO and C–N rotation, either concerted or sequential. The 2-methyl group of **3** serves to slow these two processes to the point that the four conformers become atropisomers, and, indeed, we found them to be separable at room temperature by HPLC on a chiral stationary phase. Separation of a mixture

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of ($\pm$,*exo*)-**3** and ($\pm$,*endo*)-**3** on a Chiralpak-AD column produced three fractions, one of which contained both (*R*,*exo*)-**3** and (*R*,*endo*)-**3**, which were then readily separated by HPLC on achiral silica. Both (*S*,*exo*)-**3** and (*S*,*endo*)-**3** were obtained with a purity of greater than 96% from the Chiralpak-AD column. Relative configurations were assigned by NOE experiments; absolute stereochemistry was established by comparisons between the retention times of the two enantiomers on a chiral Whelk-O1 column and by use of the Pirkle model^[19] for binding to this chiral stationary phase.

We then allowed samples of (*S*,*exo*)-**3** and (*S*,*endo*)-**3** to equilibrate with their stereoisomers by separate incubations in hexane at 33 °C, with analysis of the resulting product mixtures at regular intervals (Figures 1 and 2). Kinetic

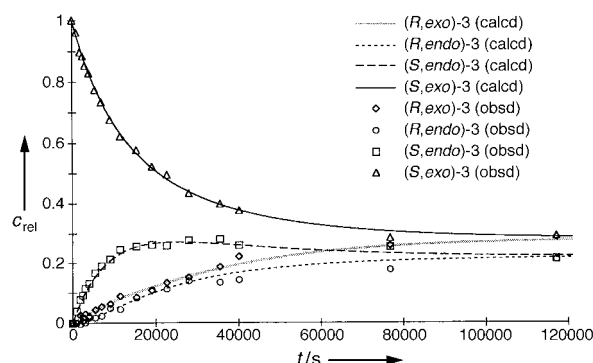


Figure 1. Equilibration of (*S*,*exo*)-**3**.

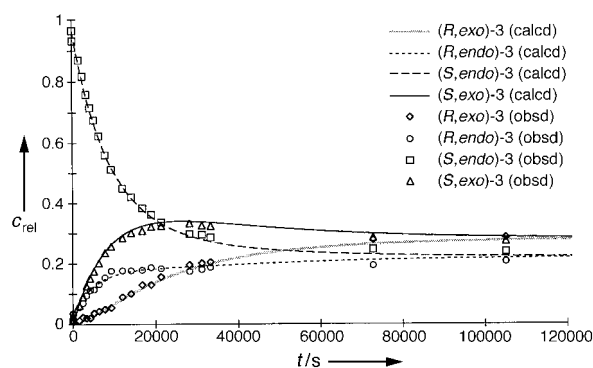


Figure 2. Equilibration of (*S*,*endo*)-**3**.

analysis is simplified by the fact that enantiomeric processes must have identical activation energies; moreover, the value of K , the quantitative ratio of ($\pm$,*exo*)-**3** to ($\pm$,*endo*)-**3** at equilibrium, could be determined accurately by HPLC to be (1.28 ± 0.02) and confirmed by NMR studies. Four mechanistic rate constants are involved: $k_{\text{Ar-CO}}$ for rotation about the aryl-CO bond (*exo* to *endo*), $k_{\text{C-N}}$ for rotation of the *exo* isomer about the C-N bond (*exo* to *endo*), and k_{exo} and k_{endo} for the proposed concerted isomerizations of the two diastereoisomers to the corresponding enantiomers. Rates for the reverse Ar-CO and C-N rotations (*endo* to *exo*) are then related to $k_{\text{Ar-CO}}$ and $k_{\text{C-N}}$ by the equilibrium constant K . Approximate values for all these rate constants were obtained when quartic curves were fitted to the early data points shown in Figures 1 and 2, and the gradient at $t=0$ was derived. It is

immediately clear from these plots that the rate at which both (*S*,*exo*)-**3** and (*S*,*endo*)-**3** enantiomerize is greater than the rate at which rotation occurs about the Ar-CO bond; therefore, rotation about the Ar-CO bond must be concerted to some degree with rotation about the C-N bond.

The system was modeled through a calculation of its evolution over time intervals of 250 s;^[21] small adjustments to the derived rate constants $k_{\text{Ar-CO}}$, $k_{\text{C-N}}$, k_{exo} , and k_{endo} permitted the resulting plots to be fitted to the experimental data. The correspondence between the modeled and observed evolution of the system is shown in Figures 1 and 2, and provides strong evidence for the validity of our kinetic analysis. Table 1 presents the rate constants for the four processes at 33 °C

Table 1. Kinetic parameters for the equilibrations of (*S*,*exo*)-**3** and (*S*,*endo*)-**3**.

	k (33 °C) [10^{-5} s^{-1}]	$\Delta G^\ddagger$ [a] [kJ mol $^{-1}$]
$k_{\text{C-N}}$	3.9 ± 0.8	100.8 ± 0.5
$k_{\text{Ar-CO}}$	0.1 ± 0.05	110 ± 1.5
k_{exo}	1.0 ± 0.1	104.3 ± 0.3
k_{endo}	2.9 ± 0.6	101.6 ± 0.5

[a] Determined at 33 °C from the Eyring equation..

along with the corresponding calculated free energy of activation $\Delta G^\ddagger$. The fact that k_{exo} and k_{endo} are not zero confirms that concerted rotation takes place; because k_{exo} and k_{endo} are an order of magnitude larger than $k_{\text{Ar-CO}}$, at least 90% of the rotations about the Ar-CO bond are concerted with rotation about the C-N bond. As $k_{\text{C-N}}$ has the same value as $k_{\text{exo}} + k_{\text{endo}}$, C-N rotations must also be free to occur without coupling to other rotations, and must occur about as frequently as concerted C-N and Ar-CO rotations. Unconcerted Ar-CO rotations are presumably rare for steric reasons; although unconcerted C-N rotations are not sterically hindered, rotation of the two bonds in concert permits the carbonyl group to exchange N-C=O conjugation, which must be lost at the transition state, for Ar-C=O conjugation.

The lower energy barrier for concerted isomerization of the *endo* isomer to the corresponding enantiomer is not unexpected: The amido nitrogen atom can pass over the 2-position of the naphthyl ring without steric crowding between the pyrrolidine methyl groups and the naphthyl 2-methyl group. Concerted isomerization of the *exo* isomer to the corresponding enantiomer requires the pyrrolidine methyl groups to straddle the naphthyl 2-methyl group, or the amido nitrogen atom to pass over the more rigidly bonded hydrogen atom at the 8-position of the naphthyl ring.

Although amide **3** displays a degree of gearing between the Ar-CO and C-N rotations, the barrier to gear slippage is low; a better interpretation of the dynamics of **3** might be that Ar-CO rotation is “gated”^[22] by C-N rotation. Simple “two-toothed” molecular gears have received little attention alongside their three-^[8] and four-toothed^[9] cousins, but they seem particularly well suited for use as devices for the storage and transmission of binary information.

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High-Pressure Soft X-Ray Absorption Spectroscopy: A Contribution to Overcoming the “Pressure Gap” in the Study of Heterogeneous Catalytic Processes

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Dedicated to Professor Sir John Meurig Thomas on the occasion of his 65th birthday

X-ray absorption spectroscopy (XAS) is an important tool in the study of gas–solid reactions and their products.^[1] In the past few years in situ techniques have attained great importance in the field of heterogeneous catalysis.^[2] Studies under reaction conditions close to those found in practice are

necessary, because the structure of a catalyst under reaction conditions can be significantly different from that after the reaction or ex situ. To allow any relevant interpretation, an in situ measurement requires the simultaneous detection of spectroscopic data together with the conversion from the gas phase. Silver, copper, or molybdenum catalysts are used in technical processes for the conversion of methanol into formaldehyde.^[3] These are well-suited to the study of the principles of chemical reactions on various surfaces due to the apparent clarity of the possible courses of reaction.^[4] The oxidation of methanol on pure silver has shown, for example, that catalytic reactions under model conditions in ultra high vacuum (UHV) can take a different course to those under practice conditions.^[5–7] Three different types of atomic oxygen were identified by surface science studies of silver that was subjected to oxygen under pressure in a manner that is used in practice;^[5, 8–10] their positions are shown in Figure 1. The critical oxygen pressure at which qualitative differences

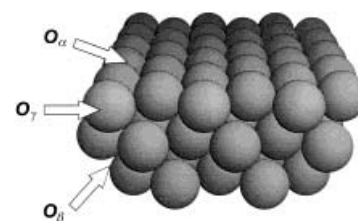


Figure 1. Schematic depiction of the Ag(111) surface treated with oxygen. The atomic oxygen species O_α , O_γ , and O_β were characterized by surface-sensitive spectroscopic techniques.^[5–13] The chemisorbed O_α species and the O_γ species bonded in the surface layer are responsible for the oxide hydrogenation and the dehydrogenation of methanol.^[12, 13] The O_β species acts as a reservoir for both surface species during the catalytic oxidation of methanol.

to the UHV model conditions in the surface chemistry of the Ag–O system were observed was 0.1 mbar. The only differences observed up to an oxygen partial pressure of 1000 mbar were in the reaction kinetics of the formation processes involved. With increasing temperature, atomic oxygen is initially formed on the surface (O_α). At a critical level of pressure and temperature, it then migrates under the surface to occupy interstitial sites in the silver crystal (O_β).^[11] On increasing the temperature still further, a new form of oxygen is formed from the O_β species and, parallel to this, directly from the gas phase. The new form is incorporated into the top atomic layer of the crystal (O_γ) and interacts strongly with the silver centers. This state differs from that of a metal oxide—silver oxide is no longer thermodynamically stable at temperatures of formation above 600 K—both in structure and in that its existence is strictly limited to a single atomic layer.^[5, 8–10]

The oxidation of a methanol molecule can either occur by dehydrogenation with loss of one hydrogen molecule and the formation of formaldehyde [Eq. (1)], or by oxide hydro-



genation or total oxidation with loss of hydrogen and simultaneous uptake of oxygen to give water and formaldehyde or water and carbon dioxide [Eqs. (2) and (3)].

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Kinetic measurements have revealed that above the critical pressure of about 1 mbar both reaction pathways are followed, and thus at least two different types of oxygen must be present.^[12, 13] Under UHV conditions, however, only reaction (2) is observed.^[14] This correlates with the results described above which show the atomic adsorbed oxygen (O_a) and the special atomic oxygen built into the surface layer (O_s) to be catalytically active centers.^[12, 15]

In contrast to the case of silver, for copper the atomic chemisorbed oxygen is thermodynamically metastable with respect to the transition to the oxide state under the conditions of the selective oxidation of methanol. One consequence of this is that different non-oxidic oxygen species are difficult to detect in conventional UHV studies, even if the surface is previously subjected to an $\text{O}_2/\text{CH}_3\text{OH}$ gas mixture at high temperature.^[16] According to ex situ UHV studies, copper(I) oxide was primarily formed.^[16] As this species can only catalyze the total oxidation of methanol [reaction (3)], it cannot be the active phase sought.^[15] In situ studies under reaction conditions close to those found in practice are thus imperative to spectroscopically characterize the selective catalytically active phase.^[17, 18]

In Figure 2 the oxygen K absorption near edges of copper(I) oxide, Cu_2O (Ib), and copper(II) oxide, CuO (Ic) as well as the corresponding copper $L_{2,3}$ absorption near-edge spectra of Cu_2O (IIb), CuO (IIc), and polycrystalline metallic copper (IIa) are shown.^[9, 10, 19, 20] The copper $L_{2,3}$ absorption spectrum of the pure metal shows the typical steplike form of the absorption edge with some fine structure that is characteristic for the formal oxidation state 0 (Cu^0 , $d^{10}s^1$ configura-

tion).^[27–29] The in situ X-ray absorption spectra measured during the reaction of polycrystalline copper with oxygen at 600 K are also presented in Figure 2. These indicate the formation of Cu_2O (d) and CuO (e) at a total O_2 pressure of 0.05 and 0.10 mbar, respectively, at the surface and in the area near the surface. The considerably different products obtained under reaction conditions which are only minimally different illustrate the high sensitivity of the system with respect to the exterior reaction conditions and confirm the specificity of the new surface-sensitive in situ XAS measurement technique.^[17]

Measurements performed on the oxygen K and the copper $L_{2,3}$ edges during the reduction of polycrystalline copper(II) oxide with methanol (total pressure 5×10^{-6} mbar) at 600 K indicate the formation of Cu_2O after about 10 min (total methanol dose ca. 3000 L^[35]). Subsequent reduction occurs after about 190 min. This reduced phase is characterized by the formation of an oxygen–copper compound on the surface or in the region near the surface. This compound does not correspond with either of the usual oxides and is characterized by a covalent $\text{O}2p$ – $\text{Cu}4sp$ bonding contribution in the oxygen K-edge spectra. In contrast, the copper $L_{2,3}$ -edge spectra of this phase show the steplike form of the absorption edge typical for metallic copper (see Figure 2IIa).^[27] According to ex situ studies on this system, however, Cu_2O is formed on the transition to UHV with simultaneous cooling to room temperature.^[16, 17] This means that it is only possible to observe the special oxygen–copper phase under in situ conditions during the treatment with methanol, as it is metastable and segregates into pure metal and copper(I) oxide on cooling and removal of the volatile components. The significance of this special phase in practice for the partial oxidation was proven by analysis of the oscillatory behavior of the $\text{Cu}/\text{O}/\text{CH}_3\text{OH}$ system.^[15]

A direct measurement of the conversion of pure methanol under comparatively high pressure (0.2 mbar) on polycrystalline copper pretreated with oxygen was first determined by the spectral proportion of CO ^[36] in the X-ray absorption spectrum of the gas phase. The copper catalyst was loaded with bulk oxygen (O_β) by an oxygen pretreatment followed by reduction in methanol. Under the reaction conditions the bulk oxygen diffuses to the surface and takes part in the oxidation reaction. Figure 3 shows the conversion of methanol as a function of reaction time. In the plot the percent spectral proportions of methanol and carbon monoxide determined from the gas-phase X-ray absorption spectra are compared with the gas-phase proportions measured simultaneously by quadrupole mass spectroscopy.^[37] The initial conversion frequency of about 0.3 methanol molecules per second and per copper surface atom lies in the range of known values for heterogeneous catalytic reactions of small molecules (between 0.01 and 100 molecules per second and per active surface atom).^[38–40]

Parallel to the gas phase spectra, X-ray absorption spectra of the active copper catalyst surface were recorded during the reaction with 0.2 mbar of methanol. Figure 4 shows the spectra of the oxygen K- (I) and the copper $L_{2,3}$ -absorption near edges (II) during the conversion of methanol at catalyst temperatures of 520 K (a) and 600 K (b). As is the case with

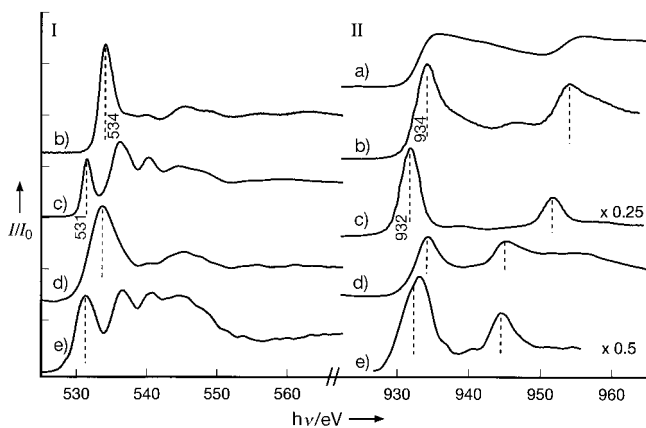


Figure 2. I) Oxygen K-absorption near-edge spectra of Cu_2O (b) and CuO (c); II) copper $L_{2,3}$ -absorption near-edge spectra of metallic copper (a), Cu_2O (b), and CuO (c). The spectra Ib, c and IIa–c were recorded under ultra high vacuum in the surface-sensitive electron-yield mode (information depth about 60 Å). The in situ spectra Id, e and II d, e were recorded at $T = 600$ K and a total O_2 pressure of $p = 0.05$ and 0.10 mbar, respectively. The in situ copper $L_{2,3}$ -absorption near-edge spectra II d, e were obtained using the second-order light of the monochromator and subsequently shifted by 466 eV to higher photon energy. This is why the difference in energy between the copper L_3 - and copper L_2 -edges is a factor of 2 smaller than in the spectra II a–c which were measured using the first-order light of the monochromator.

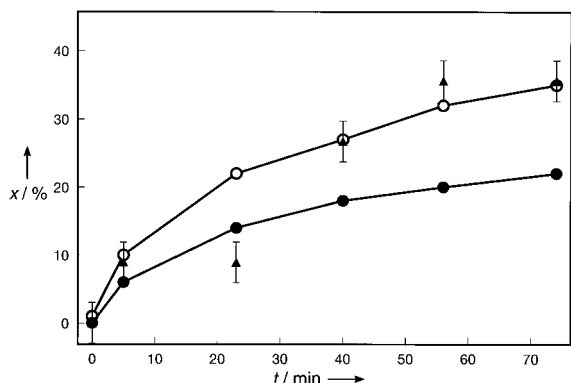


Figure 3. The catalytic conversion of pure methanol into formaldehyde on polycrystalline copper was followed in situ for the first time in a batch reactor by observing the spectral proportion of CO in the gas phase spectrum.^[17] The copper catalyst was loaded with bulk oxygen (O_β) by pretreatment with oxygen at 620 K (1 mbar O_2 , 30 min) and subsequent reduction in methanol ($p \approx 5 \times 10^{-6}$ mbar, $T = 600$ K, 90 min).^[15] The diagram shows the conversion of methanol (○) into formaldehyde (▲; multiplied by 8.4) and carbon monoxide (●) at a total pressure of 0.2 mbar and a catalyst temperature of $T = 520$ K as a function of the reaction time t [min]. The proportions of the gaseous products were determined independently by XAS (CH_3OH , CO) and mass spectroscopy (H_2CO).

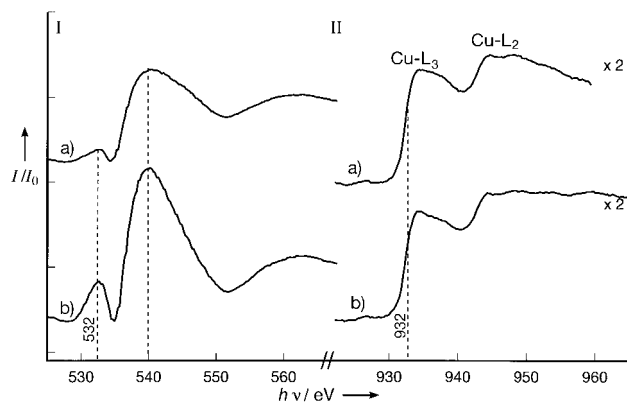


Figure 4. I) In situ oxygen K-absorption near-edge spectra measured during the conversion of methanol at catalyst temperatures of 520 K (a) and 600 K (b); II) the corresponding copper $L_{2,3}$ -edge spectra. The spectra of the pure oxides CuO and Cu_2O are depicted in Figure 2. The line profiles of the oxygen K-edge spectra of the active copper catalyst are quite different from those of known copper oxides (see Figure 2). A broad peak appears in the spectra at 540 eV which can be attributed to the selective catalytically active oxygen state. The copper L-absorption near-edge spectra were recorded with monochromated second-order X-rays (see the legend to Figure 2).

the pure copper oxides, high covalent oxygen–copper bonding contributions are also observed in the oxygen K edge spectra of the catalyst in the active state with participation of mainly $O2p-Cu4sp$ states (at 540 eV) and, to a lesser extent, of $O2p-Cu3d$ states (532 eV) (see Figure 4Ia, b). However, the spectral shapes of the oxygen K edge spectra of the active copper catalyst are completely different from those of the known copper oxides (see Figure 2II d, e). In contrast, good agreement is observed with the oxygen K-edge spectrum of the adsorbed atomic O_α species of the silver catalyst, which would indicate the same type of bonding interaction between copper and oxygen.^[9, 10] The copper $L_{2,3}$ -edge spectra have an absorption step with a form typical of metallic copper compounds (see Figure 2II a). This indicates a “catalytically active” state which is significantly different from those of the

well-known copper oxides and, in analogy to the $O_\alpha-Ag(111)$ phase, has an oxygen–copper interaction with participation of mainly $O2p-Cu4sp$ states.^[9, 10]

A comparison of the spectra of the catalyst surface with those of the gas phase shows that the formaldehyde molecules formed under the chosen reaction conditions decompose on the copper surface with the participation of covalently bonded oxygen to predominantly give CO and H_2 . If the active surface was a known copper oxide, carbon dioxide and not carbon monoxide would be the main product formed.

Thus, for the first time it has proved possible to study a catalytically active phase under reaction conditions by absorption spectroscopy not at the high-energy copper K edge, but rather at the chemically more informative oxygen K and copper $L_{2,3}$ edges. In particular, it was ascertained that the catalytically active phase is metallic and contains an atomic form of oxygen, the chemical bonding of which differs significantly from those in conventional oxides. It was not possible to identify the presence of covalently bonded oxygen in the active state during the reaction in previous in situ XAS studies at the high-energy copper K-edge.^[41, 42] Measurements performed on stoichiometric O_2/CH_3OH gas mixtures at 0.5 mbar (not detailed here) confirm that after most of the methanol has reacted, unused oxygen in the gas phase reacts with the surface to give Cu_2O . The catalyst is then no longer selective and effects complete oxidation.

The novel Cu/O phase discovered by high-pressure in situ analysis can be described as copper suboxide. However, the high surface sensitivity of this method excludes any reasonable bulk analytical characterization in the sense of an overall stoichiometric formula. The structures of different copper suboxides on surfaces^[43] and in small particles^[44] are well known. The selective active state for the application of copper as a partial oxidation catalyst was thus made analytically accessible for the first time. Considering the surface states of the pure metal (weakly active, rearranging) and copper(I) oxide (highly active, totally oxidizing), it is possible to understand the reason for the nonlinear behavior of the reaction system.^[15] Our experiment is a contribution to experimentally overcoming the “pressure gap” in catalytic science. The commissioning of the new synchrotron radiation source BESSY II will enable us to increase the upper pressure limit at which useful spectra can be obtained by at least one order of magnitude. We thus expect to gain considerable knowledge on the local electronic structure of catalytically active surfaces in the operational state.

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- [20] X-ray absorption is a process in which a core electron is promoted to an excited electronic state that is related to the original level by the dipole selection rules ($\Delta L = \pm 1$).^[21, 22] For the oxygen K-edges ($L = 0$) this means that only oxygen p states ($L = 1$) are accessible. The resulting spectrum can be interpreted to a first approximation as depicting the oxygen p projected unoccupied density of states.^[21] As X-ray absorption is a local process on the absorbing atom, this means a very high sensitivity of the X-ray absorption near-edge structures (XANES or NEXAFS) to the local bond to the neighboring atoms and thus permits detailed statements to be made on the chemical nature of the bond.^[21, 22]
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- [29] The “white-line” signal in the spectrum of CuO is about five times larger than the edge jump in metallic copper, whereas in the edge spectrum of Cu_2O it is about 2.5 times larger. These differences in the copper L-edge spectra occur in all corresponding spectra of Cu^I and Cu^{II} compounds, and can therefore be employed as reliable indicators of the copper valency.^[30] The oxygen K-edge spectra of the two oxides can be divided into two regions. The first region immediately at the absorption threshold is assigned to the covalent bonding contribution of oxygen 2p states with copper 3d states. This assignment agrees with molecular-orbital and band-structure calculations.^[30–33] The second region, which stretches from 5 to 20 eV above the absorption threshold, is assigned to the covalent bonding contribution of the oxygen p states with copper 4sp states. The occurrence of covalent oxygen p bonding contributions in a broad energy range confirms the high proportion of covalent interactions in the oxides and is typical for all transition metal oxides.^[25, 34]
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- [40] The reaction of methanol on preoxidized copper was carried out in a batch reactor at different temperatures. The conversion frequencies calculated are strongly dependent on the catalyst temperature. At 750 K, for example, the conversion frequency is 1.3 molecules per second and per surface copper atom. The active copper suboxide phase was detected to be present over a prolonged period (120 min) irrespective of the catalyst temperature; a total reduction of the catalyst, which would thus have meant the destruction of the suboxide phase, was not observed. This can be explained by the redelivery of covalently bonded oxygen by the diffusion of oxygen from the metal interior (O_β) to the surface.
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A Novel Framework Type for Inorganic Clusters with Cyanide Ligands: Crystal Structures of $\text{Cs}_2\text{Mn}_3[\text{Re}_6\text{Se}_8(\text{CN})_6]_2 \cdot 15\text{H}_2\text{O}$ and $(\text{H}_3\text{O})_2\text{Co}_3[\text{Re}_6\text{Se}_8(\text{CN})_6]_2 \cdot 14.5\text{H}_2\text{O}$ **

Nikolaj G. Naumov, Alexander V. Virovets, Maxim N. Sokolov, Sofia B. Artemkina, and Vladimir E. Fedorov*

Transition metal cyanides have been known for nearly three centuries. These compounds demonstrate unique properties, structures, and chemical reactivity.^[1, 2] The ambidentate nature of CN^- ligands with terminal and bridging bonding modes along with the wide variety of coordination numbers and arrangements for metal centers favor the formation of unusual structures both for binary and complex cyanides of transition metals. The best known examples of these compounds are Prussian Blue and analogues,^[3–5] and Hofmann clathrates.^[6–9]

Recently complex clusters with cyanide ligands and alkali metal or organic cations were described.^[10–15] They contain isolated cluster anions: $[\text{Re}_6\text{X}_8(\text{CN})_6]^{4-}$ ($\text{X} = \text{S},^{[10]} \text{Se},^{[11]} \text{Te}^{[12]}$), $[\text{Re}_4\text{X}_4(\text{CN})_{12}]^{4-}$ ($\text{X} = \text{S}, \text{Se},^{[13]} \text{Te}^{[14]}$), $[\text{Mo}_4\text{S}_4(\text{CN})_{12}]^{8-}$.^[15] Undoubtedly, the systematic study of the interactions between complex cluster cyanide anions of varying nuclearity and charge ($[\text{Re}_6\text{X}_8(\text{CN})_6]^{4-}$, $[\text{Re}_4\text{X}_4(\text{CN})_{12}]^{4-}$, $[\text{Mo}_4\text{S}_4(\text{CN})_{12}]^{8-}$) and transition metals is of major importance. Here we report the first polymeric inorganic clusters with cyanide ligands, $\text{Cs}_2\text{Mn}_3[\text{Re}_6\text{Se}_8(\text{CN})_6]_2 \cdot 15\text{H}_2\text{O}$ (**1**) and $(\text{H}_3\text{O})_2\text{Co}_3[\text{Re}_6\text{Se}_8(\text{CN})_6]_2 \cdot 14.5\text{H}_2\text{O}$ (**2**), which contain the anionic cluster $[\text{Re}_6\text{Se}_8(\text{CN})_6]^{4-}$ (Figure 1) and transition metal cations

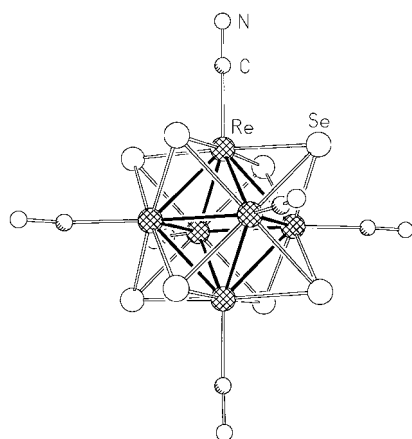


Figure 1. The structure of the cluster anion $[\text{Re}_6\text{Se}_8(\text{CN})_6]^{4-}$.

(Mn^{2+} , Co^{2+}). These compounds were prepared by reaction of $\text{Cs}_4[\text{Re}_6\text{Se}_8(\text{CN})_6]$ and $\text{K}_4[\text{Re}_6\text{Se}_8(\text{CN})_6]$ with $\text{Mn}(\text{NO}_3)_2$ and CoCl_2 in aqueous media.

The crystal structure of **1** consists of $[\text{Re}_6\text{Se}_8(\text{CN})_6]^{4-}$ units connected by $\text{Re}-\text{C}\equiv\text{N}-\text{Mn}$ bonds to an infinite lattice structure. The structure arises from the bridging behavior of the CN ligands coordinated to the Mn atoms and further similar $\text{Re}-\text{C}\equiv\text{N}-\text{Mn}$ interactions involving other CN groups of the anion, which expand the structure into a polymeric framework. No linkage isomerism of the type $\text{Re}-\text{C}\equiv\text{N}-\text{Mn}/\text{Re}-\text{N}\equiv\text{C}-\text{Mn}$ was found.^[16] Two oxygen atoms, O1 and O2, from water molecules complete the coordination shell of the Mn atom. A fragment of the crystal structure of **1** is presented in Figure 2 to show the transition metal–anion

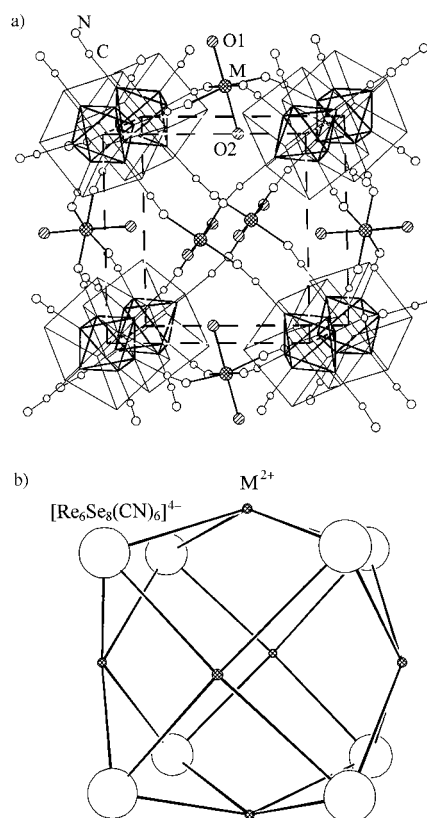


Figure 2. a) The coordination of transition metal cations by cluster anions in compounds **1** and **2**. The circles for the Re and Se atoms have been omitted for clarity. The μ_3 -Se ligands are arranged in a cubic geometry around the Re₆ octahedra. The cube of cluster anions is shown by a dashed line. b) Simplified view in which the cluster anions are presented as large circles and all atoms except M ($\text{M} = \text{Mn}, \text{Co}$) have been omitted.

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bonding. The extended crystal structure is rather complicated, as can be seen in Figure 3. Compound **2** crystallizes in a similar structure type. The Mn–N and Co–N distances in **1** and **2** are close to those encountered in polymer cyanide complexes.^[17–19]

Magnetic data show that the manganese and cobalt ions are in high-spin Mn^{2+} ($S = 5/2$) and Co^{2+} states ($S = 3/2$). Thus, the framework $\{\text{M}_3[\text{Re}_6\text{Se}_8(\text{CN})_6]_2\}^{2-}$ ($\text{M} = \text{Mn}, \text{Co}$) is negatively charged and requires additional counterions to maintain the charge balance. In **1**, caesium ions are accommodated in the

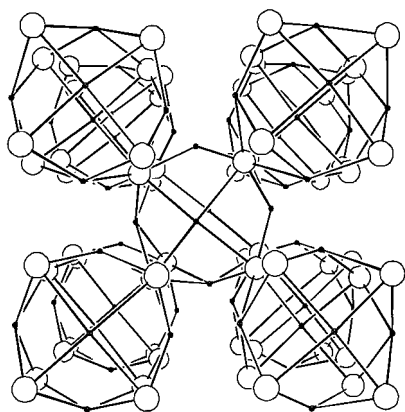


Figure 3. The extended crystal structure of **1** and **2** shown in the same style as Figure 2b. All atoms except M (M = Mn, Co) have been omitted for clarity.

cavities of the framework. In **2**, no potassium cations were found by chemical or structural analysis; the presence of one H_3O^+ cation per cluster anion $[\text{Re}_6\text{Se}_8(\text{CN})_6]^{4-}$ is deduced from the charge balance.

An increase in the wavelength of the $\nu(\text{C}\equiv\text{N})$ absorption band is observed for the transition from terminal cyanide ligands of the $[\text{Re}_6\text{Se}_8(\text{CN})_6]^{4-}$ anion to the linear bridging mode (from 2107 cm^{-1} in $\text{K}_4[\text{Re}_6\text{Se}_8(\text{CN})_6] \cdot 3.5\text{H}_2\text{O}^{[11]}$ to 2125 cm^{-1} for **1** and 2139 cm^{-1} for **2**).

Two water molecules (O1 and O2) are coordinated to the metal atom. The water molecules (atoms O1–O4) are located in the cavities of structure, and are bonded to each other and nitrogen atoms of CN ligands by hydrogen bonding. The $\text{O}\cdots\text{O}$ and $\text{O}\cdots\text{N}$ distances of $2.77\text{--}3.00\text{ \AA}$ indicate the presence of relatively weak hydrogen bonds. Some oxygen atoms have large thermal motion parameters ($U_{eq} = 0.13\text{--}0.25\text{ \AA}^2$). When **1** and **2** are heated in vacuo, irreversible decomposition (at $80\text{--}160^\circ\text{C}$) and loss of water occurs, which confirms that the water molecules play a major role in the stabilization of these structures. Powder diffractograms show that the dehydrated phases have different structures from the parent compounds.

From structures **1** and **2**, it is clear that the transition metal cations and cluster cyanide anions form three-dimensional frameworks with cavities that are occupied by cations and water molecules, as is also the case for mononuclear cyanides.^[1–9, 18] The cavities in the $[\text{M}_3[\text{Re}_6\text{Se}_8(\text{CN})_6]_2]^{2-}$ framework are large enough for the inclusion of other guest molecules.

Experimental Section

1: A solution of $\text{Mn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (0.095 g, 0.4 mmol) in H_2O (10 mL) was added to a solution of $\text{Cs}_4[\text{Re}_6\text{Se}_8(\text{CN})_6]$ (0.487 g, 0.2 mmol) in H_2O (10 mL). Product **1** was separated by filtration, washed with water, and dried in air. Yield: 0.437 g (97%). Elemental analysis (%): calcd for $\text{Cs}_2\text{Mn}_3[\text{Re}_6\text{Se}_8(\text{CN})_6]_2 \cdot 15\text{H}_2\text{O}$ (found): Cs 5.89 (5.92), Mn 3.65 (3.60), Re 49.54 (49.58), Se 28.01 (27.95), H_2O 5.99 (6.07); IR (KBr): $\nu = 2129\text{ cm}^{-1}(\text{C}\equiv\text{N})$; $\mu_{\text{eff}}(298\text{ K}) = 5.97\text{ }\mu_{\text{B}}$; powder diffraction: $a = 19.223(2)\text{ \AA}$, $\alpha = 89.50(1)^\circ$.^[20] Single crystals suitable for structural analysis were obtained by slow cooling of a hot aqueous solution of **1**.

2: A solution of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (0.119 g, 0.5 mmol) in H_2O (10 mL) was added to a solution of $\text{K}_4[\text{Re}_6\text{Se}_8(\text{CN})_6]$ (0.531 g, 0.24 mmol) in acetic buffer

(10 mL, pH 4). Product **2** was separated by filtration, washed with water, and dried in air. Yield: 0.509 g (95%). Elemental analysis (%): calcd for $(\text{H}_3\text{O})_2\text{Co}_3[\text{Re}_6\text{Se}_8(\text{CN})_6]_2 \cdot 14.5\text{H}_2\text{O}$ (found): Re 52.13 (52.15), Se 29.28 (29.32), H_2O 6.98 (7.05); IR (KBr): $\nu = 2139\text{ cm}^{-1}(\text{C}\equiv\text{N})$; $\mu_{\text{eff}}(298\text{ K}) = 4.88\text{ }\mu_{\text{B}}$; powder diffraction: $a = 18.968(2)\text{ \AA}$, $\alpha = 89.33(2)^\circ$.^[20] A solution of commercial waterglass (10 mL) in water (100 mL) was titrated to pH 4 with acetic acid (0.5 M). Then the mixture was placed into a U-tube, and the gel was allowed to set for two days. Diffusion of aqueous solutions of $\text{K}_4[\text{Re}_6\text{Se}_8(\text{CN})_6]^{[11]}$ (0.1 mol L^{-1}) and CoCl_2 (0.5 mol L^{-1}) through the silica gel for four weeks resulted in single crystals of **2** suitable for X-ray single-crystal analysis. The cubelike crystals could be easily separated from the silica gel. X-ray powder diffractometry (Philips APD 1700), IR spectroscopy (Bruker IFS-85), and TGA measurements (Sinku-Riku TA-7000) confirmed that the crystals were identical with the powder sample.

X-ray structural analyses: Data for both **1** and **2** were collected by standard techniques at room temperature on an Enraf Nonius CAD-4 diffractometer ($\theta_{\text{max}} = 25^\circ$, $\text{MoK}\alpha$ radiation ($\lambda = 0.71069\text{ \AA}$), $\theta/2\theta$ scan mode). Data were corrected for absorption with azimuthal scans. The structures were solved by direct methods and were refined by full-matrix least squares, with the SHELX-97 program package.^[21] The occupancy factors of the Cs atoms in **1** were refined under the assumption that the total number of Cs atoms in the cell is eight, in accordance with the chemical analysis and charge balance. The residual electron density peaks do not correspond to any chemically appropriate positions.

1: red prism, crystal dimensions $0.24 \times 0.54 \times 0.60\text{ mm}^3$, trigonal, space group $R\bar{3}c$, $Z = 4$, $a = 19.226(2)\text{ \AA}$, $\alpha = 89.52(1)^\circ$, $V = 7106(1)\text{ \AA}^3$, $\rho_{\text{calcd}} = 4.216\text{ g cm}^{-3}$, $\mu = 30.108\text{ mm}^{-1}$, 6076 measured reflections, 3550 independent, min/max transmission $0.579/1.421$, 237 parameters, $R(F) = 0.0399$ and $R_w(F^2) = 0.0608$ for 1840 reflections with $F_o^2 > 2\sigma(F_o^2)$, residual electron density $1.73\text{ e \AA}^{-3}$.

2: red prism, crystal dimensions $0.15 \times 0.22 \times 0.24\text{ mm}^3$, trigonal, space group $R\bar{3}c$, $Z = 4$, $a = 18.969(4)\text{ \AA}$, $\alpha = 89.35(2)^\circ$, $V = 6824(2)\text{ \AA}^3$, $\rho_{\text{calcd}} = 4.172\text{ g cm}^{-3}$, $\mu = 30.475\text{ mm}^{-1}$, 4727 measured reflections, 3250 independent, min/max transmission $0.776/1.225$, 217 parameters, $R(F) = 0.0336$ and $R_w(F^2) = 0.0546$ for 1600 reflections with $F_o^2 > 2\sigma(F_o^2)$, residual electron density $1.62\text{ e \AA}^{-3}$.

Further details of the structure investigations can 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 numbers CSD-407787 and -407788.

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Consequences of Triplet Aromaticity in $4n\pi$ -Electron Annulenes: Calculation of Magnetic Shieldings for Open-Shell Species**

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Dedicated to Professor Andrew Streitwieser on the occasion of his 70th birthday

This paper presents evidence that triplet states of $4n\pi$ -electron annulenes are aromatic^[1] rather than antiaromatic. Not only the geometric and energetic, but also the magnetic properties of open-shell species, which are generally not accessible experimentally^[2] but can be computed,^[3] may be used to assess the aromaticity and antiaromaticity of a basic set of $4n\pi$ -electron annulene singlets and triplets: C_4H_4 (**1**), C_5H_5^+ (**2**), $\text{C}_6\text{H}_6^{2+}$ (**3**), C_7H_7^- (**4**), C_8H_8 (**5**), and C_9H_9^+ (**6**).

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According to simple Hückel MO theory, planar $4n\pi$ -electron annulenes in D_{nh} symmetry have degenerate ground states^[4] and should be nonaromatic.^[5] Breslow provided experimental evidence that the cyclopropenyl anion, **1**, **2**, and **4**^[6] (or their derivatives) are destabilized and coined the “antiaromatic” designation.^[6a] As early as 1959 Berthier and co-workers found that Pariser–Parr calculations favor the D_{7h} triplet as the ground state of **4**.^[7] Borden^[8] explained why **2**^[9] and **4**^[7] should have triplet ground states, whereas **1**^[10] and **5**^[11] favor singlet ground states and undergo Jahn–Teller distortion.

The idea that triplet $4n\pi$ -electron annulenes may be regarded as being aromatic rather than antiaromatic was suggested in 1972 by Baird, who concluded that the rules for aromaticity and antiaromaticity are exactly reversed in the lowest triplet state of annulenes.^[1a] He pointed out that the proper way to evaluate the aromaticity or antiaromaticity of the lowest triplet state of a cyclic hydrocarbon is to define the aromatic stabilization energy (ASE) relative to the bonding energy for the lowest triplet state of the open-chain polyene which contains the same number of carbon atoms.^[1a] The Dewar resonance energies of triplet D_{4h} cyclobutadiene (**1T**, 14.1 kcal mol^{−1}) and of triplet D_{8h} cyclooctatetraene (**5T**, 17.7 kcal mol^{−1}), calculated on this basis (NNDO semiempirical level), supported the aromaticity of these species.^[1a] Other investigations support the aromaticity of triplet $4n\pi$ -electron annulenes.^[1b–1h] We report here the first comprehensive high level ab initio calculations^[12] of the adiabatic singlet/triplet separations ($S \rightarrow T$), the ASEs, and the magnetic properties of the six neutral or charged $4n\pi$ -electron annulenes **1–6**.

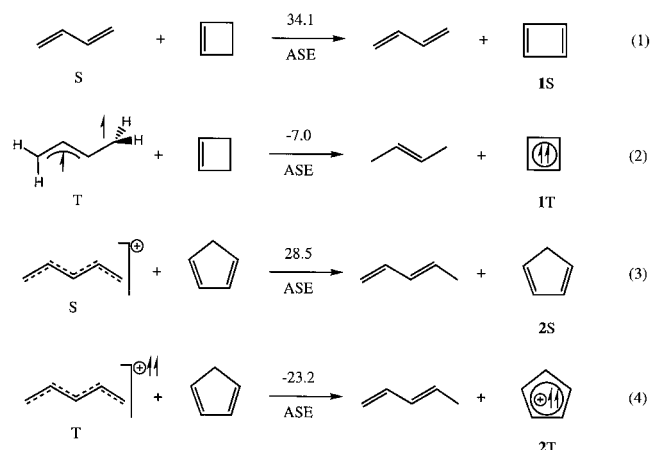
The singlet/triplet separation energies ($S \rightarrow T$, Table 1) for acyclic reference compounds butadiene and the pentadienyl cation C_5H_5^+ are much larger (57.0 and 47.1 kcal mol^{−1}, respectively) than for the cyclic species **1** (11.5 kcal mol^{−1}) and **2** (−7.6 kcal mol^{−1}). Consistent with triplet aromaticity, all triplet $4n\pi$ -electron annulenes are highly stabilized relative to the corresponding acyclic triplet reference species. The

Table 1. Singlet–triplet ($S \rightarrow T$) adiabatic transitions for $4n\pi$ -electron annulenes calculated at B3LYP and CCSD(T) ab initio levels.^[a]

Compound	Transition	B3LYP/ 6–311 + G(d,p)	CCSD(T)/cc-pVDZ// B3LYP/6–311 + G(d,p)
C_4H_4	1S → 1T	5.9	11.5 ^[b]
C_4H_6	S → T	54.2	57.0
C_5H_5^+	2S → 2T	−10.5	−7.6
C_5H_7^+	S → T	44.1	47.1
$\text{C}_6\text{H}_6^{2+}$	3S → 3T	−2.3	0.5
C_7H_7^-	4S → 4T	−2.6	−1.0
C_8H_8	5S → 5T [c]	15.5	24.3
C_9H_9^+	6S → 6T [d]	−1.2	–

[a] In kcal mol^{−1}. [b] 11.2 (CCSDT) and 12.4 (MRCCSD(T))^[10c]; 12.0 kcal mol^{−1} by flash photolysis of peralkylated cyclobutadiene (J. Wirz, A. Krebs, H. Schallstiegl, H. Angliker, *Angew. Chem.* **1981**, 93, 192; *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 192). [c] Borden, Lineberger, and co-workers found experimentally a $S \rightarrow T$ separation of 12.1 kcal mol^{−1} for cyclooctatetraene ($D_{4h} \rightarrow D_{8h}$).^[11a] The calculated^[11b] and experimentally determined (J. F. M. Oth, *Pure Appl. Chem.* **1971**, 25, 573) barrier for the ring inversion ($D_{2d} \rightarrow D_{4h} \rightarrow D_{2d}$) is around 13 kcal mol^{−1}. This gives a total $S \rightarrow T$ adiabatic transition ($D_{2d} \rightarrow D_{8h}$) of about 25 kcal mol^{−1}, which compares well with our result of 24.3 kcal mol^{−1} calculated at the coupled cluster level. [d] B3LYP/6–31G(d) geometries.

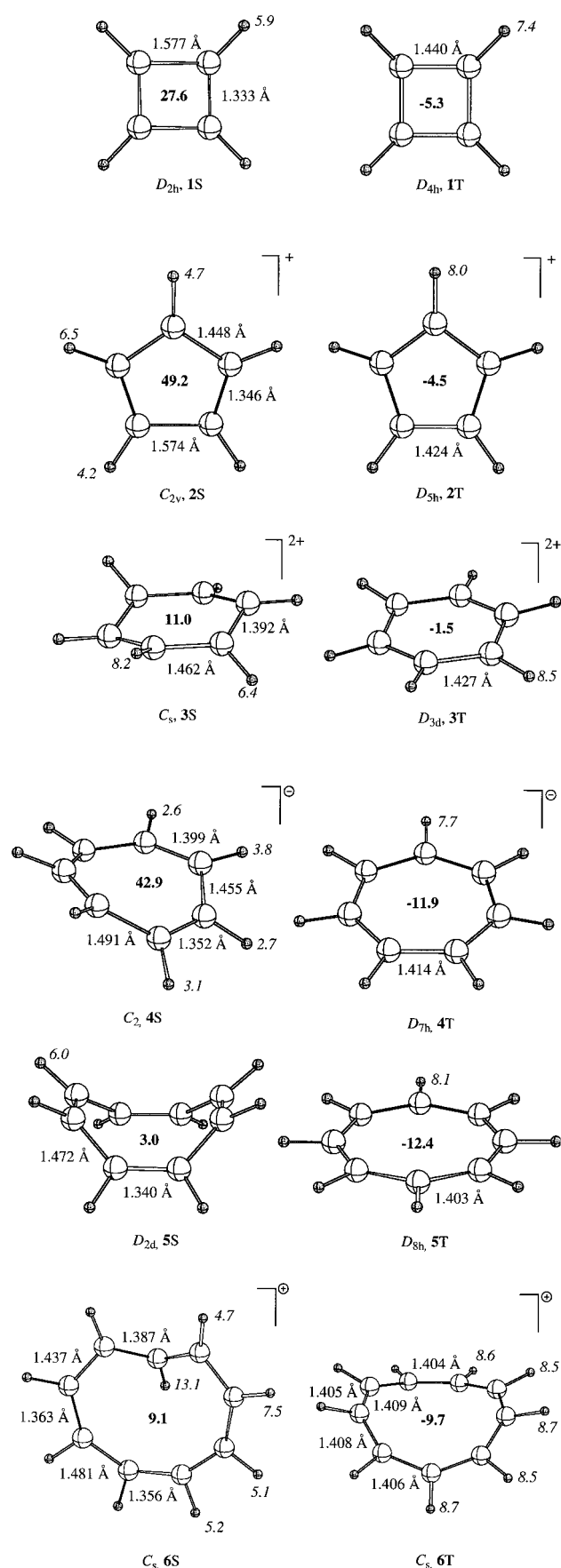
triplets **4T** and **6T** are even slightly more stable than the corresponding singlets **4S** and **6S** (Table 1). The ASEs computed at the CCSD(T)/cc-pVDZ level from isogyric equations of triplet cyclobutadiene (-7.0 kcal mol $^{-1}$) and $C_5H_3^+$ (-23.2 kcal/mol) confirm and extend Baird's proposal [Eqs. (2) and (4), Scheme 1].^[1a] Species **1T** and **2T** are stabilized with respect to triplet acyclic reference molecules



(triplet butadiene and the triplet pentadienyl cation). In contrast, Equations (1) and (3) show that the antiaromatic singlets **1S** and **2S** are destabilized with respect to singlet C_4H_6 and $C_5H_7^+$ (34.1 and 28.5 kcal mol $^{-1}$, respectively). Thus, according to the energetic criteria of aromaticity, **1T** and **2T** are aromatic.^[1f, 13]

The planar singlet $4n\pi$ -electron annulenes **1S**^[10] and **2S**^[9b] are highly antiaromatic and show the largest alternations in bond length (0.244 and 0.228 Å, respectively; Figure 1). The differences in bond lengths of the nonplanar singlets are 0.070 (**3S**), 0.139 (**4S**), 0.132 (**5S**), and 0.125 Å (**6S**). In contrast, the triplet $4n\pi$ -electron annulenes **1T**, **2T**, **4T**, and **5T** prefer D_{nh} symmetry and C–C bond lengths close to the 1.395 Å of benzene: 1.440 (**1T**), 1.424 (**2T**), 1.414 (**4T**), and 1.403 Å (**5T**). The planar D_{6h} and the nearly planar D_{3d} structures of the triplet benzene dication (**3T**) have almost the same energy. The C–C bond lengths in **3T** are all 1.427 Å. Like the Hückel-aromatic $C_9H_9^-$ anion,^[14] triplet $C_9H_9^+$ (C_s , **6T**) has two minima. The less stable C_s form has one hydrogen atom pointing inwards. The more stable **6T** also is highly planarized (Figure 1, the C–C–C–C torsion angles range from 0 to 32°), and the bond lengths are all nearly equal (1.404–1.409 Å). (The planar Hückel D_{9h} $C_9H_9^-$ anion has a C–C distance of 1.404 Å at the same level.) The planar preference of triplet $C_7H_7^-$ (**4T**), C_8H_8 (**5T**), and the planarized geometry of triplet $C_5H_3^+$ (**6T**) are particularly noteworthy because of the considerable angle strain which must be overcome to adopt such structures. The average C–C–C bond angle in **6T** is 137° (close to the 140° bond angle in the D_{9h} $C_9H_9^-$ anion), whereas **6S** has an average C–C–C bond angle of 127°.

The singlets **4S**–**6S** and the parent hydrocarbons cycloheptatriene, cyclooctatetraene, and 1,3,5,7-nonatetraene are all strongly nonplanar with strongly alternating bond lengths.



Hence, the corresponding triplet $4n\pi$ -electron annulenes **4T**–**6T** clearly are aromatic according to the geometric criteria of aromaticity.^[1f, 13]

The magnetic shieldings for open-shell species are generally not accessible by NMR measurements owing to line broadening,^[2, 15] but they can be computed.^[3] These open-shell calculations of magnetic properties^[16] may be “unphysical”,^[16b] but they are instructive and useful for many purposes. We use them here as an “index” to compare the behavior of the triplet with the singlet states. Nuclear-independent chemical shifts (NICS)^[17] and magnetic susceptibility exaltations (A)^[18] (Table 2, Figure 1) are positive for the singlets and negative for the triplets. Singlet $C_9H_9^+$ (**6S**) has a strongly nonplanar conformation and pronounced alternations in bond lengths, while triplet **6T** is clearly aromatic (NICS = -9.7 ppm). Table 2 and Figure 1 show charge-corrected^[19] ^1H NMR chemical shifts for the $4n\pi$ -electron annulenes. The average ^1H NMR chemical shifts for the singlet species are in the olefinic range, but those for the triplets are downfield (Table 2).

The consequences of triplet aromaticity in $4n\pi$ -electron annulenes **1T**–**6T** are the following: planarity or near planarity, equalization of bond lengths, low-energy triplet states (Table 1), appreciable aromatic stabilization energies (based on triplet reference states), negative nuclear-independent chemical shifts, downfield ^1H NMR chemical shifts, and, in the absence of the paramagnetic effects of unpaired electrons, significant diamagnetic susceptibility exaltations (Table 2). The stability of the triplet cyclononatetraenyl cation (**6T**), which is remarkable in view of the high degree of angle strain, extends Borden's generalization^[5, 8] to nonplanar annulenes that do not have degenerate SOMOs.^[20]

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Table 2. Nucleus-independent chemical shifts (NICS), magnetic susceptibilities, and magnetic susceptibility exaltations (A) for singlet and triplet species calculated at the GIAO-SCF level.^[a]

Compound		Point group	Electronic state	$\delta(^1\text{H})^{[\text{b}, \text{c}]}$	NICS ^[c]	Magnetic suscept. ^[c]	$A^{[\text{c}]}$
C_4H_4	1S	$D_{2\text{h}}$	$^1\text{A}_{1\text{g}}$	5.9	27.6	− 7.7	12.5[d]
	1T	$D_{4\text{h}}$	$^3\text{A}_{2\text{g}}$	7.4	− 5.3	− 22.8	− 3.5[e]
C_5H_5^+	2S	$C_{2\text{v}}$	$^1\text{A}_1$	5.2	49.2	4.8	30.5[f]
	2T	$D_{5\text{h}}$	$^3\text{A}_1'$	8.0	− 4.5	− 28.4	− 3.3[g]
$\text{C}_6\text{H}_6^{2+}$	3S	C_s	$^1\text{A}'$	7.0	11.0	− 13.7	
	3T	$D_{3\text{d}}$	$^3\text{B}_\text{g}$	8.5	− 1.5	− 28.2	
C_7H_7^-	4S	C_2	^1A	3.1	42.9	24.7	
	4T	$D_{7\text{h}}$	$^3\text{A}_1'$	7.7	− 11.9	− 64.5	
C_8H_8	5S	$D_{2\text{d}}$	$^1\text{A}_1$	6.0	3.0	− 46.2	
	5T	$D_{8\text{h}}$	$^3\text{A}_{2\text{u}}$	8.1	− 12.4	− 81.6	
TS ^[h]		$D_{4\text{h}}$	$^1\text{A}_{1\text{g}}$	3.1	30.1	4.1	60.4 ^[i, j]
C_9H_9^+	6S	C_s	$^1\text{A}'$	1.0	9.1		
	6T ^[k]	C_s	$^3\text{A}'$	8.6	− 9.7		
C_5H_5 radical		$C_{2\text{v}}$	$^2\text{A}_1$	6.5	2.6	− 30.6	
benzene		$D_{6\text{h}}$	$^1\text{A}_{1\text{g}}$	7.8	− 9.7 ^[i]	− 51.3	− 13.4 ^[i, j]

[a] B3LYP/6–311 + G(d,p) geometries. [b] Average value for species with nonequivalent protons. The ^1H NMR chemical shifts for charged species were corrected based on Haddon's suggestion that one unit of electrostatic charge on the carbon atom which binds the proton produces a change of 10 ppm in the ^1H NMR chemical shift (R. C. Haddon, V. R. Haddon, L. M. Jackman, *Top. Curr. Chem.* **1971**, *16*, 103). The charge on the carbon atom was calculated as the sum of the natural charges on the connected carbon and hydrogen atoms. [c] HF/6–31 + G*. [d] Equation (1). [e] Equation (2). [f] Equation (3). [g] Equation (4). [h] Planar transition state with alternations in bond lengths. [i] GIAO-SCF/6–31 + G(d).^[17] [j] Calculated from increments.^[17] [k] The B3LYP/6–31G(d) potential energy surface of **6T** is quite flat.

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Metal–Ligand versus Metal–Metal Redox Chemistry: Thallium(I)-Induced Synthesis of 4,9-Diaminoperylenequinone-3,10-diimine Derivatives**

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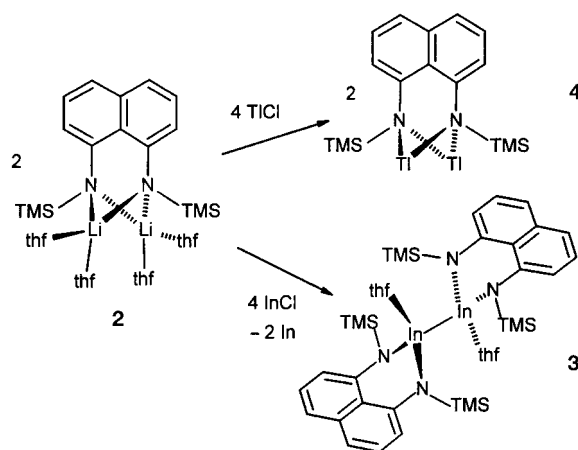
While the structural chemistry of thallium(I) amides and related molecular compounds in the solid state is characterized by supramolecular forms of aggregation defined by weakly attractive metal–metal contacts,^[1–3] redox disproportionations of the monovalent metal complexes of thallium and indium dominate their reactivity in solution.^[4] These may either lead to the mixed-valent $M^I M^{II}$ and $M^I M^{III}$ compounds ($M = \text{In, Tl}$) or, alternatively, generate the products of partial or complete thermal demetalation. In the latter case the corresponding amines are formed probably via nitrogen radical intermediates.

It was our aim to study the demetalation more closely and use it preparatively for the specific coupling of the transient intermediates generated by the demetalation. We thus set out to investigate the thallium(I) and indium(I) amide chemistry of such ligands which upon thermal demetalation would give intermediates of greater stability and lifetime. Instead of immediately abstracting hydrogen atoms from the solvent, they could undergo C–C coupling and related reactions. To this end we chose a bidentate amido ligand derived from 1,8-diaminonaphthalene which, given the known redoxchemistry of arylamines,^[5] offered the opportunity of directing the chemically induced redox conversions into pathways other than simple demetalations.

As starting material we selected 1,8-bis(trimethylsilylamino)naphthalene (**1**), which was readily converted into the lithium amide $[\text{Li}_2[\text{C}_{10}\text{H}_6(\text{NSiMe}_3)_2](\text{thf})_4]$ (**2**).^[6] The attempted metal exchange of **2** with InCl in THF led to an immediate redox disproportionation of the monovalent In^I compound and the generation of the dinuclear $\text{In}^{II}–\text{In}^{II}$ complex $[\text{In}[\text{C}_{10}\text{H}_6(\text{NSiMe}_3)_2](\text{thf})_2]_2$ (**3**; Scheme 1, Table 1). Its formulation was established by elemental analysis and the NMR spectra, while a single-crystal X-ray structure analysis^[7] of the bright yellow compound confirmed the presence of a metal–metal bond (Figure 1). The In–In distance of 2.7237(6) Å is the shortest established for a diindane to date.^[4c, 8] The midpoint of the In–In vector lies on a crystallographic center

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Scheme 1. Synthesis of the indium(II) amide **3** (In–In) and thallium(I) amide **4**.

Table 1. Selected spectroscopic data for compounds **3**–**7**.^[a]

3: ¹H NMR (C₆D₆): δ = 0.44 (s, 36H, Si(CH₃)₃), 0.88 (m, 8H, CH₂CH₂O), 3.39 (m, 8H, CH₂CH₂O), 6.95 (dd, 4H, ³J_{H,H} = 7.1 Hz, ⁴J_{H,H} = 1.2 Hz, C₁₀H₆), 7.16–7.27 (m, 8H, C₁₀H₆); ¹³C{¹H} NMR (C₆D₆): δ = 4.4 (Si(CH₃)₃), 24.5 (CH₂CH₂O), 69.7 (CH₂CH₂O), 118.6 (CH, C₁₀H₆), 120.2 (CH, C₁₀H₆), 125.8 (CH, C₁₀H₆), 126.3 (C, C₁₀H₆), 139.3 (C, C₁₀H₆), 153.7 (CN, C₁₀H₆); ²⁹Si{¹H} NMR ([D₈]THF): δ = –0.8. 4: ¹H NMR (C₆D₆): δ = 0.28 (s, 18H, Si(CH₃)₃), 6.74 (dd, 2H, ³J_{H,H} = 6.4 Hz, ⁴J_{H,H} = 2.8 Hz, C₁₀H₆), 7.33–7.38 (m, 4H, C₁₀H₆); ¹³C{¹H} NMR (C₆D₆): δ = 0.6 (br, Si(CH₃)₃), 116.1 (br, CH, C₁₀H₆), 119.4 (CH, C₁₀H₆), 122.2 (br, C, C₁₀H₆), 126.9 (CH, C₁₀H₆), 140.1 (C, C₁₀H₆), 151.0 (br, CN, C₁₀H₆); ²⁹Si{¹H} NMR ([D₈]THF): δ = –7.9. 5a: ¹H NMR (C₆D₆): δ = 0.48 (s, 36H, Si(CH₃)₃), 7.19 (d, 4H, ³J_{H,H} = 9.7 Hz, C₂₀H₈), 8.13 (d, 4H, C₂₀H₈), 14.13 (s, 2H, NH); ¹³C{¹H} NMR (C₆D₆): δ = 1.4 (Si(CH₃)₃), 112.2 (C, C₂₀H₈), 124.3 (C, C₂₀H₈), 125.4 (CH, C₂₀H₈), 126.4 (C, C₂₀H₈), 128.0 (CH, C₂₀H₈), 161.9 (CN, C₂₀H₈); ²⁹Si{¹H} NMR (C₆D₆): δ = –0.9. 5b: ¹H NMR (CDCl₃): δ = 0.41 (s, 24H, Si(CH₃)₃), 1.00 (s, 36H, Si(CH₃)₃), 7.21 (d, 4H, ³J_{H,H} = 9.8 Hz, C₂₀H₈), 8.38 (d, 4H, C₂₀H₈), 13.42 (s, 2H, NH); ¹³C{¹H} NMR (CDCl₃): δ = –2.1 (Si(CH₃)₃), 19.2 (Si(CH₃)₃), 26.9 (Si(CH₃)₃), 111.6 (C, C₂₀H₈), 123.7 (C, C₂₀H₈), 125.7 (C, C₂₀H₈), 126.0 (CH, C₂₀H₈), 127.1 (CH, C₂₀H₈), 161.8 (CN, C₂₀H₈); ²⁹Si{¹H} NMR (C₆D₆): δ = 4.9. 6: ¹H NMR ([D₆]DMSO-<i>d</i>₆): δ = 7.16 (d, 4H, ³J_{H,H} = 9.8 Hz, C₂₀H₈), 8.47 (d, 4H, C₂₀H₈), 8.65 (brs, 6H, NH/NH₂); ¹³C{¹H} NMR ([D₆]DMSO): δ = 105.7 (C, C₂₀H₈), 123.0 (C, C₂₀H₈), 125.0 (C, C₂₀H₈), 125.4 (CH, C₂₀H₈), 127.3 (CH, C₂₀H₈), 159.6 (CN, C₂₀H₈). 7: ¹H NMR (C₆D₆): δ = 0.22 (s, 36H, Si(CH₃)₃), 5.43 (brs, 4H, NH), 6.72 (d, 4H, ³J_{H,H} = 9.2 Hz, C₂₀H₈), 7.88 (d, 4H, C₂₀H₈).

[a] NMR spectra recorded at 200.13 (¹H), 50.32 (¹³C), and 39.76 MHz (²⁹Si). Correct elemental analyses obtained for all compounds. [b] DMSO = Dimethyl sulfoxide.

of symmetry, and the metal atoms are located significantly outside the planes of the aromatic ligand backbones (0.984 Å) with the SiMe₃ groups pointing in the opposite direction to generate the almost planar geometry at the amido N atoms. The coordination geometry of the indium centers may be viewed as being between the two extremes of a trigonal-planar arrangement to be expected for a non-THF-solvated complex and the distortion towards a tetrahedral geometry induced by the coordination of the THF ligands.

In contrast with the immediate disproportionation of the In^I species during the course of the metal exchange, the

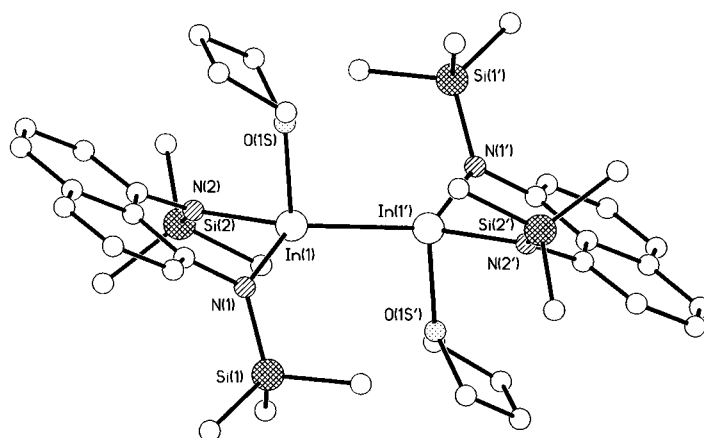
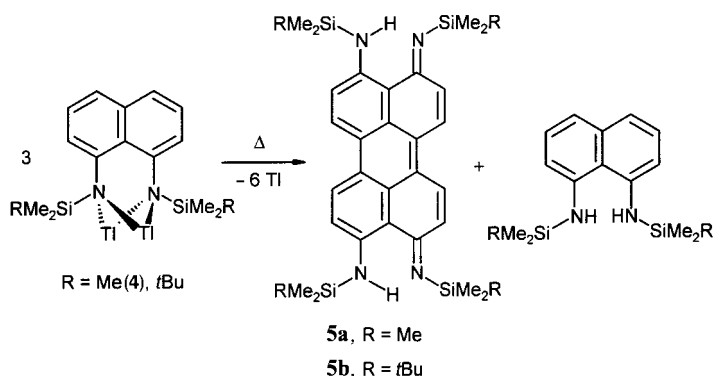


Figure 1. Molecular structure of **3** in the solid state; selected bond lengths [Å] and angles [°]: In(1)–In(1') 2.7237(6), In(1)–N(1) 2.085(3), In(1)–N(2) 2.089(3), In(1)–O(1S) 2.283(3), Si(1)–N(1) 1.722(4), Si(2)–N(2) 1.725(3); N(1)–In(1)–N(2) 90.91(13), N(1)–In(1)–O(1S) 96.75(13), N(2)–In(1)–O(1S) 93.17(12), N(1)–In(1)–In(1') 127.96(10), N(2)–In(1)–In(1') 134.45(9), C(1)–N(1)–Si(1) 125.5(3), C(1)–N(1)–In(1) 114.1(3), Si(1)–N(1)–In(1) 117.9, C(7)–N(2)–Si(2) 122.2(3), C(7)–N(2)–In(1) 114.6(3), Si(2)–N(2)–In(1) 123.1(2).

corresponding reaction of **2** with TlCl exclusively led to the monovalent synthetic target [Tl₂{C₁₀H₆(NSiMe₃)₂}] (**4**) which was isolated as a microcrystalline, orange solid and characterized by elemental analysis and NMR spectroscopy. When **4** was stirred in 1,4-dioxane at 90 °C, thallium metal precipitated and the initially orange solution turned deep green. Monitoring the reaction by ¹H NMR spectroscopy revealed a very selective conversion of **4** into the amine **1** and a hitherto unknown product **5a** in a 1:1 molar ratio. After completion of the reaction and workup **5a** was isolated in 50 % yield (based on **4**) as a black-green highly crystalline solid with a purple luster.^[9] The elemental analysis of **5a** indicated the absence of thallium, and X-ray diffraction studies of the SiMe₃-substituted compound, as well as its Si*t*BuMe₂-substituted analogue **5b**, established their identity as perylene derivatives (Scheme 2).^[10]

Both **5a** and **5b** are formulated as derivatives of 4,9-diaminoperylenequinone-3,10-dimine **6** which may be obtained by desilylation with fluoride. Compound **6** was first reported by Zinke and co-workers.^[11] However, it has received little attention since then, probably due to its



Scheme 2. Thermolytic conversion of **4** into the perylene derivative **5a** and the amine **1**.

extremely cumbersome synthesis by exhaustive nitration of unsubstituted perylene and reduction of the tetranitro derivative formed. This lack of attention is surprising in view of the close structural relationship to 4,9-dihydroxyperylene-3,10-quinones (the oxygen analogues), such as the natural product hypocrelline A; some of these compounds are employed in photodynamic therapy and display cancerostatic and antiviral activity.^[12]

The patterns of bond lengths in the molecular structures of **5a** and **5b** are similar but due to poor diffraction by the crystals of **5a**, caused by considerable rotational disorder of the trimethylsilyl groups, the estimated standard deviations in the former are relatively high and preclude detailed discussion. The structure of **5b** is well established, and the corresponding bond lengths on the two sides of the virtually planar ring system are equal within experimental error (Figure 2).

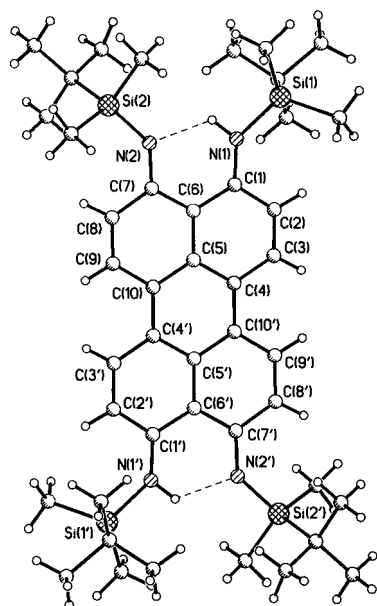


Figure 2. The structure observed for the two independent centrosymmetric molecules in the crystal of **5b**. Selected bond lengths [Å] with those for the second molecule in brackets: Si(1)–N(1) 1.748(3) [1.740(3)], Si(2)–N(2) 1.734(3) [1.738(3)], N(2)–C(7) 1.330(4) [1.326(4)], N(1)–C(1) 1.334(5) [1.332(4)], C(1)–C(2) 1.428(5) [1.430(5)], C(7)–C(8) 1.435(5) [1.436(5)], C(1)–C(6) 1.436(5) [1.439(5)], C(6)–C(7) 1.436(5) [1.433(5)], C(2)–C(3) 1.342(5) [1.337(5)], C(8)–C(9) 1.343(5) [1.339(5)], C(3)–C(4) 1.415(5) [1.420(5)], C(9)–C(10) 1.421(5) [1.426(5)], C(5)–C(10) 1.420(5) [1.426(5)], C(4)–C(5) 1.418(5) [1.410(5)], C(5)–C(6) 1.440(5) [1.441(5)], mean N–H 0.98, N⋯H 1.86.

The overall solid-state structure of the molecules is the result of a random 50:50 disorder of two tautomers throughout the crystal. There are significant differences in the bond lengths relative to the reported values of the parent compound perylene.^[13] In particular, the mean lengths of C(2)–C(3) and C(8)–C(9) of 1.341 and C(4)–C(10') of 1.421 Å are considerably shorter than the analogous values in perylene of 1.40 and 1.48 Å, respectively. A similar shortening of these bonds has been observed previously for the perylene dianion, where the respective mean values are 1.37 and 1.43 Å,^[14] as well as in the hydroxyperylenequinones mentioned above.^[15]

The solid state structures of a large number of perylene-bis(carboximide) derivatives have been studied in order to

investigate the correlation between molecular packing and color in pigments.^[16] In most cases stacked face-to-face arrangements (separation between the parallel oriented ring systems between 3.345 and 3.476 Å) of perylenes are found provided that no bulky substituent prevent this.^[17] The crystal structures in the present study are markedly different with no face-to-face interactions. Instead, in the butyldimethylsilylated derivative **5b** there are close contacts between alkyl groups and the aromatic ring, with neighboring molecules being oriented almost perpendicular to each other, whereas in **5a** the aromatic ring systems of adjacent molecules exhibit edge-to-face interactions resulting in an overall “herring-bone” arrangement in the crystal (Figure 3).

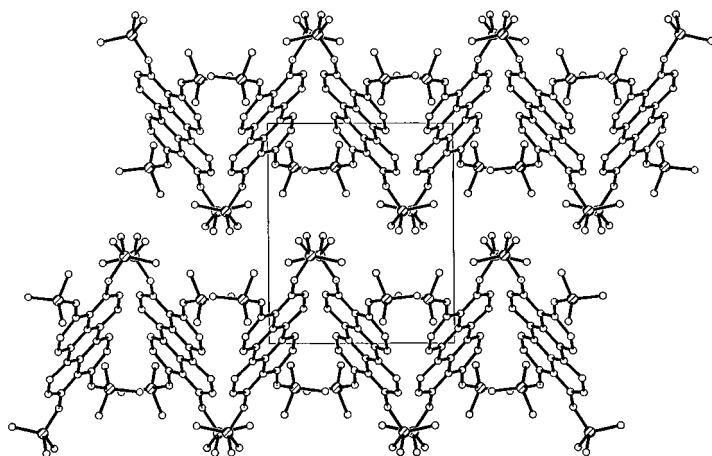
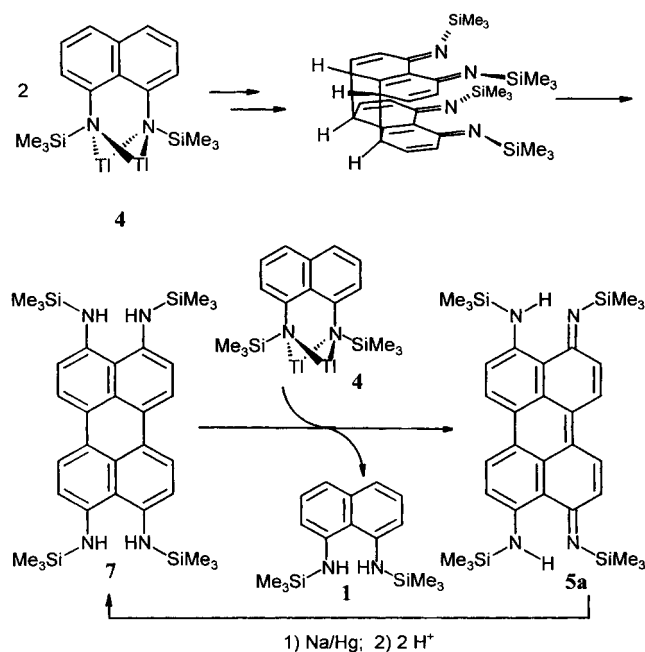


Figure 3. Packing of the perylene derivative **5a** in a “herring bone” arrangement in the crystal.

The high selectivity in the formation of **5a** from **4** and the exact 1:1 ratio in which the perylene and the diamidonaphthalene are formed raises the question of the possible mechanism of this coupling reaction (Scheme 3). ¹H NMR studies of the reaction in solution revealed the absence of any detectable intermediates, and a preliminary kinetic study suggests a rate law which is first order with respect to **4**. The demetalation of **4** may either lead to diradicals^[18] or proceed by a disproportionation step similar to the reaction observed with InCl to generate **3**. This would be followed by subsequent demetalation and coupling (possibly in a concerted step) of the two naphthalene units. A hydrogen shift and flattening of the ring system, with concomitant aromatization, produces the tetraaminoperylene **7**. This strong reducing agent, which also may be generated specifically by Na/Hg reduction and subsequent protonation of **5a**, reacts with the third equivalent of the thallium amide **4** to form **5a** and the amine **1**, as required by the observed stoichiometry. The latter step could be studied independently by allowing **7** to react with **4**.

On the basis of the generation of **5a** and **5b** described above, a convenient one-pot synthesis of these perylene derivatives has been developed starting with silylated amines such as **1**. Subsequent in situ lithiation, metal exchange, and thermolysis gives the dyes in good yields (50–52% with respect to the diamidonaphthalene starting material, the theoretical maximum being 66%) with no detectable amounts of thallium remaining in solution, as established at the ppb



Scheme 3. Proposed mechanism for the formation of the perylenes from the thallium amides generated in situ.

level by atomic emission spectroscopy. Both the diamino-naphthalenes produced and the thallium metal may be retrieved and reused in subsequent conversions.

In conclusion, we have shown that the redoxchemistry in solution of amides of the heavy monovalent Group 13 metals may vary between predominantly metal–metal disproportionation, observed for indium, and oxidation of the ligand, observed for thallium. Given the appropriate type of “ligand system”, this type of reaction can be developed into a powerful organic synthetic tool.

Experimental Section

3: Solid InCl (853 mg, 5.68 mmol) was added to a stirred solution of **2** (1.71 g, 2.83 mmol) in THF (30 mL) which was cooled to -60°C . After the mixture was warmed to room temperature and stirred for 18 h the solvent was removed under reduced pressure, and the residue extracted with toluene (30 mL). The LiCl and indium metal formed in the reaction were removed by centrifugation,^[20] and the centrifugate was evaporated to dryness. The residue was redissolved in THF (30 mL) and stored at 0°C . Compound **3** precipitated as a yellow, highly crystalline solid (yield: 1.24 g, 90%, m.p. 83°C (decomp)).

4: Solid TlCl (959 mg, 4.00 mmol) was added to a stirred solution of **2** (1.21 g, 2.00 mmol) in THF (40 mL) which was cooled at -30°C . After the mixture was stirred for 16 h at room temperature the solvent was removed in vacuo, and the residue extracted with toluene (40 mL). The LiCl formed in the reaction was separated by centrifugation, and the deep orange solution concentrated to 20 mL. Upon storing the solution at -35°C for several days, compound **4** precipitated as a microcrystalline, orange solid (yield: 380 mg, 27%).

5a, b: Solid TlCl (1.19 g, 4.98 mmol) was added at room temperature to a stirred solution of $[\text{Li}_2\{\text{C}_{10}\text{H}_6(\text{NSiMe}_2)_2\}(\text{thf})_4]$ ($\text{R} = \text{Me}, t\text{Bu}$; 2.49 mmol) in 1,4-dioxane (40 mL), and the mixture was heated at 90°C for 17 h. After removal of the solvent the residue was extracted with toluene (75 mL), and the LiCl and thallium metal formed in the reaction were removed by centrifugation. The dark green solution was concentrated to 40 mL and stored at -35°C for 24 h. Compounds **5a** and **5b** precipitated as black-

green needles with a purple luster (yield: **5a**: 373 mg, 50%, m.p. 212°C ; **5b**: 497 mg, 52%, m.p. 252°C).

7: A solution of **5a** (300 mg, 0.50 mmol) in THF (35 mL) was added at room temperature to Na/Hg (Na: 1.00 mmol). After the mixture was stirred for 24 h the Hg metal was removed by filtration, and solid NET_3HCl (138 mg, 1.00 mmol) in THF (15 mL) was added to the deep blue reaction mixture at -55°C . After the reaction mixture was stirred for another 18 h at room temperature the solvent was removed under reduced pressure, the residue extracted with toluene (75 mL), and the NaCl generated in the reaction removed by centrifugation. The deep red solution was concentrated to 15 mL and stored at -35°C for 24 h. Compound **7** was obtained as a vermillion solid (yield: 123 mg, 41%).

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- [7] Crystal data for **3**: $\text{C}_{40}\text{H}_{64}\text{In}_2\text{N}_4\text{O}_2\text{Si}_4$, $M_r = 974.95$, monoclinic, space group $P2_1/n$, $a = 10.3086(14)$, $b = 18.402(2)$, $c = 12.7880(14)$ Å, $\beta = 105.661(10)^{\circ}$, $V = 2335.8(5)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.386$ g cm⁻³, $F(000) = 1004$, $\mu(\text{MoK}\alpha) = 1.125$ mm⁻¹, $T = 298(2)$ K. A yellow crystal ($0.20 \times 0.24 \times 0.36$ mm³) was mounted in a Lindemann tube for data collection on a Siemens P4 diffractometer. The structure was determined by direct methods and refined on F^2 for 4109 independent reflections corrected for absorbance ($T_{\text{max}} 0.883$, $T_{\text{min}} 0.691$) of 5171 collected ($1.99 \leq \theta \leq 24.99^{\circ}$), $R(\text{int}) = 0.0264$. Anisotropic thermal parameters were assigned for all non-hydrogen atoms. The asymmetric unit consists of the half the centrosymmetric molecule. The hydrogen atoms were included in idealized positions and assigned the isotropic thermal parameters $U_{\text{iso}} = 1.2 U_{\text{eq}}$ of the parent carbon atom for methylene groups and aromatic hydrogen atoms, and $U_{\text{iso}} = 1.5 U_{\text{eq}}$ for methyl hydrogen atoms. At final convergence $R_1 = 0.0384$, $wR_2 = 0.0587$ ($I > 2\sigma(I)$), $R_1 = 0.0737$, $wR_2 = 0.0680$ (all data), $\text{GOF}(F^2) = 0.995$ for 490 parameters.^[10b] For programs, see reference [19].
- [8] Shorter covalent In–In bonds in a molecular compound have been reported for $[\text{In}(\text{In}(2,4,6\text{-iPr}_3\text{C}_6\text{H}_2)_2)_3]$: P. J. Brothers, K. Hübner, U. Hübner, B. C. Noll, M. Olmstead, P. P. Power, *Angew. Chem.* **1996**, *108*, 2528; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2355. Shorter In–In distances have also been established in the ternary oxide $\text{In}_{11}\text{Mo}_{40}\text{O}_{62}$ which contains linear In_3^{7+} and In_6^{8+} ions with In–In distances ranging between 2.624 and 2.689 Å.
- [9] The identical UV/Vis spectra of **5a** and **5b** (recorded in pentane) are characterized by two intense bands in the visible region corresponding

to the $\pi-\pi^*$ transition ($\lambda_{\text{max}} = 635 \text{ nm}$, $\lg \epsilon = 4.3$, vibrational progression towards lower wavelengths: 1310 cm^{-1}) and the $n-\pi^*$ transition ($\lambda_{\text{max}} = 444 \text{ nm}$, $\lg \epsilon = 4.7$) involving the N substituents.

- [10] Crystal data for **5a**: “[Me_3SiN]₄-perylene”: $\text{C}_{32}\text{H}_{46}\text{N}_4\text{Si}_4$, $M_r = 599.09$, monoclinic, space group $P2_1/c$, $a = 13.727(17)$, $b = 10.587(10)$, $c = 12.885(10) \text{ \AA}$, $\beta = 111.32(7)^\circ$, $V = 1744(3) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.141 \text{ g cm}^{-3}$, $F(000) = 644$, $\mu(\text{MoK}\alpha) = 0.197 \text{ mm}^{-1}$, $T = 293(2) \text{ K}$. All samples inspected diffracted extremely poorly. A dark green block ($0.72 \times 0.44 \times 0.32 \text{ mm}^3$) was mounted in a Lindemann tube for data collection with a Siemens P4 diffractometer. The structure was determined by direct methods and refined on F^2 for 1198 independent reflections of 2189 collected ($1.59 \leq \theta \leq 18.00^\circ$), $R(\text{int}) = 0.1955$. Anisotropic thermal parameters were assigned for all non-hydrogen atoms, and chemically equivalent bonds in the structure were constrained to common values. Hydrogen atoms were included in idealized positions and assigned $U_{\text{iso}} = 1.5 U_{\text{eq}}$ or $U_{\text{iso}} = 1.2 U_{\text{eq}}$ of the parent carbon atom for methyl groups and aromatic carbon atoms, respectively. The amino hydrogen was disordered over two sites of equal occupancy and assigned a fixed isotropic thermal parameter of $0.10 \text{ \AA}^2$. At final convergence $R_1 = 0.1063$, $wR_2 = 0.2020$ ($I > 2\sigma(I)$), $R_1 = 0.2421$, $wR_2 = 0.3195$ (all data), $\text{GOF} (F^2) = 1.053$ for 181 parameters. For programs, see reference [19]. Crystal data for **5b**: “[tBuMe_2SiN]₄-perylene”: $\text{C}_{44}\text{H}_{70}\text{N}_4\text{Si}_4$, $M_r = 767.40$, triclinic, space group $P1$, $a = 11.034(2)$, $b = 13.852(2)$, $c = 15.485(2) \text{ \AA}$, $\alpha = 84.411(8)$, $\beta = 79.200(10)$, $\gamma = 80.047(9)^\circ$, $V = 2284.5(6) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.116 \text{ g cm}^{-3}$, $F(000) = 836$, $\mu(\text{MoK}\alpha) = 0.164 \text{ mm}^{-1}$, $T = 198(2) \text{ K}$. A dark green block ($0.60 \times 0.50 \times 0.34 \text{ mm}^3$) was mounted in a Lindemann tube for data collection on a Siemens P4 diffractometer. The structure was determined by direct methods and refined on F^2 for 8055 independent reflections corrected for absorption ($T_{\text{max}} 0.954$, $T_{\text{min}} 0.532$) of 16109 collected ($1.34 \leq \theta \leq 25.00^\circ$), $R(\text{int}) = 0.0591$. Anisotropic thermal parameters were assigned for all non-hydrogen atoms. The asymmetric unit consists of the halves of two independent molecules each of which is exactly centrosymmetric. The two amino hydrogen atoms in the asymmetric unit were disordered over the four independent nitrogen atoms and were assigned half occupancy and a common isotropic thermal parameter which refined to $0.04 \text{ \AA}^2$. The remaining hydrogen atoms were included in idealized positions and assigned $U_{\text{iso}} = 1.2 U_{\text{eq}}$ of the parent carbon atom for methylene groups and aromatic hydrogen atoms, and $U_{\text{iso}} = 1.5 U_{\text{eq}}$ for methyl hydrogen atoms. At final convergence $R_1 = 0.0674$, $wR_2 = 0.1525$ ($I > 2\sigma(I)$), $R_1 = 0.1228$, $wR_2 = 0.1858$ (all data), $\text{GOF} (F^2) = 0.981$ for 490 parameters. For programs, see reference [19]. 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-101183. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+49)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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 [18] All attempts to observe diradical intermediates by performing the thermolysis in an ESR tube and subsequent quenching the reaction in liquid N_2 were unsuccessful. The use of spin-trapping reagents was precluded by the extremely high reactivity of **4**, which thermally and unspecifically reacted with the trapping agents prior to its thermolysis. Attempts to detect radical intermediates by NMR spectroscopy at different field strengths and temperatures through observation of a CIDNP effect were equally unsuccessful. These results either indicate the absence of a free radical species in the coupling reaction or, alternatively, their short-lived nature.
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The Behavior of $[\text{RAlX}_2 \cdot \text{THF}]$ Compounds under Reductive Conditions: Tetrakis[tris(trimethylsilyl)methylaluminum(III)]—A Neutral Aluminum(III) Compound with σ -Bound Alkyl Groups and a Tetrahedral Structure**

Christoph Schnitter, Herbert W. Roesky,* Cord Röpken, Regine Herbst-Irmer, Hans-Georg Schmidt, and Mathias Noltemeyer

Dedicated to Professor Bernt Krebs on the occasion of his 60th birthday

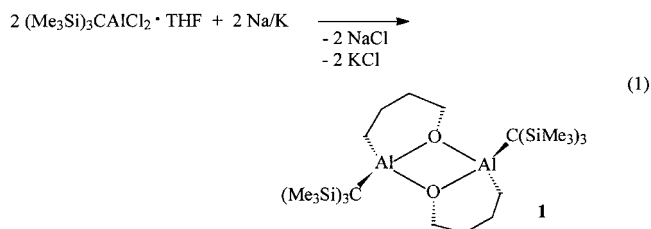
The great interest in low-valent compounds of the higher homologues of Group 13 is reflected in several recent reviews on this class of compounds.^[1] The first univalent aluminum compound that is stable at room temperature— $[\{\text{AlCp}^*\}_4]$, $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$, which contains π -bound C_5Me_5 groups—was synthesized and structurally characterized in 1991 by Schnöckel et al. It was prepared by the treatment of $(\text{AlCl})_x$ with $[\text{MgCp}^*]_2$.^[2] Somewhat later we reported a more facile synthesis of this compound: the reductive dehalogenation of $[\{\text{Cp}^*\text{AlCl}(\mu\text{-Cl})\}_2]$ with potassium.^[3] Despite many attempts, only two further neutral organoaluminum(III) compounds of type $[\{\text{AlR}\}_n]$ ($[\{\text{AlCH}_2\text{CMe}_3\}_4]$ ^[4a] and $[\{\text{AlSi}(\text{tBu})_3\}_4]$ ^[4b,c,e]) have been reported; this is due to the tendency of this type of compound to disproportionate into elemental aluminum and AlR_3 . The disproportionation reaction can be largely inhibited by the use of very bulky substituents. However, it has not as yet been possible to characterize these two compounds by diffraction methods.^[4c,e]

The tris(trimethylsilyl)methyl group (trisyl group) is regarded as a particularly bulky group with electronically stabilizing properties.^[5] The use of this substituent permitted the synthesis of the tetrameric compounds $[\{\text{MC}(\text{SiMe}_3)_3\}_4]$ of gallium,^[6] indium,^[7] and thallium.^[8] We recently reported the synthesis of the trisylaluminum dihalides $[\{(\text{Me}_3\text{Si})_3\text{AlF}_2\}_3]$ and $[(\text{Me}_3\text{Si})_3\text{AlX}_2 \cdot \text{THF}]$ ($\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$),^[9] which should be suitable precursors for the synthesis of low-valent trisylaluminum compounds.

We began our reduction experiments with the THF-free difluoride $[\{(\text{Me}_3\text{Si})_3\text{AlF}_2\}_3]$; however, it could not be dehalogenated, even with Na/K alloy in refluxing toluene. In contrast, the reaction of the THF-containing dichloride compound $[(\text{Me}_3\text{Si})_3\text{AlCl}_2 \cdot \text{THF}]$ with the appropriate reducing agent in toluene did not lead to the expected $[\{\text{AlC}(\text{SiMe}_3)_3\}_n]$, but to the tricyclic chiral compound **1** in high yields [Eq. (1)]. During the reductive dehalogenation the ring of the coordinated THF molecule had opened, which resulted in dimerization. Compound **1** is a colorless solid (m.p. 246°C) that was completely characterized by ^1H NMR, ^{29}Si NMR, and IR spectroscopy as well as by mass spectrom-

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etry, elemental analysis, and X-ray crystal structure analysis (Figure 1).^[10] It consists of a central four-membered Al_2O_2 ring, in which two oppositely positioned Al–O units are bridged by a C_4 chain. The distorted Al_2O_2 ring (Al–O–Al 99.9° , O–Al–O 77.9°) is not planar (average deviation

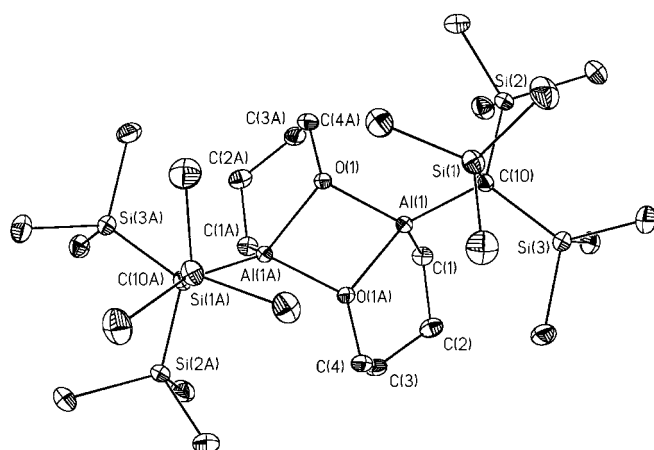
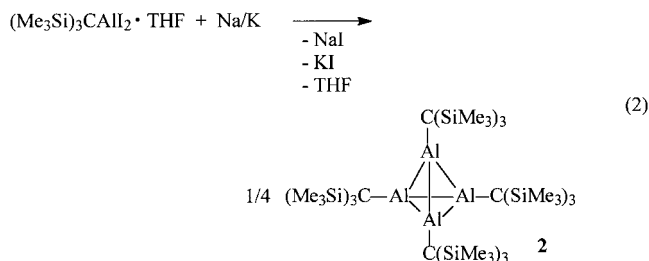


Figure 1. Crystal structure of **1** (thermal ellipsoids at the 50% probability level). The H atoms are omitted for clarity. Selected bond lengths [pm] and angles $^\circ$: Al(1)–C(1) 198.5(2), Al(1)–C(10) 202.4(2), Al(1)–O(1) 186.3(2), Al(1)–O(1A) 188.4(2), O(1A)–C(4) 145.6(2), C(1)–C(2) 154.1(3), C(2)–C(3) 152.4(3), C(3)–C(4) 151.0(3); C(1)–Al(1)–C(10) 116.2 (1), C(1)–Al(1)–O(1) 115.4(1), C(1)–Al(1)–O(1A) 96.6(1), C(10)–Al(1)–O(1) 115.4(1), C(10)–Al(1)–O(1A) 129.6(1), O(1)–Al(1)–O(1A) 77.9(1), Al(1)–O(1)–Al(1A) 99.9(1), Al(1)–O(1)–C(4A) 124.2(1), Al(1A)–O(1)–C(4A) 121.4(1).

from the best plane: 13.0 pm). The two Al–O–C₄ rings take up a *cis* conformation with an angle of 118.8° to the Al_2O_2 plane, which gives the molecule the appearance of a thumb screw. This is in contrast to the comparable other tricyclic compound known ($[\{\text{Trip-Al}(\mu\text{-O}(\text{CH}_2)_3\text{CH}_2)\}_2]$ (Trip = 2,4,6-*i*Pr₃C₆H₂),^[11] in which the Al_2O_2 ring is planar and the two Al–O–C₄ rings are *trans* to one another. The average Al–O distance in **1** (187.4 pm) is similar to the Al–O distances in the dimeric aluminum alkoxides $[\{\text{Me}_2\text{Al}(\mu\text{-O}t\text{Bu})\}_2]$ (186.4 pm),^[12a] $[\{t\text{Bu}_2\text{Al}(\mu\text{-O-2,6-Me}_2\text{C}_6\text{H}_3)\}_2]$ (187.2 pm),^[12b] and $[\{\text{Me}_2\text{Al}(\mu\text{-OCH}_2\text{-2,4,6-}i\text{Bu}_3\text{C}_6\text{H}_2)\}_2]$ (184.9 pm).^[12c] This result shows clearly the influence of the THF molecule in the reduction of the aluminum center.

As a result of the strongly decreasing aluminum–halogen bond energies in the series Al–F > Al–Cl > Al–Br > Al–I,^[13] the reductive dehalogenation of $[(\text{Me}_3\text{Si})_3\text{AlI}_2 \cdot \text{THF}]$ ^[9] should be more facile. The reaction of the diiodide in toluene with Na/K alloy (2 equiv) gave after workup $[\{\text{AlC}(\text{SiMe}_3)_3\}_4]$ (**2**) as orange platelets in yields of up to 24% [Eq. (2)]. So far,



we have only been able to unambiguously identify the side product $\text{HC}(\text{SiMe}_3)_3$, which is formed in low yields.

Compound **2** is thermally very stable and only starts to decompose at 282°C with a brown discoloration (for comparison: $[\{\text{AlCp}^*\}_4]$ decomposes at 205°C ,^[3] and $[\{\text{GaC}(\text{SiMe}_3)_3\}_4]$ decomposes at 255°C).^[6] In the EI mass spectrum, signals from $[\{\text{AlR}\}_n^+]$ ($n = 1-3$, $\text{R} = \text{C}(\text{SiMe}_3)_3$) are present along with the signal from the ion fragment $M - \text{R}$. This is in contrast to $[\{\text{GaC}(\text{SiMe}_3)_3\}_4]$, for which only the monomeric unit $[\text{GaC}(\text{SiMe}_3)_3]$ is observed.^[6] This indicates a successive decomposition of **2** in the gas phase. In the UV/Vis spectrum of **2**, the absorption band with the longest wavelength (418 nm with a shoulder at 444 nm) only has a slight hypsochromic shift with respect to that for the analogous gallium compound (435 nm). The ^1H and ^{29}Si NMR spectra of **2** each exhibit, in addition to the expected singlet, further singlets of lower intensity which could not be unequivocally assigned. It could not be ascertained whether these are due to impurities (oxidation products), in spite of repeated measurements (with variation of the concentration and the temperature) on different samples.^[14]

The crystal structure analysis^[15] of **2** showed the presence of an almost perfect tetrahedral Al_4 skeleton, with an average Al–Al–Al angle of 60.00° (Figure 2). The Al–Al bonds in the Al_4 cluster ($\bar{d} = 273.9$ pm) are shorter than those in both elemental aluminum (286 pm)^[16] and $[\{\text{AlCp}^*\}_4]$ ($\bar{d} = 276.9$ pm).^[2] However, they are somewhat longer than the

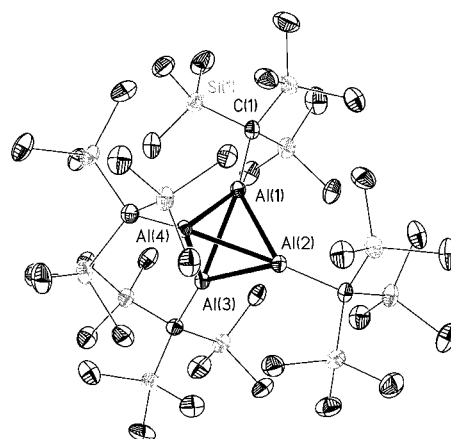


Figure 2. Crystal structure of **2** (thermal ellipsoids at the 50% probability level). The H atoms are omitted for clarity. Selected bond lengths [pm] and angles $^\circ$: Al(1)–Al(2) 274.7(2), Al(1)–Al(3) 274.5(2), Al(1)–Al(4) 273.3(2), Al(2)–Al(3) 273.5(2), Al(2)–Al(4) 274.7(2), Al(3)–Al(4) 273.0(2), Al(1)–C(1) 202.7(5), Al(2)–C(2) 202.8(5), Al(3)–C(3) 202.7(5), Al(4)–C(4) 203.1(5); Al–Al–Al 59.67(5)–60.36(5), Al–Al–C 144.2(2)–145.3(2).

Table 1. Properties of the tetrahedranes $[\{MC(SiMe_3)_3\}_4]$ ($M = Al, Ga, In, Tl$).

Compound	Color	$\bar{d}_{M-M}$ [pm]	$\bar{d}_{M-C}$ [pm]	$\angle_{M-M-M}$	M.p. [°C]	$\lambda_{max.}^{[a]}$ [nm]
2	orange	273.9	202.8	60.0	282 (decomp)	418 (444)
$[\{GaC(SiMe_3)_3\}_4]^{[6]}$	dark red	268.8	208	60.1	255 (decomp)	435
$[\{InC(SiMe_3)_3\}_4]^{[7]}$	black-violet	300.2	225	60.0	180 (decomp)	487 (570)
$[\{TlC(SiMe_3)_3\}_4]^{[8]}$	black	332.2–363.8	233–238	54.9–64.7	65 (decomp)	515

[a] UV/Vis band with the longest wavelength; shoulders at even greater wavelengths are given in brackets.

metal–metal distances in $[\{GaC(SiMe_3)_3\}_4]$ ($\bar{d} = 268.8$ pm)^[6] and in the compounds $[K_2\{Al_{12}tBu_{12}\}]$ ($\bar{d} = 268.5$ pm)^[17a] and $[R_2AlAlR_2]$ ($R = CH(SiMe_3)_2$) (266.0 pm) synthesized by Uhl et al.^[17b] The Al–Al distances in $[\{AlSiRtBu_3\}_4]$ ^[4b,c] were calculated by Ahlrichs et al. to be 263.8 pm.^[4d] That these Al–Al distances are markedly shorter than in **2** could be due to the Al–Si bonds in $[\{AlSiRtBu_3\}_4]$ (260 pm), which are longer than the Al–C bonds in **2** ($\bar{d} = 202.8$ pm), and the associated smaller ligand repulsion. This effect has already been observed for the only other two reported tetrahedral Ga₄ clusters, $[\{GaC(SiMe_3)_3\}_4]$ (Ga–Ga 268.8, Ga–C 208 pm)^[6] and $[\{GaSi(SiMe_3)_3\}_4]$ (Ga–Ga 258.4, Ga–Si 240.6 pm).^[18] However, the exchange of one carbon atom for a silicon atom should also have an electronic effect on the substituents. The average Al–C distance in **2** (202.8 pm) is somewhat larger than that in the starting material $[(Me_3Si)_3CAI_2 \cdot THF]$ (198.1 pm),^[9] but almost identical to that in $[(Me_3Si)_3-CAI_2Me_2 \cdot THF]$ (203.0 pm).^[19] Table 1 gives some physical and crystallographic data for **2** and the tetrahedranes $[\{MC(SiMe_3)_3\}_4]$ ($M = Ga, In, Tl$).

Compound **2** is the first neutral, crystallographically characterized aluminum cluster that contains σ -bound alkyl groups. The new compounds illustrate impressively that the THF ring can be opened and fixed to an aluminum center, and that it is moreover expedient to use THF–aluminum adducts for the reduction. The systematic investigation of RAI_2 compounds under reductive conditions should lead to the isolation of further aluminum clusters.

Experimental Section

All the reactions were carried out under N₂ in anhydrous solvents.

1: To Na/K alloy in toluene (20 mL), prepared from sodium (0.06 g, 2.61 mmol) and potassium (0.19 g, 4.86 mmol), was added dropwise at room temperature a solution of $[(Me_3Si)_3CAI_2 \cdot THF]$ (1.45 g, 3.61 mmol) in toluene (40 mL). The colorless solution was stirred for 2 d at room temperature and then heated at reflux for 2 h. The yellow solution was filtered through Celite and concentrated (10 mL), and pure **1** was obtained as colorless rods upon crystallization at -26°C ; yield: 0.86 g (72%). M.p. 246°C ; IR (Nujol, KBr): $\nu[\text{cm}^{-1}] = 1437$ (s), 1287 (m), 1262 (vs), 1250 (vs), 1121 (s), 1082 (m), 1021 (s), 998 (s), 924 (s), 888 (vs), 850 (vs), 807 (vs), 785 (s), 752 (s), 721 (s), 670 (vs), 654 (vs), 635 (s), 617 (m), 593 (s), 575 (s), 555 (vs); ¹H NMR (200.13 MHz, C₆D₆, 25°C , TMS): $\delta = 4.20$ – 3.85 (m, 4H, OCH₂CH₂CH₂CH₂Al), 2.20–1.75 and 1.35–1.20 (m, 8H, OCH₂CH₂CH₂CH₂Al), 0.80–0.40 (m, 4H, OCH₂CH₂CH₂CH₂Al), 0.39 (s, 54H, Si(CH₃)₃); ²⁹Si NMR (49.69 MHz, C₆D₆): $\delta = -4.4$; MS (EI): m/z (%): 660 ($[M^+]$, 5), 645 ($[M^+ - Me]$, 25), 429 ($[M^+ - C(SiMe_3)_3]$, 86), 315 ($[(M/2)^+ - Me]$, 100); elemental analysis calcd for C₂₈H₇₀Al₂O₂Si₆ (661.34): C 50.85, H 10.67; found: C 50.3, H 10.4.

2: To Na/K alloy in toluene (20 mL), prepared from sodium (0.04 g, 1.74 mmol) and potassium (0.13 g, 3.32 mmol), was added dropwise at room temperature a solution of $[(Me_3Si)_3CAI_2 \cdot THF]$ (1.46 g, 2.50 mmol) in toluene (30 mL). The colorless solution was stirred for 2 d at room

temperature and then heated at reflux for 4 h. The solvent was removed from the red-brown solution in vacuo, and the red-brown viscous residue taken up in *n*-hexane (15 mL). The mixture was filtered through Celite, the solvent removed in vacuo, and the dark orange residue recrystallized twice from toluene (10 mL) at 2°C to give pure **2** as orange platelets; yield: 0.16 g (24%). Single crystals suitable for X-ray diffraction analysis were obtained by recrystallization from diisopropyl ether at 2°C . Decomposition (under nitrogen) at 282°C . ¹H NMR (200.13 MHz, [D₈]toluene, 25°C , TMS): $\delta = 0.51$ (s, 4H), 0.49 (s, 12H), 0.42 (s, 1H), 0.41 (s, 1H), 0.40 (s, 1H); ¹³C NMR (100.60 MHz, C₆D₆, 25°C , TMS): $\delta = 17.13$, 8.06, 7.50, 6.98, 6.45, 6.34; ²⁹Si NMR (49.69 MHz, C₆D₆, 25°C , TMS): $\delta = -4.09$ (s), -4.16 (s), -4.55 (s), -6.37 (s); MS(EI): m/z : 801 ($[M^+ - C(SiMe_3)_3]$, 5), 774 ($[(3/4M)^+]$, 8), 516 ($[(M/2)^+]$, 35), 258 ($[(M/4)^+]$, 55), 201 ($[C(SiMe_3)_3^+ - 2Me]$, 100); IR (Nujol, CsI): $\nu[\text{cm}^{-1}] = 1261$ (vs), 1098 (s), 1018 (s), 863 (vs), 844 (vs), 800 (vs), 679 (m), 659 (m), 393 (m); UV/Vis (*n*-hexane): λ_{max} [nm] (ϵ) = 243 (shoulder, 31 000), 249 (shoulder, 39 000), 255 (49 000), 261 (54 000), 269 (52 000), 418 (3000), 444 (shoulder, 1600); elemental analysis calcd for C₄₀H₁₀₈Al₄Si₁₂ (1034.25): C 46.45, H 10.53; found: C 46.2, H 10.2.

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- Crystal structure analysis of **1**: C₂₈H₇₀Al₂O₂Si₆, $M_r = 661.34$, monoclinic, space group C2, $a = 1531.2(3)$, $b = 967.5(2)$, $c = 1457.7(3)$ pm, $\beta = 116.07(2)^\circ$, $V = 1.9398(7)$ nm³; $Z = 2$, $\rho_{\text{calcd}} = 1.132$ g cm⁻³, $F(000) = 728$, $\lambda = 71.073$ pm, $\mu(\text{MoK}\alpha) = 0.283$ mm⁻¹. The data were

recorded on a Stoe-Siemens-Huber four-circle diffractometer equipped with a Siemens SMART CCD area detector. The reflections were collected at -140°C on a shock-cooled crystal of dimensions $0.4 \times 0.3 \times 0.2\text{ mm}^3$ in a drop of oil^[20] with a $2\theta/\omega$ -scan in the range $5.0 \leq 2\theta \leq 49.6^{\circ}$. Of the 21552 observed reflections, 3333 were independent ($R_{\text{int}} = 0.033$). The structure was solved by direct methods (SHELXS-97)^[21] and refined against F^2 ^[22]. The hydrogen atoms were placed in ideal positions and refined with a riding model that allows the rotation of the methyl groups about their local axes; max./min. residual electron density after the final difference Fourier synthesis $207/-174\text{ e nm}^{-3}$, $R1 = 0.027$ ($I > 2\sigma(I)$) and $wR2 = 0.060$ (all data). The values of $R1$ and $wR2$ are defined as $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$; $wR2 = \{[\sum w(F_o^2 - F_c^2)^2] / [\sum w(F_o^2)^2]\}^{1/2}$. The absolute structure was determined by refinement of the Flack parameter^[23] to 0.0(1). A total of 181 parameters were refined.^[15b]

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TeS₂⁻ Radical Anions in CuBrCu_{1.2}TeS₂**

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*Dedicated to Professor W. H. E. Schwarz
on the occasion of his 60th birthday*

Copper(I) halides have recently proven to be "solid solvents" for molecules of the elements of Groups 15 and 16. Thus, neutral and low-charged phosphorus polymers were detected and structurally characterized in, for example, $(\text{CuI})_3\text{P}_{12}$ ^[1] and $(\text{CuBr})_{10}\text{Cu}_2\text{P}_{20}$.^[2] Compounds of copper(I) halides with selenium or tellurium contain neutral homoa-tomic chains, such as ${}^{\infty}[\text{Te}]$ in CuClTe_2 ,^[3] or six-membered rings, as in CuISe_3 .^[4] Heteroatomic chalcogen chains in which selenium and tellurium (${}^{\infty}[\text{SeTe}]$ ^[5]) or sulfur and tellurium atoms alternate (${}^{\infty}[\text{STe}]$ ^[6]) can also be obtained in a copper(I) halide matrix. In $\text{CuISe}_{1.93}\text{Te}_{1.07}$ tellurium-rich six-membered rings $\text{Se}_{6-x}\text{Te}_x$ ($x \leq 3$) were detected for the first time in the solid state.^[7] Degradation of the neutral chalcogen chains ${}^{\infty}[\text{STe}]$ led to $(\text{CuI})_3\text{Cu}_2\text{TeS}_3$, which is the first copper chalcogenide halide to contain a complex thiotellurate(IV) ion.^[8] Like $(\text{CuI})_2\text{Cu}_3\text{SbS}_3$,^[9] this compound can be described as a composite compound of copper(I) iodide and a copper thiometalate.

Here we report the preparation, crystal structure determination, and ESR spectroscopic investigations of $\text{CuBrCu}_{1.2}\text{TeS}_2$ (**1**). In this compound the novel $\text{TeS}_2^{\cdot-}$ radical anion and the unknown polychalcogenide ion $\text{TeS}_2^{\cdot-}$ were identified and structurally characterized. Compound **1** crystallizes as very thin, square or rectangular black platelets. Top illumination of the crystals indicates their tendency for twinning by a characteristic reflection pattern. Scanning electron micrographs of the edge of a broken platelet (Figure 1) show the pronounced two-dimensional character of the solid compound. The thickness of the single sheets is significantly smaller than $1\text{ }\mu\text{m}$. Nevertheless, the crystal structure could be determined.^[10] Figure 2a shows the three-dimensional structure of **1**. The copper atoms Cu4, which are located between the layers on a position with an occupancy of 20%, are omitted in order to emphasize the two-dimensional character of the structure. The layers are stacked along [001] and are made up of tetrahedrally coordinated copper atoms. The coordination polyhedra are $[\text{CuBr}_2\text{S}_2]$ for Cu1 and Cu2, and $[\text{CuS}_4]$ for Cu3. The Cu–S distances are $2.288\text{ }\text{\AA}$, and the Cu–Br distances $2.512\text{ }\text{\AA}$. The $[\text{CuS}_4]$ polyhedra are located in the center, and the $[\text{CuBr}_2\text{S}_2]$ polyhedra at the upper and lower borders of the layers. Further building blocks are bent TeS_2

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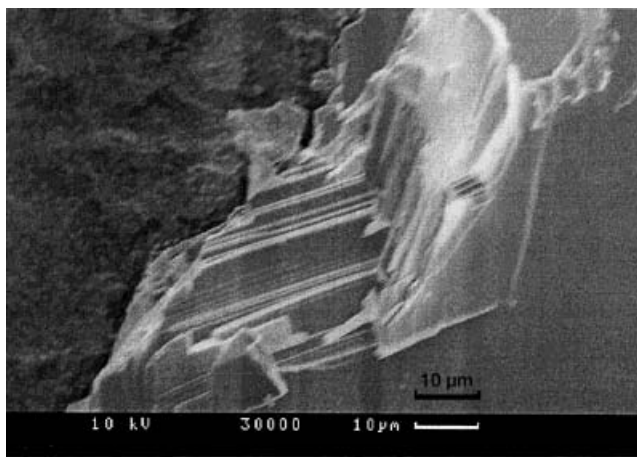


Figure 1. Scanning electron micrograph ($\times 1200$) of the edge of a broken platelet of **1**. The thickness of the layers is significantly smaller than $1\ \mu\text{m}$.

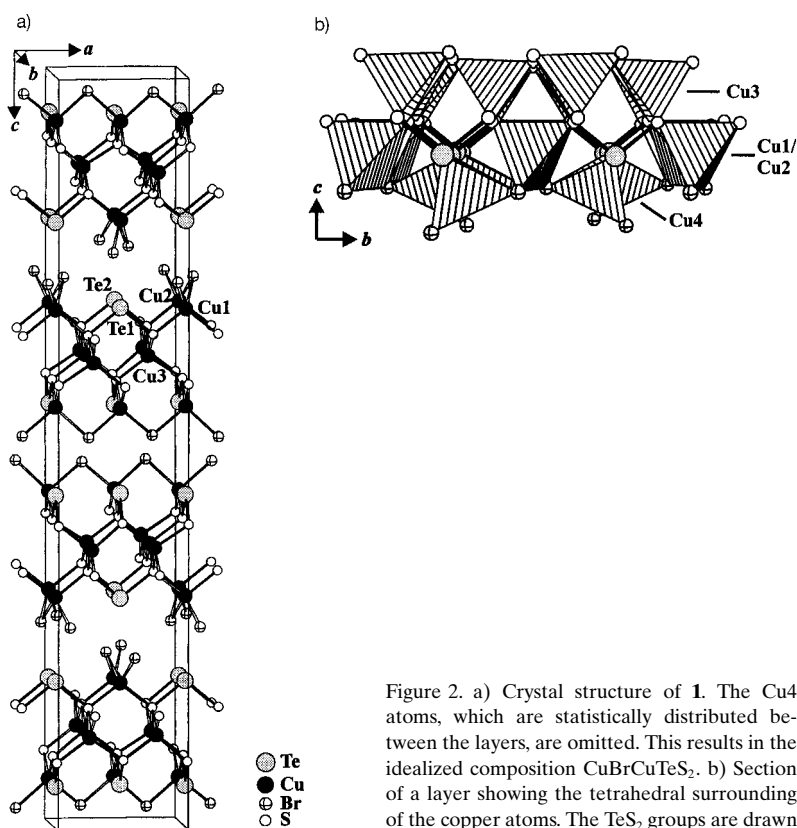


Figure 2. a) Crystal structure of **1**. The Cu4 atoms, which are statistically distributed between the layers, are omitted. This results in the idealized composition CuBrCuTeS_2 . b) Section of a layer showing the tetrahedral surrounding of the copper atoms. The TeS_2 groups are drawn in bold.

groups. Assuming a composition of CuBrCuTeS_2 (see Figure 2a) these groups bear a total charge of -1 ; that is, they are radical anions $\text{TeS}_2^{\cdot-}$.

However, the corresponding stoichiometric compound CuBrCuTeS_2 has not yet been obtained. The structure of **1** can be formally derived from this hypothetical compound by intercalating 0.2 copper atoms per formula unit between the layers. The resulting compound can be described as $(\text{CuBr})_5\text{Cu}_6[\text{TeS}_2]_4^{\cdot-}[\text{TeS}_2]^{2-}$. Despite the mixed-valent character, copper occurs exclusively as tetrahedrally coordinated Cu^+ ions. The $\text{TeS}_2^{\cdot-}$ and TeS_2^{2-} units cannot be distinguished

by X-ray diffraction data at room temperature. Two almost identical TeS_2 groups with Te–S distances of $2.375\ \text{\AA}$ are present in the crystal structure. The Te–S bond length is similar to those in the TeS_3^{2-} ions of $(\text{CuI})_3\text{Cu}_2\text{TeS}_3$,^[8] ACuTeS_3 , and AAgTeS_3 (A = alkali metal^[12]), but is about $0.11\ \text{\AA}$ shorter than that in the formally neutral chalcogen chains ($^1[\text{STe}]$) of CuXSTe (X = Cl, Br).^[6] This unexpected finding can be explained by the number of covalent S–Te bonds, that is, one per sulfur atom in TeS_2 and in TeS_3^{2-} , but two in $^1[\text{STe}]$. The average S–Te–S bond angle of 101.9° in $\text{TeS}_2^{\cdot-}$ is slightly larger than that of $^1[\text{STe}]$ and about $3\text{--}5^\circ$ larger than that of TeS_3^{2-} in $(\text{CuI})_3\text{Cu}_2\text{TeS}_3$. In contrast to the heteroatomic polychalcogenide ions $[\text{S}_x\text{Se}_{4-x}]^{2-}$ in $\alpha\text{-CsCu}(\text{S}_x\text{Se}_{4-x})$ and $[\text{S}_x\text{Se}_{6-x}]^{2-}$ in $\text{CsCu}(\text{S}_x\text{Se}_{6-x})$,^[13] the positions of the different chalcogen atoms in the TeS_2 groups can be clearly distinguished. Tellurium occupies exclusively the central position, whereas sulfur is located only at the terminal positions.

The crystal structure arrangement is responsible for the pronounced layer character of **1**. The $[\text{CuS}_4]$ groups are located in the center and the $[\text{CuS}_2\text{Br}_2]$ polyhedra at the borders of the layers. However, it is not possible to extend the layers to form a regular three-dimensional tetrahedral structure. Both sulfur and tellurium are coordinated to copper (Figure 2b), but tellurium occupies “cation sites” in the structure. As a consequence, the construction of a three-dimensional tetrahedral structure is terminated at the tellurium positions (Figure 2b).

The novel anion $\text{TeS}_2^{\cdot-}$ is a further member of the large group of triatomic radicals with 19 valence electrons and a $^2\text{B}_1$ ground state.^[14] Other relatively stable compounds that predominantly consist of light atoms are the radicals $\text{ClO}_2^{\cdot-}$ ^[15] and $\text{SO}_2^{\cdot-}$ ^[16] (which is in equilibrium with $\text{S}_2\text{O}_4^{2-}$) as well as the homologous radicals $\text{SeO}_2^{\cdot-}$,^[17] $\text{NO}_2^{\cdot-}$,^[18] $\text{NF}_2^{\cdot-}$,^[19] the ozonide ion $\text{O}_3^{\cdot-}$,^[20] and the deep blue $\text{S}_3^{\cdot-}$ ion^[21] (a component of lapis lazuli^[22]). A survey of ESR investigations of this class of radicals, including a discussion of correlations and an estimation of the participation of d orbitals, has been already published.^[14]

A powder sample of **1** was investigated at $3.5\ \text{K}$ in an X-band ESR spectrometer. An intense signal was observed with axial splitting of the g components within the limits of the linewidth (Figure 3, Table 1). Hyperfine splitting could not be detected.^[23] Owing to very fast relaxation, the ESR signal broadens at higher temperature and is no longer visible. A similar observation was made for the main group radical $\text{B}_6\text{I}_6^{\cdot-}$,^[24] which is similar to $\text{TeS}_2^{\cdot-}$ in that a 5p element with numerous available atomic states participates in the spin distribution.

$\text{SeO}_2^{\cdot-}$, a lighter homologue of $\text{TeS}_2^{\cdot-}$, also shows an almost axial splitting of the g components with $g_1 \gg g_2, g_3$; a similar pattern was observed for $\text{O}_3^{\cdot-}$ (Table 1). As expected, the deviation of g_1 from the free electron value of 2.0023 and the g anisotropy $\Delta g = g_1 - g_3$ increase when light atoms are sub-

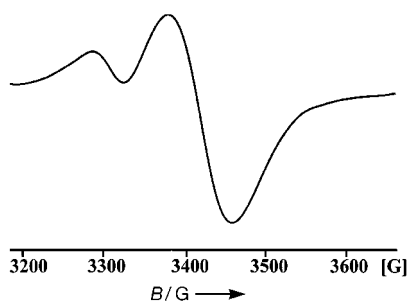


Figure 3. ESR spectrum of $\text{CuBrCu}_{12}\text{TeS}_2$ at 3.5 K and 9.64281 GHz.

Table 1. ESR data of radicals with 19 valence electrons.

	g_1	g_2/g_3	$(g_{\perp})$	$\Delta g = g_1 - g_3$	T [K]	Ref.
O_3^-	2.0174	2.0025/2.0013	(2.0019)	0.0161	77	[20]
SeO_2^-	2.0317	2.0066/1.9975	(2.0021)	0.0342	77	[17]
TeS_2^-	2.0804	2.0085/2.0085 ^[a]	(2.0085)	0.0719	3.5	this work

[a] g_2 and g_3 can differ by at most 0.01.

stituted by heavier homologues with much higher spin–orbit coupling constants (Table 1).^[14, 17] Since a major part of the spin density of, for example, SeO_2^- is located at the central atom, g_1 and Δg are significantly higher when tellurium is present instead of selenium. The results of the ESR investigations (Figure 3), including the considerable linewidth and the fast relaxation, are in accord with the structural identification of TeS_2^- . Thus, a new example has been added to this group of well-known inorganic radicals.

Experimental Section

$\text{CuBrCu}_{12}\text{TeS}_2$ (**1**) was prepared by the reaction of stoichiometric amounts of CuBr, Cu, Te, and S in the ratio 1:1.2:1:2 in evacuated silica ampoules. The mixture of starting materials was melted at 600 °C, homogenized by grinding, and then tempered at 390 °C. Black, shiny square or rectangular platelets were obtained together with a microcrystalline powder after 14 d. The purity and the sample quality was checked by X-ray powder diffraction. Microcrystalline samples with the composition $\text{CuBrCu}_{12}\text{TeS}_2$ were investigated at 3.5 K with an Bruker ESP300 X-band ESR spectrometer. The composition of selected single crystals was determined by semi-quantitative energy dispersive X-ray analysis (EDX): found: Cu:Br:Te:S = 0.350:0.169:0.158:0.324 (calcd: 0.355:0.161:0.161:0.322).

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Rapid Phosphodiester Hydrolysis by Zirconium(IV)

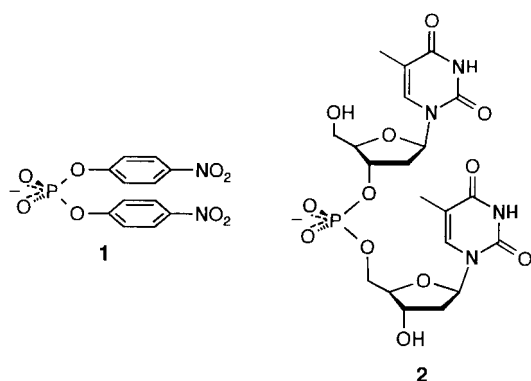
Reina Ott and Roland Krämer*

Nonenzymatic hydrolysis of the phosphodiester backbone of nucleic acids is an attractive research aim in molecular biology. Bioconjugates of hydrolytically active metal complexes and antisense-oligonucleotides may have important applications as artificial restriction enzymes since they have much greater sequence-specificity than their natural counterparts.^[1] In addition, the treatment of incurable diseases by the in-vivo silencing of the genetic code of pathogenic proteins on the RNA or DNA level has been attempted.^[2] RNA is more susceptible to hydrolysis than DNA and various low molec-

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ular weight cleaving agents are available for this. The efficient hydrolysis of linear DNA^[3] under mild conditions is possible with Ce^{IV}, a hard Lewis acid with a high charge/size ratio that will strongly activate the phosphate group. Heterogeneous systems (Ce^{IV}–hydroxide gels) are particularly efficient and accelerate the rate of DNA cleavage up to 10¹¹ fold at pH 7 and 30 °C.^[4, 5a] Homogeneous Ce^{IV} solutions also display high reactivity. Other metal ions, for example trivalent lanthanides, hydrolyze linear DNA either very slowly or only at high temperature.^[6] A disadvantage of Ce^{IV} compounds in potential applications in molecular biology is their sensitivity to reduction (formation of Ce^{III}). While many studies on phosphodiester hydrolysis by middle and late transition metal ions have been reported, little is known about the d⁰ ions of the early transition metals. No evidence of Zr^{IV} compounds having outstanding reactivity has so far been discussed.^[7]

We have investigated the hydrolysis of the “activated” phosphodiester bis(*p*-nitrophenyl)phosphate **1**. Cleavage of **1**



is monitored spectrophotometrically by the release of *p*-nitrophenol in weakly acidic solutions ($\lambda_{\text{max}} = 317 \text{ nm}$, $\epsilon = 10000 \text{ M}^{-1} \text{ cm}^{-1}$). The pH-dependence of the hydrolysis of **1** in the presence of excess ZrCl₄ at 20 °C is shown in Figure 1.

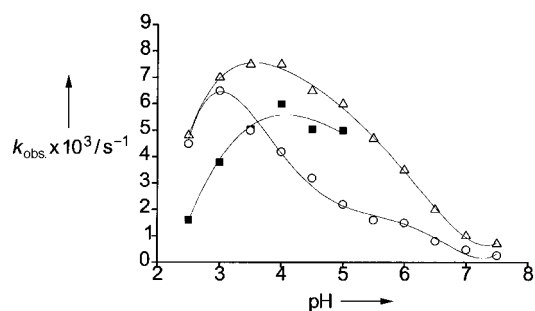


Figure 1. The pH-dependence of the hydrolysis of **1** in the presence of 5 mM ZrCl₄ (■), 5 mM ZrCl₄ + 5 mM **1** (○), 5 mM ZrCl₄ + 10 mM **1** (△). Conditions: H₂O, (20 ± 0.5) °C, 2 × 10^{−5} M **1**. The data are average values of two measurements with a reproducibility within 20 %.

Kinetic studies were carried out in unbuffered, aqueous solutions since the metal salt solutions themselves have sufficient buffer capacity. Maximum reactivity is observed at pH 4; at a pH greater than 5 zirconium hydroxide is formed. The Zr^{IV}-mediated hydrolysis of **1** is 5 × 10⁸ times faster than the spontaneous hydrolysis at pH 7 and 25 °C ($k = 10^{-11} \text{ s}^{-1}$).^[8] Conclusions on the reaction mechanism are not possible from

the pH–rate constant profile. The chemistry of aqueous ZrCl₄ solutions is complicated, and governed by the formation of cationic polynuclear polyhydroxo species.^[9] Nucleophilic attack of the Zr-coordinated hydroxide to the P atom of the coordinated phosphodiester is likely since [Zr(OH)]³⁺ species form at a pH less than 1. The first-order rate constant (k_{obs}) for the reaction of **1** to the monoester *p*-nitrophenylphosphate and nitrophenol was determined from the initial rate of reaction (<10% conversion). *p*-Nitrophenylphosphate is cleaved to phosphate and *p*-nitrophenol at a similar rate ($k_{\text{obs}} = 3.4 \times 10^{-3} \text{ s}^{-1}$). In the determination of k_{obs} for the hydrolysis of **1** the release of *p*-nitrophenol from the monoester was ignored.

Additionally, the cleavage rate of **1** was investigated at various ZrCl₄ concentrations. Michaelis–Menten behavior is observed as shown by a linear relationship between 1/ ν and 1/[ZrCl₄] (Figure 2). From Figure 2 the cleavage rate for the

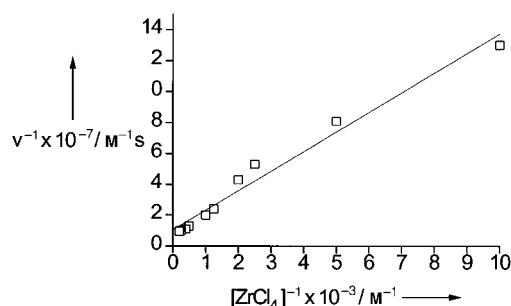


Figure 2. Relationship between the reciprocal rate (1/ ν) of the hydrolysis of **1** and the reciprocal concentration of ZrCl₄. Conditions: H₂O, pH 3.5, (20 ± 0.5) °C, 2 × 10^{−5} M **1**. The data are average values of two measurements with a reproducibility within 20 %.

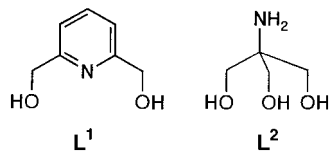
Zr-coordinated phosphodiester **1** ($k_{\text{cat}} = 4.9 \times 10^{-3} \text{ s}^{-1}$ (20 °C, pH 3.5)), and the Michaelis constant K_{M} , whose reciprocal value 1/ $K_{\text{M}} = 770 \text{ M}^{-1}$ corresponds to the formation constant of the **1**–Zr complex, were determined. Application of the Michaelis–Menten law implies a fast equilibration occurs in the formation of the complex between Zr and **1**. The coordination chemistry of the zirconium(IV) ion is determined by fast ligand-exchange kinetics.^[9] To confirm this an NMR study was performed using the less reactive dimethylphosphate derivative; after several hours virtually no hydrolysis was observed. In a D₂O solution containing ZrCl₄ (10 mM) and dimethylphosphate (2 mM) at pH 3.5 a broad CH₃ signal of coordinated dimethylphosphate ($\delta = 3.7$) and a sharp signal of small intensity for free dimethylphosphate ($\delta = 3.52$) are observed after approximately 30 s. The equilibrium ratio of complexed to uncomplexed dimethylphosphate is in the range expected from the stability constant of the **1**–Zr complex. The relative intensities of the signals remain unchanged even after several hours. Thus, thermodynamic equilibrium is also reached after 30 s.^[10]

When substrate **1** is added in excess the initial hydrolysis rate is still high, but a deviation from Michaelis–Menten behavior is apparent. For [ZrCl₄] = 10^{−4} M and [**1**] = 4 × 10^{−4} M at pH 3.5 and 20 °C the rate of *p*-nitrophenol release is $\nu = 6 \times 10^{-8} \text{ M s}^{-1}$ (expected: $\nu = 11 \times 10^{-8} \text{ M s}^{-1}$). Catalytic turnover is

not observed. After the release of one equivalent of *p*-nitrophenol per zirconium ion the reaction rate is very slow, possibly because of the formation of unreactive zirconium(IV) phosphate complexes. A noticeable decrease in the reaction rate in the presence of excess substrate was also described for the hydrolysis of **1** with lanthanide(III) ions.^[11]

Kinetic investigations with Ce^{IV} salts under the same conditions are complicated by the intense UV absorption of the metal center. Recent studies on aqueous micellar solutions of Ce^{IV} and Th^{IV} salts have confirmed that **1** is hydrolyzed much faster ($k \approx 2 \times 10^{-2} \text{ s}^{-1}$ at 37 °C) than by transition metal or lanthanide(III) salts.^[12] The reactivity of ZrCl₄ at 37 °C ($k_{\text{obs}} = 1.3 \times 10^{-2} \text{ s}^{-1}$) is comparable to those of the micellar Ce^{IV} and Th^{IV} systems.

Carboxylate-containing ligands such as ethylenediamine-tetraacetate (EDTA) form stable 1:1 complexes with Zr^{IV} ions at neutral pH, but they quench reactivity.^[11] In contrast, with the amino alcohols 2,6-bis(hydroxymethyl)pyridine (**L**¹) and especially with tris(hydroxymethyl)aminomethane (**L**²) high reactivity is retained in weakly acidic solutions. ¹H NMR



spectra were recorded of D₂O solutions containing **L**¹ and ZrCl₄ under the conditions of the kinetic experiments (pH 4.0, 5 mM ZrCl₄). For **L**¹:Zr ratios of 0.5:1 and 1:1 broad signals

of the coordinated ligand are observed at $\delta = 8.1$ (py-H4), 7.3 (d, py-H3,5), and 5.6 (s, CH₂) (py = pyridine). At a **L**¹:Zr ratio of 2:1 the excess **L**¹ does not coordinate and is present in its protonated form ($\delta = 8.5$ (py-H4), 7.9 (d, py-H3,5), and 5.0 (s, CH₂)). ¹H NMR data indicate formation of a complex containing one equivalent of **L**¹ per zirconium ion although oligomerization by formation of hydroxo- or alkoxo-bridged complexes cannot be excluded. The significant decrease of the reactivity of the complexes at high pH may be a result of aggregation (Figure 1).

The complex derived from **L**² forms homogeneous solutions up to pH 6 and pH 8 with one and two equivalents of **L**², respectively, while in the absence of the ligand precipitates are formed in a ZrCl₄ solution (5 mM) at pH > 5.0. Addition of one equivalent of **L**² to the ZrCl₄ solution causes a significant increase in the reactivity (Figure 1), but no further change in the reactivity is apparent on addition of a second equivalent of **L**². This indicates formation of a 1:1 complex. Even with an excess of **L**² only one CH₂ signal is seen in the ¹H NMR spectrum, a consequence of the exchange between the free and coordinated **L**² being fast on the NMR timescale. The observation that the dialcohol 2-amino-1,3-propanediol neither prevents the formation of zirconium hydroxide precipitates nor affects the reactivity of the complex suggests that **L**² is bound as a tridentate *O,O,O*-chelating ligand. Solutions of Ce^{IV} salts are not stabilized by **L**¹ and **L**² at pH > 4.

Hydrolysis of the phosphodiester linkage in the DNA-dinucleotide thymidylyl(3' → 5')thymidine (**2**) by ZrCl₄ (5 mM) was analyzed by quantification of the reaction products by reversed-phase HPLC (Figure 3). While **2** is cleaved into two equivalents of thymidine and phosphate, only trace amounts of the intermediates thymidine 3'phosphate and thymidine 5'-

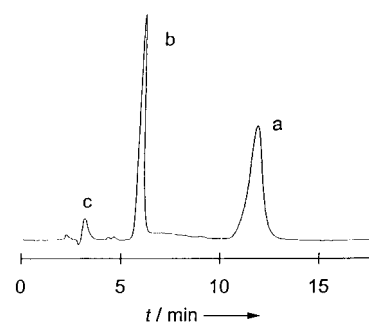


Figure 3. HPLC elution profile of an aqueous solution of **2** (10^{-4} M) in the presence of ZrCl₄ (5 mM) and **L**² (10 mM) after 440 h at pH (5.5 ± 0.1) and (20 ± 0.5) °C. a) **2**; b) thymidine; c) thymidine-3' phosphate and thymidine-5' phosphate.

phosphate are detectable owing to rapid monoester hydrolysis. At pH 3.0 and 20 °C, where the initial rate of the reaction was constant at less than 15 % conversion, $k_{\text{obs}} = (1.4 \pm 0.3) \times 10^{-7} \text{ s}^{-1}$. The DNA-dinucleotide **2** is converted into thymidine and phosphate a little faster by (NH₄)₂Ce^{IV}(NO₃)₆ ($k_{\text{obs}} = 2.0 \pm 0.4 \times 10^{-7} \text{ s}^{-1}$). Considering the strong temperature dependence of the Ce^{IV}-mediated cleavage,^[4c] this value is comparable to literature data for the hydrolysis of **2** by homogeneous Ce^{IV} solutions.^[5a]

The Zr^{IV} complex of **L**² (5 mM ZrCl₄, 10 mM **L**²) hydrolyzes **2** with $k_{\text{obs}} = (2.9 \pm 0.4) \times 10^{-7} \text{ s}^{-1}$ at pH 5.5 and 20 °C, a rate that corresponds to a half-life of 28 days. The zirconium-mediated hydrolysis proceeds 3×10^9 times faster than the spontaneous hydrolysis of the DNA – phosphodiester linkage at pH 7 and 25 °C with an estimated k_{obs} of 10^{-16} s^{-1} .^[8] Under physiological conditions (pH 7.0, 37 °C) we have determined $k_{\text{obs}} = (1.3 \pm 0.2) \times 10^{-7} \text{ s}^{-1}$.

In conclusion, Zr^{IV} salts and Zr^{IV} complexes display high reactivity toward activated and nonactivated phosphodiester in weakly acidic, homogeneous solution and an efficiency similar to that of Ce^{IV} compounds. In potential applications in molecular biology nonredox-active Zr^{IV} compounds should be an alternative to the reduction-sensitive Ce^{IV} ion.

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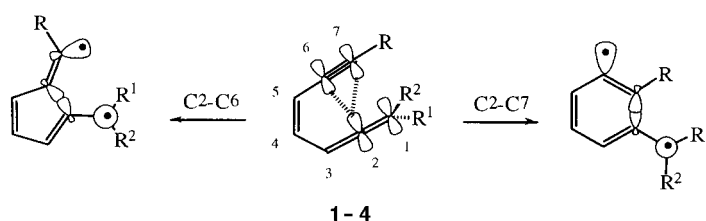
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Regioselectivity of Biradical Cyclizations of Enyne-Allenes: Influence of Substituents on the Switch from the Myers–Saito to the Novel C^2 – C^6 Cyclization**

Bernd Engels,* Christian Lennartz, Michael Hanrath, Michael Schmittel,* and Marc Strittmatter

The Myers–Saito C^2 – C^7 cyclization of enyne-allenes^[1] has recently received a lot of attention owing to the involvement of the $\alpha,3$ -didehydrotoluene biradicals (Scheme 1) in DNA-cleavage reactions^[2] and subsequent reactions of synthetic interest.^[3]

The synthetic potential of thermal enyne-allene reactions was extended when Schmittel and co-workers found a complete switch from the Myers–Saito C^2 – C^7 cyclization to



Scheme 1. Thermal reaction of enyne-allenes: C^2 – C^6 cyclization (left) and Myers–Saito C^2 – C^7 cyclization (right). **1**: R = H, **2**: R = Ph, **3**: R = *t*Bu, **4**: R = NH_2 ; $\text{R}^1 = \text{R}^2 = \text{H}$.

a C^2 – C^6 cyclization (Scheme 1).^[4] For different groups R^1 and R^2 , the new C^2 – C^6 cyclization takes place if the terminal hydrogen atom of the alkyne group (R = H) is replaced by an aryl group (R = Ph) or by sterically bulky groups (e.g., R = *t*Bu, SiMe_3). Later Gillmann et al.^[5] and Rodriguez et al.^[6] found a similar reaction switch, which indicates that the new C^2 – C^6 cyclization constitutes a general reaction motif.

As indicated on the right-hand side of Scheme 1, the rate-determining step of the Myers–Saito reaction is the formation of a (σ, π) biradical. Experimental studies^[7, 8] on the new C^2 – C^6 cyclization (shown on the left-hand side of Scheme 1) also suggest that biradical formation is the rate-determining step, but the final proof for a biradical intermediate was missing so far. Although the switch from the C^2 – C^7 to the C^2 – C^6 cyclization is experimentally well established, the reasons are still unclear.

In the present investigation quantum-chemical calculations^[9] address for the first time the regioselectivity of biradical cyclizations in enyne-allenes with different substituents—namely, R = H (**1**), Ph (**2**), *t*Bu (**3**), and NH_2 (**4**)—at the alkyne terminus (with $\text{R}^1 = \text{R}^2 = \text{H}$). In addition, the hitherto postulated biradical intermediate of the C^2 – C^6 cyclization could be trapped by hydrogen transfer, thus providing the most direct proof of its biradical nature.

The theoretical results are summarized in Table 1, and the optimized geometrical structures of the reactants and of the transition states are shown in Figure 1. We will first compare

Table 1. Summary of the theoretical data. Energy differences are given with respect to the reactants (in kcal mol^{-1}). Thermochemical corrections were made at a temperature of 298 K.

		R =			
		H	Ph	<i>t</i> Bu	NH_2
C^2–C^7 cyclization					
TS ^[a]	$R_{\text{C}^2-\text{C}^7}$ ^[c]	2.07	2.06	2.07	2.08
	ΔE^*	22.4	28.0	29.0	20.9
	ΔH^*	21.4	26.7	27.9	19.8
	ΔG^*	24.0	29.8	31.1	22.7
product ^[b]	$R_{\text{C}^2-\text{C}^7}$ ^[c]	1.43	1.41	–	1.50
	ΔE_{r}	–21.3	–23.3	–	–34.7
C^2–C^6 cyclization					
TS ^[a]	$R_{\text{C}^2-\text{C}^6}$ ^[c]	1.90	1.96	1.90	2.13
	ΔE^*	30.8	27.2	33.0	16.9
	ΔH^*	29.0	25.1	31.4	15.4
	ΔG^*	31.4	28.7	33.3	17.8
product ^[b]	$R_{\text{C}^2-\text{C}^6}$ ^[c]	1.51	1.50	–	1.47
	ΔE_{r}	12.0	1.3	–	–37.0

[a] DF(B3LYP) in combination with a 6-31G* basis set. TS = transition state. [b] MR-CI in combination with a DZP basis set. [c] Distance in Å.

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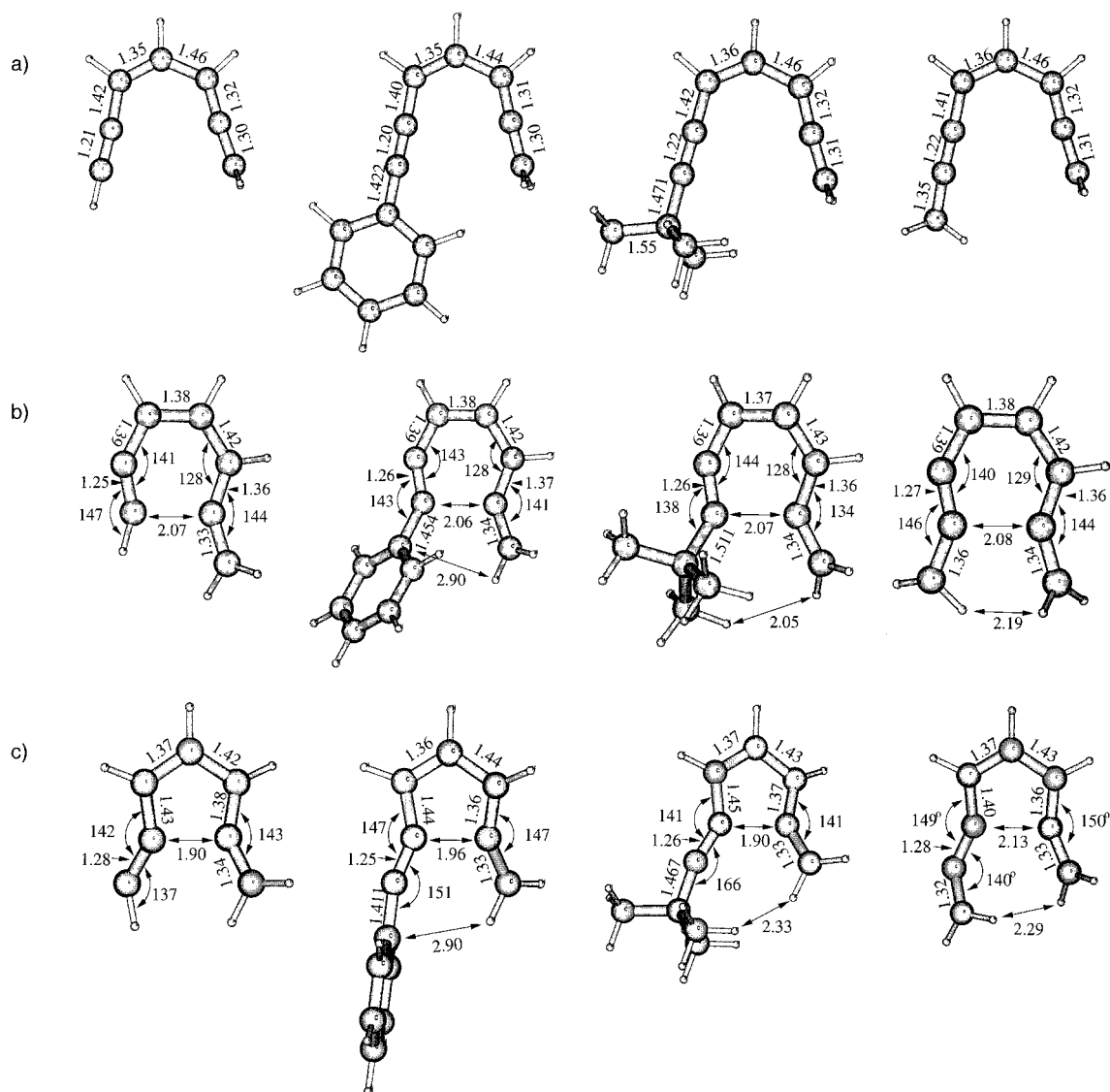
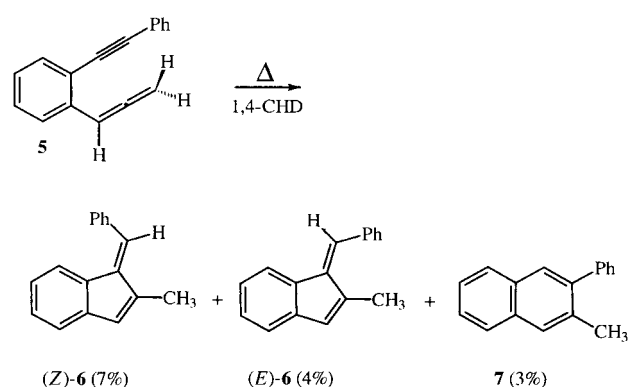


Figure 1. Geometry-optimized (DFT/6-31G*) structures of the reactants of the thermal biradical cyclization of the enyne-allenes **1–4**. a) Reactants; b) transition states for the Myers–Saito reaction; c) transition states for the new C²–C⁶ cyclization. Selected distances [Å] and angles [°] are given.

the results for **1** (R = H) and **2** (R = Ph).^[10] While the activation energy of the C²–C⁷ cyclization increases by about 6 kcal mol^{–1} if the terminal hydrogen atom in **1** is replaced by a phenyl ring (**2**), the activation energy of the C²–C⁶ cyclization falls by about 3 kcal mol^{–1}. As a result, the computed reaction barrier to the C²–C⁶ cyclization for **2** ($\Delta G^\ddagger \approx 29$ kcal mol^{–1}) is somewhat smaller than that of the C²–C⁷ cyclization ($\Delta G^\ddagger \approx 30$ kcal mol^{–1}).

The calculated slight preference for the C²–C⁶ cyclization was confirmed experimentally by the thermolysis of the novel enyne-allene **5** (Scheme 2). When **5** was heated for 18 h in neat 1,4-cyclohexadiene, the benzofulvene derivatives (*Z*)-**6** (7%) and (*E*)-**6** (4%) were formed along with the C²–C⁷ cyclization product **7** (3%). Clearly (*Z*)-**6** and (*E*)-**6** are both derived from the corresponding fulvene biradical (Scheme 1) through hydrogen abstraction, which constitutes the strongest proof thus far for the biradical nature of the C²–C⁶ cyclization.

An analysis of the theoretical data reveals that the differences in the activation energies between **1** and **2** result from



Scheme 2. Preferential formation of the products during the thermolysis of **5**. 1,4-CHD = 1,4-cyclohexadiene.

electronic interactions between the alkyne group and the phenyl ring. The bond distance between C⁷ and the phenyl ring in **2** is 1.422 Å. In the transition state of the C²–C⁷ cyclization this bond is elongated to 1.454 Å, while it is

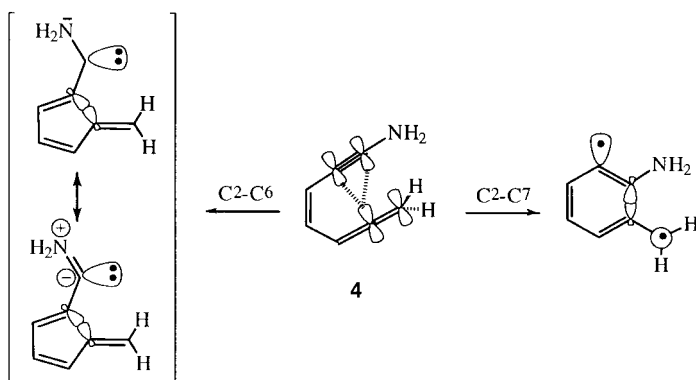
shortened to 1.411 Å in the transition state of the C²–C⁶ cyclization. This indicates that the mesomeric interaction between the alkyne group and the phenyl ring strengthens along the reaction path of the C²–C⁶ cyclization, but weakens along the Myers–Saito pathway. Clearly a stabilization of the emerging radical center through mesomeric interactions at the alkyne terminus is only possible for the C²–C⁶ cyclization, where the vinyl radical center develops in the position α to the phenyl ring. No mesomeric stabilization between the radical center and the phenyl group is possible in the C²–C⁷ cyclization.

Steric interactions are unimportant in both cyclizations of **2** (R¹ = R² = H), because in both transition states the orientation of the phenyl ring permits large distances between the two terminal groups (Figure 1b, c). However, since the experimental preference for the C²–C⁶ cyclization of substituted enyne-allenes (R¹, R² ≠ H) is much more pronounced than in **2**,^[4] steric effects between the substituents of the alkyne and allene termini are apparently relevant.

Indeed, steric effects can be detected by calculations in a comparison of the cyclization of **1** (R = H) and **3** (R = *t*Bu). Substitution of H by *t*Bu leads to an increase in the activation energies of both reactions. Although the increase for the C²–C⁷ cyclization (ca. 7 kcal mol^{–1}) is much larger than for the C²–C⁶ cyclization (ca. 2 kcal mol^{–1}), the C²–C⁷ cyclization still possesses a smaller activation energy. At first this finding seems to contradict the experimental results, as the switch from the C²–C⁷ to the C²–C⁶ cyclization is experimentally well documented with *t*Bu groups.^[11] The geometries of the transition states of the reactions of **3** rationalize this behavior on the basis of differential steric effects. In line with strong steric interactions in the C²–C⁷ cyclization, the allene unit is increasingly bent in the transition state from 144° (**1**) to 141° (**2**) to 134° (**3**). Similarly, the bending of the alkyne terminus is increased from 147° (**1**) to 143° (**2**) to 134° (**3**). This shows that both terminal groups repel each other for R = *t*Bu.

In contrast, the geometrical parameters of the transition state of the C²–C⁶ cyclization clearly indicate that the steric interactions are weaker than in the C²–C⁷ cyclization. Therefore, on the basis of the smaller distance between the repelling alkyne and allene substituents in the C²–C⁷ cyclization than in the C²–C⁶ cyclization, the introduction of bulky substituents at the allene terminus is expected to raise the activation energy of the C²–C⁷ cyclization above that of the C²–C⁶ cyclization. Our findings agree with new results of Gillmann et al., who showed that the switch from the C²–C⁷ cyclization to the C²–C⁶ cyclization takes place only if both the alkyne and the allene terminus possess bulky substituents.^[12] Electronic effects, as discussed for R = Ph, also seem to increase the barrier to the C²–C⁷ cyclization. This can be seen from the bond between the alkyne group and the substituent (*t*Bu), which is elongated by about 0.04 Å on going from the reactant to the transition state of the C²–C⁷ cyclization.

The reaction energies (ΔE_r) have been calculated for both cyclization pathways of **1** and **2**.^[13] Notably, for both substituents at the alkyne terminus the C²–C⁷ cyclization is favored thermodynamically over the C²–C⁶ cyclization, which indicates that the switch from the C²–C⁷ cyclization to the C²–C⁶ cyclization is kinetically controlled.



Scheme 3. The intermediates in the C²–C⁶ (left) and C²–C⁷ cyclization (right) of **4**.

To test the influence of increasing mesomeric interaction on the activation energy, the cyclization of **4** (R = NH₂) was investigated. Interestingly, the activation energy for the C²–C⁶ cyclization is reduced by about 17 kcal mol^{–1}, while the activation energy of the C²–C⁷ cyclization is only lowered about 1 kcal mol^{–1}. In addition, both cyclizations become strongly exothermic, with ΔE_r = –37 kcal mol^{–1} for the C²–C⁶ cyclization and –34 kcal mol^{–1} for the C²–C⁷ cyclization. The reasons for the drastic changes are outlined in Scheme 3 and Figure 1b, c. Because of the influence of the substituent NH₂, the product of the C²–C⁶ cyclization no longer is a biradical, but a carbene in which the C²–C⁷–N plane is rotated by about 40° toward the fulvene plane. The planarity at the NH₂ group is indicative of strong mesomeric interactions between the lone pair of the NH₂ group and the p orbital localized at the C⁷ center, which lies perpendicular to the doubly occupied orbital at the same center (a'' symmetry). In contrast, the intermediate of the C²–C⁷ cyclization is still a biradical. The change in the value of ΔE_r for the C²–C⁷ cyclization results from mesomeric interactions between the NH₂ group and the benzene ring.

Our study rationalizes the switch between the two biradical cyclizations on the basis of mainly steric (R = *t*Bu) or electronic effects (R = Ph). Moreover, the results for R = NH₂ predict that the activation energy of the C²–C⁶ cyclization can be reduced even further. However, a change in the reaction mechanism is found. An experimental verification of this prediction is currently being undertaken.

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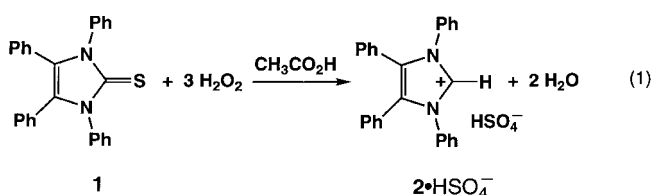
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- [9] A correct description of biradical intermediates needs a multireference configuration interaction (MR-CI) approach. However, because the biradical nature of the wavefunction develops after the transition state—that is, in the density functional theory (DFT) calculations $\langle S^2 \rangle = 0$ was found for all transition states (B. Engels, M. Hanrath, *J. Am. Chem. Soc.*, in press)—the influence of substituents on the activation energy of both processes can be obtained from less demanding DFT calculations. Consequently, in the present work the influence of the substituents at the alkyne terminus on the activation energy of both cyclizations was studied with the density functional approach in combination with a 6-31G* AO basis set, while an individually selecting MR-CI approach in combination with a DZP basis set (T. H. Dunning Jr., *J. Chem. Phys.* **1970**, *53*, 2823) was used for the computation of the reaction energies (ΔE_r). The reference space of the individually selecting MR-CI computations consisted of up to 15 configurations, leading to total MR-CI configuration spaces of more than 500×10^6 configuration state functions (CSFs). The secular equations actually solved were in the order of 4×10^6 CSFs. The influence of the neglected CSFs was estimated by the Buenker–Peyerimhoff extrapolation (R. J. Buenker, S. D. Peyerimhoff, *Theor. Chim. Acta* **1975**, *39*, 217; R. J. Buenker, S. D. Peyerimhoff, W. Butscher, *Mol. Phys.* **1978**, *35*, 771; R. J. Buenker, R. A. Phillips, *J. Mol. Struct. THEOCHEM* **1985**, *123*, 291, and references therein). The influence of higher excitations are estimated by the normalized form of the Davidson correction (J. E. Del Bene, E. A. Stahlberg, I. Shaviat, *Int. J. Quantum. Chem. Symp.* **1990**, *24*, 455). In these calculations, abbreviated in the following as MR-CI+Q, all valence electrons were correlated. The calculations were performed with the DIESEL-MR-CI program package (B. Engels, M. Hanrath, DIESEL-MR-CI (direct internal external separated individually selecting MR-CI) program package, Universität Bonn, Germany, **1997**; M. Hanrath, B. Engels, *Chem. Phys.* **1997**, 225, 197). The transition states were optimized and characterized by frequency calculations. As discussed above, the DFT (B3LYP) approach was used (A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785). These calculations were performed with the Gaussian 94 program package (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, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1995**) and the TurboMol program package (R. Ahlrichs, M. Baer, M. Haeser, H. Horn, C. Koelmel, *Chem. Phys. Lett.* **1989**, *162*, 165; O. Treutler, R. Ahlrichs, *J. Chem. Phys.* **1995**, *102*, 346).
- [10] Experimental studies^[7] provided an activation energy of 24–25 kcal mol^{−1} for the C²–C⁶ cyclization for R=Ph, R¹=nBu, R²=POPh₂ (Scheme 1), while for R=H, R¹=nBu, R²=POPh₂ an activation energy of about 22 kcal mol^{−1} was measured for the C²–C⁷ cyclization. Test calculations for R=H showed that the POPh₂ group lowers the barrier by about 3–4 kcal mol^{−1}.
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- [13] Our calculations for R=H and R=Ph identify both biradical intermediates as minimum structures on the potential surface. A zwitterionic mechanism could be ruled out, because the first excited singlet state of the biradical intermediate, which has a zwitterionic structure, lies above the singlet ground state.

1,3,4,5-Tetraphenylimidazol-2-ylidene: The Realization of Wanzlick's Dream**

Anthony J. Arduengo III,* Jens R. Goerlich, Roland Krafczyk, and William J. Marshall

In 1970 H.-J. Schönherr and H.-W. Wanzlick postulated the formation of the title compound **3** upon deprotonation of the corresponding imidazolium perchlorate **2**·ClO₄[−] with potassium *tert*-butoxide.^[1] However, carbene **3** was neither observed nor isolated, but rather allowed to react in situ with water in the presence of oxygen from the air. The resulting ketone, 1,3,4,5-tetraphenylimidazol-2-one, was characterized as the secondary reaction product. The apparent absence of any attempt to isolate the putative carbene **3** or its dimer may have been a result of the then prevalent idea that such imidazol-2-ylidenes really exist as the corresponding dimers (olefins)^[2] or are at best highly labile intermediates.^[3] Nonetheless, for steric and energetic reasons, Wanzlick postulated the presence of the carbene **3**.

We now report the synthesis, characterization, and X-ray crystallographic structure determination of **3**. A modification of the procedure published by Wanzlick makes it possible to isolate the carbene.^[1] The imidazolium salt **2**·HSO₄[−] was obtained by oxidation of 1,3,4,5-tetraphenylimidazol-2-thione (**1**)^[4] with a solution of 30% aqueous hydrogen peroxide in acetic acid [Eq. (1)].^[1] The amount of hydrogen peroxide



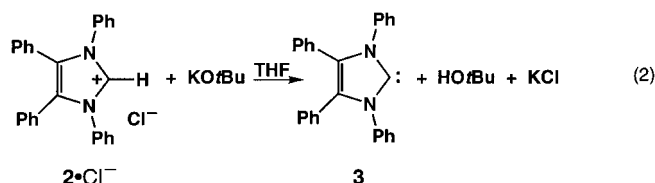
specified in Wanzlick's procedure for the preparation of this salt is insufficient to form the hydrogensulfate quantitatively. Three moles of hydrogen peroxide are required per mole of thione because sulfur remains in the product in the form of a hydrogensulfate counterion; it is not lost as sulfur dioxide as assumed by Wanzlick et al. Wanzlick and co-workers also reported conversion of the initially formed imidazolium salt into a perchlorate, which was in turn used in their attempts to generate the carbene. It is possible that traces of the hydrogensulfate anion (similar in size and molecular weight to perchlorate) contaminated their imidazolium perchlorate and

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thus interfered with the deprotonation reaction because of the additional acidic proton. Our experience shows that imidazolium chlorides are more effective in subsequent deprotonation reactions than salts with other anions. Thus, the hydrogensulfate ion in $2 \cdot \text{HSO}_4^-$ was exchanged for chloride by treatment with barium chloride.

When $2 \cdot \text{Cl}^-$ is treated with potassium *tert*-butoxide in tetrahydrofuran (THF) at room temperature, the stable carbene **3** is formed through elimination of KCl and *tert*-butyl alcohol [Eq. (2)]. Carbene **3** is a colorless crystalline



solid that melts at 199–202 °C with decomposition. Solid **3** tends to be microcrystalline and does not easily lend itself to satisfactory purification by recrystallization. This complication may be another reason why Wanzlick and co-workers did not report isolation of the carbene itself. However, we find that nice crystals of **3** can be grown by cooling solutions in THF/hexamethyldisiloxane.

The ^1H NMR spectrum of **3** shows a collection of multiplets at $\delta = 6.9$ –7.4, but this provides little information about the compound. A signal at $\delta = 219.6$ in the ^{13}C NMR spectrum ($[\text{D}_8]\text{THF}$) of **3** clearly identifies the compound as a carbene and is very similar to resonances observed for other reported *N,N'*-diarylimidazol-2-ylidenes.^[5, 6] The nitrogen centers in **3** produce a signal at $\delta = -161.2$ in the ^{14}N NMR spectrum, again providing data similar to that from previously reported *N,N'*-diarylimidazol-2-ylidenes.^[5, 6]

Crystals suitable for X-ray diffraction studies were grown by cooling a solution of **3** in THF/hexamethyldisiloxane. The compound crystallizes in the orthorhombic space group $P2_12_12_1$.^[7] Molecules of **3** are positioned such that a twofold symmetry axis passes through the carbene center and bisects the C4–C5 bond of the imidazole ring. Similar local symmetry is observed for 1,3,4,5-tetramethylimidazol-2-ylidene (**4**)^[5] and 1,3-dimesityl-4,5-dichloroimidazol-2-ylidene.^[6] Selected bond lengths and angles for **3** and **4** as well as for 1,3-di-*p*-tolylimidazol-2-ylidene (**5**) are provided in Table 1. The crystalline structure of **3** is depicted as a KANVAS^[8] drawing in Figure 1. The imidazole ring of **3** is nearly planar; only C4 and C5 lie respectively 0.5 pm above and below the average

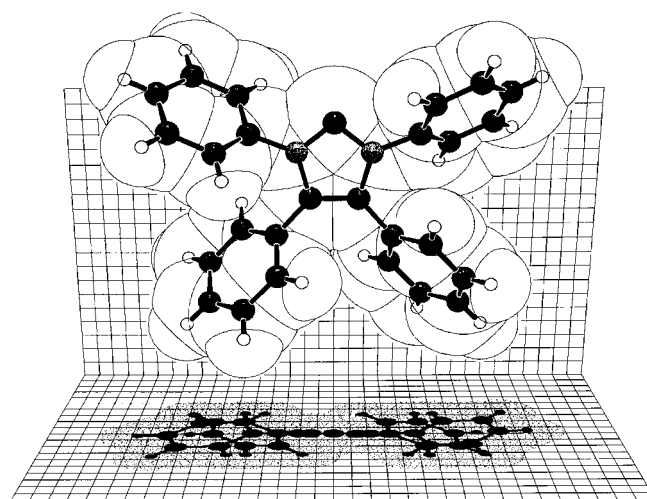


Figure 1. Space-filling KANVAS drawing of the crystalline structure of **3**.

plane of the imidazole ring. The valence angle at the carbene center of **3** is 102.1°, which is characteristic of singlet carbenes.^[5, 9] The nitrogen atoms are slightly pyramidalized; each lies 2.3 pm above the plane defined by its three attached substituents. The phenyl rings are twisted an average of 52° with respect to the imidazole plane and display a propellerlike geometry.

The carbene **3** originally reported by Wanzlick and co-workers in 1970 does, in fact, exist as a monomeric carbene and not as a dimer. Furthermore, under the conditions described above it is possible to isolate **3** as a solid that is stable at room temperature in the absence of moisture and oxygen. The inconvenient physical properties of the carbene, possible problems with respect to purity of the starting material, and the then widely accepted idea that imidazol-2-ylidenes are too labile to be isolated in pure form probably all contributed to the fact that Wanzlick et al. did not actually isolate **3**.

Experimental Section

2 · Cl⁻: To a solution of **1** (24.60 g, 60.81 mmol) in acetic acid (160 mL) was added dropwise at 100 °C of 30% aqueous solution of H_2O_2 (22 mL, ca. 190.0 mmol). The resulting brown solution was heated under reflux for 1 h and subsequently allowed to cool to 23 °C. After 15 h the solvent was concentrated in vacuo to give a brown oil that contained $2 \cdot \text{HSO}_4^-$ together with traces of water and acetic acid. This crude product was dissolved in methanol (250 mL) and treated with a solution of $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ (14.85 g, 60.81 mmol) in water (50 mL). After removal of the BaSO_4 by filtration, the solution was concentrated in vacuo and the residue was triturated with ether (250 mL) to give crude $2 \cdot \text{Cl}^-$ as a beige solid. This was dried in vacuo and recrystallized from chloroform/toluene; yield: 16.2 g (65.1%). M.p. 228 °C (decomp); ^1H NMR (CDCl_3): $\delta = 7.1$ –7.7 (m, Ph), 10.1 (s, C2-H).

3: A 100-mL round-bottom flask was charged with $2 \cdot \text{Cl}^-$ (2.03 g, 4.96 mmol) and THF (20 mL). The resulting suspension was stirred for 15 min. Solid potassium *tert*-butoxide (0.59 g, 5.29 mmol) was added to the suspension at room temperature. A dark red solution was obtained immediately. The reaction mixture was stirred for 20 min, after which all volatiles were removed in vacuo. The residue was extracted into warm toluene (2 × 10 mL) and filtered through celite. The filtrate was concentrated and cooled to -25 °C, which caused **3** to crystallize; yield: 1.52 g (82.2%). M.p. 199–202 °C (decomp); ^1H NMR ($[\text{D}_8]\text{THF}$): $\delta = 6.9$ –7.4 (m, Ph); $^{13}\text{C}\{^1\text{H}\}$ NMR ($[\text{D}_8]\text{THF}$): $\delta = 127.121, 128.345$ (C_{para}), 127.256, 131.466

Table 1. Selected bond lengths [pm] and angles [°] for **3**–**5**.

	3	4	5
$r(\text{C2-N1(3)})$	136.9(3)	136.3(1)	137.1(2), 137.5(2)
$r(\text{C4-C5})$	136.9(5)	135.2(2)	133.4(2)
$r(\text{N1(3)-C5(4)})$	140.9(3)	139.4(1)	139.2(2), 139.4(2)
$r(\text{N1(3)-Ph})$	144.0(3)	145.4(1)	143.0(2), 143.0(2)
$r(\text{C4(5)-Ph})$	147.7(3)	149.0(1)	95.6(16), 96.5(19)
$\theta(\text{N1-C2-N3})$	102.1(3)	101.5(1)	101.2(1)
$\theta(\text{C5(4)-N1(3)-C2})$	113.3(2)	113.47(8)	112.9(1), 113.0(1)
$\theta(\text{N1(3)-C5(4)-C4(5)})$	105.7(1)	105.78(5)	106.6(2), 106.2(1)
$\theta(\text{C2-N1(3)-Ph})$	119.5(2)	122.9(1)	123.1(1), 122.9(1)
$\theta(\text{N1(3)-C5(4)-Ph})$	123.3(2)	122.8(1)	124(1), 123(1)

(C_{ortho}), 128.871, 128.994 (C_{meta}), 131.197 (C_{ipso} on C4,5), 131.894 (C4,5), 142.505 (C_{ipso}), 219.587 (C2); ^{14}N NMR ($[D_8]THF$): $\delta = -161.21$ (s); EI-MS (70 eV): m/z : 372.1600 [M^+], calcd for $C_{27}H_{20}N_2$: 372.1626.

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- [7] Crystal data for **3**: $T = -95^\circ C$, MoK_{α} radiation (Rigaku RU300 diffractometer, R-Axis image plate area detector), crystal dimensions $0.18 \times 0.03 \times 0.25$ mm³ (parallelepiped): $a = 1010.8(2)$, $b = 963.9(2)$,

$c = 1035.2(2)$ pm, orthorhombic, space group $P2_12_12_1$ (no. 18), $Z = 2$, $\mu_{Mo} = 0.67$ cm⁻¹, $M_r = 372.47$, $V = 1008.6$ Å³, $\rho_{calcd} = 1.226$ g cm⁻³, filament size 12×2 mm, anode power 55 kV $\times$ 200 mA, crystal-to-plate distance 85.0 mm, 105- μ pixel raster, 45 frames, oscillation range 4.0° per frame, exposure time 25.0 min per frame, box sum integration, 5472 measured reflections, $4.0^\circ \leq 2\theta \leq 48.2^\circ$, max. $h, k, l = 11\ 11\ 11$, 1501 duplicates ($R_{merge} = 0.023$), 772 independent reflections with $I > 3\sigma(I)$. The structure was solved by direct methods (MULTAN) and refined by full-matrix least squares on F (scattering factors from *Int. Tables for X-ray Crystallography*, Vol. IV). Carbon and nitrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed in idealized positions with isotropic temperature factors calculated as $1 + B_{iso}$ of the corresponding carbon centers. The data/parameter ratio was 5.83. $R = 0.035$, $R_w = 0.032$, GOF = 1.43, $(\Delta/\sigma)_{max} = 0.00$, max. residual electron density 0.12 e Å⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101067. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[8] The drawing was made with the KANVAS computer graphics program. This program is based on the program SCHAKAL by E. Keller (Kristallographisches Institut der Universität Freiburg, Germany), which was modified by A. J. Arduengo III (E.I. du Pont de Nemours & Co., Wilmington, DE) to produce the back and shadowed planes. The planes bear a 50-pm grid, and the lighting source is at infinity so that shadow size is meaningful.

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Deposition of Data from X-Ray Structure Analyses

In order to make life easier for authors and referees the Cambridge Crystallographic Data Centre (CCDC) and the Fachinformationszentrum Karlsruhe (FIZ) have unified their procedures for the deposition of data from single-crystal X-ray structure analyses.

Prior to submitting a manuscript please deposit the data for your compound(s) **electronically** at the appropriate data base, that is, at the CCDC for organic and organometallic compounds and at the FIZ for inorganic compounds. Both data bases will be pleased to provide help (see our *Notice to Authors* in the first issue of this year). In general, you will receive a depository number from the data base within two working days after electronic deposition; please include this number with the appropriate standard text (see our Notice to Authors) in your manuscript. This will enable the referees to retrieve the structure data quickly and efficiently if they need this information to reach their decision.

This is now the uniform procedure for manuscripts submitted to the journals *Advanced Materials*, *Angewandte Chemie*, *Chemistry—A European Journal*, *the European Journal of Inorganic Chemistry*, and *the European Journal of Organic Chemistry*.