

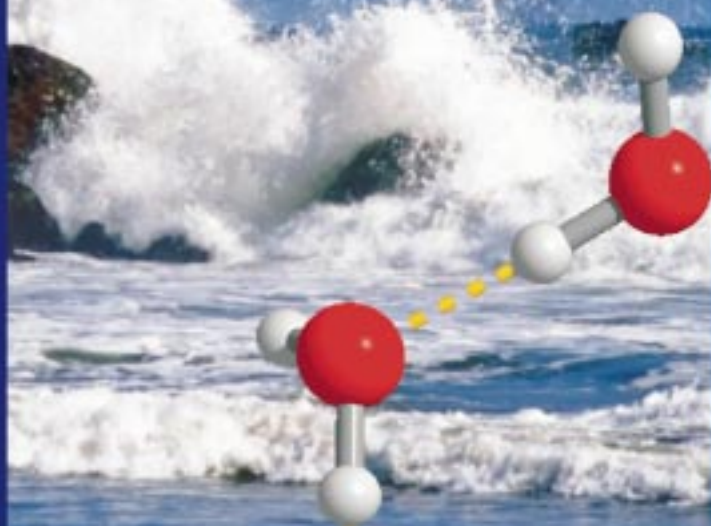
Cover Picture

Todd Bosanac, Jaemoon Yang, and Craig S. Wilcox

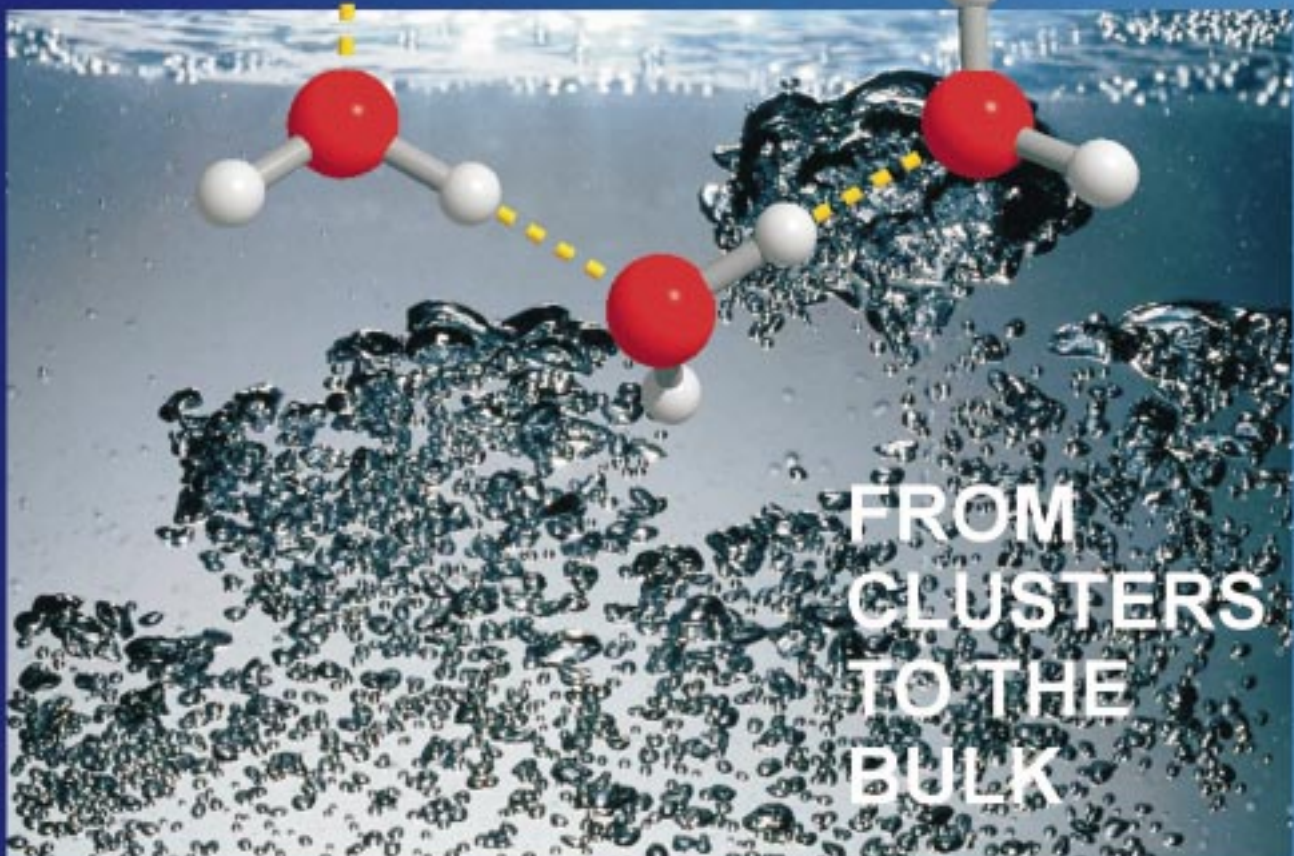
The cover picture shows a thought-provoking new approach to one of chemistry's oldest and most important challenges—the isolation of pure substances from complex homogeneous solutions. A product may be targeted for isolation by attaching its corresponding starting material to a latent phase tag. This latent phase tag (or “precipiton”) is designed to be very soluble in the required reaction solvent and thus supports homogeneous reaction conditions (1→2). After the reaction, the labeled product may be separated from a homogeneous mixture of solvent, excess reagents, catalysts, and nonlabeled by-products (4) through activation of the precipiton tag (4→5). Separation is effected because structural isomerization of the precipiton renders the precipiton-tagged product nearly insoluble in all solvents: only the product precipitates from the mixture (5). The product (6) is easily isolated by filtration or centrifugation and may be further purified by trituration. Sometimes it may be desirable to remove insoluble catalysts or by-products, or to replace the reaction solvent with another solvent (2→4) before activating the precipiton. This clever strategy for chemical separation based on tactical isomerization may be applied to reactions of any scale and can be automated. More about this method is reported by C. S. Wilcox et al. on p. 1875 ff.



WATER



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FROM
CLUSTERS
TO THE
BULK

Water: From Clusters to the Bulk

Ralf Ludwig*

*Dedicated to Professor Manfred Zeidler
on the occasion of his 65th birthday*

Water is of fundamental importance for human life and plays an important role in many biological and chemical systems. Although water is the most abundant compound on earth, it is definitely not a simple liquid. It possesses strongly polar hydrogen bonds which are responsible for a striking set of anomalous physical and chemical properties. For more than a century the combined importance and peculiarity of water inspired scientists to construct

conceptual models, which in themselves reproduce the observed behavior of the liquid. The exploration of structural and binding properties of small water complexes provides a key for understanding bulk water in its liquid and solid phase and for understanding solvation phenomena. Modern ab initio quantum chemistry methods and high-resolution spectroscopy methods have been extremely successful in describing such structures. Clus-

ter models for liquid water try to mimic the transition from these clusters to bulk water. The important question is: What cluster properties are required to describe liquid-phase behavior?

Keywords: ab initio calculations • hydrogen bonds • molecular clusters • vibrational spectroscopy • water chemistry

1. Introduction

Water has probably received more scientific and technological interest than any other substance—mainly for two reasons. Firstly, water is a major chemical constituent of our planet's surface and as such it has been indispensable for the genesis of life. Secondly, it exhibits a fascinating array of unusual properties in pure form and as a solvent. The importance of water is clearly described in monographs such as “Properties of Ordinary Water Substance” by Dorsey (1940),^[1] the compendium “Water. A Comprehensive Treatise, Volumes 1–7”, edited by Franks (1972–1982),^[2] the book “Metastable Liquids” by Debenedetti (1996),^[3] and Ball's popular survey of the “history” of water “H₂O—A Biography of Water” (1999).^[4] Those standard works go along with thousands of reviews, proceedings, and articles which all show that water is one of the most appealing of the open puzzles in science. Among those highlights, Bernal and Fowler's “A theory of water and ionic solution, with particular reference to hydrogen and hydroxyl ions”,^[5] Narten and Levy's “Observed

diffraction pattern and proposed models of liquid water”,^[6] Stillinger's “Water Revisited”,^[7] and Mishima and Stanley's review about “The relationship between liquid, supercooled and glassy water”^[8] should be emphasized.

Recent progress in some fields of water science makes it worthwhile to summarize important results obtained during the last five years. Topics concern the discovery of new ice phases,^[9, 10] new insight into supercooled and glassy water,^[8, 11, 12] and a better understanding of high-mobility transport of water ions.^[13, 14]

In this review I would like to focus on recent progress in calculating and measuring water clusters and their properties. This interest is mainly a consequence of the fact that investigations on small water clusters are a perfect means with which to characterize structural changes and bonding mechanisms in passing from isolated molecules to bulk states. Thus we can ask whether there is a continuous path from the gas to the liquid phase. Is there some evidence from experiments or theoretical models that gas-phase structures may also be important constituents of the liquid phase?

An outline of this review is as follows: First we describe some of the anomalies of water. The fascinating array of unusual properties can be qualitatively understood from water-bonding characteristics. Thus we discuss hydrogen bonds (H-bonds) and their possible arrangements in water. The crystal structures of hexagonal ice I_h and clathrate

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hydrates are presented as typical three-dimensional networks. Many-body effects are crucial for the size and arrangement of water complexes. Consequently we discuss recent theoretical and experimental evidence for cooperativity in H-bonded systems. This chapter is followed by a brief introduction into two common water models: the mixture and the continuum model approaches.

A survey of calculated water clusters ranges from small ring structures up to icosahedral networks. The main features and properties of the water structures are discussed in respect to experimental findings and their possible relevance for water models.

In the following chapter we describe exciting spectroscopic methods which recently allowed the detection of small water clusters: small quasi-planar ring structures ($n = 3-5$), isomeric hexamers ($n = 6$) representing the transition from cyclic to three-dimensional structures, and larger clusters in the “cage” regime ($n = 7-12$). Finally we present recent cluster models for liquid water. All models are based on calculated water structures and it is assumed that these may be constituents of the liquid phase. We discuss whether these models are able to explain the properties of liquid water including some of its anomalies.

2. Water Anomalies

The behavior of liquid water deviates strongly from that expected of a simple liquid in almost every respect. The liquid-phase density maximum is the most prominent and publicized of the water anomalies.

The density of liquid water at atmospheric pressure increases as it is cooled to 277 K, at which temperature the density has a maximum value of $0.999972 \text{ g cm}^{-3}$.^[15, 16] As shown in Figure 1a, the density decreases rapidly below 277 K, a trend which continues if the liquid density is followed into the supercooled region below the freezing point at 273 K.^[17-19] Although water is not the only liquid to exhibit a density maximum, the phenomenon only appears in a few other liquids, such as SiO_2 ^[20] and Ga ^[21] melts. Water also possesses a negative volume of melting (Figure 1b). The density of most liquids increases as they freeze, however,

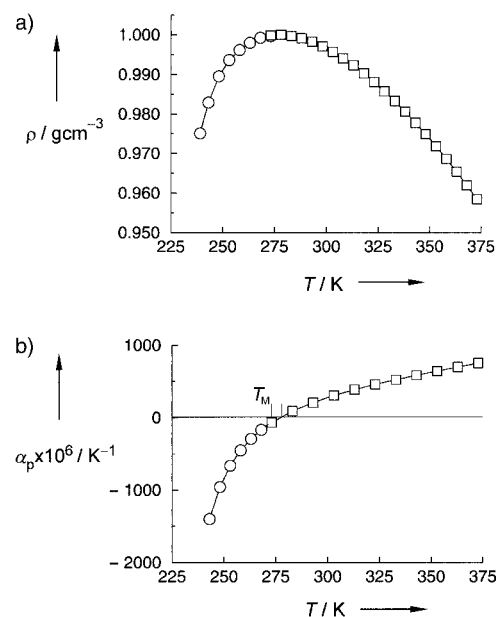


Figure 1. Temperature dependence of the isobar density ρ (a)^[16, 18] and the thermal expansivity α_p (b).^[19]

water expands by about 11 %. It is that process that allows a sheet of ice to float on liquid water. Both effects, the density maximum and the negative volume of melting, cause lakes and rivers to freeze from the top down.

The isothermal compressibility κ_T ^[22] passes through a minimum in the normal liquid-water range at 319 K. It then increases further as the temperature decreases and becomes more pronounced in the supercooled region (Figure 2a). The same behavior is found for the heat capacity C_p at constant pressure.^[23, 24] As shown in Figure 2b, the minimum value of C_p occurs at 308 K, which is right in the middle of the liquid-water range. Supercooling leads to a strong increase in the heat capacity. It takes more heat to raise the temperature of water than to warm up most other substances by the same amount. This occurrence results in ocean circulation effects that strongly influence local and global climates.

The dynamic properties of water also show strong deviations from simple liquid behavior. The diffusion constant D normally decreases as pressure increases at constant temper-



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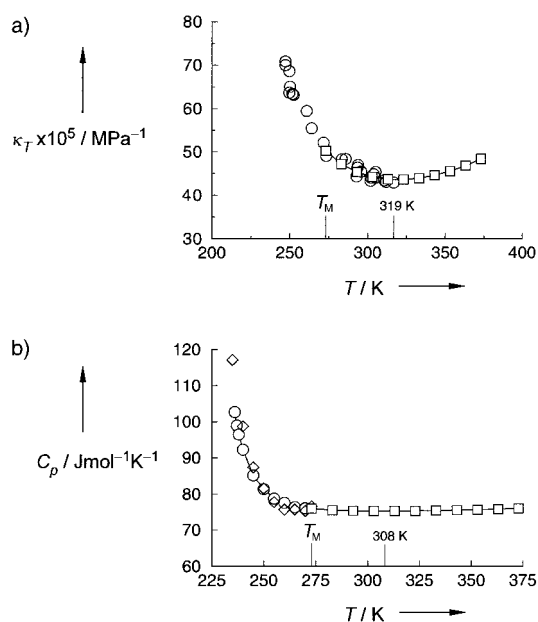


Figure 2. Temperature dependence of the isothermal compressibility κ_T (a)^[21] and the constant-pressure specific heat C_p (b).^[22, 23]

ature. Again, liquid water displays a reversal of this behavior. As shown in Figure 3a, the diffusion coefficient actually increases with increasing pressure up to about 200 MPa, above which the usual decrease in D is observed.^[25] Cold water gets more fluid when it is squeezed, whereas most

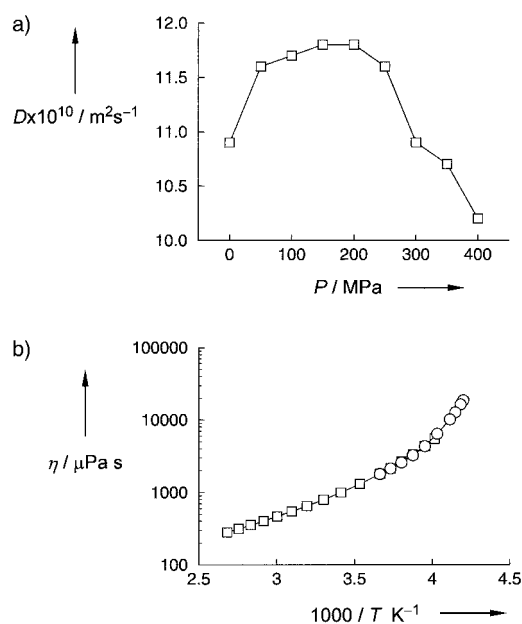


Figure 3. Pressure dependence of the isothermal diffusion coefficient D at 273 K (a)^[24] and the temperature dependence of the isobaric viscosity η at atmospheric pressure (b).^[25, 26]

liquids become more viscous under pressure. The pressure and temperature dependence of another transport property, the viscosity η , is also anomalous.^[17, 26] Figure 3b shows an Arrhenius plot at atmospheric pressure. The deviation of the data from a straight line indicates that the activation energy

E_A for the molecular motion increases with decreasing temperature, which indicates there is a change in the mechanism of molecular mobility.^[27] Many other dynamic properties of the liquid, such as the dielectric relaxation time^[28] and the nuclear spin relaxation times,^[29, 30] show the same kind of accelerating deviation from simple liquid behavior as the liquid is cooled far from the glass transition temperature.

Another surprising characteristic of water is its preferential orientation in the hydration shell of nonpolar solutes and nonpolar side groups attached to biopolymers. The structure adopted by liquid water which is in close proximity to nonpolar solutes is a fundamental characteristic of modern theories of hydrophobic hydration and hydrophobic effects, which are of great relevance to our understanding of many important chemical and biological processes.^[31]

Placing a solute molecule in liquid water leads to a rearrangement of the random H-bond network. Besides making some space for the guest molecule, water tries to strengthen its network around the nonpolar solute. This can best be done by placing its tetrahedral bonding directions in a straddling mode^[32] as shown in Figure 4 (left). The water

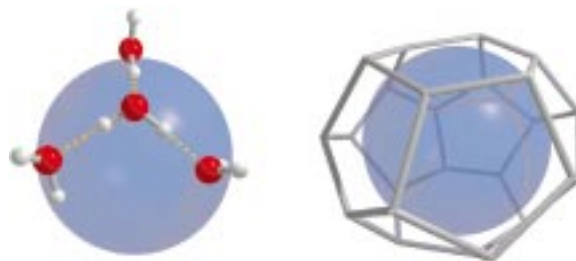


Figure 4. Water molecules next to a nonpolar solute. Each water molecule prefers to place its tetrahedral bonding directions in a straddling mode (left). A possible full arrangement of such a H-bonded network is shown for a crystal structure of a clathrate hydrate (right).

molecule is aligned with three tetrahedral directions tangential to the surface of the occupied space in order to preserve the maximum number of H-bonds. This orientational restraint leads to a negative entropy contribution for the solution. The crystal structures of the clathrate hydrates of many nonpolar substances show that such arrangements are possible in principle (Figure 4 (right)).

3. Hydrogen Bonds and their Arrangements

3.1. Structure and Properties of the Water Molecule

Qualitatively, insight into the origin of these peculiar liquid properties is available from a consideration of the shape and bonding characteristics of the water molecule (Figure 5). A simple molecular orbital description provides a useful qualitative picture of the electron distribution in the water molecule. Four localized regions of excess charge appear in a tetrahedral arrangement around the central oxygen atom. Two positive regions are associated with the hydrogen atom

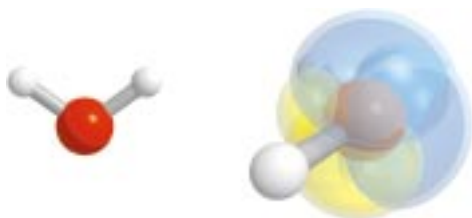


Figure 5. The water molecule (left). The two positive regions at the hydrogen atoms and the negative “lone pair” orbitals of the oxygen atom (right) obtained by an NBO analysis.

nuclei, which are significantly stripped of their attendant electrons by the highly electronegative oxygen atom.

The excess negative charge that thus appears around the oxygen atom is organized primarily in two lobes, or “lone-pair” orbitals, which complete the tetrahedral arrangement of the local electron deficit or excess. Overall, the electron distribution in an isolated water molecule can be related to the value of the equilibrium bond angle (104.5°), the value of the dipole moment (1.85 D), and the tetrahedral coordination of water molecules in condensed phases.^[2]

3.2. Hydrogen Bonding in the Water Dimer

The intermolecular attraction between the hydrogen atom of one water molecule and the lone-pair electrons on another represents an H-bond. Hydrogen bonds are the dominant interactions between water molecules. Thus much experimental and theoretical effort has been directed toward understanding the nature of the water dimer, which represents the archetype for hydrogen bonding.

The water dimer (Figure 6) exists in the vapor phase and was measured for the first time by Dyke and co-workers.^[33, 34] Their molecular beam resonance experiments clearly showed

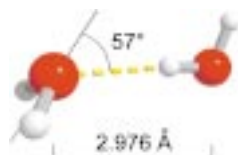


Figure 6. Experimental structure of the water dimer as measured from molecular beam resonance studies by Dyke et al.^[33, 34] Covalent chemical bonds are shown as solid lines and H-bonds as dashed lines.

that the lowest energy arrangement has a plane of symmetry containing the hydrogen donor molecule to the right and the symmetry axis of the molecule to the left. As shown in following sections, experiments using advanced techniques as well as high-level quantum-mechanical calculations fully support the notion of linear H-bonds. The measured bond length in the water dimer of about $2.98 \text{ \AA}$ is significantly longer than the observed distances in both liquid water and regular ice (about 2.85 and $2.74 \text{ \AA}$, respectively).

The shortening of the $R(\text{O}\cdots\text{O})$ distance in stronger H-bonded networks can be attributed to the cooperative nature of hydrogen bonding which will be discussed in detail in following chapters.

3.3. Tetrahedral Structures

The tetrahedral arrangement of the bonding groups in a single molecule results in the possibility of the molecule only

forming four H-bonds with nearby molecules (Figure 7). In a so-called “Walrafen” pentamer,^[35–40] the two hydrogen atoms of the centered molecule act as acceptors and the two lone pairs as donors. It is possible to fill three-dimensional space with tetrahedrally coordinate units, and some realization of this is the solid ice I_h crystal, which water forms on freezing at atmospheric pressure, as well as clathrate hydrates, which are described in detail in the next section. This possibility indicates that all microscopic and macroscopic properties arise from the fact that liquid water is a three-dimensional tetrahedral H-bonded (HB) network.



Figure 7. Tetrahedral configuration of water molecules spanned by two covalent bonds and two “lone pairs” of the central monomer.

3.4. Ice I_h and Ice Polymorphs

Thirteen crystalline phases are presently known: I_h (h = hexagonal), I_c (c = cubic), ice II–XI^[41, 42] and XII.^[43, 44] Two distinct amorphous water structures, low- and high-density amorphous ice, have also been reported.^[8] This uncommonly large number of different solid phases attests to the structural versatility of the water molecule. Relative to ice I_h , all the other phases exist at lower temperatures and/or higher pressures. Those phases differ in the connectivity of the rings and in the position of the hydrogen atom between the oxygen atoms, and show bent H-bonds.^[45] We will now take a closer look at ordinary hexagonal ice I_h , which is shown in Figure 8 along with cubic ice I_c . The oxygen atoms in ice I_h possess almost tetrahedral coordination. Each water molecule is involved in four H-bonds, with the two lone pairs as donors and both hydrogen atoms as acceptors. Compared to the gas-phase geometry, the distance $R(\text{O}\cdots\text{O})$ is shortened to $2.74 \text{ \AA}$ and the bond length $R(\text{O}-\text{H})$ is lengthened to $1.01 \text{ \AA}$ as a result of hydrogen bonding. Simultaneously, the intramolecular bond angle $\angle(\text{H}-\text{O}-\text{H})$ is widened to the typical tetrahedral angle of 109.5° . All these structural changes can be attributed to cooperative effects in hydrogen bonding. I_h and I_c are presented here

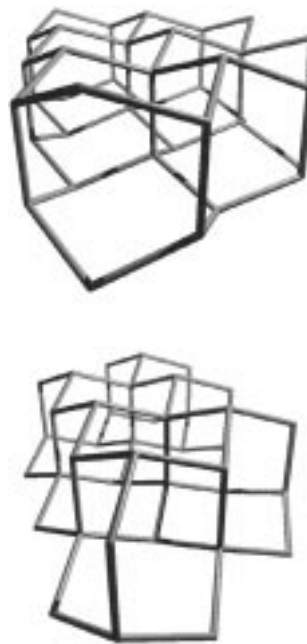


Figure 8. The structure of hexagonal ice I_h (top) and cubic ice I_c (bottom).

because of their structural motifs of chair- and boatlike hexamers, which play a significant role in the experimental and theoretical studies discussed later.

3.5. Clathrate Hydrates

Clathrate hydrates present the greatest variety and most intensively studied of H-bond inclusion compounds. The ability of water molecules to form a wide variety of four-coordinate networks, which results in the polymorphism of ice, is also apparent in the hydrate inclusion compounds. The voids in clathrate hydrates are much larger than in ice, and the H-bonded networks are unstable unless they are occupied by guest molecules. After the discovery of crystalline hydrates of chlorine by Davy^[46] and Faraday^[47] in 1823 it took more than a century before von Stackelberg and Müller^[48] and Pauling and Marsh^[49] could determine the structure of this chlorine hydrate and its gas hydrates. In the meantime the crystalline structures of the gas hydrates had been well characterized. Generally the structures are of the cage-like type-I or type-II clathrate structures. The structure-type formed depends upon the size of the guest gas molecule,^[50] which stabilizes the lattice through nonbonding repulsive interactions.^[51, 52] These structures have a pentagonal dodecahedron (5^{12}) of radius 3.9 Å as a principle building block. As this is not a space-filling polyhedron, the crystalline form of those hydrates contain a second larger polyhedra to form the lattice; that is a tetrakaidecahedron ($5^{12}6^2$) unit for type-I and a heccaidecahedron ($5^{12}6^4$) unit for type-II clathrates. All the principle building blocks are shown in Figure 9. Ripmeester and

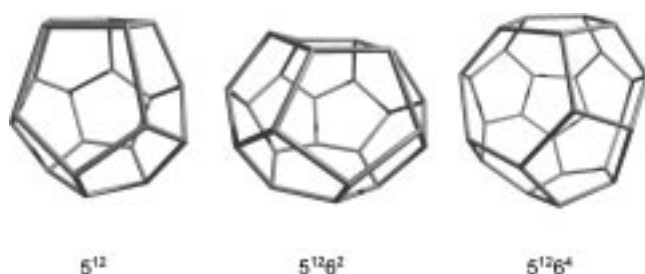


Figure 9. Clathrate structures of cage type I and II: dodecahedron (5^{12}), tetrakaidecahedron ($5^{12}6^2$), and heccaidecahedron ($5^{12}6^4$).

Ratcliffe^[53] used ^{129}Xe NMR spectroscopy to identify a new clathrate hydrate. An X-ray powder pattern diffraction study has shown this clathrate to have a host lattice isostructural with a known clathrasil structure, which contains the polyhedra 5^{12} , $4^35^66^3$, and a larger one, $5^{12}6^8$. More recently, Udachin and Ripmeester reported a complex clathrate hydrate structure showing bimodal guest hydration.^[54] Formally this structure consists of alternating stacks of structure H and II hydrates, and might conceivably be found in those settings in which clathrate hydrates form naturally. The ubiquity of such motifs in crystalline hydrates led Pauling to formulate a “clathrate theory” of liquid water^[55] that was built upon dodecahedral and tetrakaidecahedral clusters as structure units, but this picture has not received widespread support.

However, in a computer simulation study of the hydrogen-bond network, Geiger et al.^[56] found some evidence for the existence of numerous clathrate-like holes in liquid water. The same shape of orientational distribution functions have been observed when studying the orientation of water molecules in the hydration shell of hydrophobic solutes.^[32] Thus the structure was characterized as “clathrate-like”, since the hydration shell molecules are oriented in such a way that one of the four tetrahedral bond directions points radially outward and the remaining three bonding directions straddle the dissolved particle (Figure 4 (left)).

The academic interest concerns the water–water interaction in these topologically rather complex systems and the guest–host interaction with guest species that range from noble gas atoms to large and polar organic molecules. Clathrates are also believed to occur in some outer planets at fairly high temperatures. The interest is, however, not only academic: The petrol industry suffers from the nuisance of hydrocarbon clathrates blocking gas pipelines in arctic regions, and has just started to show interest in the giant natural methane deposits in the deep ocean floor and in permafrost regions.^[57, 58]

3.6. Statistical Networks

So far we have characterized some of the structures which occur in the gas phase of water or polymorphs of ice. The precise nature of the H-bonded disorder of water in the liquid phase is still unknown. Scattering experiments of liquid water give a precise description of atomic position disorder, but simply do not lead to a uniquely clear picture of the H-bonded network. Thus computer simulation methods, such as molecular dynamics (MD) or Monte Carlo (MC) simulations, are helpful for generating a representative set of configurations for a small region within the solid or liquid of interest. These calculations predict a totally connected random network of H-bonds as shown in Figure 10. The melting of ice results in a latent heat of $1.4 \text{ kcal mol}^{-1}$ being absorbed. This value is equivalent to breaking about 10% of the H-bonds and the system becoming “frustrated”. The water structure at any instant and on any length scale is amorphous, with many dangling bonds. Its structure becomes “random” and contains many five- and seven-membered rings, as well as the ice six-membered ring.^[59, 60]



Figure 10. Statistical network of liquid water. Snapshot from molecular dynamics simulations.

4. Many-Body Effects/Cooperativity

The nature of the physical interaction that contributes to hydrogen bonding has been the subject of numerous discussions in the chemical literature.^[61] On one side, H-bonds are attributed to purely electrostatic interactions, or to electrostatic plus polarization interactions; on the other side covalent interactions are considered to be extremely important. As discussed, there is increasing experimental evidence for the partial covalence of the H-bond. The more recent and prominent ones are the Compton scattering experiments on ice I_h by Isaac et al.^[62, 63, 64] and NMR measurements of ^1H - ^{15}N and ^{15}N - ^{15}N scalar couplings of several H-bonded biological systems by Grzesiek et al.^[65, 66] It should be noted that the covalent contributions to H-bonding concluded from Compton profiles is highly controversial. Parrinello et al.^[67] calculated the same features of the electron distribution in ice I_h , but come to a different chemical interpretation.

Cooperativity of H-bonding in water was originally an idea of Frank and Wen.^[68] The formation of a first H-bond (Figure 11) results in a change in the charge distribution



Figure 11. Hydrogen-bonded water dimer in the framework of an NBO analysis.^[74] The overlap of an oxygen lone pair orbital and an antibonding OH orbital is shown.

within the participating monomer in such a way that the hydrogen acceptor molecules becomes potentially an even better H-bond donor than before. It is capable of forming a stronger second bond because of the existence of the first bond. The same is true for the proton donor, which has an enhanced ability to accept a proton as a result of the bond that it has already formed. This idea has been supported for many years by quantum mechanical studies. Kollman and co-workers used a Morokuma analysis^[69, 70] of the results from an ab initio calculation to break down the interaction energy of the water dimer into four components: electrostatic, polarization, charge transfer, and dispersion. The authors found out that the contributions of various components varied with intermolecular distance. Roughly half the interaction at the equilibrium distance of about 2.98 Å could be attributed to electronic interactions.

Weinhold and co-workers performed a natural bond orbital (NBO) analysis to eliminate the charge-transfer component from the Hamiltonian operator of H-bonded dimers.^[71] They reported that this component constituted the major energetic contribution to many H-bonds, whereas electrostatic attraction was largely canceled out by exchange repulsion. Thus, the interaction energy can be considered to be a consequence of a

charge-transfer interaction. In this Lewis-type picture the donor–acceptor interaction between a lone pair on an oxygen atom and an O–H antibond leads to an energetic stabilization as a result of progressive charge transfer (CT).^[72, 73] This CT interaction is responsible for both enthalpic and entropic factors that stabilize certain H-bond clusters over others. For example, the cooperative effects in a water pentamer (Figure 12) lead to H-bonding energies that are almost twice as



Figure 12. Overlapping of the oxygen lone pair orbital and the antibonding OH orbital in an equilibrium structure of the $(\text{H}_2\text{O})_5$ pentamer. The average H-bond strength is almost twice that in the dimer as a result of cooperative effects.

strong as the linear dimer H-bond.^[74, 75] Some of the consequences are: Strong CT interactions tend to lengthen the covalent O–H bond and to shorten the noncovalent $\text{H}\cdots\text{O}$ hydrogen bond, thus reducing the overall $R(\text{O}\cdots\text{O})$ separation as given in Table 1. On enthalpic grounds, cooperative

Table 1. Calculated average distance $R(\text{O}\cdots\text{O})$ and bond length $R(\text{O–H})$ [Å], NBO delocalization energies $\Delta E_{n\rightarrow n+1}$ [kcal mol^{−1}] from oligomer W_n to oligomer W_{n+1} , and natural charge transfer q_{CT} [e] in water clusters (RHF/6-31 + G*⁺).^[75]

	$R(\text{O}\cdots\text{O})$	$R(\text{O–H})$	$\Delta E_{n\rightarrow n+1}$	q_{CT}
W_1	–	0.9476	–	–
W_2	2.964	0.9491	9.73	0.009560
W_3	2.872	0.9514	8.70	0.008917
W_4	2.847	0.9531	15.04	0.015397
W_5	2.837	0.9536	16.72	0.016404
W_6	2.833	0.9535	16.94	0.016673

bicoordinate ring structures are intrinsically favored over open-chain and starlike topologies (Figure 13). On entropic grounds, two-coordinate connectivities such as chains and cycles are favored over three- or four-coordinate networks. Compared with two-coordinate closed CT ring forms, higher three- and four-coordinate clusters are disfavored at higher temperature because of strongly hindered intermolecular bending or stretching modes. These reduce the librational entropy contributions and the unfavorable cooperative H-bond directionality patterns which lead to significant enthalpy loss. The occurrence of the three-dimensional structures at lower temperatures is caused by the high connectivity and the resulting larger total H-bond energy.

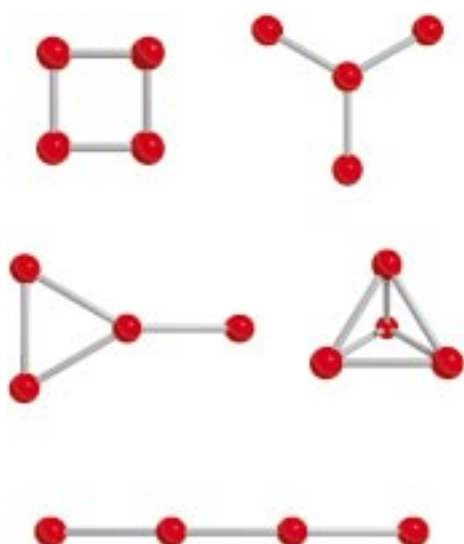


Figure 13. H-bond formations of water molecules: ring, star, lasso, tetrahedron, and chain.

5. Water Models

5.1. Mixtures Models

The combined importance and peculiarity of water has inspired scientists for more than a century to construct conceptual models which reproduce the observed behavior of the liquid. The earliest attempt probably goes back to Röntgen in 1892. He explained the density maximum as resulting from a shifting equilibrium between small ice crystallites suspended in a liquid of dissociated individual molecules.^[76] Röntgen's concept was based on the idea that liquid water can be modeled by a mixture of two locally less- and more-dense structures. It thus represents the first of a family of so-called "mixture models" for the liquid structures.^[77] Such models focus on the H-bond structures of the liquid and distinguish between a population of "intact" and "broken" H-bonds. This view was naively confirmed in infrared studies of liquid water.^[78] A strong overtone of the OH stretching mode was found with two distinct components in the 1.4 to 1.6 μm region. The absorbance of the lower wavelength component decreases with decreasing temperature, while the higher wavelength component increases. This behavior has been associated with the expected decrease in the population of "broken" H-bonds as the liquid cools. Although other explanations do not require two distinct states of bonding, those experimental results encouraged several scientists to follow the idea of bonded and nonbonded structures for modeling the properties of liquid water.^[79–81] Stanley and Teixeira^[82] presented a more modern model in this spirit. Their statistical model does not require that water molecules are strictly H-bonded or not H-bonded; it simply describes the degree of connectivity that is observed to occur in a lattice of four-coordinate sites when some random fraction of the nearest neighbors are considered bonded, and the rest are considered unbound. The two groups of interacting water molecules are distinguished for example by an

energetic criterion. It could be shown that clusters of four-bonded molecules will be observed as the probability of bonding to a nearest neighbor increases. The thermodynamic anomalies of water could be explained by considering those four-bonded clusters to be associated with regions of larger molecular volume, lower energy, and higher order. The authors results held when random configurations of molecular sites in the continuum, taken from computer simulations of water, were used.^[83, 84]

5.2. Continuum Models

"Continuum models" contrast to the mixture models in that in the former it is considered that the H-bonds are never broken in the liquid, but are only more or less distorted from their optimal form. A more modern example is the "continuous random network" (CRN) model of Sceats and Rice.^[85] This approach is supported by the observation that H-bonds need not necessarily break for molecules to have the mobility that is characteristic of the liquid. The model is based on continuous modifications of the topology of the H-bonded network rather than disruption of local H-bonded associates. This view implies there are "bifurcated" H-bonds or shared H-bonds between two atoms of one molecule.^[86]

The picture of continuous modification of the H-bonded network has been proven useful in explaining the mobility of water molecules in the liquid.^[87–89]

A distinction between mixtures and continuous models could be made as follows: in the former there are intact and broken H-bonds, while in the latter there is a fully H-bonded network. There is a continuous transition between these extremes. For example, the model of Stanley and Teixeira,^[82] which is given above as a modern mixture model, can also be regarded as a continuous model. The introduction of a threshold for H-bonds into a continuous model picture leads to a mixture model.

6. Survey of Calculated Water Clusters

Semi-empirical and ab initio quantum mechanical studies on water clusters are numerous.^[90–120] This development went along with improved methods and better computational capabilities. Our survey concentrates on recent ab initio Hartree–Fock (HF) and density functional (DFT) calculations. For clusters larger than $n=30$, only semi-empirical calculations are taken into consideration. The presented water clusters are discussed as a function of size and connectivity so that most of them can play a significant role in the experimental and theoretical investigations described later.

6.1. Small Cyclic Water Clusters ($n=3-6$)

The optimal structures and harmonic vibrational frequencies of small water clusters including ring structures W_n , $n=3-6$, have been determined by Xantheas et al.^[121–124] with

Hartree–Fock (HF) and density functional (DFT) methods, as well as Møller–Plesset second order perturbation theory (MP2) with an augmented correlation-consistent double-zeta basis set (Figure 14). The density functional B-LYP used

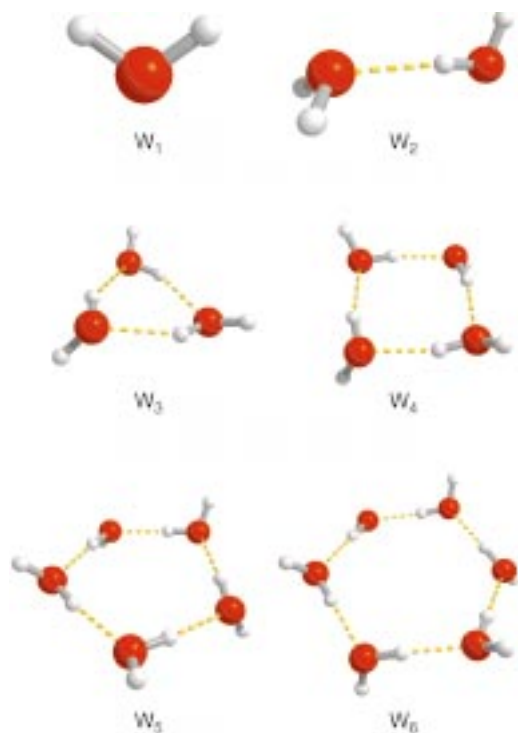


Figure 14. Small water clusters ($n = 1-6$) as calculated by ab initio and DFT methods.^[121]

combines the Becke's gradient-corrected exchange functional with the gradient-corrected correlation functional of Lee, Young, and Parr.^[123] The authors were particularly interested in the correlation of various properties with cluster size. Thus they performed benchmark studies of the water monomer and H-bonded dimer to ascertain the minimum level of theory and basis set that would yield meaningful results for the larger clusters. Accurate structure, harmonic frequencies, dipole moments, and polarizability components for the water molecule, along with several measured properties for the water dimer, such as the structure and rotational constants, were chosen as benchmarks. The most important results concern the structural and spectral trends in small cyclic water clusters. The study of cyclic clusters ($n = 3-6$) reveals a systematic contraction of the nearest $R(O \cdots O)$ separation with increasing size, a fact which can be attributed to nonpairwise additive (cooperative) many-body interactions as discussed earlier. As given in Table 2, the $R(O \cdots O)$ distance decreases nearly exponentially with increasing cluster size. The HF results, although not as accurate as the correlated data, exhibit the same trends as the DFT and MP2 results. While the $R(O \cdots O)$ separation decreases, the length of the bridged OH bonds increase monotonically with increasing ring size. The $R(O-H)$ bond length in the MP2 tetramer is about 2 pm longer than in the water monomer.

Table 2. Calculated average $R(O \cdots O)$ distances [Å] in water clusters W_n ($n = 2-6$) at various levels of theory with the aug-cc-pVDZ basis set.^[121-123]

Cluster	HF	B-LYP	MP2
W_2	3.032	2.939	2.911
W_3	2.927	2.808	2.799
W_4	2.880	2.743	2.743
W_5	2.867	2.727	–
W_6	2.855	2.714	–

The vibrational spectra of small water clusters ($n = 4-6$) show a blue shift of about 70 cm^{-1} for the intramolecular bending mode with respect to the monomer. The corresponding red-shifts in the OH stretches were estimated to be about 50 and 500 cm^{-1} for the free and bridging hydrogen atoms, respectively, with respect to the monomer. These values are in excellent agreement with experimental observations both on small water clusters as well as the bulk, as we will see later. Xantheas et al. pointed out that geometries, harmonic frequencies, and IR intensities can provide guidance to research groups studying water clusters; they demonstrated that the shifts in the OH stretching frequencies correlate well with the changes in the corresponding equilibrium bond distances and obey the well-known Badger's rule.^[125]

6.2. Isoenergetic Water Hexamer Clusters ($n = 6$)

An accurate theoretical description of the water hexamer is an interesting and fundamental subject. The cyclic hexamer, as discussed above, is the building block of many ice forms and it appears to be relevant for liquid water as well.

Prompted by the surprising experimental results for the water hexamers in the gas phase, Kim and Kim^[126] performed extensive ab initio and DFT calculations on the five lowest energy structures of the water hexamers (Figure 15). The authors demonstrated that the ring, book, bag, cage, and

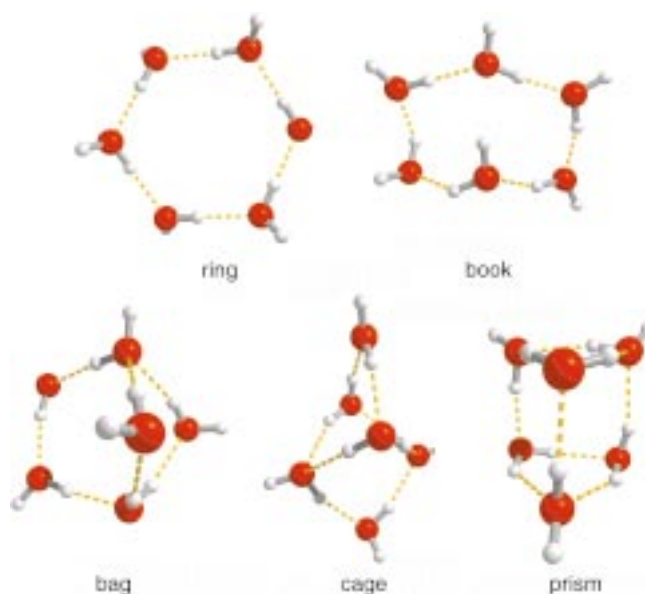


Figure 15. Calculated water hexamer isomers showing quasiplanar and cagelike clusters.^[126]

prism structures have energies that are within $0.7 \text{ kcal mol}^{-1}$ of each other, that is, they are nearly isoenergetic. Their MP2 calculations showed that the lowest energy conformer is the cage followed by the book (within $0.1 \text{ kcal mol}^{-1}$) and the prism structure (within $0.2 \text{ kcal mol}^{-1}$). The ring and the bag structures are only slightly higher in energy (0.5 and $0.7 \text{ kcal mol}^{-1}$, respectively) than the cage hexamer. The free energy of the book hexamer above 40 K is slightly lower than the cage, which might imply that the book structure would be more populated and thus be detectable. At higher temperatures the populations of the five hexamers would be almost the same. Deuteration did not change the nearly isoenergetic behavior of the clusters. The cage structure is still the lowest energy conformer, followed by the two competing structures of the book and the prism, whose energies are only $0.2 \text{ kcal mol}^{-1}$ higher at 0 K . Above 55 K the book form would again be more populated than the cage structure. The nearly isoenergetic nature of the water hexamers suggests that the kind of structure that will be detected experimentally strongly depends on the physical and chemical environment.

6.3. Variety of Water Heptamers ($n = 7$)

In spite of a spate of studies of various water clusters, only a few theoretical investigations on the water heptamer are available. The experimental vibrational spectra of water heptamers encouraged Kim et al.^[127] to perform ab initio and DFT calculations on twelve possible water heptamer structures to explore the conformations as well as the spectroscopic properties of these water clusters. Two three-dimensional cagelike structures comprised of a seven-membered ring with three additional H-bonds were found to be the lowest energy heptamer conformers (Figure 16). The global

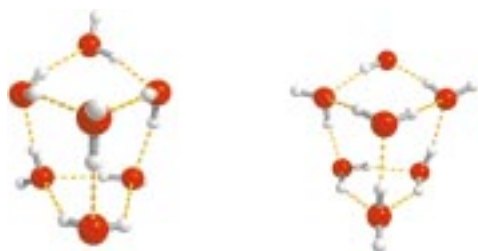


Figure 16. Energetically low-lying isomers of calculated water heptamers.^[127]

minimum energy of the most stable species was found to be $0.5 \text{ kcal mol}^{-1}$ lower than the other. The Gibbs free energy calculations using HF and B3LYP frequencies have shown that both structures are stable up to 100 K . An almost two-dimensional ring conformer lies only 1 kcal mol^{-1} above the global minimum at 0 K . Above 150 K , this ring structure is more stabilized than the three-dimensional heptamers for entropic reasons. The vibrational spectra of different heptamer conformers were discussed and compared with spectra of the hexamer and octamer water clusters.

6.4. Water Octamers: Cubic or Cyclic?

Some of the forementioned water heptamers can be generated from the two most important water octamer conformers. These cube water structures with D_{2d} and S_4 symmetry present isoenergetic global minima.^[128] They contain two kinds of water monomer: donor-donor-acceptor and acceptor-acceptor-donor molecules. Both cubic octamers are shown in Figure 17 along with a nearly cyclic and a bicyclic

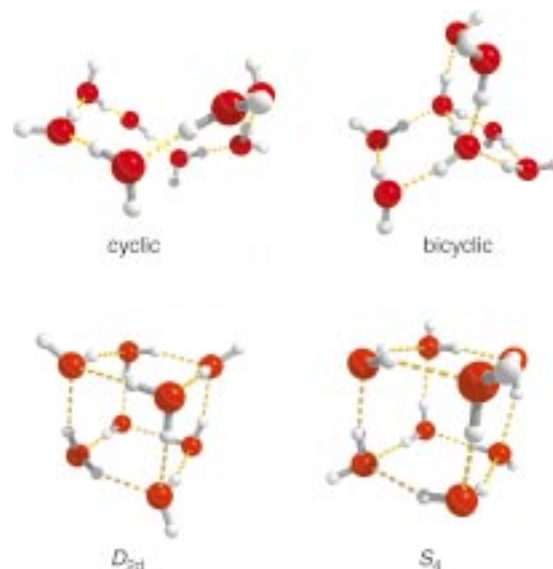


Figure 17. Cyclic, bicyclic, and cubic octamers of water obtained from ab initio calculations.^[128, 129]

octamer calculated by Weinhold.^[129] The cyclic topology has less H-bonds than the polycyclic octamers (8 versus 12) and is thus energetically disfavored. Its strong thermodynamic stability is caused by entropic factors. A virtually free torsion about the H-bond axis in the cyclic octamer leads to lowest frequency vibrations whereas angular strain factors in the cubic structures cause higher vibrational temperatures of the lowest H-bond modes.^[129]

6.5. Ice-Like and Clathrate-Like Structures ($n = 12 - 26$)

Larger water clusters with up to 26 water molecules were calculated by Ludwig and Weinhold.^[130] The species W_{12} , W_{18} , and W_{26} (Figure 18) were chosen as representative clusters with hexagonal units. Those hexagonal facets are well known structural elements of known crystallographic ice forms.^[42] The W_{12} cluster has two W_6 rings directly coupled face to face in a charge-balanced fashion, with each vertex (oxygen atom) having trigonal coordination. A more ice-like fragment is the W_{18} cluster, which contains an adamantane-like core buttressed with three W_2 side chains. Although this polycyclic cluster exhibits hexagonal elements of a tetrahedral lattice, it has no four-coordinate vertices that could truly resemble a typical interior site of bulk ice I_h . The W_{26} cluster was initially formulated as a tetrahedral diamond-like microcrystal with central water molecules concentrically surrounded by succes-

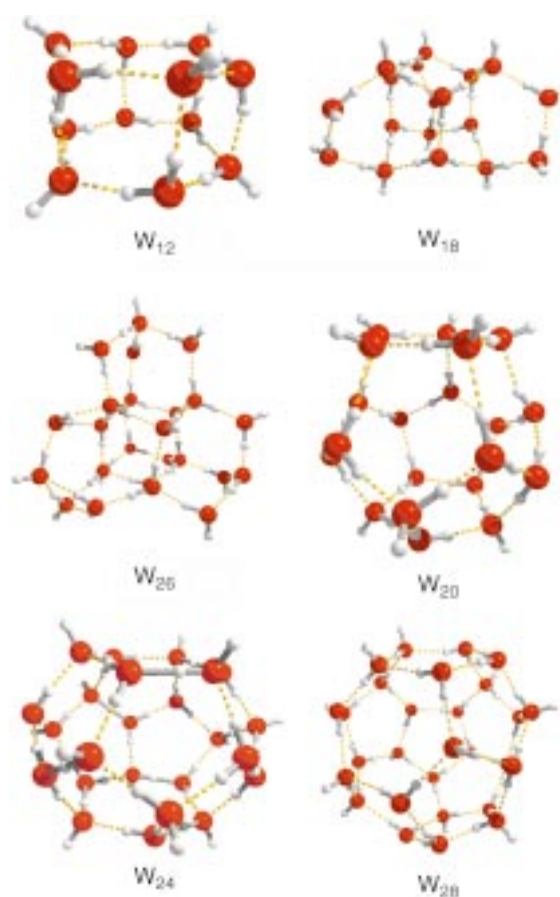


Figure 18. Ice- and clathrate-like water clusters.^[130]

sive shells of tetrahedral coordination to give increased numbers of “interior” four-coordinate monomers at each shell. However, even the W_{26} cluster contains only six four-coordinate (plus eight three-coordinate and twelve two-coordinate) monomers, which leads to an average coordination number of 2.77. This value is less than in the trigonal coordination of the fullerene-like topologies W_{20} , W_{24} , and W_{28} (bucky water). While pentagonal and hexagonal facets are well-known structural elements of crystallographic ice forms,^[42] the intact bucky-water polyhedra are principally recognized as crystallographic elements in certain clathrate-type hydrates, such as the pentagonal dodecahedral (5^{12}), tetrakaidecahedral ($5^{12}6^2$), and the hekkaidecahedral ($5^{12}6^4$) units. The large number of calculated clusters are topologically similar; they differ only in the proton ordering around each vertex. The most stable species of the cage types are shown in Figure 18. The comparable tetrakaidecahedral cluster structures W_{24} , W_{25} , and W_{26} were also calculated by Khan.^[131] He used semi-empirical methods for his calculations and described the structural features and stability of these clusters.

Most recently, Khan calculated multiple-cage clusters to examine whether these fused structure formations became more favorable as the cluster-size increases.^[132] Indeed, the 35-mers having two fused dodecahedral cages consistently show a greater stability than their single-cage isomers.

6.6. Larger Clusters: Icosahedral Networks ($n = 280$)

Chaplin^[133] formed an icosahedral three-dimensional network of 280 hydrogen-bonded water molecules. In this structure each water molecule is involved in four H-bonds, two as donors and two as acceptors. The network is based on the regular arrangement of 20 slightly flattened tetrahedral 14-molecule units as shown in Figure 19. Within these units

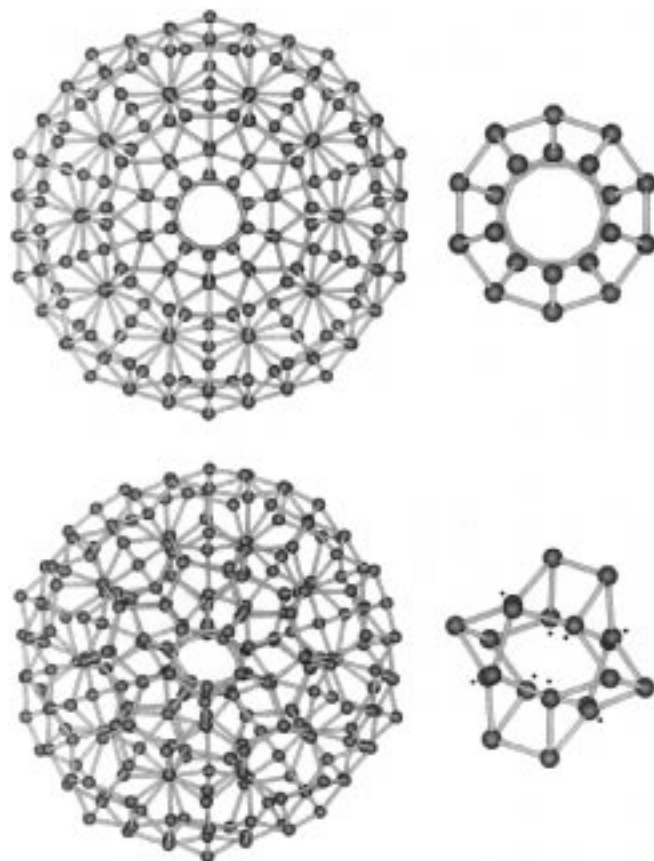


Figure 19. An expanded icosahedral water cluster consisting of 280 water molecules with a central dodecahedron (top) and the same structure collapsed into a puckerd central dodecahedron (bottom). The figure is reproduced with the kind permission of Elsevier Science and M. F. Chaplin. ^[133]

four water molecules form the corners of the tetrahedron and are involved in both boat-form hexamers and pentamers. The remaining ten molecules form an adamantane-type ring structure, identical to a 10-molecule unit recently found in a crystalline supramolecular complex,^[134] and also as found within the 18-molecule cubic ice cell. Four of these molecules are involved in hexamers in both the boat and chair conformation, with the remaining six molecules form pentamers and hexamers in the chair conformation.

Pentamers of water have bond angles of 108° , which are 1.47° closer to the supposedly most stable $\angle(\text{H-O-H})$ angle in water vapor (104.52°) than are the tetrahedral angles (109.47°) in ice. The clusters can grow in three dimensions; each cluster has twelve potential sites at its icosahedral vertices for use as centers for neighboring, overlapping clusters. The structure becomes more distorted as the network grows.

7. Survey of Measured Water Clusters

7.1. Small Cyclic Water Clusters ($n = 3-6$)

Enormous progress in laser spectroscopy has facilitated new, highly detailed studies of water clusters. Studies of the structure and dynamics of isolated small clusters of water molecules provide a means of quantifying the intermolecular forces and hydrogen-bonded rearrangements that occur in condensed phases. Far-infrared (FIR) vibration-rotation-tunneling (VRT) spectroscopy of clusters has recently been developed by Saykally and co-workers^[135–145] to address such questions. Low-frequency van der Waals vibrations in clusters can be measured with tunable FIR lasers to resolve rotational and tunneling motions. The resulting VRT spectra can be analyzed in terms of permutation-inversion (PI) group theory and scattering theory to yield pair potentials of unprecedented accuracy and detail for weakly bonded systems. FIR-VRT spectroscopy is also a powerful probe of the tunneling dynamics that occur in hydrogen-bonded clusters. This method should allow for the investigation of the cooperative (nonpairwise) effects of hydrogen bonding in water clusters. In a series of beautiful experiments Saykally and co-workers characterized the water dimer,^[135] the cyclic water trimer,^[136] the tetramer,^[137] and the pentamer.^[138] The results unambiguously established that the structures of the water clusters responsible for the observed spectra were indeed the quasi-planar rings predicted by theory.^[139] These spectra permitted estimates of the $R(\text{O}\cdots\text{O})$ distances to be determined for each of the clusters and yielded a quantitative experimental measure of the hydrogen-bond cooperativity. The $R(\text{O}\cdots\text{O})$ distance obtained from VRT spectroscopy and theoretical studies of water clusters are plotted in Figure 20. Consistent

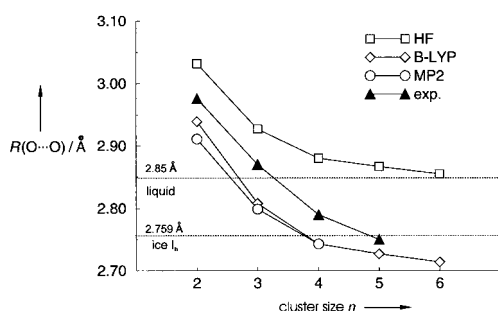


Figure 20. The $R(\text{O}\cdots\text{O})$ distance versus cluster size obtained from VRT spectroscopy^[136–139] and three different levels of theory: Hartree–Fock (HF), Møller–Plesset second-order perturbation theory (MP2), and density functional theory (B-LYP).^[121–123] The experimental $R(\text{O}\cdots\text{O})$ distances in liquid water at 298 K^[155] and hexagonal ice I_h at 183 K^[41, 42] are given for comparison and are indicated by dotted lines.

with the occurrence of cooperative effects, all the methods produced an exponential contraction of the $R(\text{O}\cdots\text{O})$ distance with increasing cluster size which converged to the bulk (ordered ice) value of about 2.74 Å. Experiment and theory strongly suggest that the water trimer, tetramer, and pentamer have cyclic, quasi-planar minimum energy structures. Larger water clusters were expected to have three-dimensional geometries, with the hexamer representing the transition from a cyclic to a three-dimensional structure.

7.2. Water Hexamers: Cage, Quasiplanar Ring, or Chair?

7.2.1. The Cagelike Hexamer in the Gas Phase

As discussed in Section 6, ab initio studies on the hexamer reveal the existence of several low-lying structures, but predict that the minimum-energy form is the three-dimensional cage shown in Figure 21. This cagelike hexamer agrees best with



Figure 21. Experimentally found water hexamers: the cage structure detected in the gas phase,^[146] the quasi-planar cyclic structure trapped in liquid helium,^[147] and the chairlike cyclic structure measured in organic hosts.^[148]

the measured rotational constants from VRT measurements performed by the Saykally group.^[146] The fact that both high-level ab initio calculations and diffusion quantum Monte Carlo (DQMC) results^[147–149] predict the cage as the lowest energy form, and that no structures other than the most stable have ever been detected by VRT spectroscopy in super-sonic argon jets, is fairly compelling evidence that the cage form is indeed the most stable water hexamer. Clearly the water molecules have enough time to find the absolute minimum structure in these gas-phase experiments at 5 K. Ab initio studies also predict that zero-point vibrational effects are crucial for the stability and that they can alter the energy ordering of the low-lying hexamer structures. Thus, there were some hints that other hexamer isomers could be detected by changing the chemical environment and temperature.

7.2.2. Quasiplanar Hexamers in Liquid Helium

Nauta and Miller recently reported the experimental observation of the cyclic water hexamer, which was a higher energy isomer than Saykally's cage structure previously characterized in the gas phase.^[150] The ring hexamer shown in Figure 21 was formed in liquid helium droplets and studied by infrared spectroscopy. Three main results of this beautiful study are remarkable. Firstly, this isomer is formed selectively as a result of unique cluster-growth processes in liquid helium. The experimental results indicate that the cyclic hexamer is formed by insertion of water molecules into smaller, pre-formed cyclic complexes such as trimers,^[151] tetramers, and pentamers. Buck and co-workers^[152] obtained different results for growing methanol clusters in helium. Once the cyclic trimer was formed and cooled, insertion of the fourth methanol molecule into the ring was inhibited by the lack of energy needed to open the ring. The result was a tetramer structure corresponding to a cyclic trimer with the fourth molecule hydrogen bonded to the outside. As a possible

explanation for the difference between the water and methanol systems Nauta and Miller suggested that insertion into the water ring is facilitated by tunneling of the hydrogen atoms through associated barriers. In contrast, ring insertion may be inhibited in methanol because it involves more motion of heavy atoms. Secondly, the infrared spectrum for the OH stretches of water clusters formed in liquid helium were compared with those of the corresponding complexes formed in a free jet expansion experiment. The vibrational frequency shifts resulting from the interaction with the helium were negligible and the bonds for the dimer, trimer, tetramer, and pentamer essentially coincidence with the gas-phase bands.^[153] An additional peak red-shifted relative to the pentamer was assigned to the cyclic isomer of the water hexamer. The most compelling support for this assignment comes from comparing the frequency shifts for all of these cyclic complexes with the corresponding *ab initio* and DFT calculations on the clusters (Figure 22). As already shown for intra- and inter-molecular geometries, the frequency shifts vary smoothly with

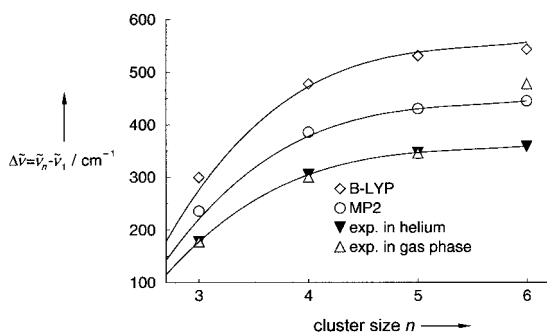


Figure 22. Experimental^[150, 153] and calculated^[121–123] red-shifts of the OH vibrational frequency for cyclic water clusters from the trimer to the hexamer. The shifts are taken in both cases relative to the average of the symmetric and asymmetric OH stretches of the monomer. The frequency shifts are essentially the same for the gas-phase and liquid helium data up to the pentamer. The band for the cage hexamer detected in the gas phase is more red-shifted than that of the hexamer in liquid helium relative to a quasi-planar ring structure. The solid curves present guidelines for the eye. They are obtained by scaling the fitted experimental curve to the theoretical data.

cluster size. The cyclic hexamer peak is precisely where it is expected theoretically, whereas the cage band is shifted further to the red region. Better agreement with experimental and theoretical values can not be expected given that the theoretical values are based on harmonic frequency calculations. From a theoretical viewpoint it is important that the calculated shifts can be scaled to the experimental data by one scaling factor for all cyclic clusters. Increasing cluster sizes clearly do not require different scaling factors. Thirdly, Nauta and Miller used superfluid liquid helium as a growth medium to access a different portion of the energy surface as in the gas-phase experiment, and could observe the cyclic water hexamer. This species is one of the prominent morphologies found in computer simulations of liquid water^[60] and is the structural motif of ice I_h .^[41, 42] The cage isomer characterized previously by Saykally and co-workers^[146] has a most intense OH vibrational band which has a much greater red-shift. Several calculated local minima^[126] lie lower in energy than the cyclic hexamer. Clearly the path between this hexamer

and the three-dimensional cage structure will involve a great deal of H-bond rearrangement, which is expected to be difficult in liquid helium.

7.2.3. The Chairlike Hexamer in Organic Matrices

Recently, the supramolecular association of cyclic water hexamers with an ice-like chair conformer into one-dimensional chains inside an inclusion organic host was reported.^[154] The geometric parameters of the hexamers are summarized in Table 3. The average $R(O \cdots O)$ distance of 2.776 Å is about the same as the analogous value of 2.759 Å in ice I_h at 183 K.

Table 3. Experimentally determined distances [Å] and angles [°] for water hexamers detected in an organic host.^[154]

$R(O-H)$	$R(O \cdots O)$	$R(H \cdots O)$	$\angle O-H \cdots O$	$\angle O \cdots O \cdots O$
0.960	2.711	1.758	171.3	113.2
0.956	2.785	1.844	167.6	96.0
1.264	2.833	1.703	145.0	140.2

However, there is a wide variation of the angles $\angle(O-O-O)$; the average value is 116.5°, which is considerably deviated from the corresponding value of 109.3° which occurs in hexagonal ice. The hexamers are self-assembled by $O-H \cdots O$ H-bonds into extended chains along the channels, which consist of fused four- and six-membered water rings. The observed interhexamer oxygen–oxygen distance of 2.854 Å is very similar to the separation of 2.85 Å found in liquid water.^[155] This supramolecular association of water molecules in chains is presumably enforced by the shape of the host's channels, whose relatively narrow openings preclude the formation of the more stable three-dimensional clusters found in the gas phase. There are no $O-H \cdots N$ H-bonds between the water chains and the organic host. Thus the water clusters can be removed by heating without changing the structure of the host. In contrast to previously described inclusion complexes of water clusters that have strong interactions with the host, the water clusters more closely resemble structures found in liquid water or ice. The IR spectra suggest that the water chains have more similarities with liquid water than with hexagonal ice.

Ice-like clusters with chair and boat conformations were also observed by Barbour et al.^[134, 156] in the solid state. The intervening voids of a cobalt cage complex are filled with clusters of ten water molecules that adopt an ice-like conformation. The water cluster is sufficiently flexible to respond to small changes in its environment, but the overall conformation is robust.

However, free chair- or boatlike hexamers can not be detected. It clearly requires neighbors in a periodic system such as are present in hexagonal and cubic ice or organic matrices.

7.3. From Heptamers to Decamers

The understanding of the evolution of clusters larger than hexamers in the “cage” regime was the challenge of Buck and

co-workers.^[157–159] Prior to their measurements, experimental results focused on the OH stretch of large clusters without size selection^[160, 161] and $n = 7, 8$ clusters attached to benzene.^[162–164] Recently, Buck et al. presented the first infrared measurements of the OH stretch mode of pure water clusters with size $n = 7–10$. Their experimental method is a combination of size selection (by momentum transfer in collisions with rare gas atoms) with an infrared depletion technique.^[165] In the first step the different clusters are dispersed into different angles according to their masses and detected by a mass spectrometer. Then the OH stretch vibrational mode of the water molecules is excited by IR laser radiation. The detector records the depletion in the cluster signal caused by dissociation of the clusters by the absorbed radiation. Additional calculations on the heptamers resulted in numerous energy minima, which can be divided into two structural families. The experimental spectra are reproduced quite well using the lowest energy structures similar to those found by Kim et al.^[127] and shown in Figure 16. Inclusion of the zero-point motion effects was crucial for reproducing the spectra. The spectra of the two lowest isomers can be derived from the cubic S_4 octamer by removal of either one double donor or one double acceptor water molecule. The two cubic octamer isomers with D_{2d} and S_4 symmetry were characterized, along with nonamers and decamers, earlier by Buck et al.^[157] using the same experimental method. The proposed lowest energy nonamer and decamer structures (Figure 23) are derived from

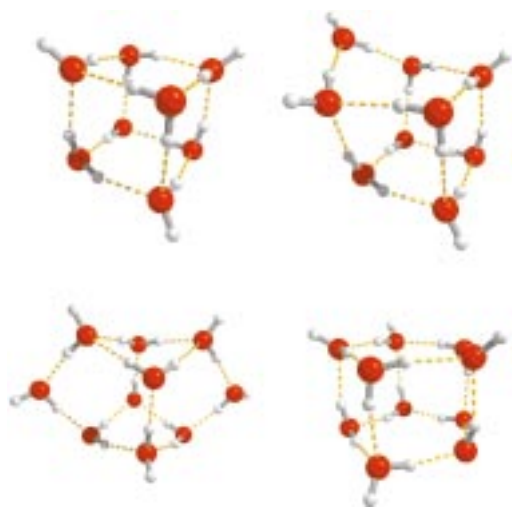


Figure 23. Structures of water clusters ($n = 8–10$): one cubic octamer (top left), one nonamer (top right), and two decamers (bottom) as measured by IR depletion techniques.^[157–159]

the octamers by insertion of one and two two-coordinate molecules, respectively, into the cube edges. The two lowest energy decamers can be viewed as two fused pentamers with the same and the opposite orientation of H-bonds in the two cycles, respectively. However, the spectrum calculated for these two minima did not match the experiment very well. A better agreement was obtained for another “butterfly” minimum structure, which can be viewed as a D_{2d} octamer with two extra two-coordinate donor–acceptor molecules inserted at opposite edges.

The authors reported that the presented experimental technique will allow the measurements to be extended down to cluster sizes of $n = 6$ and up to $n = 20$ by changing the carrier gas and the collision partner.

8. Cluster Models for Liquid Water

8.1. Quantum Cluster Equilibrium Theory of Liquid Water

Weinhold^[129] developed a method for calculating equilibrium properties of liquids by extending the standard statistical thermodynamic treatment of chemical equilibria to the analogous equilibria between molecular clusters, as characterized by modern ab initio techniques. The quantum cluster equilibrium (QCE) theory of liquids is based on the role of H-bonded molecular clusters as fundamental constituent units. Standard quantum statistical thermodynamic methods are used to treat the equilibria between clusters in the canonical ensemble, which leads to predictions of macroscopic thermodynamic and spectroscopic properties. Meanwhile QCE has been shown to provide practical, quantitative, or semiquantitative descriptions of H-bonded fluids such as amides^[166–169] and alcohols.^[170–173] The quantum cluster equilibrium formalism was first applied to the most important H-bonded fluid, namely, liquid water. In these first papers, emphasis was not placed on achieving high quantitative accuracy, but rather to illustrate qualitatively how the QCE model “works”, and included the interplay between microscopic water clusters and macroscopic phase behavior, the stability of QCE predictions with respect to changes in the theoretical model or inclusion of other clusters, and the importance of nonpairwise additive cooperative effects in aqueous condensation phenomena. The simple seven-cluster QCE(7)/3-21G model for liquid water comprised clusters from the water monomers W_1 up to the cyclic n -mers W_5 , W_6 , and W_8 .

It could be shown that structures found in the gas-phase experiments, such as the cubic octamer with D_{2h} symmetry are completely negligible in the QCE population, even though they are lower in energy. The reason for these dramatic differences in thermodynamic stability can be traced to energetic and entropic factors. The H-bonds in the cubic clusters are much more highly strained by the severe non-linear O–H–O angles required along the cube edges, since the ideal 90° angle at each corner is much smaller than the equilibrium H–O–H bond angle. Severe angular strain in polycyclic octamers lead to higher vibrational temperatures of the lowest H-bond modes and result in much larger unfavorable entropic contributions. Such a process renders this species essentially irrelevant for describing equilibrium properties of water.

The QCE liquid-phase population as shown in Figure 24 consists mainly of cyclic octamers W_8 . The next highest concentration of clusters are W_5 and W_6 . Thus the equilibrium liquid phase is pictured as a mobile distribution of ring isomers that are packed roughly with van der Waals contact separation. This packing leads to characteristic near neighbor

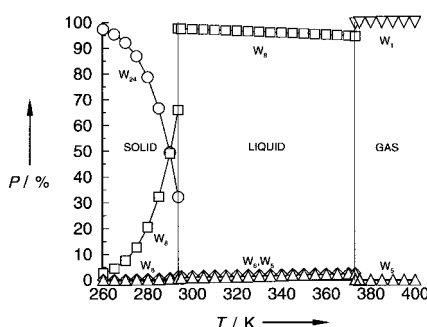


Figure 24. Cluster population P [mass %] from QCE(18)/3-21G model water at one atmosphere of pressure. The contributions of leading clusters are shown in each phase: W_{24} , W_8 , and W_6 in the solid phase, W_8 , W_6 , and W_5 in the liquid phase, and W_1 and W_5 in the gas phase.^[130]

$R(O\cdots O)$ distances of about 2.8 Å within the rings and a next-nearest $O\cdots O$ separation of about 4.5 Å. These values are crudely consistent with known features of the radial distribution function of liquid water. What is certainly not in agreement is the low number of nearest neighbors compared to the experimentally found number of 4.4. Also most of the thermodynamic properties, such as the liquid–vapor coexistence curve and heats of vaporization, could be reproduced in reasonable agreement. It was more difficult to reproduce a liquid–solid(ice) phase transition; for that it was necessary to calculate three-dimensional four-coordinate water structures similar to crystalline ice. Thus Ludwig and Weinhold^[130] extended the QCE model of liquid water to include larger ice-like clusters, such as the tetrahedral and fullerene-like clusters with up to 26 water molecules. A low-energy tetrakaidecahedral W_{24} cluster (Figure 18) leads to a new low-temperature phase that borders on both liquid and vapor regions in first-order transition lines and gives rise to a true QCE triple point (Figure 25). The authors characterized

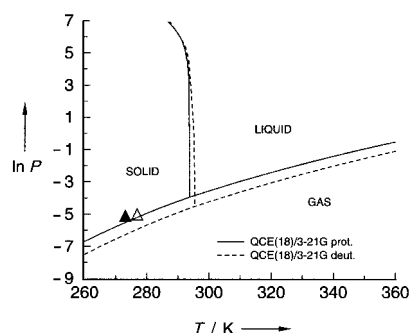


Figure 25. Phase diagram of the light and heavy QCE(18)/3-21G model water. The available experimental triple points for light (▲) and heavy (△) water are given for comparison.^[130]

the microstructural composition and macroscopic properties of this “bucky ice” phase. Although it differs significantly from physical ice I_h (for example, the melting point is 20 K too high and the molar volume is 5% too low), it manifests qualitatively correct thermodynamic features of true ice polymorphs, which suggests an important role of voluminous clusters in the liquid/solid transition region. In further studies Ludwig and Weinhold extended the QCE theory to deuter-

ated^[174] and recently to tritiated^[175] water clusters. They characterized the microstructural composition and macroscopic properties relative to those obtained for protonated species. The main goal was to compare the phase diagrams and thermodynamic properties of isotopically substituted water. It was found that the QCE triple point is shifted to higher temperatures by about 2.0 K upon deuteration and by about 3.0 K upon tritiation compared to the measured 3.8 K in heavy and 4.5 K in super-heavy water. The shifts of the melting point to higher temperature is also modeled correctly. The QCE theory allows for a change in the properties of light, heavy, and super-heavy water clusters (masses, momentum of inertia, zero-point energies, and vibrational frequencies) individually and/or in any combination. In this way the influence of different properties on cluster populations can be investigated. An interesting result is that the shift of the triple point to higher temperatures is a net effect: Lower zero-point energies for deuterated and tritiated water alone strongly raise the melting points, whereas a reduction in the vibrational frequencies for the isotopically substituted species alone lowers the melting point. The combination of the opposite effects result in a small net shift of the melting point to higher temperatures as shown in Figure 26. The larger masses and rotational temperatures in heavy and super-heavy water clusters have practically no effect on the melting point.

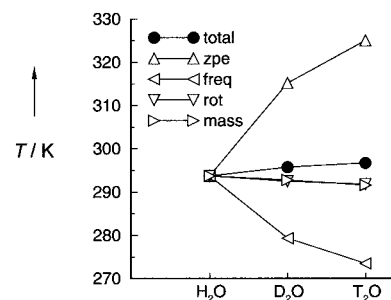


Figure 26. Calculated QCE triple points (●) for light, heavy, and super-heavy model water. The partial triple points are obtained by individually replacing zero-point energies (zpe), vibrational frequencies (freq), translational masses (mass), and rotational temperatures (rot).^[175]

It is also interesting to note that isotopic substitution leads to different cluster populations in the liquid range. The dominant cyclic octamers W_8 are slightly replaced by W_5 and W_6 ring structures. It is usually assumed that shifts in thermodynamic and dynamic properties in going from H_2O to T_2O can be ascribed to zero-point-energy-induced thermal offset and keep the structural properties nearly identical.

8.2. Icosahedral Networks—A Structure Proposal for Water

Chaplin^[133] proposed a fluctuating network of water molecules with localized icosahedral symmetry to explain many of the anomalous properties of water. This structure is built up from a mixture of hexamer and pentamer rings and contains cavities capable of enclosing small solutes. The model was developed by arranging alternating sheets of boat

and chair conformations of water hexamers from the lattices of hexagonal and cubic ice. This structure was folded to form an icosahedral three-dimensional network with capacious pores that is capable of partial collapse as a result of competition between the formation and destruction of H-bonded interactions. The stability of the network is balanced; it is able to fluctuate between an expanded low-density one of about 0.94 g cm^{-3} (Figure 19 (top)) and a denser collapsed one of about 1.00 g cm^{-3} (Figure 19 (bottom)) without breaking any H-bonds during the small changes that occur in the H-bond strength relative to the nonbonded interactions. The expanded structure is formed when structuring solutes or surface interactions are present which result in stronger H-bonds. Weak H-bonds yield the partially collapsed structure as a consequence of the formation of puckered dodecahedra. The resulting densities of both structures as given above can be related to well-known measured densities. The lower density structure may be compared with that of low-density water found around macromolecules^[176] (0.96 g cm^{-3}), of supercooled water (-45° ; 0.94 g cm^{-3}), and of low-density amorphous ice (0.94 g cm^{-3}).^[177, 178] The high-density structure compares with the density of water at 273 K (1.00 g cm^{-3}). The collapse of all dodecahedral structures gives a density of 1.18 g cm^{-3} , which is similar to that of high-density amorphous ice at 1.17 g cm^{-3} .^[178]

The structures allow the explanation of many of the anomalous properties of water, such as its density maximum as a function of temperature, and the viscosity minimum as a function of pressure. Additionally, the radial distribution pattern, the presence of both pentamers and hexamers, the change in properties and the “two-state” model of supercooling, as well as the solvation properties of ions, hydrophobic molecules, carbohydrates, and macromolecules can be reproduced.

The strongest direct evidence for this model is the agreement with the radial distribution functions. The high-density structure showed comparable radial distribution functions with that from X-ray^[179] and neutron scattering^[156, 180] data. As shown in Figure 27 there is a peak maximum at $2.8 \text{ \AA}$. The

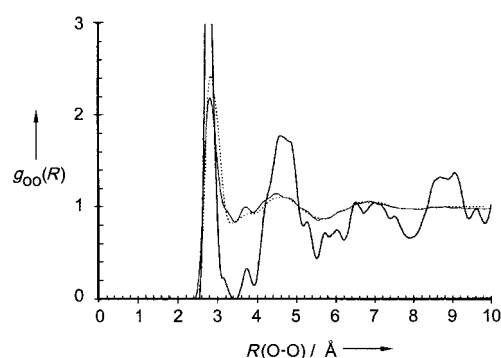


Figure 27. Comparison of the calculated radial distribution function $g_{\text{OO}}(R)$ of the high-density structure (—) with the X-ray diffraction data of water^[179] at 277 K (---). The X-ray data yield a weighted sum of all atom pair distribution functions, which is mainly determined by the O...O contribution. The model peaks have been broadened by using a normal distribution with a standard deviation of $0.1 \text{ \AA}$. The radial distribution function of oxygen atoms, as determined by neutron scattering,^[156] is also shown (· · · · ·). The figure is reproduced with the kind permission of Elsevier Science and M. F. Chaplin.^[133]

number of nearest neighbors of about 4.34 is also in good agreement with the reported 4.4 nearest neighbors calculated from diffraction data.^[42] The radial distribution functions for the low-density structure can be compared with experimental data obtained for solutions, supercooled water, and the low-density amorphous ice. The distance between the cavities of $5.4 \text{ \AA}$ is close to the value of about 5.5 and $6 \text{ \AA}$ for supercooled water^[56] and the Ne...Ne distance in water,^[56] respectively. The radial distribution function of the low-density structure also shows similarities to those of the low-density amorphous structure. Both include features similar to cubic and hexagonal ices.^[181] Neutron-diffraction data has been used to suggest the presence of pentamers, boat and chair conformers of hexamers, and partial dodecahedra.^[182] By using Gaussian broadening for the high-density structure, the resulting four peaks at 2.8 , 4.6 , 6.7 , and $9.0 \text{ \AA}$ show close agreement with the values of 2.79 , 4.56 , 6.95 and $8.60 \text{ \AA}$ measured by X-ray experiments.^[183] The agreement with neutron scattering data^[184] was even better.

8.3. A Simple Two-Structure Model for Liquid Water

A simple two-structure model for liquid water was proposed by Benson and Siebert.^[185] The authors were able to construct a model involving isomerization between clusters which reproduces, within two per cent, the anomalous heat capacity of liquid water from the melting up to the boiling point. The clusters are polycyclic, cubic-shaped octamers which can dissociate into two cyclic tetramers. These clusters (Figure 28) are held together by H-bonds and although very

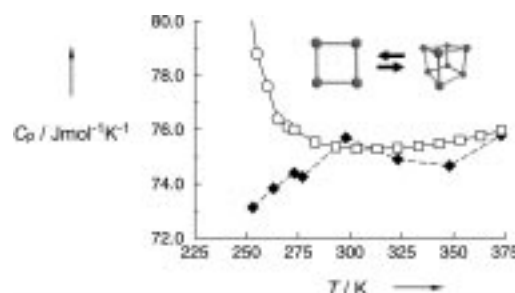


Figure 28. Heat capacity C_p of water as a function of temperature as calculated by Benson and Siebert^[185] in comparison to measured data. The two-structure model includes tetramers and cubic octamers only.

labile, they appear to be the principal species present in liquid water according to this model. The fact that this two-structure model is capable of giving reasonable heat capacities is not too surprising. Structural theories of liquid water depend on the assumption that H-bonds can be considered as “intact” or “broken”. Benson and Siebert fitted their model directly to bulk data, such as the sublimation energy of ice, the enthalpy of melting, and estimates of broken H-bonds. A satisfactory description of one or more of the properties of water over a particular range of temperature and density is usually obtained when an equilibrium of two species differing significantly in structural order and the number of H-bonds is used. As Benson and Siebert pointed out, the heat capacity

of water could also be obtained by assuming equilibria between polycyclic decamers and monocyclic pentamers. However, results from scattering experiments are not in agreement with the proposed structures.^[186] If an $R(\text{O}\cdots\text{O})$ distance of about 2.89 Å is assumed, then maxima in the pair correlation function should result at about 4.09 and 5.01 Å.^[2] A maximum at 4.5 Å is found experimentally, which supports a tetrahedral structure.

Recently, Rodriguez et al. considered the water hexamer and octamer in a theoretical study of isomerization, melting, and polarity of model water clusters.^[106] The model includes five hexamers of similar energy with different geometries and dipole moments, as well as two nonpolar octamers with D_{2d} and S_4 symmetry. The melting transitions were studied by using ab initio methods and empirical force field models. The melting transitions for the hexamer and the octamer were found at 50 and 160 K, respectively. The authors conclude that their results provide a comprehensive picture of the relationship that exists between the spatial and polarization fluctuations that occur in small water aggregates.

9. Summary and Outlook

Small water clusters and their properties can be calculated by high quality ab initio and DFT methods using extended basis sets. Most of the theoretical predictions for geometries and vibrational frequencies, as well as their behavior with increasing cluster size, are supported by experimental information. To the best of our knowledge these state of the art calculations are applied to clusters comprised of up to eight water molecules. For larger clusters Hartree–Fock calculations are performed on smaller basis sets. DFT is the method of choice for including electron correlation where post-Hartree–Fock methods are too expensive or impossible. These calculations are known for clusters with up to 30 water molecules. For most larger clusters, such as Chaplin's icosahedral water structures with 280 water molecules, only semi-empirical methods can be applied. The problem with these methods is that H-bonds and their cooperative behavior are certainly not calculated in an appropriate way. Although calculations yield accurate structures and properties for small clusters, there remain shortcomings. Growing cluster sizes may lead to a dramatic increase in the number of isomers for each species which is no longer manageable. It requires a lot of experience and knowledge to pick out the plausible low-energy structures. The harmonic approximation is a further limit for calculating reasonable vibrational frequencies. The calculated frequencies are usually overestimated and corrected by a factor typical for the chosen method and basis set. It is some comfort that the measured trend of red-shifting of the OH stretch in water clusters can be smoothly reproduced by using only one correction factor. However, this is no longer true for low-lying frequency vibrations, which are particularly important for the use of calculated frequencies in the vibrational partition function. Another deficiency is the calculation of true minimum structures. Molecular dynamics and Monte Carlo simulations have shown that bifurcated structures may play a significant role in liquid water, particularly for

describing its dynamics. These configurations are never present in low-lying minimum structures in ab initio calculations at 0 K.

The combination of calculated clusters and their properties with new laser spectroscopy experiments are likely to generate a wealth of information regarding the intricate details of how water molecules interact. Recent experiments have yielded detailed information about structural and dynamic aspects of small clusters. The clusters occur as nearly planar ring structures up to pentamers, whereas three-dimensional clusters are energetically favored with clusters larger than the pentamers. Large intermolecular zero-point energies of the H-bonds become crucial, and can alter the energy ordering of the low-lying hexamer structures. This is the reason why the cage hexamer is found in the gas phase and the quasi planar ring hexamer in liquid helium. The physical and chemical environment strongly determine the occurrence of different isomers. The geometries and vibrational frequencies have both been experimentally characterized up to the hexamer structures. The measured bond distances and vibrational frequencies provide strong support for the cooperative nature of hydrogen bonding. Growing cluster size, and thus increasing H-bond strength, lead to a shortage of intermolecular distances and a red-shift of the OH stretching modes as predicted by ab initio calculations. These findings certainly support theoretical predictions and experimental results that show the covalent character of hydrogen bonding.

Three water models based on the assumption that calculated molecular clusters and structures may be constituents of the liquid phase were recently presented. The quantum cluster equilibrium (QCE) model assumes that water species calculated from current ab initio methods are adequate representatives of the “flickering clusters” of the liquid-phase structure. This treatment of liquids is thus in the tradition of mixture models. The QCE model exhibits many characteristic features of a true gas/liquid phase transition (macroclustering, volume collapse, specific heat increase, Clausius–Clapeyron pressure dependence). The inclusion of larger ice- and fullerene-like clusters leads to a new low-temperature phase that bounds both liquid and vapor regions in first-order transition lines, and gives rise to a true triple point. Although the bucky-ice phase differs in significant respects from physical ice I_h , it manifests qualitatively correct thermodynamic features of true ice polymorphs, which suggests an important role of voluminous clusters in the liquid–solid transition. Nevertheless quantitative differences between theory and experiment currently remain. For example, the absence of a density maximum cannot be reproduced. The failure to accurately describe higher order temperature derivatives suggests the importance of incorporating vibrational anharmonic frequencies. Improved ab initio treatments of cluster–cluster interactions and molecular excluded-volume effects are also desirable. Although the current QCE model permits description of many interesting liquid properties at a useful level of chemical accuracy, rather high levels of theory as well as larger clusters may be necessary to achieve convergence to a quantitatively realistic water phase diagram.

Chaplin calculated large icosahedral structures, including 280 fully H-bonded molecules, to investigate long-range

ordering. This network can be converted between lower and higher density forms without breaking H-bonds. The structures allow explanation of many of the anomalous properties of water, such as its temperature–density and pressure–viscosity behavior, the radial distribution pattern, the presence of both pentamers and hexamers, the change in properties and the “two-state” model on supercooling, and the solvation properties of ions, hydrophobic molecules, carbohydrates, and macromolecules. As in the foregoing models, dynamic information is not obtainable. The calculation of dynamic properties is still the domain of molecular dynamics simulations.

Benson and Siebert could reproduce the anomalous heat capacity of liquid water from the melting to the boiling point by using a simple two-structure model. On the other hand, the proposed structures of a planar tetramer and a cubic octamer are certainly not suitable for describing the data obtained from X-ray and neutron scattering experiments of liquid water.

Among the proposed cluster models for water, QCE is the only unbiased approach. In the models of Chaplin and Benson discrete structures are proposed and their properties compared to those of liquid water. On the other hand, the QCE model yields equilibrium cluster populations as a result of quantum statistical calculations. Although the model does not give a continuously restructured random network, it does yield a hierarchy of species and structural motifs that may be important constituents of liquid water. Improving the quality of the calculated water clusters, as well as increasing their number and size, should permit an even better description of condensed-phase properties. However, there still remain certain limits to the capability of cluster-based approaches to understanding associated liquids in detail. Future theoretical and experimental investigations of larger water complexes showing new H-bond arrangements should ultimately enable a quantitative description of the complexity of the behavior liquid water to be made.

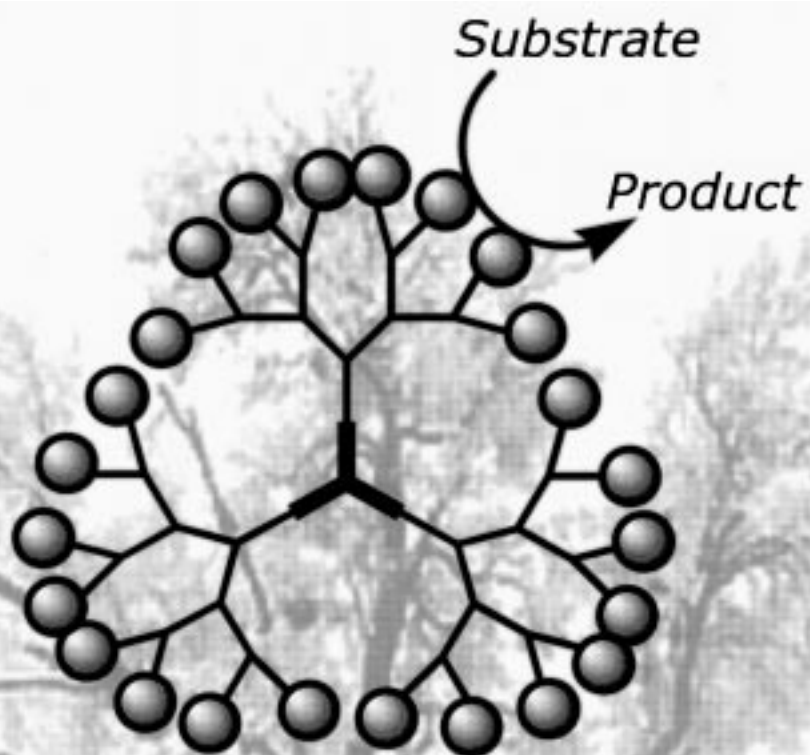
The author thanks A. Geiger, T. Farrar, and F. Weinhold for numerous discussions about the phenomena of water. Thanks are also due to A. Geiger and A. Benbow for carefully reading the manuscript. Financial support provided by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

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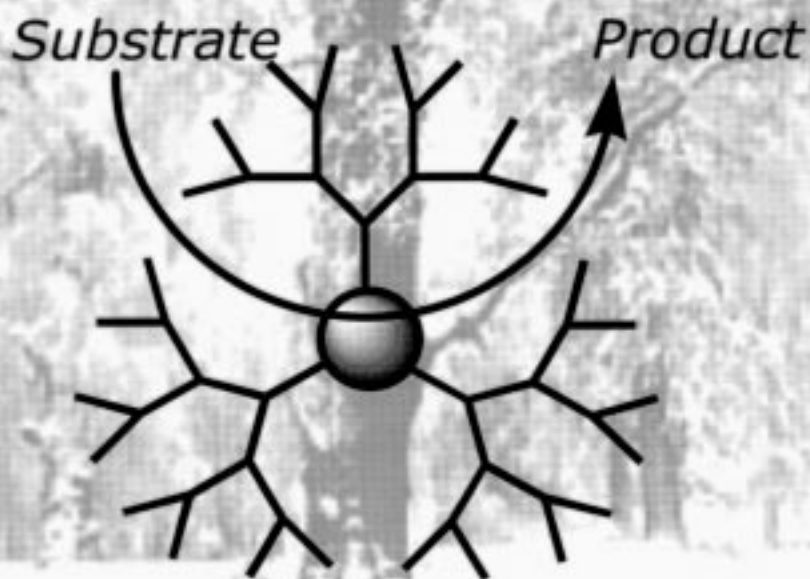
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Transition Metal Catalysis
Using Functionalized Dendrimers



Transition Metal Catalysis Using Functionalized Dendrimers

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Dendrimers are well-defined hyper-branched macromolecules with characteristic globular structures for the larger systems. These novel polymers have inspired many chemists to develop new materials and several applications have been explored, catalysis being one of them. The recent impressive strides in synthetic procedures increased the accessibility of functionalized dendrimers, resulting in a rapid development of dendrimer chemistry. The position of the catalytic site(s) as well as the spatial separation of the catalysts appears to be of crucial importance. Dendrimers that are func-

tionalized with transition metals in the core potentially can mimic the properties of enzymes, their efficient natural counterparts, whereas the surface-functionalized systems have been proposed to fill the gap between homogeneous and heterogeneous catalysis. This might yield superior catalysts with novel properties, that is, special reactivity or stability. Both the core and periphery strategies lead to catalysts that are sufficiently larger than most substrates and products, thus separation by modern membrane separation techniques can be applied. These novel homogeneous catalysts can be used in

continuous membrane reactors, which will have major advantages particularly for reactions that benefit from low substrate concentrations or suffer from side reactions of the product. Here we review the recent progress and breakthroughs made with these promising novel transition metal functionalized dendrimers that are used as catalysts, and we will discuss the architectural concepts that have been applied.

Keywords: catalysts • chirality • dendrimers • immobilization • transition metals

1. Introduction

Dendrimers are highly branched macromolecules, obtained by an iterative sequence of reaction steps, having precisely defined molecular structures. This new class of macromolecules, pioneered by the groups of Vögtle,^[1] Tomalia,^[2] Newkome,^[3] and Fréchet,^[4] has inspired many chemists in several fields. The initial focus was on the efficient synthesis and characterization of dendrimers.^[5] The development of new and better analytical techniques such as high-field NMR spectroscopy, matrix-assisted laser-desorption/ionization time of flight (MALDI-TOF) and electrospray mass spectrometry, and size-exclusion chromatography has assisted this development significantly.

Generally two synthetic strategies can be applied:

- The divergent route starting from the core building layers around it.
- The convergent route making wedges that can be connected to a core in the last step of the synthesis.

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Although the development of novel types of dendrimers still continues, the synthesis of different types of dendrimers is now well established and some are even commercially available. Obviously this is of major importance when considering applications of dendrimers. Furthermore, detailed knowledge about the macromolecular structure of dendrimers is required to understand and predict the properties of functionalized dendrimers.^[6] In several examples it has been shown that dendrimers do not adopt the ideal spherical structures their drawings might suggest. Especially amphiphilic dendrimers have structures that are far from spherical.^[7]

In several scientific fields the application of dendrimers has been explored. The different properties of large dendrimers compared to their conventional polymeric counterparts make these molecules interesting compounds for materials science. Furthermore, it has been shown that dendrimers can possess cavities within their macromolecular structure that can be used to accommodate guest molecules.^[8] Several groups are exploring the use of this property for the development of sophisticated drug-delivery systems; host–guest complexes based on dendrimers have often been reported in the light of this application. Other potential applications are artificial antennae for the efficient conversion of light energy, magnetic resonance imaging (MRI) agents, immuno-

diagnostics, gene-delivery vectors, and unimolecular micelles.^[6, 9]

Transition metal catalysis based on functionalized dendrimers is another very promising application of dendrimers.^[10] Here we review the progress that has been made in the exciting field of dendritic transition metal catalysis.

1.1. Dendritic Transition Metal Catalysts: The New Generation?

To give an answer to the question “what can dendrimers add to the field of catalysis?” we have to take a closer look at the ideal catalyst. From a catalytic point of view the ideal catalyst is highly active and selective under mild conditions, very stable and can be separated from the product using a relatively simple process. Right from the start, the regular monodisperse structure and multiarm topology of dendrimers inspired chemists to propose dendrimers with peripheral catalytic sites as soluble supported catalysts. In 1994, Tomalia and Dvornic discussed the promising outlook of surface-

functionalized dendrimer catalysts.^[11] Dendritic catalysts are often proposed to fill the gap between homogeneous and heterogeneous catalysts. However, keeping in mind that heterogeneous systems generally contain at least 10^{12} active sites per conglomerated particle,^[12] it is fair to state that the class of dendritic catalysts, containing at most 1000 active sites, is closer to the monomeric homogeneous systems. A better formulation is that functionalized dendrimers potentially can combine the advantages of both homogeneous and heterogeneous catalytic systems. Moreover, their globular shape makes these systems more suitable for recycling than soluble polymer-supported catalysts.

In principle, dendritic catalysts can provide systems that... show the kinetic behavior and thus the activity and selectivity of a conventional homogeneous catalyst. Catalysts supported on highly cross-linked polymer beads generally suffer from diminished activity compared to the homogeneous analogues, which is because of a reduced accessibility.^[13] Organic polymers show solvent-dependent swelling properties that can strongly influence the catalytic performance.



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G. Eric Oosterom studied chemistry at the University of Utrecht. His undergraduate research concerning benzo-bis-crownethers was supervised by Prof. Dr. L. W. Jenneskens (1996). He is currently completing his PhD research project in the laboratory of Prof. van Leeuwen on the application of core-functionalized carbosilane dendrimers in batch and continuous catalytic reactions.

Joost N. H. Reek did his PhD in supramolecular (organic) chemistry at the University of Nijmegen. In 1996 he went to the University of Sydney as a postdoctoral fellow, where he was involved in porphyrin chemistry. In 1998 he joined the group of Prof. van Leeuwen at the University of Amsterdam, where he currently is working as a lecturer. His research interests are homogeneous catalysis, catalysis in water, molecular recognition and supramolecular catalysis, dendrimers and dendritic catalysis, molecular modeling, and electron- and energy-transfer processes.

Paul C. J. Kamer did his PhD in organic chemistry at the University of Utrecht. As a postdoctoral fellow of the Dutch Cancer Society (KWF) he spent one year at the California Institute of Technology and one year at the University of Leiden, where he worked on the development of phosphorothiate analogues of nucleotides. He now is a senior lecturer in the group of Prof. van Leeuwen at the University of Amsterdam. His current research interests are (asymmetric) homogeneous catalysis, organometallic chemistry, combinatorial synthesis, and enzyme mimics.

Piet W. N. M. van Leeuwen has been the professor of homogeneous catalysis at the University of Amsterdam since 1989. He spent much of his career at Shell Research in Amsterdam working in the area of homogeneous catalysis and organometallic chemistry. His present research concerns the development of novel homogeneous catalysts using the full range of available tools and techniques.

- ... can easily be removed from the reaction mixture by membrane or nanofiltration techniques because of their large size compared to the products (an advantage of heterogeneous catalysts).
- ... allow mechanistic studies, because of the monodisperse, uniform character of their catalytic sites and the symmetry of the molecules (an advantage of homogeneous catalysts),
- ... allow fine-tuning of their catalytic centers by precise ligand design (an advantage of homogeneous catalysts),
- ... require relatively low metal loading (an advantage of homogeneous catalysts over heterogeneous catalysts).

In the first instance dendritic catalysts were proposed to be easily recyclable homogeneous catalysts. The question is, however, if they also can provide systems that are either more active or selective or more stable than their homogeneous monomeric analogues? This would yield systems with interesting novel catalytic properties providing an intrinsic solution for the homogenous catalyst separation problem. These novel properties induced by the dendritic framework depend on the location of the functional group within the structure. One should distinguish periphery-functionalized (dendrimer or a dendritic wedge), core-functionalized, and focal-point-functionalized (dendritic wedge) systems (see Figure 1). A combination of these conceptual approaches might lead to systems with different catalytic centers, which are ideally suited for cascade reactions. Such systems, however, have not been reported yet.

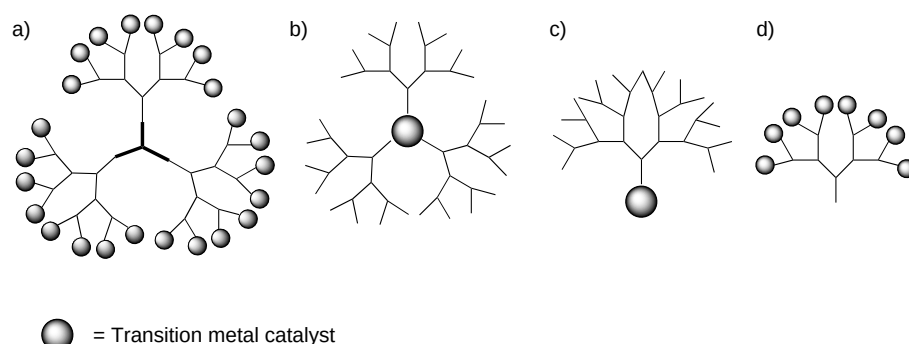


Figure 1. Catalytically active transition metal complexes can be attached to the periphery (a), the core (b), at the focal point of a wedge (c), and at the periphery of a wedge (d).

Periphery-functionalized dendrimers have their ligand systems, and thus the metal complexes, at the surface of the dendrimer. The transition metals will be directly available for the substrate, in contrast to core-functionalized systems, for example, in which the substrate has to penetrate the dendrimer prior to reaction. This accessibility allows reaction rates that are comparable with homogeneous systems. On the other hand, the periphery-functionalized systems contain multiple reaction sites and ligands, which results in extremely high local catalyst and ligand concentrations. For example, a second-generation carbosilane dendrimer functionalized with phosphine ligands (with 36 terminal phosphines; section 2.3) results in local concentrations of 8 M of ligand (dendrimer-PPh₂) and 4 M of catalysts ((dendrimer-PPh₂)₂Pd). In reactions where excess ligand is required to stabilize the catalyst this local-concentration effect can indeed result in stable

systems. Furthermore, if a reaction proceeds by a bimetallic mechanism, the dendritic catalysts might show better performance than the monomeric species.^[14] On the other hand, several deactivation mechanisms operate by a bimetallic mechanism, for example, ruthenium-catalyzed metathesis,^[15a] palladium-catalyzed reductive coupling of benzene and chlorobenzene,^[15b] and reactions that involve radicals.^[16] These deactivation pathways will be invigorated in periphery-functionalized systems.

In core- (and focal-point-) functionalized dendrimers the catalyst could benefit especially from the site isolation created by the dendritic environment. Site-isolation effects in dendrimers can be beneficial for other functionalities and a general review on this topic has recently appeared.^[17] For reactions that are deactivated by excess ligand or in cases in which a bimetallic deactivation mechanism is operative, core-functionalized systems can specifically prevent such deactivation pathway, whereas periphery-functionalized systems might suffer from relative low activity. Core-functionalized dendrimers may benefit from the local catalyst environment created by the dendrimer. Effects of desolvation of the substrate during the penetration of the dendrimer might be of importance, but very little is known about these effects. In nature, enzymes make use of these effects when substrates enter the active site of such systems.

Another significant difference between core- and periphery-functionalized dendrimers is the molecular weight per catalytic site. Much higher costs will be involved in the application of core-functionalized systems and application can also be limited by the solubility of the system (to dissolve 1 mmol of catalyst 20 g L⁻¹ is required (M_w 20000 Da, 1 active site) compared to 1 g L⁻¹ (M_w 20000 Da, 20 active sites)). On the other hand, for core-functionalized systems the solubility of the dendritic catalyst can be tuned by changing the end groups.

1.2. Dendritic Catalysts in Continuous Processes

Membrane reactors have been investigated since the 1970s.^[18] Although membranes can have several functions in a reactor, the most obvious application is the separation of reaction components. Initially the focus was mainly on polymeric membranes for enzymatic reactions. The membrane materials have improved significantly ever since, and nowadays nanofiltration membranes suitable to retain relatively small compounds are commercially available (e.g. mass cut-off 400 Da). Two forms of leaching have to be considered when using dendritic transition metal catalysts in membrane reactors: leaching of the dendritic catalyst through the membrane and metal leaching from the dendrimer (and further leaching through the membrane). For practical applications the overall retention of the (dendritic) catalyst

Flow

Dendritic Catalyst
 Substrate
 Product
 Nanomembrane

Retention = 0.999

0.990

0.950

0.900

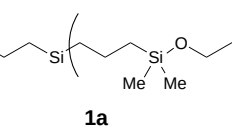
N_L

This review is divided in the following topics: periphery-functionalized dendrimers, core-functionalized dendrimers, enantioselective dendritic catalysis using periphery and core-functionalized systems, and metal nanocomposites in the dendrimer interior as catalysts. Within each topic we have chosen to organize the systems by reaction type.

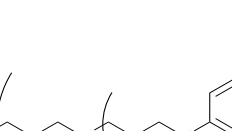
2.1. Terpolymerization of Ethene, Propene, and CO

2.2. Nickel-Catalyzed Kharasch Addition

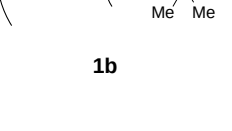
1a



1b



1c


$$CX_3Y + \text{CH}_2=\text{CHCH}_2\text{CH}_3 \xrightarrow{\text{catalyst}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CX}_3$$

Scheme 1. The Kharasch addition reaction (X = halogen; Y = H, halogen, or CF₃).

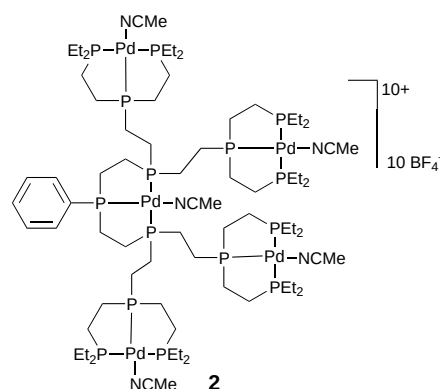
compound; 80% of the activity was found for G0 (four Ni centers) and 70% for G1 (**1a**, twelve Ni centers). The selectivity was the same in all experiments resulting in a clean and regiospecific formation of the 1:1 addition product.

Molecular models showed that the accessibility of the catalytic sites was similar for dendrimers and monomer, and it was proposed that the lower rates were because of the high local concentration of nickel centers. In a subsequent paper this effect was studied in more detail using dendrimers with different spacer lengths.^[21] An even larger decrease in activity was observed on using larger dendritic catalysts, which was attributed to surface congestion. This was strongly supported by the results of the more flexible dendrimers. The more flexible system **1c** with 12 active sites yielded a much better catalyst for the Kharasch addition reaction than **1b** (the turnover frequency (TOF) increased from 39 for **1b** to 85 for **1c**). It was proposed that the catalyst deactivation was caused by an interaction between neighboring Ni^{II} and Ni^{III} sites, which is clearly more pronounced in systems where surface congestion is larger. Alternatively one might propose that local high radical concentrations lead to termination and Ni^{III} formation. For this reaction core-functionalized systems that are large enough to induce site isolation might lead to more stable and active systems. Amino acid based dendritic wedges that were functionalized at the periphery with up to four NCN pincerlike nickel(II) groups also showed activity in the Kharasch addition reaction. No significant influence of the sterically different and more polar amino acid backbone was observed.^[22]

Some preliminary results on membrane filtration experiments have been reported. Compound **1a** exhibited decomposition while being applied in a continuous membrane reactor,^[23] which was ascribed to hydrolysis of the Si–O bond of the linker between ligand and carbosilane backbone, thus the catalytically active complexes were disconnected from the support and subsequently washed out of the reactor. In **1b** the NCN ligands are directly attached to the carbosilane backbone and therefore much more stable.^[24] Initial tests showed that **1b** was retained to 80% in the continuous membrane reactor after 100 reactor volumes (retention 0.9975) which is acceptable for many practical applications.^[25]

Similar to the nickel–nickel interaction in the pincer-functionalized dendrimers, DuBois et al. observed metal–metal interactions in palladium-functionalized systems. Dendrimers were constructed containing up to 15 phosphines in both the periphery and backbone and the palladium complexes (**2**) were prepared by the addition of [Pd(CH₃CN)₄](BF₄)₂.^[26] These systems catalyze the electrochemical reduction of CO₂ to CO, and the rates and selectivities observed for the dendritic systems were comparable to those of the monomeric complex. The electrochemical data, however, suggested the formation of Pd–Pd bonds during the electrochemical reactions. To avoid this type of dimerization a better spatial separation of the palladium sites in the dendrimer should be arranged.

Astruc et al. recognized this problem and suggested constructing star polymeric structures instead of dendrimers.^[27] In their opinion the steric congestion around the catalytic centers located at the periphery of these functionalized star



polymers would be sufficiently reduced to overcome interactions between the catalytic sites. Star shaped hexanuclear polymeric catalysts **3a** containing six CpFe^I(arene) complexes (Figure 3) were indeed as efficient as single-site complexes in the redox-catalyzed reduction of nitrite and nitrate to ammonia.^[28]

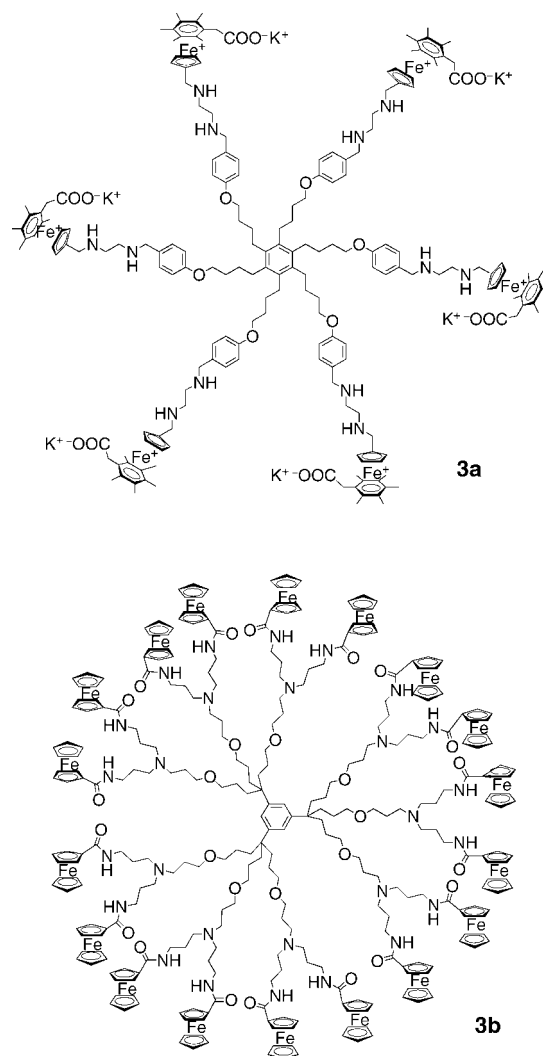
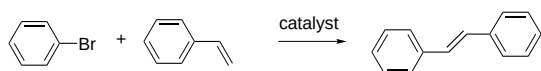


Figure 3. The star-shaped catalyst (**3a**) having electrochemically active iron centers for the redox-catalyzed reduction of nitrite at the periphery, and for comparison, the corresponding dendritic system (**3b**).

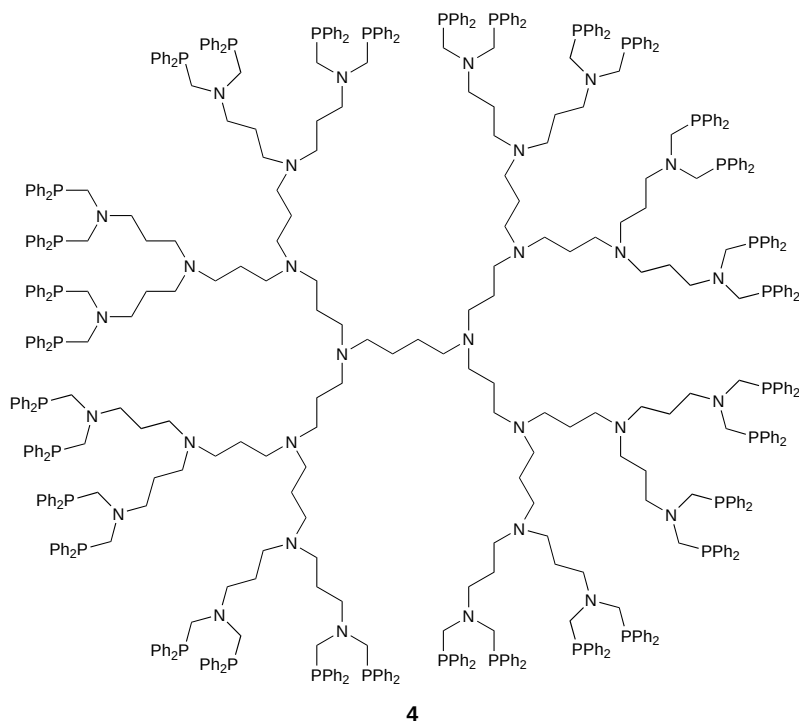
2.3. Palladium-Catalyzed Coupling Reactions

Several groups prepared systems that were functionalized with phosphine ligands at the periphery of the dendrimer (Sections 2.3–2.7). Commercially available DAB-dendrimers were equipped with diphenylphosphane groups at the periphery (**4**) by Reetz et al. by a double phosphination of the amines with diphenylphosphane and formaldehyde.^[29] The transition metal complexes **4a** to **4d** were prepared in which the dendrimer-N-(CH₂PPh₂)₂ groups act as bidentate ligands (cod = cycloocta-1,5-diene). Well-defined chelate complexes were obtained and complexes with metals bridging between different branches were not observed. The palladium complexes of these dendrimers (**4b**) were used as catalysts in the Heck reaction of bromobenzene and styrene to form stilbene (Scheme 2). Interestingly, the dendrimers showed



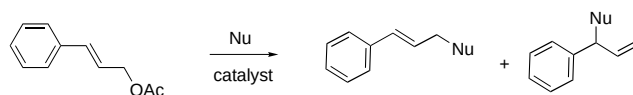
Scheme 2. The palladium-catalyzed Heck reaction of bromobenzene and styrene to form stilbene.

larger turnover numbers than the monomeric parent compounds, which was ascribed to the higher thermal stability of the dendritic palladium complexes. Palladium black formation was only observed when the monomeric species was used. The catalytic activity using a 50 % palladium loading (M:L = 1:4) was similar to systems with 100 % loading. After the reaction the dendritic palladium catalyst completely precipitated upon addition of diethyl ether. In this way the catalyst was recycled and a second catalytic run gave similar results in the Heck reaction.



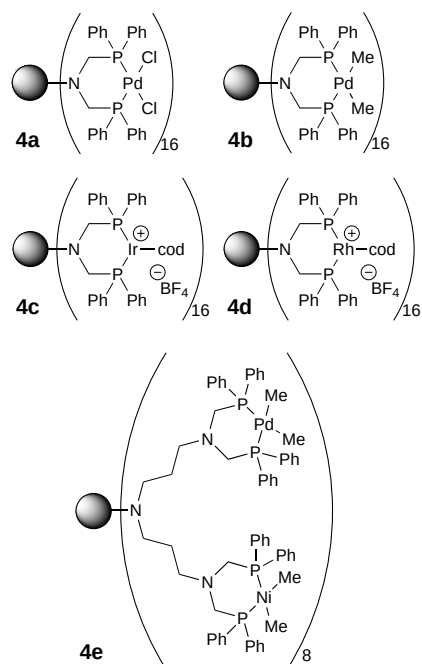
Heterobimetallic complexes **4e** have also been prepared. Half of the diphosphine ligands were used for complexation with palladium after which the remaining 50 % were treated with nickel. This strategy resulted in a statistical distribution of the metal atoms on the dendrimer surface. No catalysis using these systems has been reported to date, but interesting properties can be expected for a reaction in which a heterobimetallic mechanism is operative.^[30]

Reetz and Kragl et al. reported the use of phosphine-based dendritic catalysts for allylic substitution reactions in a continuous membrane reactor.^[31] Prior to catalysis retentions up to 0.999 were measured photometrically for G3 dendrimer **4b** (molecular weight of 10212 g mol⁻¹). Although the dendrimer stayed in the reactor, some palladium leaching was observed. Metal–ligand dissociation gives a low molecular weight palladium species that will be washed out of the reactor. During the reaction the leaching was compensated by the addition of allyl palladium chloride to the feed solution. Applying G3 **4b** in palladium-catalyzed allylic substitution (Scheme 3) the continuous reactor could be operated for over



Scheme 3. The palladium-catalyzed allylic substitution reaction (Nu = nucleophile).

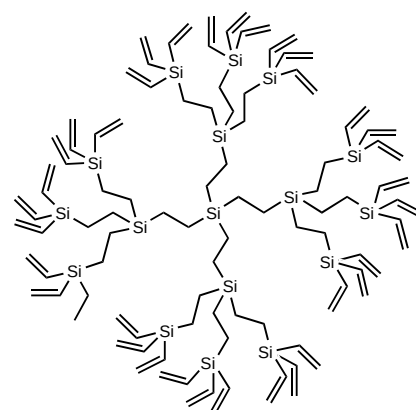
60 residence times with a conversion of up to 12 %, but obviously the product was contaminated with palladium. Better results were obtained using in situ prepared Pd complexes of a G4 dendrimer (calculated molecular weight 20564 g mol⁻¹ for 100 % palladium loading of the 32 diphosphines). After 100 residence times, the conversion had



decreased from 100% to around 75%. Only very little palladium leaching was observed during this experiment (0.14% per residence time), which could only partly explain the decrease in conversion. The formation of inactive PdCl_2 complexes was proposed to account for the additional drop in activity. The conditions were significantly altered compared to the previous experiment (different reactor material and 10-fold increase in catalyst concentration) however, for definite conclusions about the effect of the dendritic catalyst used more experiments are required.

Several groups have reported the synthesis of carbosilane dendrimers functionalized with phosphine ligands.^[32–35] These systems can be synthesized by a reaction with silicon chloride end groups (after hydrosilylation with $\text{HSiCl}_x\text{Me}_{3-x}$ of the terminal allyls) or by direct phosphination of the alkene. Van Leeuwen et al. reported carbosilane based dendritic catalysts with terminal mono- ($-\text{SiMe}_2\text{CH}_2\text{PPh}_2$) and diphosphine ($-\text{SiMe}(\text{CH}_2\text{PPh}_2)_2$) groups.^[32] The largest dendrimer (G2) contained 36 terminal monodentate phosphines. Allyl palladium complexes of these ligands were formed upon the addition of $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$. The bidentate ligands gave well-defined complexes like those observed for the DAB systems (**4**) whereas the dendrimers with the monodentate phosphines formed a mixture of complexes, differing in ring size ($-\text{P-Pd-P-dendrimer}-$). All the complexes were active in the palladium-catalyzed allylic alkylation using sodium diethyl methylmalonate as the nucleophile (batch reaction).^[32] The rates were virtually independent of the dendrimer size, suggesting that all the active sites behaved independently.

Dendrimer **5** containing 12 diphosphine–palladium complexes was studied in a continuous membrane reactor. The

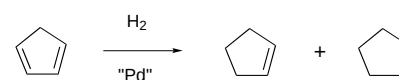


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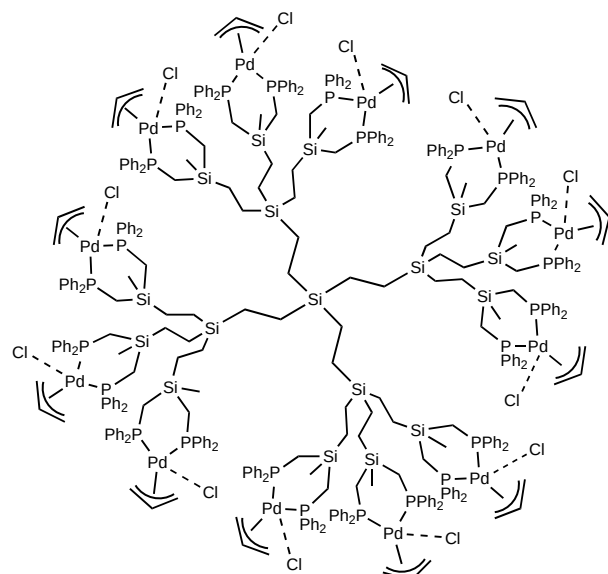
leaching of dendritic catalyst cannot account for the observed drop in activity. This suggests that the catalyst decomposed or leached through the membrane probably as small soluble metal clusters that were dissociated from the dendrimer. The similarity of these observations with those of Reetz et al.^[31] show that the practical application of dendritic palladium catalysts for the allylic substitution reaction in continuous processes is not straightforward and more investigations are required to understand the deactivation and leaching mechanisms.

2.4. Palladium-Catalyzed Hydrogenation

$\text{Pd}^{\text{II}}\text{Cl}_2$ complexes of **4** (G3) were used as catalysts in the hydrogenation of a series of conjugated dienes and compared with the corresponding monomeric complex, the catalyst immobilized on non-cross-linked polystyrene, and heterogeneous palladium catalysts.^[36] Higher activity in the hydrogenation of cyclopentadiene was found for **4** than for the corresponding monomeric complex and the polystyrene-bound catalyst (Scheme 4). The dendrimer backbone was



Scheme 4. Hydrogenation of cyclopentadiene.



5

catalytic activity (space–time yield) dropped dramatically to 10% of its initial activity within 10 residence times. The retention of unfunctionalized G2 dendrimer **6** was determined to be 0.981, that of dendritic catalyst **5** should be much higher since its molecular volume is three times larger. Therefore,

proposed to act as a base to capture HCl , thereby accelerating the formation of the catalytically active (diphosphine) PdHCl species. In line with this, the monomeric complex was also much more active in the presence of a base. The heterogeneous systems (Pd/C and $\text{Pd/Al}_2\text{O}_3$), however, were still more active than the dendritic catalyst.

Remarkably, excellent selectivity to cyclopentene was obtained on using the dendritic catalyst based on **4** in the hydrogenation of cyclopentadiene. This is a result of the relatively slow successive hydrogenation of cyclopentene as can be clearly seen in Figure 4 (slower hydrogen uptake); no explanation for this selectivity has been given. Although Pd/C

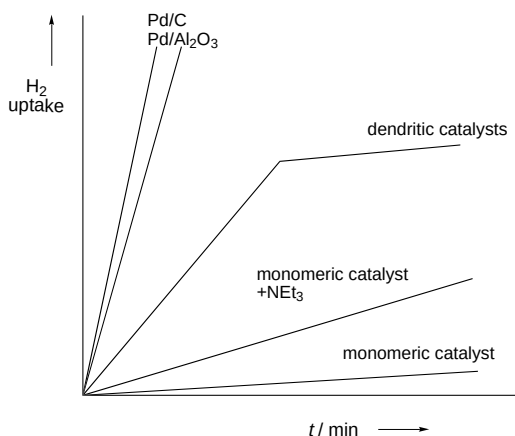


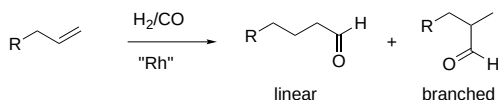
Figure 4. Schematic time courses of H_2 uptake in the hydrogenation of cyclopentadiene for various Pd catalysts.

and $\text{Pd}/\text{Al}_2\text{O}_3$ where more active catalysts the reaction was not selective; the rates of hydrogen uptake remained unchanged after conversion of cyclopentadiene into cyclopentene, yielding cyclopentane.

In the hydrogenation of 1,3-cyclooctadiene, dendritic **4**- PdCl_2 showed much higher rates than monomeric $[\text{PhN}(\text{CH}_2\text{PPh}_2)_2\text{PdCl}_2]$. The reaction was most efficient in ethanol while it was very slow in DMF. This is interesting since the dendritic complexes are not soluble in ethanol suggesting that in this solvent the catalyst system is heterogeneous, whereas in DMF the reaction proceeded homogeneously. Apparently, under heterogeneous conditions the active sites on the surface are still accessible. The hydrogenation rate was independent of the size of the substrates used, which supports this accessibility. In contrast, the polystyrene-immobilized system has the catalytic sites buried partially *within* its structure resulting in poor performance with DMF as the solvent. The heterogeneous dendritic catalyst could be recycled by centrifugation and showed only a slight decrease in activity in consecutive reactions.

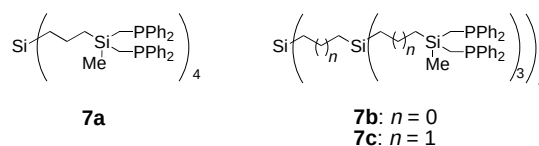
2.5. Rhodium-Catalyzed Hydroformylation

Rhodium complexes of the phosphine-functionalized carbosilane dendrimers are active in the hydroformylation of alkenes (see Scheme 5). The influence of the flexibility of the



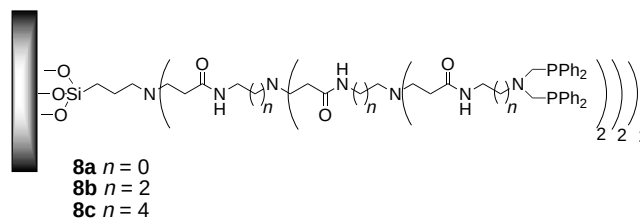
Scheme 5. Rhodium-catalyzed hydroformylation of alkenes.

dendritic backbone on the catalytic performance was studied by comparing dendritic ligands **7a–c** (conditions: toluene, 80°C , 20 bar CO/H_2).^[37] Remarkably, an increase in steric congestion on going from **7a** to **7b** and finally to **7c** did not affect the catalytic performance in this reaction, which is in contrast with the results of the Kharasch addition reaction (Section 2.2).



Reetz et al. reported preliminary results on the rhodium-catalyzed hydroformylation using the multiphosphine DAB dendrimer **4** as the ligand and they observed activities and selectivities similar to that of the parent ligand.^[29] The monodentate analogues of the phosphine-functionalized carbosilane dendrimers with the $\text{SiMe}_2\text{CH}_2\text{PPh}_2$ end groups showed a decrease in activity for the more congested systems.^[37] By changing these steric properties the structure of the peripheral rhodium complexes also changes, metal complexes are formed between phosphines of different branches. This was proposed to be the origin of the lower activity.

A similar study has been performed by Alper et al; they prepared phosphine-functionalized poly(amido amine) (PAMAM) branches **8a** that were anchored to the surface of silica particles. Primary amines were stepwise converted into



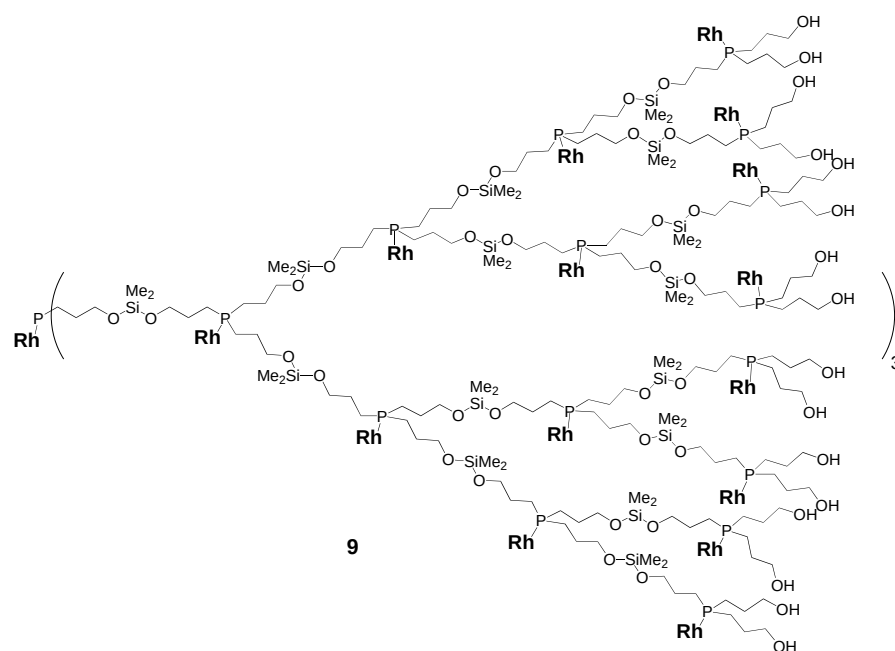
G0 to G4.^[38a] Phosphination of the terminal amine groups occurred completely for G0 to G2, but for G3 and G4 steric crowding prevented complete functionalization. Subsequent reaction with $[\{\text{RhCl}(\text{CO})_2\}_2]$ gave the corresponding dendrimer complexes, which were tested in catalytic alkene hydroformylation. Using styrene as a substrate, the G0–G2 dendritic catalysts afforded aldehydes in nearly quantitative yield even at room temperature. They showed good regioselectivity to the branched product (linear to branched ratios as high as 1:30). G3 and G4 catalysts showed only considerable activity at elevated temperatures. To study the impact of steric congestion on the hydroformylation reaction a new series of ligands was prepared (**8a–c**), differing in flexibility because of variation in spacer length.^[38b] From comparison of the catalytic activity of these ligands it was concluded that steric congestion indeed lowered the activity. This is in contrast with the results obtained with the homogeneous dendritic systems. A detailed study using both systems under similar conditions should be performed before any conclusions can be drawn. The reusability of the immobilized catalysts has been tested by performing recycling experiments. Recovery of the catalyst was relatively easy since the particles were large enough to be separated by microporous filtration. No significant loss of activity or selectivity (for the branched product) was observed during five consecutive runs.

Carbosilane dendrimers based on polyhedral oligosilsequioxane cores containing up to 72 vinyl groups (vinyl-POSS)

have been phosphinated with HPR_2 ($\text{R} = \text{Me}, \text{Et}, \text{Hexyl}, \text{Cy}, \text{or Ph}$).^[35] The rhodium complexes of the alkyl–phosphine-functionalized systems were catalytically active in hydroformylation reactions yielding alcohols instead of aldehydes. Interestingly, the dendritic catalyst with 24 PET_2 end groups was slightly more selective for the linear product (linear: branched = 3.1) than the monomeric ligand PET_3 (linear: branched = 2.4), whereas for the other dendritic catalyst the selectivity was lower. It was suggested that this higher selectivity was because of a subtle steric control over the reaction.

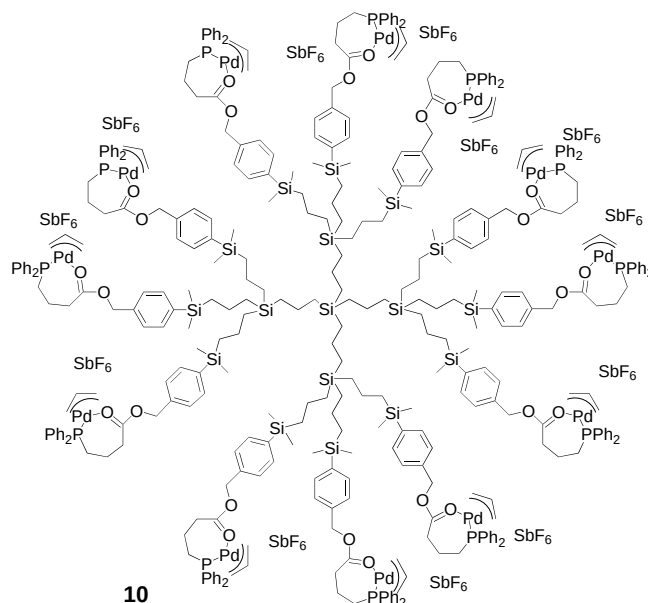
2.6. Rhodium-Catalyzed Hydrogenation

In the group of Kakkar, dendrimers such as **9** ($\text{Rh} = [\text{Rh}(\text{cod})\text{Cl}]$), having phosphines as branching points, were synthesized by acid–base hydrolysis of aminosilanes with alcohols.^[39] The synthesis of these dendritic systems is relatively straightforward, but the dendrimers contain labile silicon–oxygen bonds making them less suitable for application in continuous processes. The phosphorus donor atoms can be used to complex a variety of transition metals. Interestingly, the complexes can be formed before or after the acid–base reaction that forms the dendrimer. The Rh^{I} metallodendrimers were catalytically active in the hydrogenation of decene, and the larger system **9** showed only a small decrease in activity compared to the monomeric rhodium complex. Rates around $400 \text{ mol}(\text{molrhodium})^{-1} \text{ h}^{-1}$ were obtained in THF at 25°C and 20 bar of hydrogen. After extraction and recrystallization the catalysts were reused showing 95% of the original activity in the second run. Unfortunately, the catalytic performance of the complexes at the periphery was not compared with those located in the interior.



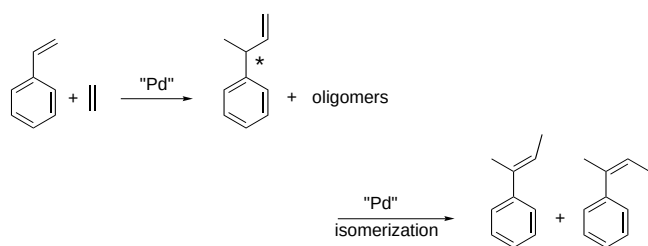
2.7. Palladium-Catalyzed Hydrovinylation

Van Koten and Vogt et al. prepared carbosilane dendrimers **10** that were functionalized with hemilabile P,O -ligands at the surface.^[40] The palladium complexes of this system are active



catalysts in the hydrovinylation reaction of styrene (Scheme 6), an important reaction since it potentially provides easy access to chiral building blocks for the preparation of fine chemicals. Key problems in this reaction are the selectivity of the reaction, oligomerization and isomerization side reactions, and the stability of the catalyst. The dendritic catalysts were found to be rather stable in the batch process. Isomerization of the product, which normally occurs at high

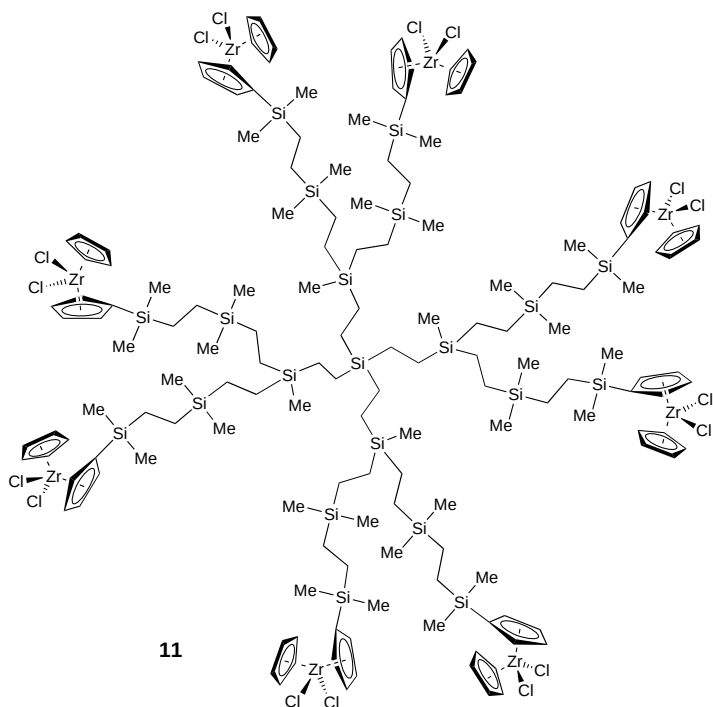
conversion, could be suppressed by stopping the reaction at low conversion. Performing this reaction continuously is therefore interesting since it can combine a high space–time yield with a low conversion and thus a high selectivity.^[40] Retention of the dendrimers with four or twelve palladium sites in a membrane reactor was at least 85%, which should be sufficient to prove the concept. Indeed the selectivity to the desired chiral 3-phenylbut-1-ene was very high in the continuous hydrovinylation of styrene, but the rate of the reaction decreased rapidly because of decomposition of the catalyst **10**. This decomposition was confirmed by the observation of palladium precipitate on the membrane.



Scheme 6. Hydrovinylation of styrene.

2.8. Metallocene-Catalyzed Polymerization

Seyferth synthesized carbosilane dendrimers with 4, 8, and 12 peripheral zirconocene, hafnocene, and titanocene groups.^[41] Dendrimer **11** containing eight zirconocene dichlorides was applied in the methylaluminoxane (MAO) activated olefin (co)polymerization (Table 1) and in silane polymerization.



Considerable activity of **11** in the ethylene polymerization and copolymerization (of two different alkenes) was found (5760 kg polyethylene (mol metal)⁻¹ h⁻¹). However, these systems are ten times less active than monomeric zirconocenes (Kaminsky et al.^[42] reported activities as high as

Table 1. (Co)polymerization of alkenes using zirconocene-functionalized dendrimer **11**.

Substrate 1	Substrate 2	Activity [kg mol (Zr) ⁻¹ h ⁻¹]
ethylene		5760
1-hexene		11
cyclopentene		29
ethylene	propylene	1460
1-hexene	cyclopentene	15

60 900 kg (mol metal)⁻¹ h⁻¹). Hyperbranched polymers based on dimethylvinylsilane were prepared,^[41b] which are attractive because in one step large dendrimerlike structures can be obtained. After functionalization of their irregular surface with zirconocenes, they were tested in ethylene polymerization. Unexpectedly, a higher activity (12 400 kg mol⁻¹ h⁻¹) was observed for these hyperbranched polymers than for **11**.

3. Core-Functionalized Dendritic Transition Metal Catalysts

In this section we will discuss the important contributions of core- and focal-point-functionalized dendrimers in catalysis. These two approaches result in similar systems intended to have similar properties. The choice of either the core- or focal-point-functionalization has mainly been based on synthetic accessibility. There is a difference, however, in that core-functionalized systems are more efficient in shielding the catalysts than the focal-point-functionalized ones. The latter require higher generations to give similar effects. To demonstrate this difference we performed molecular dynamics calculations of a first-generation (phosphine) core-functionalized and a second-generation focal-point-functionalized system (Figure 5).^[43] In the core-functionalized dendrimers the phosphine ligand is located at the center of the molecule, thereby being shielded from the exterior environment by the dendritic architecture. In the focal-point-functionalized system the phosphine is located closer to the surface of the dendrimer, and the dendrimer shielding is less effectively.

The specific micro-environment created by dendritic structures shows great similarity to biological systems such as enzymes. This has greatly stimulated chemists to prepare systems based on core-functionalized dendrimers that mimic certain properties of biological systems, but these systems are generally not used for transition metal catalysis.^[44] By using these mimics natural features, such as, hemoprotein–dioxygen binding, selective recognition of guest molecules, and stabilization of, for instance, iron–sulfur clusters have been studied. Dendritic iron porphyrins were examined as cytochrome mimics, reproducing the buried electroactive heme core (with the Fe^{III}/Fe^{II} couple) within a dendrimer superstructure, which is a model for the natural protein shell.^[44i] Several groups have studied recognition of guest molecules by dendritic receptors.^[44f–h, 45] With respect to catalysis, core-functionalized systems can potentially mimic enzyme properties.

3.1. Polymerization

The first example of a catalytic reaction at the core of a dendrimer was provided by Fréchet et al. using dendritic alcoholates such as **12** as macro-initiators for anionic ring-opening polymerization of ϵ -caprolactone (Scheme 7).^[46] Usually, in the polymerization of ϵ -caprolactone, alkali metal alcoholates yield low molecular weight (M_w) polymers with

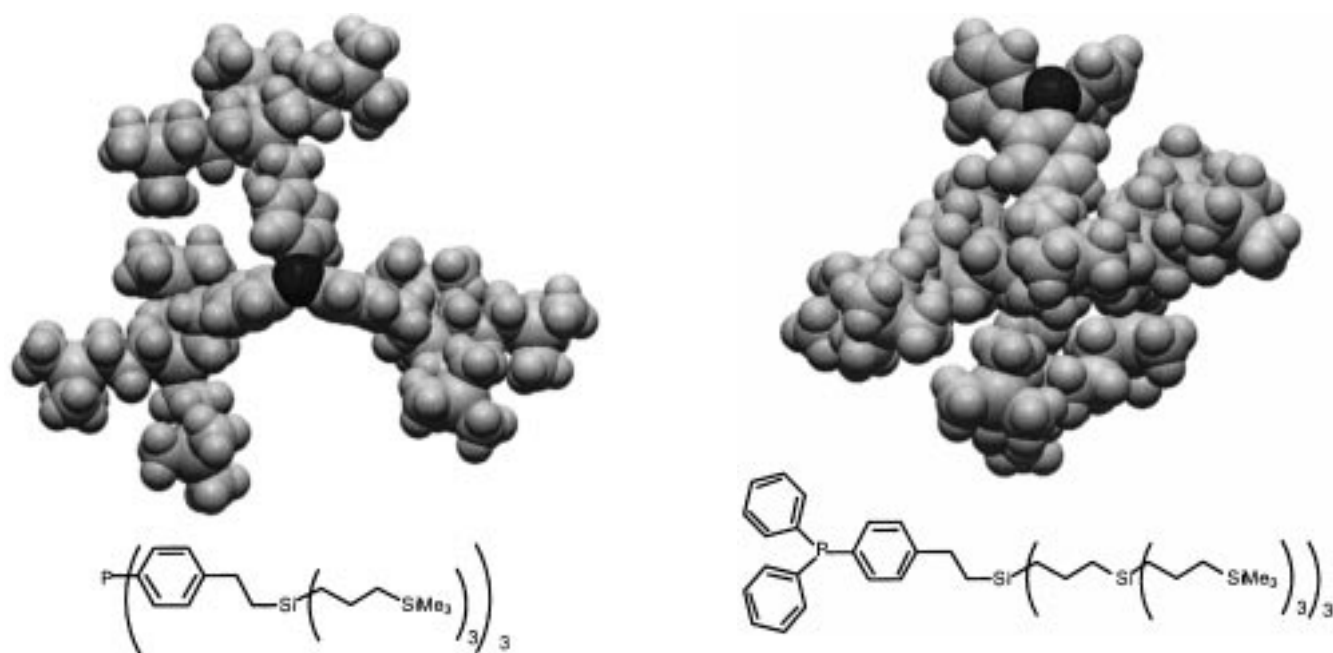
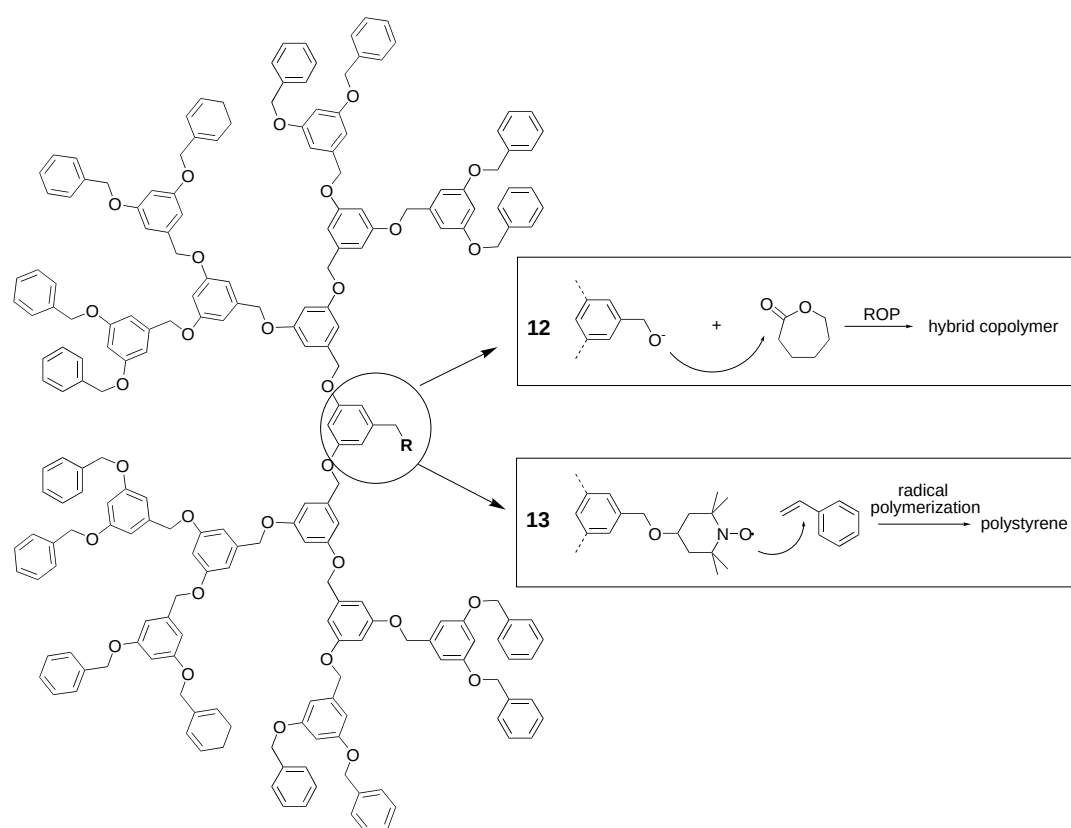


Figure 5. Molecular modelling (dynamics) clearly shows the efficient embedding of the phosphine ligand in the core-functionalized system (left) compared to the focal-point-functionalized wedge (right).



Scheme 7. Polymerization reactions at the focal point of a dendron: anionic ring-opening polymerization (ROP) of ϵ -caprolactone (**12**), and styrene radical polymerization (**13**).

broad M_w distribution. Earlier studies had shown that steric bulk around the reaction center leads to suppression of side reactions as well as to a decrease of “backbiting”, which is responsible for low M_w products. Furthermore, solubility problems usually result in low M_w polymers. The dendritic

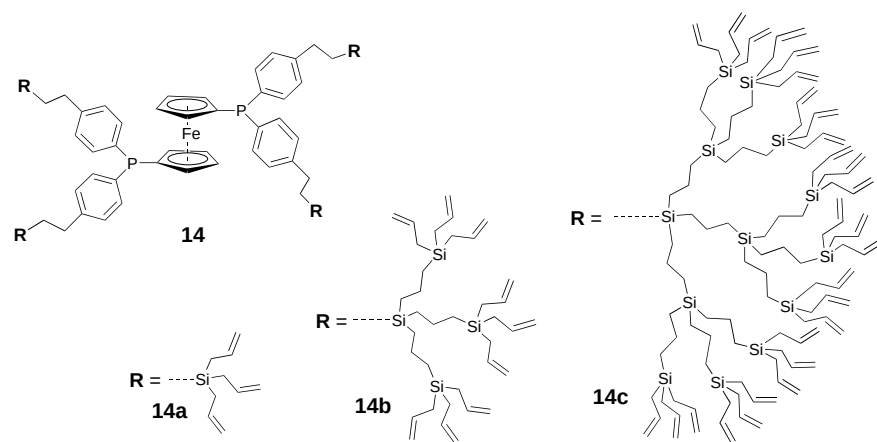
initiators appeared suitable initiators because of their excellent solubility in THF and their steric bulk prevented “backbiting”. The G4 alcoholate acts as a highly effective initiator (Scheme 7) producing high M_w polymers with a narrow M_w distribution of 1.07. The initiator efficiency was

estimated to be close to 100%, confirming the good accessibility of the reactive core. The G1 analogue produced only oligomers in very low conversions, which resembles the behavior of potassium *tert*-butoxide. Thus, the large dendrimers prevent termination of the polymerization by shielding the growing tip from reaction with a chain of another growing tip.

Similarly, dendritic wedges were designed for use in the synthesis of living polymers and living block copolymers by controlled radical polymerization.^[47] A nitroxyl radical (TEMPO) was attached at the focal point of G1 to G3 wedges (**13**, Scheme 7). In polymerization reactions low polydispersities were obtained using the high generation dendrimers because of the irreversible release of the growing chains and slow recombination. This result shows the necessity of having polymer chains that are compatible with the dendrimers. Unfortunately, insolubility of the polymer–dendrimer complexes limited the growth of the chains.

3.2. Palladium-Catalyzed Allylic Alkylation

In our group core-functionalized dendritic catalysts based on carbosilane dendrimers have been prepared.^[48] A novel route was developed to synthesize dendritic wedges with arylbromide as the focal point. These wedges were divergently coupled to a ferrocenyl diphosphine core to obtain dpfp-like ligands **14** (dpfp = bis(diphenylphosphanyl)ferrocene). Other phosphine ligand core-functionalized systems have also been prepared using the same strategy.^[49]



Bidentate palladium complexes of **14** were formed upon the addition of PdCl_2 , as evidenced by ^{31}P NMR spectroscopy. Even the largest systems formed *cis* complexes. Crotylpalladium chloride complexes were prepared in situ and used as catalysts in allylic alkylation reactions (Table 2, Scheme 3). The rate of alkylation of 3-phenylallyl acetate with sodium diethyl methylmalonate slightly decreased upon increasing generation number. More importantly, a change in product regioselectivity was observed on going to higher generations, resulting in an increase of branched product from 10% for dpfp to 21% for the largest system. It was proposed that the apolar microenvironment created within the carbosilane

Table 2. Activities and selectivities in the allylic alkylation reaction of 3-phenylallyl acetate with sodium diethyl methylmalonate using carbosilane dendrimers with a dpfp core.

L	TOF [$\text{mol mol}^{-1} \text{h}^{-1}$] ^[a]	Branched product [%] ^[b]
dpfp	72	10 (± 0.7)
14a	76	12 (± 1.2)
14b	58	13 (± 0.8)
14c	17	21 (± 0.4)

[a] All catalytic reactions reached full conversion in 24 h. [b] The selectivity of the reaction was independent of the conversion.

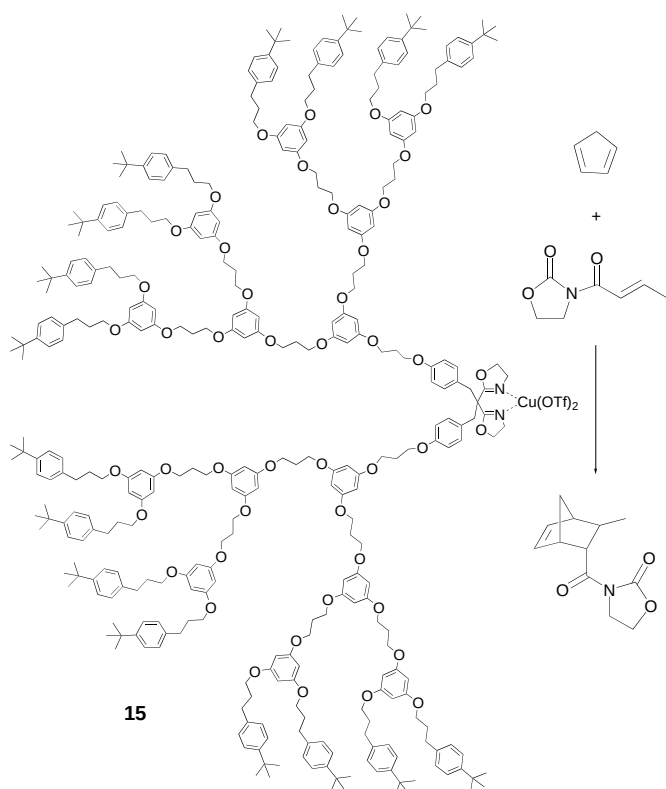
dendrimers caused this change in selectivity.^[50] Recent studies of allylic alkylation and Heck reactions confirmed this relationship between solvent polarity and product regioselectivity.^[51] In contrast, steric hindrance of the branches and an increase in the P–Pd–P bite angle because of increasing steric interactions between the dendritic substituents on the phosphorus atoms would preferentially lead to the linear product (for this substrate).^[49, 52] Allylic alkylation using **14c** was also performed in a continuous membrane reactor. Catalytic activity was retained for at least 20 residence times without significant loss, suggesting that the stability of core-functionalized systems is larger than that of their periphery-functionalized analogues.^[49]

The rhodium complexes of analogues of **14** (trimethylsilyl instead of allyl end groups) are active in the hydroformylation of 1-octene.^[53] In contrast to the palladium-catalyzed allylic alkylation the activity for all generations of dendritic catalyst was similar. This clearly demonstrates that the relative activity

for the higher generation core-functionalized dendrimers varies, depending on the type of reaction. This obviously depends on the steric demands of the rate limiting step of the reaction.

3.3. Copper-Catalyzed Diels–Alder Reactions

Chow et al. reported the synthesis of a series of poly(alkyl aryl ether) dendrons (G0–G3; G3 (**15**) is shown in Scheme 8) functionalized at the focal point with dendritic bis(oxazoline) ligands.^[54] Cu^{II} complexes of these dendrimers catalyze the Diels–Alder reaction between cyclopentadiene and *N*-2-butenoyl-2-oxazolidinone. A detailed study revealed that the reaction follows enzymelike Michaelis–Menten kinetics. A reversible formation of the copper–dienophile complex is followed by the rate-limiting conversion into the Diels–Alder adducts. The association constants of the catalyst–dienophile complex (k_1/k_{-1}) decreased slightly with the higher generation dendrimer. Upon complexation of the dienophile at the focal point the geometry at the metal center changes. This results in an increase in steric repulsion between the dendritic wedges which is more pronounced for the larger systems. Since the dienophile was used in large excess during the catalytic experiments the copper was present as a dienophile complex



Scheme 8. Diels–Alder reactions using Cu^{II} –bis(oxazoline) complexes located at the core of polyether dendrimers.

in all the systems, thus under these conditions no effect of this difference on the catalytic activity was expected. Indeed the activity of the dendritic catalysts G0–G2 was very similar. However, a marked drop in activity was observed when G3 was used as the catalyst. The size of this dendritic system results in a change in spatial structure around the catalytic core from planar to globular. The decrease in reaction rate is proposed to be because of a decrease in steric accessibility, with G3 thus acting more like a core-functionalized dendrimer.

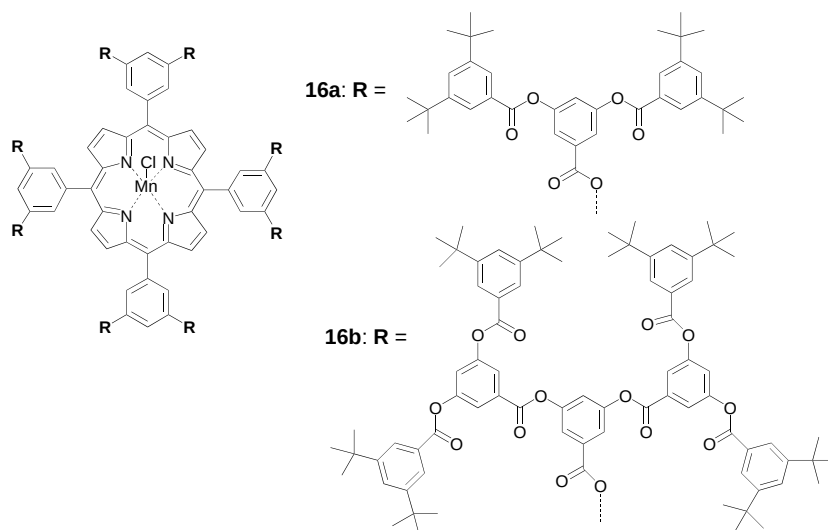
This encapsulation effect was further studied by determination of the substrate selectivity using substrates of different sizes. Dienophiles with different tail lengths were applied in a 1:1 molar ratio to react with cyclopentadiene in the presence of catalyst. The smaller dienophile reacted slightly faster than the bulkier one for all the catalysts studied (non-dendritic parent complex, G1- $\text{Cu}(\text{OTf})_2$, and G3- $\text{Cu}(\text{OTf})_2$). More importantly, G3- $\text{Cu}(\text{OTf})_2$ ($k_{\text{rel}} = 1.18$) displayed higher substrate selectivity than G1- $\text{Cu}(\text{OTf})_2$ ($k_{\text{rel}} = 1.05$).

3.4. Manganese-Catalyzed Epoxidation

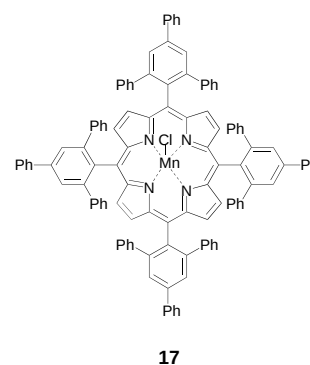
Introduction of dendritic wedges on metalloporphyrins results in core-functionalized dendrimers in which the por-

phyrin unit is shielded from the bulk solution. These type of systems were mainly prepared to mimic the microenvironment effect of hemoproteins since this plays a crucial role in dioxygen binding. Suslick et al. used steric shielding of the porphyrin unit to establish regio- and shape-selective catalysis.^[55] Eight bulky G1 and G2 poly(aryl ester) dendrons were connected to the porphyrin core to give the manganese(III)-porphyrin complexes **16**. These bulky catalysts have been tested as regioselective epoxidation catalysts, using iodosylbenzene as the oxygen donor, employing nonconjugated dienes that differ in steric hindrance. The dendritic epoxidation catalysts show greater preference for the least hindered double bond than less sterically hindered porphyrins do: 1,4-octadiene epoxidation of the terminal C=C bond is four times more selective using **16b**. A similar effect, but less pronounced, was observed for a moderately hindered (2',4',6'-OMeC₆H₄)Mn^{III}-porphyrin.

Epoxidation of 1-alkenes is generally slower than that of the more electron-rich internal alkenes, but steric effects can reverse this trend; up to threefold higher selectivities for 1-alkenes compared to internal alkenes have been observed when using the dendritic catalysts. Remarkably, there was no significant rate difference between parent and dendrimer-encapsulated catalysts. Molecular modeling studies showed that, although access from “above” is completely restricted by the dendrimer branches on both faces of the porphyrin, significant cavities at the “sides” of the porphyrin plane



exist which permit the entry of the substrates. Compounds **16a** and **16b** have larger pockets (ca. 7–10 Å) than the double pocket 5,10,15,20-tetrakis(2',4',6'-triphenylphenyl)porphyrin **17** (~4 Å), which is fully consistent with the higher selectivity obtained using **17**.^[56]



4. Enantioselective Transition Metal Catalysis using Dendrimers

Chirality in dendritic architectures has been reviewed in a recent “Concepts” article by Meijer et al.^[57] The traditional concepts of chirality for small molecules are not sufficient to explain the chiroptical properties of some of the chiral dendrimers. Some hypotheses have been proposed, but more detailed studies on novel systems are required to confirm these ideas.

Seebach et al.^[58] classified the several ways to introduce chirality in a dendrimer:

- 1) It can have a chiral core (Figure 6a).
- 2) The chirality can be introduced at the periphery (Figure 6b).
- 3) Chiral branching units can be used (Figure 6c).
- 4) Constitutionally different branching units can be attached to a chiral core (Figure 6d).

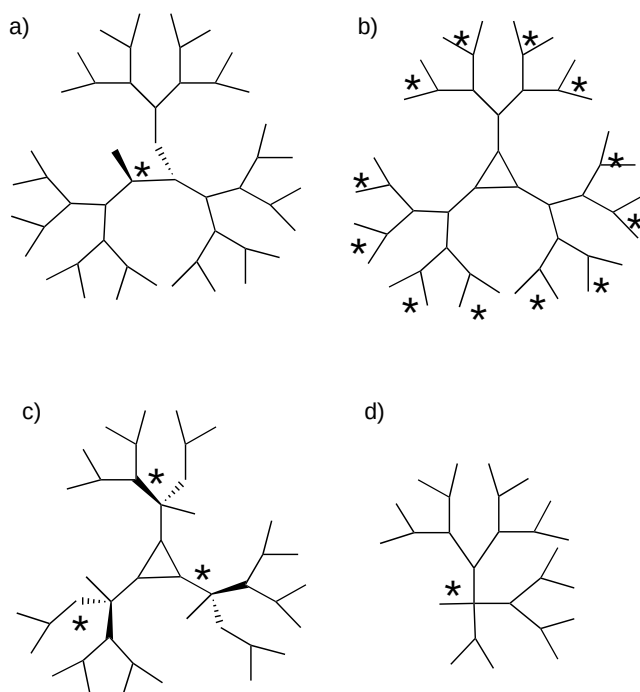


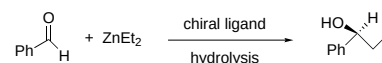
Figure 6. Schematic picture of the positions where chirality can be introduced in the framework of dendrimers.

Moreover, one can prepare systems that combine these types of chirality. Some examples show that the local chirality in the core of a dendrimer can result in a cryptochiral dendrimer that exhibits no optical activity. Also, in systems that are functionalized at the periphery with chiral groups, the optical rotation can strongly depend on the number of end groups. Generally, the rigidity of the system and the dense packing of chiral groups can have a huge impact on the stereochemical properties. For enantioselective transition metal catalysis using chiral dendritic catalysts these factors are likely to be of similar importance. In the field of enantioselective dendrimer catalysis, several reports have appeared and are summarized in ref. [10d].

4.1. Periphery-Functionalized Chiral Dendritic Catalysts

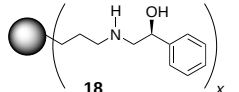
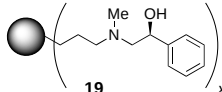
4.1.1. Diethylzinc Addition

Meijer et al. used poly(propylene imine) dendrimers, that were functionalized with chiral amino alcohol ligands, for the Et_2Zn addition to benzaldehyde (Scheme 9).^[59] Preliminary results using **18** and **19** are given in Table 3, showing high



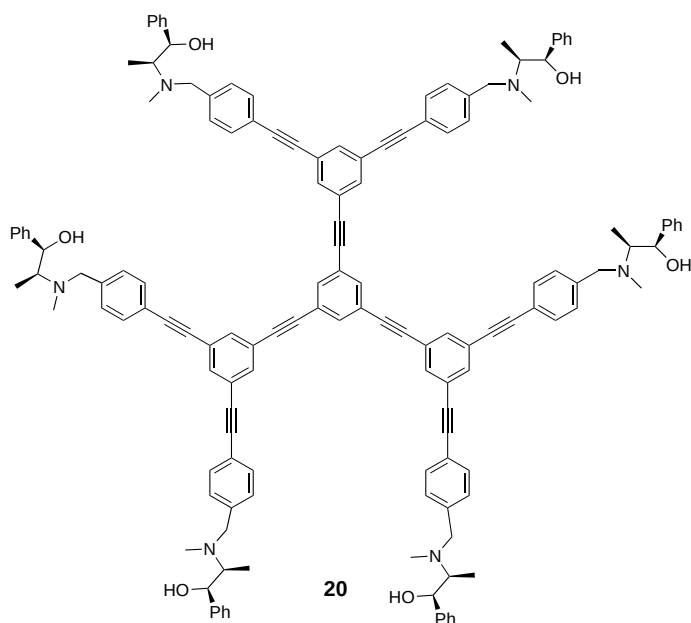
Scheme 9. The diethylzinc addition to benzaldehyde yielding optically active secondary alcohols.

Table 3. The use of modified poly(propylene imine) dendritic catalysts **18** and **19** for the addition of diethylzinc to benzaldehyde.

Number of end groups (x)	 18		 19	
	Yield [%]	ee [%]	Yield [%]	ee [%]
1	82	36	86	27
2	75	36	77	25
4	54	11	86	25
8	58	6	64	24
16	63	13	57	18
32	49	10	70	18
64	57	7	68	18

yields of 1-phenylpropanol for all generations. Moderate enantioselectivities were obtained for the smaller dendritic catalysts and the *ee* decreased with increasing generation number: upon using G5 almost no selectivity was observed, which was proposed to be a result of the dense packing of the chiral end groups at the periphery. Presumably, this leads to several “frozen-in” conformations (this was also observed for the “dendritic box”^[8, 60]), which is directly related to the presence of different catalytic sites. Introducing spacers between the dendrimer surface and the chiral functionalities to minimize steric interactions might solve this problem.^[57]

Poly(amido amine) dendrimers were functionalized with four and eight chiral amino alcohol groups.^[61] In the presence of these chiral ligands, enantioselective addition of Et_2Zn to various *N*-diphenylphosphinylimines was examined. With *N*-diphenylphosphinylbenzaldehyde as the substrate the monomeric parent ligand gave 92% *ee*, whereas the dendritic catalysts showed only moderate enantioselectivities (43% *ee* for G0 and 30–39% *ee* for G1). The reaction rates also decreased for the larger systems. Thus a similar effect was observed for these systems as for those of Meijer et al.;^[59] the high local concentration of chiral active sites leads to a diminishing of the overall enantioselectivity of the reactions. In a subsequent paper it was reported that similar ligands linked to a more rigid dendrimer **20**^[62] gave enantioselectivities similar to the parent compound in the addition reaction of Et_2Zn to *N*-diphenylphosphinylimines and at similar rates. In **20** the chiral ligands are effectively separated by the rigid



backbone yielding systems that do indeed have independent catalytic sites.

Seebach et al. prepared G0 and G1 poly(phenyl benzyl ether) dendrimers functionalized with three or six terminal $\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs; for the structure of the TADDOLs see Scheme 10).^[63] The $\text{Ti}(\text{OCHMe}_2)_2$ complexes of these TADDOLs were applied in the catalytic nucleophilic addition of Et_2Zn to benzaldehyde. The yields are generally lower than for mononuclear Ti-TADDOLates, but the enantioselectivity of the reaction for (*S*)-1-phenylpropanol was high for all the systems used (94% *ee* for the largest dendritic catalyst compared to 96–98% *ee* for the other systems). The dendritic catalysts could be separated from the reaction mixture on a silica column, but reuse was not reported.

4.1.2. Rhodium-Catalyzed Hydrogenation

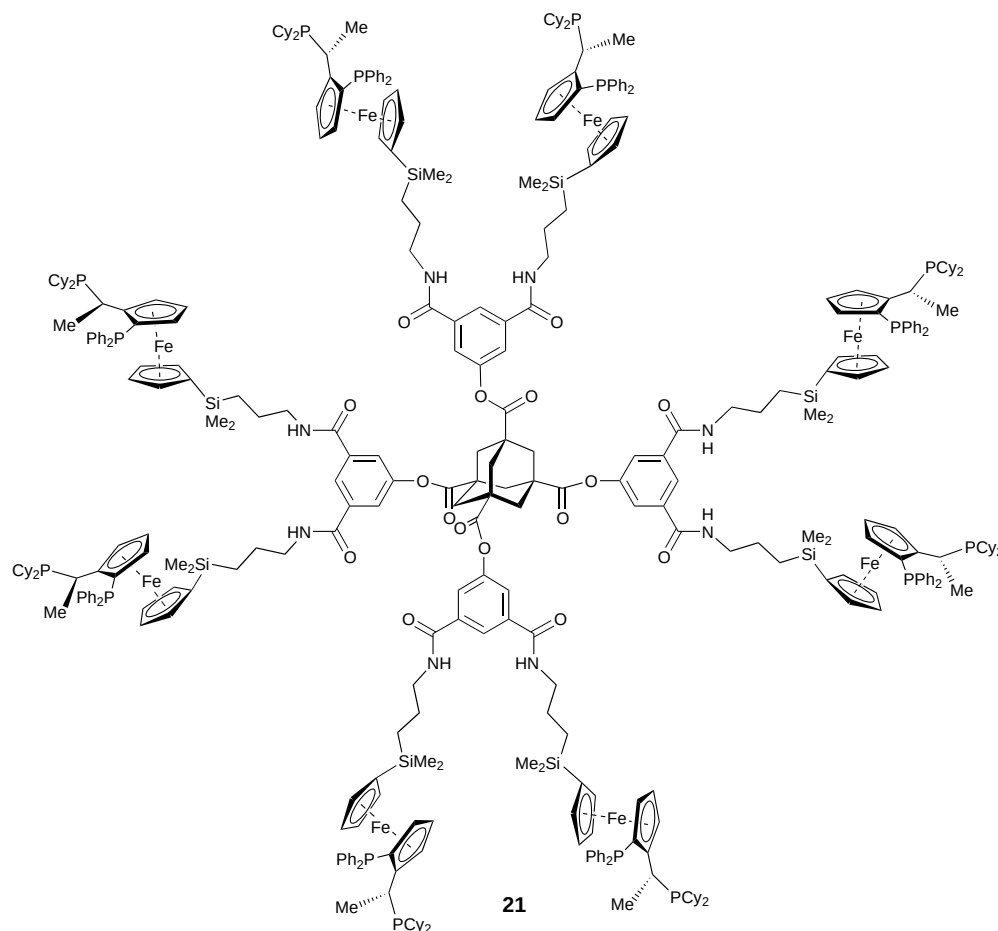
Togni et al. reported dendritic catalysts based on chiral ferrocenyl diphosphine ligands. Using different cores they obtained systems with 3, 6, 8^[64] (complex **21**) 12, 16,^[65] and 24^[66] “Josiphos” units (Cy = cyclohexyl). Rhodium complexes of these systems were obtained by stirring one equivalent of ligand with

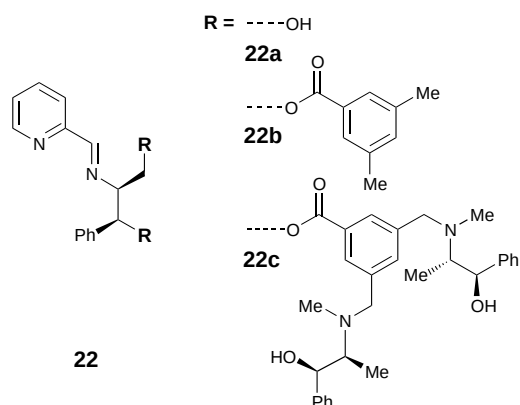
$[\text{Rh}(\text{cod})_2]\text{BF}_4$ in dichloromethane. These complexes were used as precursors in the hydrogenation of dimethylitaconate (conditions: 1 mol % rhodium, methanol, 1 bar H_2 pressure). Remarkably, all the reactions went to completion in 20 min and all the dendritic catalysts gave 98% *ee* or higher, which is comparable with mononuclear Rh-Josiphos complexes (99% *ee*). In the lower generations no significant steric interactions between the catalytic sites are expected. The observed high enantioselectivity for the largest dendritic systems, however, clearly suggests that also in these systems the catalysts work as independent sites without significant obstruction by steric congestion. Preliminary nanofiltration experiments indicated that **21** could be completely retained, but catalysis in a continuous process using **21** has not been reported.

4.2. Core-Functionalized Chiral Dendritic Catalysts

Brunner introduced the term “dendrzymes” for core-functionalized transition metal catalysts developed for enantioselective catalysis.^[67] Diphosphine and diimine ligands were coupled to the focal point of chiral dendritic branches to create a chiral pocket around the transition metal.

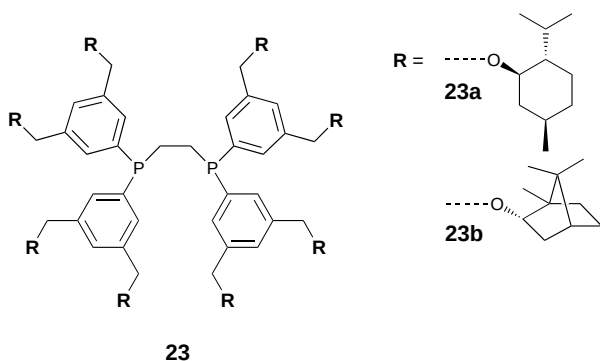
The “dendrzyme” **22a–22c** were used in the Cu^{I} -catalyzed cyclopropanation of styrene and a slight increase from <2% *ee* to about 10% *ee* on changing from parent





pyridine aldimine **22a** to **22b** was observed showing that the chiral pocket slightly enhances the enantioselectivity of the reaction. Further expansion with a second layer of chiral substituents (**22c**) did not result in higher *ee* values.^[68]

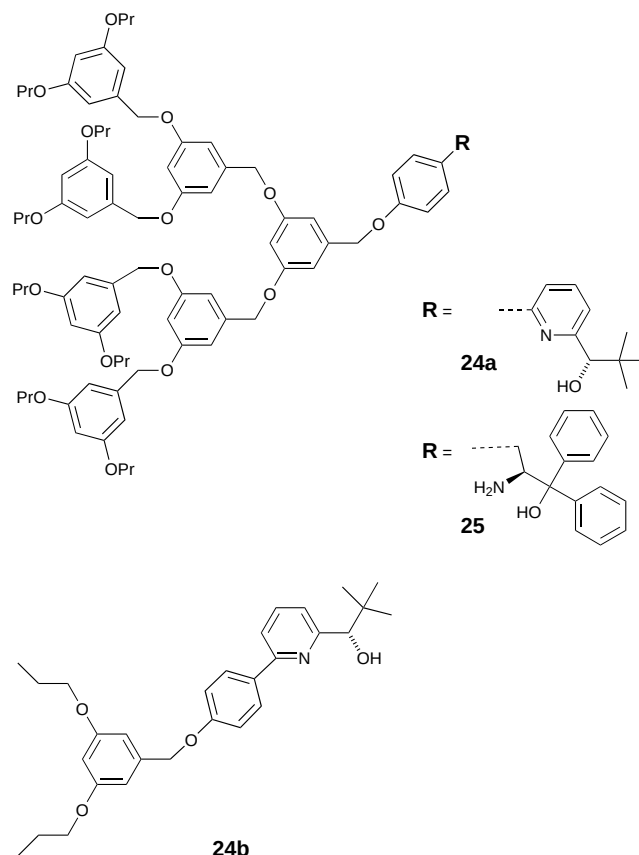
Two-layer chiral diphosphine dendrizymes such as **23** were synthesized by a divergent route.^[67, 69] As the chiral functionalities around the P atoms varies, a modification of the enantioselectivity in asymmetric reactions was anticipated. However, only poor enantioselectivities have been reported



for all the reactions tested so far (hydrogenation, hydrosilylation, allylation, and Grignard cross-coupling). A lack of rigidity in the outer layer of chiral groups was held responsible for these low enantioselectivities. Detailed kinetic studies were performed to investigate the effect of different dendritic branches on the reaction rate of the hydrogenation of acetamidocinnamic acid. Remarkably, the expanded ligand system **23a** resulted in a faster hydrogenation catalyst than the parent ligand 1,2-bis(diphenylphosphanyl)ethane (dppe). No clear explanation has been given, but the rate of catalyst formation might be involved. The catalysts were prepared in situ, and dppe showed an incubation time whereas the mixture with ligand **23a** immediately started to consume H₂. Only a relatively small change in the structure of the dendritic wedge, a 2,5-substituted analogue of **23b** (which contains 3,5-substituted wedges), resulted in a hydrogenation catalyst that was 300 times slower.^[70] Blocking of the catalytic site by *ortho* substituents on the P phenyl ring was proposed to cause this lower activity.

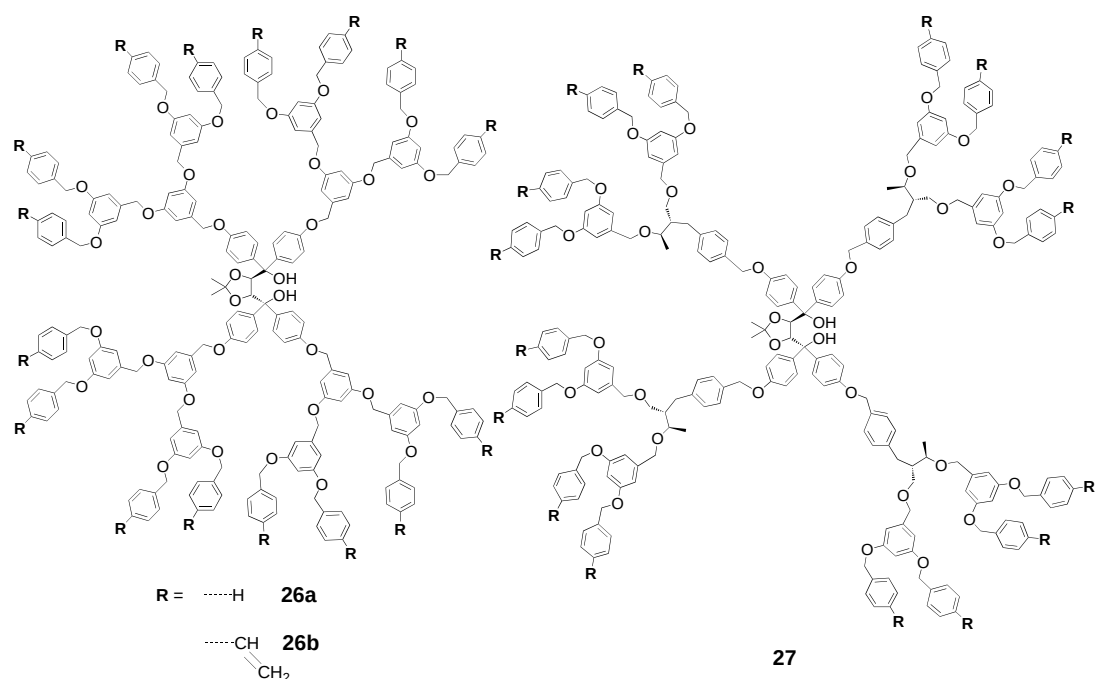
4.2.1. Diethylzinc Addition

The group of Bolm reported asymmetric catalysis using focal-point-functionalized Fréchet-type wedges. Similar to the chiral parent compound, dendritic catalysts such as **24a** were



catalytically active in diethylzinc additions to benzaldehyde yielding optically active secondary alcohols (Scheme 9).^[71] Enantiomeric excesses were only slightly lower (85–86% *ee*) than those of the parent pyridyl compound (5 mol% catalyst; 88% *ee*). The chiral amplification using **24b** was also studied. Using 5 mol% of **24b**, which was 76% enantiopure, resulted in a 84% *ee* for the product. The observed positive nonlinear effect is similar to that observed for the reference pyridyl compound. For larger dendritic systems such nonlinear effects might not be observed since the formation of complexes with a metal:ligand ratio of 1:2 is involved, but experiments with such systems have not been reported.

Seebach et al. described the synthesis of dendrimers with TADDOLs as asymmetric active sites in the core.^[72] Achiral Fréchet-type wedges of G₀ to G₄ were coupled to the *para* positions of the four phenyl groups of the TADDOL core (**26**, Scheme 10).^[72b] Styrene-functionalized derivatives of these systems have been prepared for immobilization purposes (**26b**). Interestingly, this group also reported TADDOL ligands such as **27**, functionalized with both the *R,S* (shown) as well as the *S,R* chiral wedges. The molar rotation value of the chiral dendrimers was not significantly affected by the size or by the chirality of the wedges.



Scheme 10. G2 dendrimers with TADDOL ligands at the core for homogenous reactions (**26**) and for immobilization with styrene functionalized derivatives (**26b**). The dendrimer **27** contains chiral wedges.

The Ti-catalyzed enantioselective nucleophilic addition of Et_2Zn to benzaldehyde was studied using these dendritic catalysts. The dendrimers with achiral branches gave slightly slower reaction rates and a small decrease in enantioselectivity with increasing generation number (G0 to G3) was observed. A large drop in both the activity and selectivity was observed for the largest system G4. On going from G3 to G4, the structure changes from roughly planar to globular and densely packed which provides an explanation for the drop in catalytic activity. This is a similar effect to that observed for the copper-catalyzed Diels–Alder reaction reported by Chow et al.^[54] (see Section 3.3). The chiral branches in **27** did not significantly affect the rates and selectivities of the addition reaction. This was probably because the distance between the central catalytic site and the stereogenic centers of the branches is too large.

The TADDOL-cored dendrimers were immobilized by copolymerization^[72a] of styryl-substituted TADDOLs in cross-linked polystyrene using divinylbenzene and TADDOL-centered dendrimers with peripheral styryl groups (**26b**, Scheme 10) as cross-linkers. These ligands were coordinated to Ti by exchange with $\text{Ti}(\text{OCHMe}_2)_4$ and their activities and enantioselectivities in the Et_2Zn addition to benzaldehyde were then evaluated. As shown before, the branches of the dendritic catalyst (**26b**) have only a minor influence on the selectivity of the homogeneously catalyzed reaction.^[73] Using the immobilized systems *ee* values comparable to the homogeneous systems were obtained (98% versus 96% *ee*). However, using polymers with a high TADDOLate content (thus higher cross-linking) resulted in much lower enantioselectivities. This effect was proposed to be the result of “frozen-in” conformations of the ligand. The immobilized dendritic catalysts did not perform better when higher generation

dendrimers were used, but generally the activities of the dendritic immobilized systems were between those of the polymer-bound analogues and the homogeneous counterparts. This confirms the hypothesis that catalytic sites within the polymer beads show intermediate accessibility.^[72a]

The selectivity drops considerably with the introduction of spacers between the Ti-TADDOLates and the styryl-functionalities of **26** which might be caused by a less control of the active site and the swelling properties of the polystyrene beads.^[74] All the polymeric systems were recycled in 20 consecutive reactions by decanting/filtration and subsequent washing with toluene. The dendritic polymer showed the highest enantioselectivity of 98:2 in 20 sequential runs.

4.2.2. Asymmetric Borane Reduction

Optically active amino alcohols were attached to the focal point of dendritic branches (G0 to G3), and the resulting ligands (**25** $\triangleq$ G2) were employed in asymmetric borane reductions.^[75] Compared to the parent catalyst (87% *ee*) slightly higher enantioselectivities (88–91% *ee*) and good yields were obtained for various generations using acetophenone as a substrate. The highest *ee* values (up to 96%) for the reduction of α -chloroacetophenone were observed using the catalyst based on G2. The slightly lower selectivity of the G3 was proposed to be an effect of steric hindrance whereas the smaller systems (G0 and G1) are less efficient because of their flexibility.

4.2.3. Titanium-Catalyzed Asymmetric Allylation

Yoshida et al. prepared chiral 1,1'-binaphthol derivatives having poly(benzyl ether) wedges at the 6,6'-positions.^[76] The

molecular optical rotation was identical for all generations, which is in agreement with the presence of a single chiral group. From circular dichroism (CD) spectroscopy it was concluded that the chiral environment of the binaphthol remained unchanged for all systems. In titanium-catalyzed asymmetric allylation of aldehydes the enantioselectivity decreased only slightly for the larger dendritic catalysts (92–88 % *ee* compared to 87 % for the parent (*R*)-binaphthol).

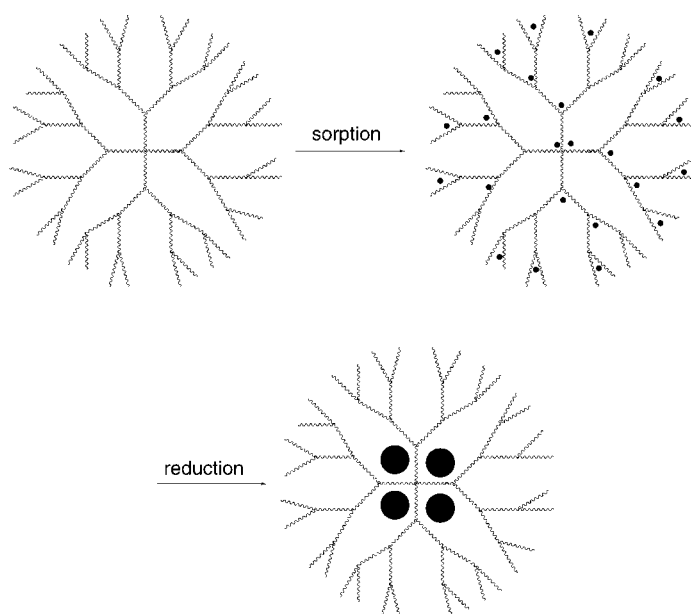
5. Metal Nanocomposites in the Dendrimer Interior

So far we have only discussed catalysts in which the metal ions are *coordinated* to appropriate donor atoms such as P, N, O. Recently, a new concept was reported independently by the groups of Crooks,^[77] and Tomalia.^[78] Hydroxyl-terminated poly(amido amine) dendrimers were found to be excellent templates for the preparation of precise metal nanoclusters within the dendrimer interiors.

Among the potential applications of nanoclusters, catalysis is an important one and metal clusters have been shown to be very active catalysts.^[79] However, clusters tend to aggregate into larger (less active) systems under catalytic conditions which complicates the application of these systems. Precise construction of nanocomposites in the cavities of dendrimers might lead to both cluster stability and full control over size and size distribution, while the dendrimer branches still allow substrates access to the catalytically active clusters. Additionally, dendrimers could enhance the solubility of the metal clusters, a result of their solubility in a wide-range of solvents.

Cu^{2+} ions have been extracted into poly(amido amine) dendrimers bearing terminal hydroxyl groups and bind to pairs of the outermost tertiary amine groups. This results for G2-OH, G4-OH, and G6-OH in sorption of 4, 16, and 64 Cu^{2+} ions respectively, as shown by spectrophotometry.^[77a] Chemical reduction leads to stable, perfectly soluble nanocluster complexes (Scheme 11). Evidence for the formation of these clusters comes from an immediate color change from dark blue to gold brown, and from the loss of signal in the EPR spectrum upon reduction.^[77a, 78] The absorbance bands at 605 and 300 nm disappear and a characteristic peak at 590 nm appears (its exponential shape points to a band-like electronic structure of metal clusters). Metal particle diameters of 1–2 nm were found based on transition electron micrographs (TEM), CPK modelling, and optical absorption spectroscopy. Samples of intradendrimer copper clusters remained unaggregated for over 90 days at room temperature in oxygen-free aqueous solutions. Similarly, Pd^{II} and Pt^{II} ions were sorbed into poly(amido amine) dendrimers, and subsequently reduced to yield dendrimer-embedded nanoclusters.^[77b] TEM clearly shows that the clusters are monodisperse, roughly spherical, with diameters of 1.3–1.6 nm.

Dendrimer-encapsulated Au, Ag, Pd, and Pt metal particles can be prepared by multiple in situ replacement reactions in which the Cu atoms being less noble are exchanged.^[80] Such intradendrimer reactions are fast and quantitative. Moreover, the resulting particles are stable, small (1–3 nm) and rela-



Scheme 11. Sorption of metal ions and subsequent reduction forming dendrimer-stabilized nanocluster complexes.

tively monodisperse. The Ag nanoclusters G6-OH(Ag_{110}), which were prepared by primary metal-exchange reactions from G6-OH(Cu_{55}), could be converted further into the more noble G6-OH(Au_{37}), G6-OH(Pt_{55}), and G6-OH(Pd_{55}) by secondary replacement reactions. Using this replacement method, catalytically active encapsulated nanoparticles were prepared.

The water-soluble and stable composite G4-OH(Pd_{40}) exhibits high catalytic activity for the hydrogenation of alkenes in water. Turnover frequencies were higher than for water-soluble polymer-bound Rh^{I} catalysts and comparable to PVP-stabilized colloidal palladium dispersions in water (PVP = poly(vinyl pyrrolidone)). These nanocluster-dendrimer catalysts are sufficiently stable for recycling and reuse. Moreover, choice of the dendrimer generation can control the hydrogenation activity.^[77b] The end groups of higher generation dendrimers are more densely packed together resulting in there being less free space in the dendrimer surfaces, which thus give limited access of substrates to the Pd nanoclusters. G6-OH(Pd_{40}) and G8-OH(Pd_{40}) show rates of only 10 % and 5 %, respectively, of that for G4-OH(Pd_{40}). In principle this could add substrate selectivity to the dendrimer. In a subsequent paper^[81] dendrimer-encapsulated palladium nanoparticles were applied in fluororous biphasic catalysis.^[82] PAMAM dendrimers were functionalized with perfluoropolyether groups by complexation of the carboxylic end groups with the terminal amino groups of the dendrimer. The nanoparticles were active in the catalytic hydrogenation and could be recycled at least 12 times without significant decrease in activity. Moreover, polar substrates were hydrogenated much faster than non-polar substrates, which is a result of the polar microenvironment within the dendrimer. Using these dendritic nanocomposites substrate selectivity can be achieved on the basis of size and polarity.

6. Summary and Outlook

The field of dendritic transition metal catalysis is very new, but already numerous examples based on different dendritic backbones functionalized at different locations have appeared. At this stage it is pivotal to focus on the fundamental aspects of dendritic catalysis and many points of interest stated in the introduction have been addressed. Periphery-functionalized dendrimers, which have extremely high local concentrations of catalysts/ligands, can on the one hand lead to more stable catalysts than their monomeric analogues (e.g., in the Heck reaction). On the other hand this high local concentration could promote deactivation and thus lead to lower activities (as observed in the Kharasch addition reaction). To date no examples have been reported in which the catalytic sites at the periphery of a dendrimer showed (chiral) cooperativity; heterobimetallic catalysis using dendritic catalysts has not been studied yet. The dendrimer surface seems to be very suitable for catalytic reaction sequences that require two (or more) metals, and the quest for this highly interesting behavior is still ongoing.

Also the core-functionalized dendrimers have huge potential as transition metal catalysts and the analogy with natural systems is evident. Large dendritic branches positioned around the catalytic site can induce substrate-, regio-, and enantioselectivity, albeit often at the price of lower reaction rates. The precise tuning of the microenvironment (polarity, steric constraints) is still a difficult task, but might provide a tool to enhance the selectivity of a reaction. Construction of molecular recognition sites close to the catalytically active core in combination with the specific microenvironment created by the dendrimer will provide interesting systems that might increase selectivities by using noncovalent interactions, analogous to the working principles of enzymes.

Preliminary results show that dendrimers are suitable supports for transition metal catalysts and the larger systems can be used in continuous processes. Using dendritic catalysts the common problems involved in catalyst recycling can still occur, such as dendrimer or catalyst decomposition, dendrimer leaching, metal leaching and catalyst deactivation. These problems can be solved for most reactions by proper choice of ligands and dendrimer backbone. Whether dendritic catalysis can compete successfully in commercial applications with other systems such as two-phase catalysis remains to be seen. High turnover numbers are required considering the sophisticated dendritic ligands.

Generally, positioning of the catalytic sites and their spatial separation are determined by the geometry of the dendrimer and are very important for the performance of the catalyst. This is especially true for dendritic catalysts with chiral ligands at the periphery. In the near future more examples of dendritic transition metal catalysts are required to substantiate this principle for a broad range of reactions. Ideally we would like to accumulate enough information and synthetic knowledge to implement the dendritic framework in the rational design of new catalyst systems. Dendritic systems functionalized with different catalytic sites at several well-defined locations can potentially be used for tandem reactions. Also the assembly of dendritic catalysts into larger

aggregates^[7, 83] and systems organized on surfaces will have a bright future in high precision nanotechnology. Multistep reactions using these “nanofactories” are getting closer to the sophisticated natural systems such as the multiprotein respiratory assembly.

After submitting this manuscript several interesting reports on dendritic catalysis appeared, and references to these are included.^[84]

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Blue Fluorescent Exciplexes Consisting of *trans*-Stilbene and Antibodies

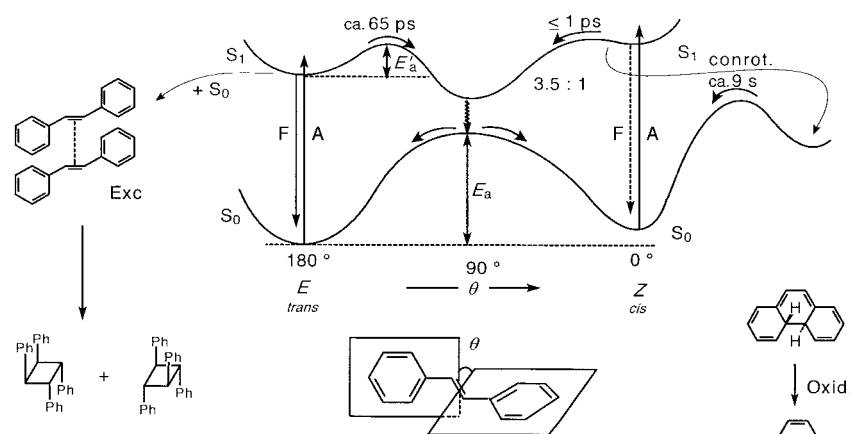
Herbert Meier*

Stilbene and its derivatives belong to the best investigated molecules in organic photochemistry and photophysics.^[1–4] Besides the variety of deactivation processes that follow an electronic excitation, it is mainly aspects of materials science^[2] that have awakened interest in stilbenoid systems over the last two decades. Recently a completely new area of application was conceived by Simeonov et al.^[5] They studied the influence of protein–ligand interactions on electronically excited states with monoclonal antibodies against stilbene haptens.^[6]

Scheme 1 shows a survey of the photochemistry of stilbenes. The *trans*/*cis* isomerization (*E*/*Z* isomerization) has, in the

through the potential energy hypersurface S_1 in an analogous way, so that the torsion around the C–C double bond represents the decisive parameter on the reaction coordinate.

The S_1 state has, on the side of the *E* configuration, an activation barrier E_a' , which can be rationalized by an avoided crossing with a higher excited singlet state. This barrier provokes temperature-dependent competition with the fluorescence. The fluorescence quantum yield Φ_F increases from 4–8% at room temperature to almost 100% at very low temperatures.^[1, 2] A very small barrier exists on the side of the *Z* configuration; moreover, the deactivation by fluorescence plays an inferior role: $\Phi_F \approx 10^{-4}$ at room temperature in *n*-hexane.^[8] The reaction coordinate on the S_1 potential energy hypersurface leads from both starting configurations to a state that has a $\theta = 90^\circ$ angle of twist and whose average lifetime is in the femtosecond range. In the nonadiabatic photoreaction, the ground state S_0 is reached through a funnel,^[9] whereby the rotation relaxation to the *E* or the *Z* configuration has about the same probability.^[1, 2] As a competing reaction to the isomerization, a stereoselective dimerization via nonfluorescent excimers Exc has to be considered on the *trans* side; this process becomes the dominating product channel, especially at concentrations above 10^{-2} M. The conrotatory electrocyclic reaction that yields 4a,4b-dihydrophenanthrene represents a monomolecular competitive reaction on the *cis* side. The cyclization is thermally and photochemically



Scheme 1. An overview of the *E*/*Z* isomerization of stilbene and the competitive processes.^[1–3] F = fluorescence, A = absorption.

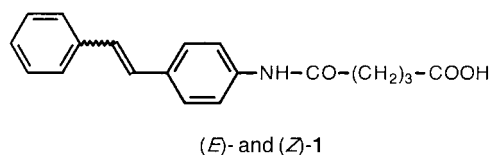
ground state S_0 , a high activation barrier ($E_a = 180 \pm 20 \text{ kJ mol}^{-1}$), which can be strongly reduced by a variety of catalysts. Much easier is the decoupling of the olefinic π bond in the electronically excited singlet state S_1 . The first detailed reaction model was proposed by Saltiel^[7] more than 30 years ago; all later models^[1–4] have positioned the cross-section

reversible in the absence of oxidants. Internal conversion ($S_1 \rightarrow S_0$) and intersystem crossing ($S_1 \rightarrow T_1$) are not important, either for (*E*)- or (*Z*)-stilbene.^[10, 11] The critical question to ask here is now: How do the properties, described above and summarized in Scheme 1, change when stilbene molecules are complexed in monoclonal antibodies?

To increase the solubility in water and to insure a better binding to the carrier protein, Simeonov et al.^[5] used the glutaric acid monoamide derivative **1** instead of the unsubstituted stilbene; the electronic nature of **1** differs only slightly from that of the parent compound.

An intense fluorescence appeared under UV light during the stoichiometric addition of (*E*)-**1** to a number of mono-

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clonal antibodies (EP2 mAb: **19G2**, **20F2**, **21C6**, **16H10**, etc.). The color varies from powder blue to faint purple according to the complex mAb–(E)-**1**. From amongst the investigations with a total of 15 antibodies,^[5, 12] two examples shall be selected here for comparison with the uncomplexed stilbene **1**: the blue fluorescent complex **19G2**–(E)-**1** and the purple fluorescent complex **16H10**–(E)-**1** (Table 1).

Table 1. Comparison of selected thermodynamic and spectroscopic data for **1** and its complexes with the antibodies **19G2** and **16H10** in an aqueous buffer solution^[a] at 20–21 °C.^[5, 12]

	(E)- 1	19G2 –(E)- 1	19H10 –(E)- 1
dissociation constants:			
K_d ((E)- 1) [μM]	–	0.16	0.31
K_d ((Z)- 1) [μM]	–	1.7	2.3
UV absorption:			
λ_{max} [nm]	320	325	320
$10^{-4} \epsilon_{\text{max}}$ [$\text{cm}^{-1}\text{M}^{-1}$]	3.32	3.15	2.82
fluorescence:			
λ_{max} [nm]	388	410	380
quantum yield Φ_F	0.02	0.78	0.28
fluorescence lifetime τ_F [ns]	0.071	22.9, 7.6, 1.1, 0.086	0.864, 0.375
intrinsic lifetime ^[b] τ [ns]	3.6	31	4.3
photostationary state: ^[c] E/Z	< 1	32.3	2.2

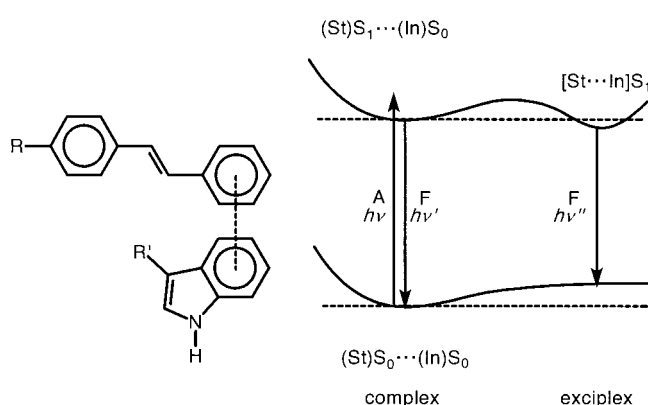
[a] Buffer solution: 10 mM Na_3PO_4 , 150 mM NaCl (pH 7.4) with 5% N,N -dimethylformamide as cosolvent. [b] $\tau = \tau_F/\Phi_F$. [c] $\lambda \geq 300$ nm.

The dissociation constants of the complexes mAb–(E)-**1** have an average value of 0.37 μM at room temperature in the applied buffer solution; those of the corresponding complexes mAb–(Z)-**1** have a value of about 2.16 μM . With one exception, the *E* configuration of **1** is always bound a bit more strongly than the *Z* configuration. There is no significant difference between **19G2**–**1** and **16H10**–**1**. The X-ray measurements of **19G2**–(E)-**1** show that, at 4 °C, the hapten that is not covalently bound represents a planar (*E*)-stilbene, whose longitudinal axis points towards the center of the monoclonal antibody. The phenyl group, which is distal to the glutaric acid chain, lies parallel to the benzene ring of the indole belonging to tryptophan 103 on the H chain of the antibody. Therefore, the π,π interaction of the two benzene rings has a significant meaning.^[13]

The UV and the fluorescence excitation spectrum of **19G2**–(E)-**1** exhibit a red-shift respective to free (E)-**1** (Table 1) and a modified vibrational fine structure at room temperature. Analogous effects can be found for the fluorescence band. However, much more dramatic is the increase of the fluorescence quantum yield Φ_F from 2% for (E)-**1** to 78% for **19G2**–(E)-**1**. On cooling, the fluorescence band of the

complex **19G2**–(E)-**1** is hypsochromically shifted and becomes more structured. The main change occurs in the temperature interval between –13 and –33 °C where the intensity of the blue fluorescence decreases; the fluorescence has completely disappeared at –60 °C, but reappears on warming. This result is surprising and is contrary to the behavior of free (*E*)-stilbene. As shown in Scheme 1, cooling favors the fluorescence, because the activation barrier of the isomerization route is less easily overcome. The photostationary states of stilbene and the stilbene derivative **1** are characterized by *E/Z* ratios smaller than one for longwave irradiations ($\lambda \geq 300$ nm).^[14] The *E* → *Z* photoisomerization^[15] of **19G2**–(E)-**1** hardly appears at room temperature (Table 1). Hence, the stilbene **1** complexed in the antibody fundamentally modifies its photophysical and photochemical behavior.

Further information is provided by time-resolved emission spectroscopy in the picosecond range. The fluorescence of (E)-**1** at room temperature in the buffer solution shows a monoexponential decay with an average lifetime τ_F of 71 ps, which is equivalent to the value for the unsubstituted (*E*)-stilbene (Scheme 1). On the contrary, the decay function of **19G2**–(E)-**1** consists of four components, whereby the long-lived component, with $\tau_F = 22\,900$ ps, is the most important one. The, in principal, very problematic fit of the decay curve with four exponential functions is supported by four different emission spectra, which relate to the different time regimes: The weak emissions with maxima between 380 and 400 nm correspond more or less to the emission of free (E)-**1** and can be probably explained by complexes that have small differences in the surroundings of the stilbene chromophore. The long-lived component with an intense and bathochromically shifted emission ($\lambda_{\text{max}} = 420$ nm) is due to an exciplex which is created and degraded in the nanosecond range. The π,π interaction between the stilbene and the indole building blocks (St...In) seems to be a decisive factor for this effect (Scheme 2).



Scheme 2. Exciplex formation and deactivation by fluorescence.

The exciplex corresponds to a dissociative term in the ground state, that is, a spontaneous dissociation occurs on the energy hypersurface of the ground state. How much the ground-state complexes and the exciplexes differ in their

geometrical parameters or activated vibrational modes, remains a speculation.^[5] The temperature-dependent dynamics of the systems, which do not permit a reorganization to the exciplex below about -30°C , are an important feature.

The difference between the purple (violet) fluorescent systems, for example, **16H10**–(*E*)-**1**, and the blue fluorescent complexes, like **19G2**–(*E*)-**1**, still remains to be explained. The data shown in Table 1 reveal *one* difference in particular: **16H10**–(*E*)-**1** is not capable of generating a long-lived exciplex—the intrinsic radiation lifetime is nearly unchanged compared to that for free (*E*)-**1**. The reduced quantum yield Φ_{F} relative to **19G2**–(*E*)-**1** is due to an increased amount of *Z* configuration in the photostationary state.

Photodimerization is not relevant in the monoclonal antibody as a competitive process to fluorescence and isomerization (Scheme 1), but the electrocyclic ring-closure reaction with subsequent oxidation by the oxygen present (from air) can be observed. Simeonov et al. explain the total absence of fluorescence after 60 minutes of UV illumination by the irreversible production of phenanthrene.^[5]

How do the photophysics and photochemistry of stilbene chromophores in antibodies differ from other host systems with stilbene guests, like cyclodextrins,^[16] clathrates,^[17] inclusion compounds in deoxycholic acid,^[18] or liquid crystals?^[19] Steric constraints, symmetry of the cavity, local polarity, local viscosity, and energy transfer between guest and host induce a variety of modified characteristics compared to stilbene in solution. The “fine-tuning” that is based on the molecular dynamics of the antibody–stilbene complexes is new. Photochemical sensors of the type described here promise interesting applications, for example, in immunochemistry, histological investigations, and genomic studies.

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- [11] With an energy transfer from triplet sensitizers it is possible to populate T_1 and so to induce an *E/Z* isomerization.
- [12] Details about the preparation and characterization are available from *Science Online* at the website: <http://www.sciencemag.org/feature/data/1052306.shl>.
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Retracing Enzyme Evolution in the $(\beta\alpha)_8$ -Barrel Scaffold

James D. Stevenson, Stefan Lutz, and Stephen J. Benkovic*

The structure–function relationship and evolutionary origin of enzymes containing the $(\beta\alpha)_8$ -barrel fold has been extensively studied in recent years.^[1] The high abundance of this particular fold in nature (found in approximately 10 % of all soluble proteins), coupled with an apparent flexibility in the chemistry carried out by these enzymes, has made the $(\beta\alpha)_8$ -barrel an interesting target for protein engineers. Two recent papers^[2, 3] report the successful engineering of the chemistry and binding properties of $(\beta\alpha)_8$ -barrel enzymes using rational and nonrational design approaches. In conjunction with structural^[4] and computational studies,^[1a] these results support the theory of widespread recruitment of ancestral $(\beta\alpha)_8$ -barrel scaffolds in the evolution of multiple metabolic pathways.

The core $(\beta\alpha)_8$ -barrel structure itself is composed of an eightfold repeat of β -strand–loop– α -helix–loop secondary structure elements.^[5] These assemble with the eight β -strands forming a central cylindrical parallel β -sheet and with the α -helices forming the outer surface of the barrel (see Figure 1).

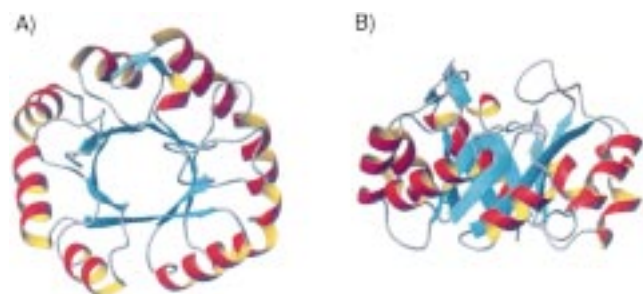


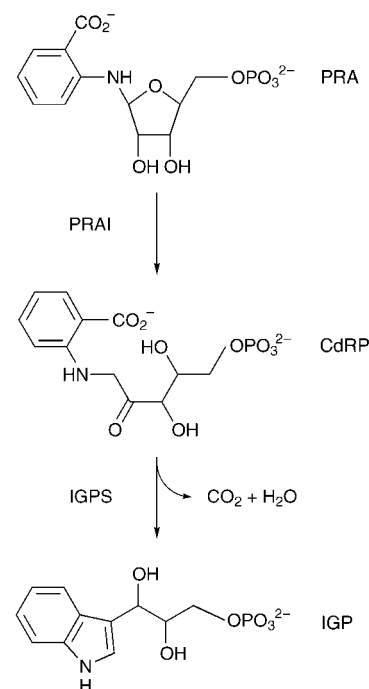
Figure 1. Ribbon representation of the structure of the $(\beta\alpha)_8$ -barrel enzyme PRAI. A) Top view from the C-terminal face of the barrel showing the active site of the enzyme. B) Side view of the barrel structure.

Particularly appealing to protein engineers is the apparent spatial separation of the different elements responsible for binding and catalysis. Typically the residues involved in catalysis are located on the loop regions, while the substrate-binding residues are located within the barrel itself.

This enables the elements of binding and catalysis to be separately addressed in mutagenesis approaches to modifying enzyme function.

Changing Chemistry, Retaining Binding

Altamirano et al. reported the conversion of one $(\beta\alpha)_8$ -barrel into a functional equivalent of another using a combination of rational design and directed evolution.^[2] The two enzymes, *N*-(5'-phosphoribosyl)anthranilate isomerase (PRAI) and indole-3-glycerol phosphate synthase (IGPS), catalyze consecutive steps in the tryptophan biosynthetic pathway (see Scheme 1) and are thought to have evolved from



Scheme 1. The consecutive reactions in the tryptophan biosynthetic pathway catalyzed by enzymes PRAI and IGPS. PRAI catalyzes the Amadori rearrangement of *N*-(5'-phosphoribosyl)anthranilate (PRA) to 1'-(2'-carboxyphenylamino)-1'-deoxyribulose 5'-phosphate (CdRP), and IGPS catalyzes the ring closure of CdRP to indole-3-glycerol phosphate (IGP) with release of CO₂ and H₂O.

an ancestral IGPS enzyme through gene duplication.^[6] The authors sought to reproduce this evolutionary divergence by converting IGPS from *E. coli* into a functional PRAI. In so doing, they would not only support the evolutionary link

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between these two enzymes, but would also demonstrate the conversion of one enzyme activity into that of another.

The experimental design employed demonstrates an impressive combination of rational and nonrational design (directed evolution) and exploits the power of in vivo metabolic selection (see Figure 2). The authors initially

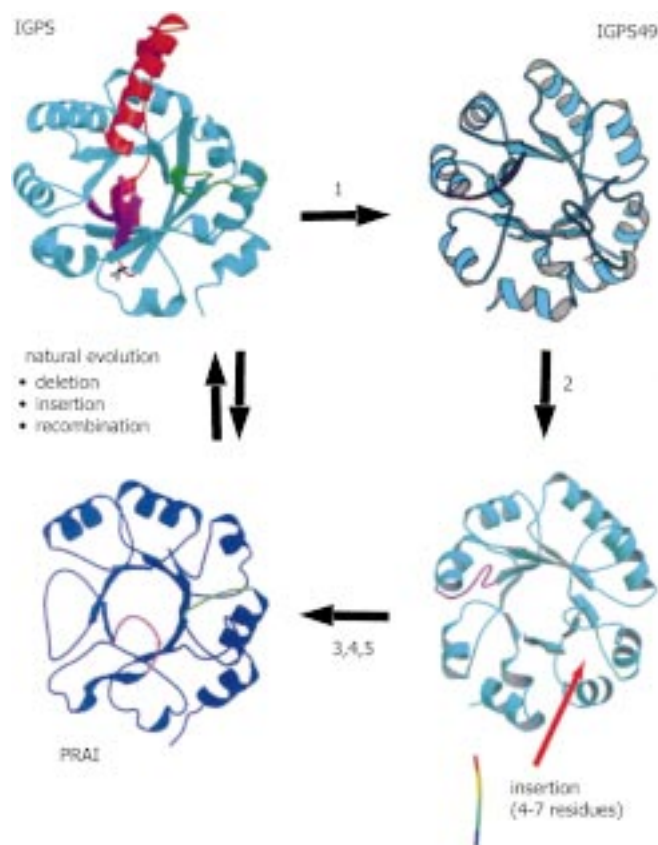


Figure 2. Stepwise-directed evolution approach employed to convert IGPS into a functional PRAI. 1) Deletion of the 48-residue N-terminal extension (shown in red). 2) Substitution of IGPS loop $\beta 1\alpha 1$ (15 residues in length) with the loop library sequence GK(X)₂₋₅, which ranges from 4–7 residues in length. 3) Replacement of IGPS loop $\beta 6\alpha 6$ with the PRAI consensus sequence DGXGGQG. 4) In vivo metabolic selection. 5) Two rounds of DNA shuffling and StEP polymerase chain reaction recombination mutagenesis, followed by in vivo metabolic selection to generate in vitro evolved PRAI (ivePRAI). Reproduced with permission from ref. [2]. Copyright (2000) Macmillan Magazines Ltd.

identified the regions in the tertiary structure of IGPS which differ significantly from that of PRAI; they reasoned that these regions would primarily account for the differences in the chemistry carried out by the two enzymes. In a series of structural modifications, the authors removed the N-terminal helix from IGPS (which is not present in PRAI) and introduced loop library sequences into the equivalent loop regions in PRAI (loops $\alpha 1\beta 1$ and $\alpha 6\beta 6$). This strategy essentially switches the active sites between the two enzymes.

In order to select functional members from this combinatorial library with different loops, an auxotrophic *E. coli* strain (JA300) deficient in PRAI activity was employed. In the absence of exogenous tryptophan only cells which express a functional PRAI enzyme will grow. Although none of the

library members were able to grow in the absence of tryptophan, at very low concentrations (0–25 $\mu\text{g mL}^{-1}$ of tryptophan), a small proportion (1.7 %) of the library was able to grow. This was taken to indicate the presence of weak PRAI activity in some of the library members. To further enhance this activity, the authors employed a directed evolution approach to generate random diversity in the selected library members. Two rounds of DNA shuffling^[7] and staggered extension procedure^[8] (StEP) were carried out to generate a large library of random mutants. In vivo library selection identified 360 colonies that were able to grow in the complete absence of tryptophan. The most active mutant protein, termed ivePRAI (in vitro evolved PRAI), displayed sixfold-improved PRAI activity in vitro over the wild-type enzyme, mainly due to an increase in substrate binding, and completely lacked the original IGPS activity.

Sequence analysis revealed that ivePRAI had 90 % sequence identity to wild-type IGPS, but only 28 % to PRAI, clearly demonstrating the central role of the loop regions to the activity of this ($\beta\alpha$)₈-barrel enzyme. That the function can be so readily altered by targeting these regions for mutagenesis indicates a clear functional plasticity in the ($\beta\alpha$)₈-barrel scaffold. This may account for the prevalence of this structure in nature.

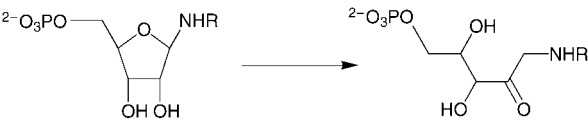
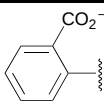
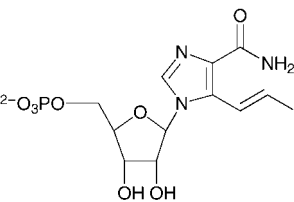
In terms of protein engineering, a number of lessons can be learned from this study. Firstly, that rational and nonrational design may be used in tandem. The initial approach of rational loop grafting was unsuccessful in obtaining a functional enzyme. Only when the diversity-generating power of in vitro recombination was applied, were functional enzymes obtained. To say that this step merely fine-tuned the mutagenesis already in place is possibly understating the importance of this technology. That said, it is unlikely that DNA shuffling alone would have been capable of generating PRAI activity in the IGPS scaffold.

Retaining Chemistry, Changing Binding

In addition to the use of existing enzymes as structural scaffolds, nature has also employed the strategy of tailoring the binding specificity of existing activity to recognize different substrates. This is again apparent with the enzyme PRAI, which has a related homologue in the histidine biosynthetic pathway. The enzyme *N*'-[5'-(5'-phosphoribosyl)formimino]-5-aminoimidazole-4-carboxamide ribonucleotide isomerase (ProFARI) catalyzes the Amadori rearrangement of ProFAR to *N*'-[5'-(5'-phosphoribulose)formimino]-5-aminoimidazole-4-carboxamide ribonucleotide (PRFAR; see Table 1). This is the same chemical transformation catalyzed by PRAI, but using a different substrate. Like PRAI, ProFARI is also a ($\beta\alpha$)₈-barrel enzyme, and, while the two enzymes share only 10 % sequence identity, this similar structure and chemistry suggests a clear evolutionary link.

Jürgens et al. set out to retrace the divergent evolution of PRAI and ProFARI from a proposed ancestral enzyme displaying broader substrate specificity, by generating variants of ProFARI that were capable of catalyzing both the PRAI and ProFARI reactions.^[3] Such a mutant would support the evolutionary link between PRAI and ProFARI. The authors

Table 1. The substrate specificity of ProFARI and PRAI.

			
R	Substrate	Product	Enzyme
	ProFAR	PRFAR	ProFARI
	PRA	CdRP	PRAI

employed a combination of random mutagenesis and in vivo selection to obtain ProFARI mutants with PRAI activity. In contrast to the elaborate mutagenesis procedure carried out by Altamirano et al.,^[2] Jürgens et al. needed only to perform a single round of DNA shuffling in order to achieve their aims. Two variant ProFAR enzymes capable of isomerizing PRA to CdRP were identified from a randomly mutated ProFAR library, by in vivo selection in an auxotrophic *E. coli* strain deficient in PRAI activity. Kinetic analysis showed that both mutants displayed significant PRAI activity, although $3-11 \times 10^4$ times less than wild-type PRAI in terms of the specificity constant ($k_{\text{cat}}/K_{\text{M}}^{\text{PRA}}$). In addition, significant ProFARI activity was retained in one of the mutants (26-fold lower than wild-type), while the other displayed much lower levels of activity. It would be expected that carrying out additional rounds of mutagenesis and in vivo selection would result in the further enhancement of PRAI activity at the expense of ProFARI activity. This is due to the focus of the selection criterion purely on PRAI activity.

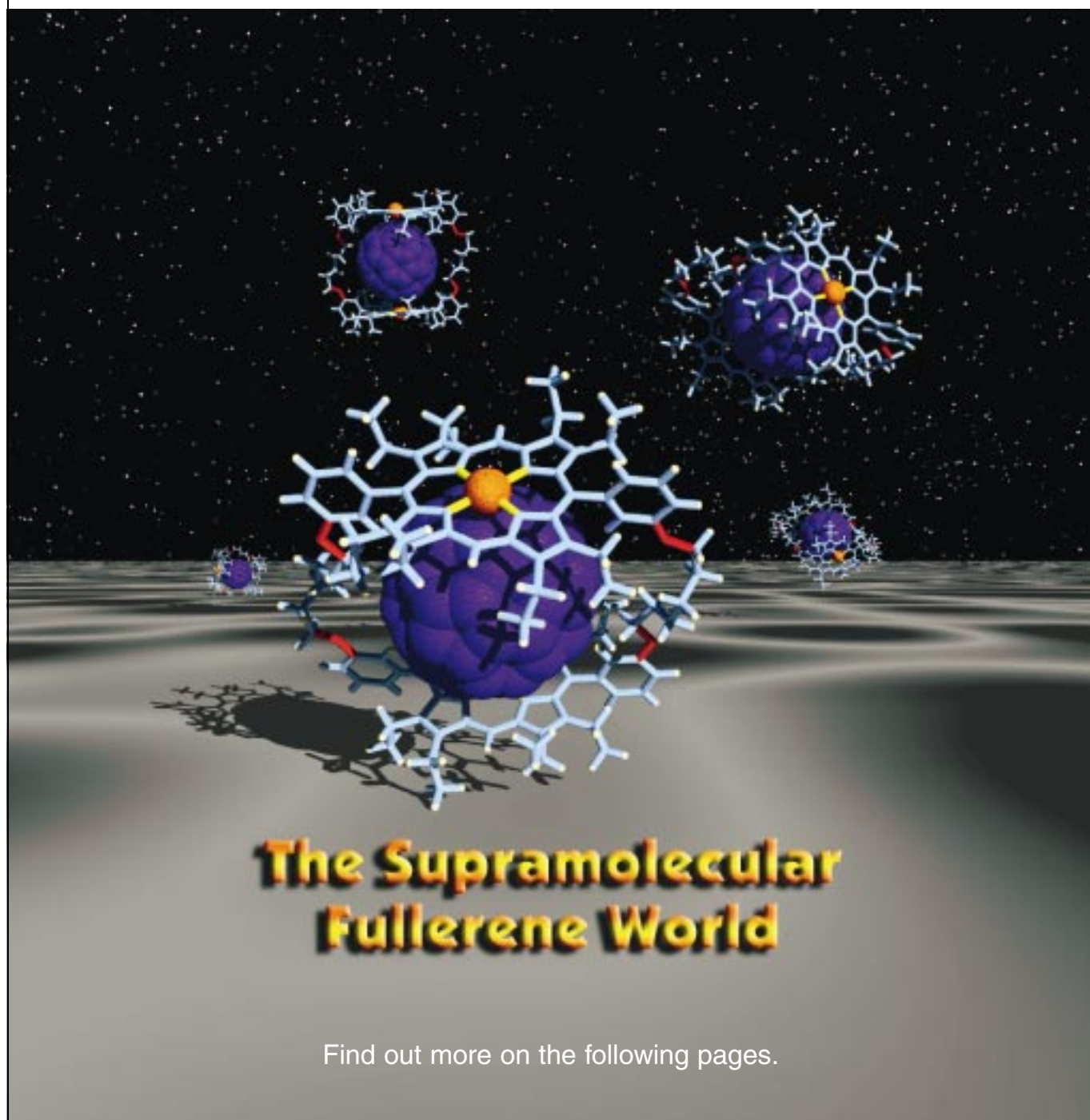
Of the seven point mutations identified in the two ProFARI variants, only the single point mutation D127V conveyed PRAI activity when reproduced by site-directed mutagenesis. However, this single-site mutant was significantly less active in either reaction than the two selected mutants; this indicates that multiple mutations were acting cooperatively to alter the activity of ProFARI. In turn, the fact that a single amino acid substitution was capable of altering the specificity of ProFARI supports the hypothesis of an evolutionary connection between these two enzyme activities.

In conclusion, while the de novo creation of efficient tailor-made protein catalysts is currently an unattainable goal for protein engineers, this approach of “refitting” an existing enzyme scaffold offers a powerful route to new enzyme activities.^[9] As shown by the cases of the two $(\beta\alpha)_8$ -barrel enzymes discussed here, either the chemistry or the binding properties can be altered to obtain variant enzymes with the desired new activity. The $(\beta\alpha)_8$ -barrel structure is thus being used as a generic scaffold, into which new activities can be introduced. This essentially copies nature itself which, in the course of natural evolution, has generated new enzyme functionality by recruiting existing protein structural and functional folds.

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Supramolecular Architectonics with Carbon Nanoclusters

A host-guest interaction between fullerenes and cyclic dimers of metalloporphyrins results in the formation of doubly layered π -electronic supramolecules, whose thermodynamic stability and dynamics in guest exchange can be tuned by the selection of the metal ions at the outer porphyrin layer. In particular, the host molecule with rhodium ions exhibits an extremely high affinity toward fullerenes.



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

Jian-Yu Zheng, Kentaro Tashiro, Yusuke Hirabayashi, Kazushi Kinbara, Kazuhiko Saigo,* Takuzo Aida,* Shigeru Sakamoto, and Kentaro Yamaguchi

With regard to multiwalled graphitic nanoparticles such as carbon nanopolyhedrons,^[1] nanocapsules,^[2] and buckyonions,^[3] wrapping of fullerenes in large π -conjugated molecular envelopes is an interesting subject, which may extend the π -electronic conjugation of fullerenes in a three-dimensional fashion. Recently, we found that a cyclic dimer of zinc porphyrin (**1-Zn**) forms an inclusion complex with C_{60} (**1-Zn** $\supset$ C_{60}), of which the association constant K_{assoc} of $6.7 \times 10^5 \text{ M}^{-1}$ is the highest value reported to date in organic

media.^[4] This finding prompted us to investigate whether the central metal ions play an essential role in this supramolecular interaction.^[5] Here we report the results of a study on the interaction of fullerenes such as C_{60} and C_{70} with a series of metalloporphyrin cyclic dimers (**1-M**; $M = 2\text{H}$, Co, RhMe, Ni, Cu, Ag, and Zn), with emphasis on the extremely high affinity of the host molecule for Group 9 metal ions such as rhodium(III).^[6]

X-ray crystallography is informative of fullerene–metalloporphyrin interactions.^[7] By slow diffusion of acetonitrile into a CH_2Cl_2 solution of a mixture of C_{60} and **2-Zn**, a black prismatic crystal of a 1:1 complex of C_{60} with **2-Zn**, appropriate for X-ray crystallography, was obtained.^[8] Figure 1

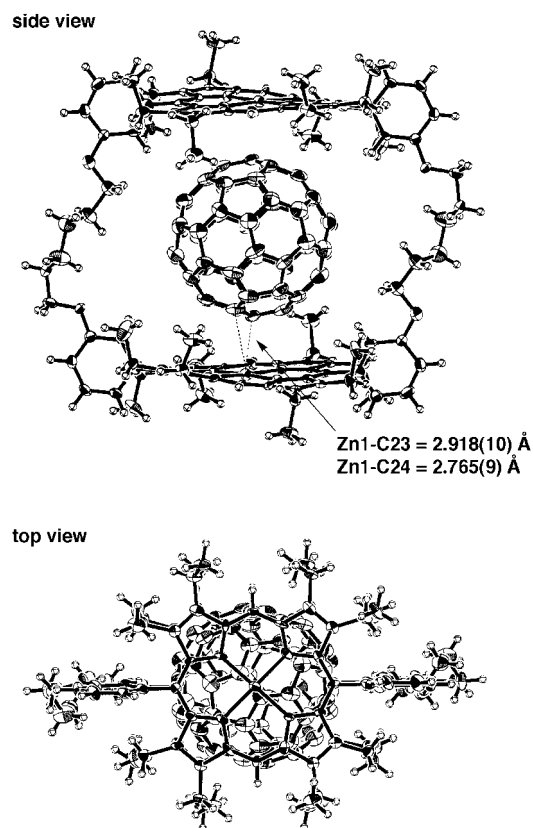
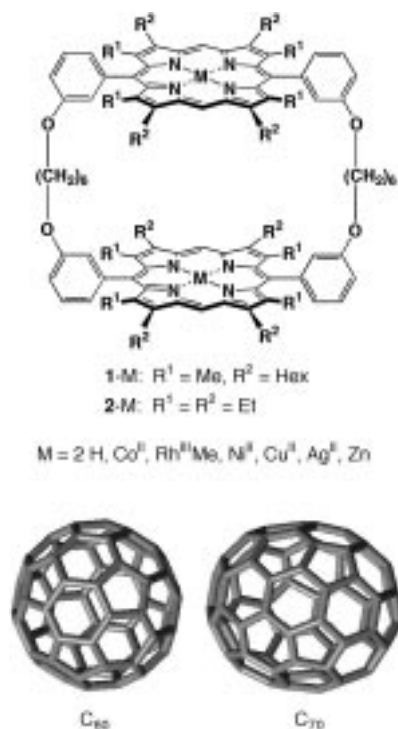


Figure 1. ORTEP plot of an inclusion complex of C_{60} with **2-Zn** (**2-Zn** $\supset$ C_{60}).

shows an ORTEP plot of the complex at -110°C ,^[9] where **2-Zn** in the crystal adopts a C_i -symmetric conformation, the inversion center of which is shared with that of included C_{60} . The hexamethylene linkers of **2-Zn** are folded to adjust the porphyrin–porphyrin distance, and the porphyrin macrocycles are slightly distorted from planarity so as to accommodate the convex shape of C_{60} . One of the 5:6 ring-juncture C–C bonds of C_{60} is located on the central metal ion. The distances between the zinc atom and these two unique carbon atoms are 2.765(9) and 2.918(10) Å, which are clearly shorter than the sum of the van der Waals radii (3.09 Å).^[10] Furthermore, the distances between the pyrrole α -C atoms of the porphyrin moieties and three proximal carbon atoms of C_{60} (3.320–3.346 Å) are slightly but definitely shorter than the typical interlayer distance of graphite (3.354 Å).^[11] These observations suggest the presence of a π interaction between

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

the zinc porphyrin moieties and the included fullerene in the solid state.^[7]

Similarly to our previous study,^[4] we conducted spectroscopic titration of the metalloporphyrin cyclic dimers bearing Group 9–11 metal ions (**1-M**; M = Co, Ni, Cu, Ag) in addition to free-base **1-2H**, with C₆₀ in benzene at 25 °C, in which the Soret absorption band of each host molecule showed a clear red shift with a decrease in absorbance.^[12] From the observed spectral change profiles, the association constants K_{assoc} were evaluated as shown in Figure 2a, whereby K_{assoc} of **1-2H** is

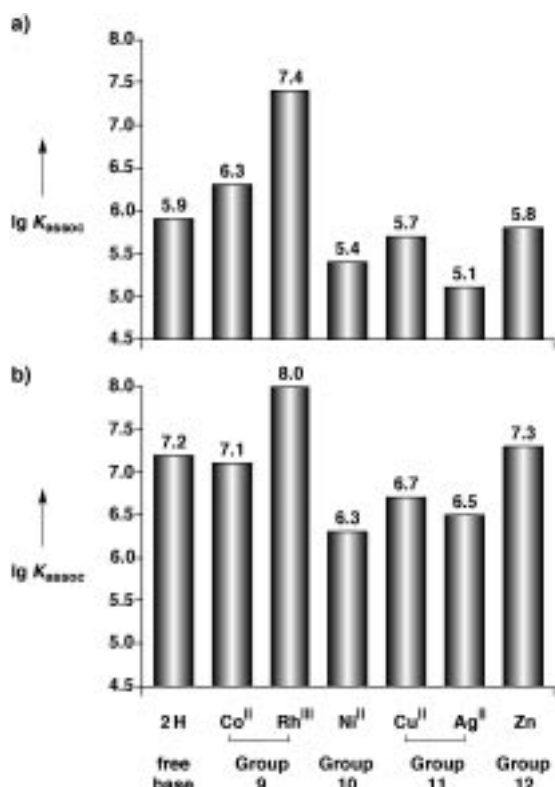


Figure 2. Association constants K_{assoc} of metalloporphyrin cyclic dimers **1-M** with C₆₀ (a) and C₇₀ (b) in benzene at 25 °C.

comparable to that of **1-Zn**,^[4] while **1-Ni**, **1-Cu**, and **1-Ag** with Group 10 and 11 metal ions are inferior to these two host molecules. On the other hand, a host molecule with Group 9 metal ions such as **1-Co** is clearly superior to all these host molecules. Therefore, we synthesized **1-RhMe** with rhodium(III) ions at the porphyrin center. Interestingly, the K_{assoc} value of **1-RhMe** with C₆₀ ($2.4 \times 10^7 \text{ M}^{-1}$) was even higher than that of **1-Co**.^[13] For the interaction with C₇₀, the affinities of the cyclic host molecules **1-M** displayed essentially the same dependency on the central metal ion as in Figure 2a, whereby the observed K_{assoc} values were nearly or more than one order of magnitude larger than those with C₆₀ (Figure 2b). In particular, **1-RhMe** again exhibited an extremely high affinity; the K_{assoc} value of about 10^8 M^{-1} apparently exceeds the experimental upper limit of accuracy for the spectroscopic titration. The K_{assoc} values of **1-2H**, **1-Co**, and **1-Zn** were also greater than 10^7 M^{-1} , whereas the other three host molecules with Group 10 and 11 metal ions (**1-Ni**, **1-Cu**, and **1-Ag**) were inferior to the above host molecules ($K_{\text{assoc}} < 10^7 \text{ M}^{-1}$). With

respect to the extremely high affinity of **1-RhMe** toward fullerenes, the inclusion complex **1-RhMe** ⊂ C₆₀ eluted as a single component not only in GPC on Polystyragel (CHCl₃) but also in HPLC on Buckyprep (toluene), while other complexes such as **1-Zn** ⊂ C₆₀, in contrast, dissociated completely under the same chromatographic conditions.

For the interaction of **1-RhMe** with fullerenes, the axial methyl groups of the host serve as an NMR probe: the ¹H NMR spectrum of **1-RhMe** alone in C₆D₆ at 25 °C showed eight inequivalent doublets assigned to MeRh at $\delta = -5.15$, -5.30 , -5.36 , -5.67 , -5.77 , -5.79 , -5.84 , and -5.85 , which indicate the presence of several conformational isomers.^[4] When C₆₀ was added to this solution, **1-RhMe** underwent a conformational change to give only a single doublet for MeRh (**1-RhMe** ⊂ C₆₀) at $\delta = -5.06$. In the ¹³C NMR spectrum in CDCl₃, **1-RhMe** ⊂ C₆₀ showed a signal assigned to MeRh in a region downfield (d, $\delta = -6.9$, $\Delta\delta = 6.9$) from that of **1-RhMe** ($\delta = -13.8$), while included C₆₀ displayed a signal in a region upfield ($\delta = 139.4$; $\Delta = -3.6$) from that of free C₆₀ ($\delta = 143.0$). In contrast, upon coordination of an electron-donating ligand such as bipyridine (bpy) to **1-RhMe** (**1-RhMe** ⊂ bpy), the ¹³C NMR signal for MeRh shifted upfield^[14] to $\delta = -16.0$ ($\Delta\delta = -2.2$). Therefore, it is likely that **1-RhMe** ⊂ C₆₀ involves a rhodium-to-fullerene charge transfer interaction.

The much higher affinities of the host molecules toward C₇₀ than C₆₀ are considered to be a result of the ovality of C₇₀ (7.1/7.9 Å). Because of this elliptical shape, C₇₀ itself shows five inequivalent ¹³C NMR signals.^[15, 16] When ¹³C-enriched C₇₀ was mixed with **1-Zn** in CDCl₃/CS₂ (1:1), all the C₇₀ signals shifted upfield, whereby the change in chemical shift was more pronounced for the equatorial carbon atoms than for those at the pole over a wide temperature range ($\Delta\delta_{\text{equator}} = -3.8$, $\Delta\delta_{\text{pole}} = -2.4$ at 25 °C; $\Delta\delta_{\text{equator}} = -4.1$, $\Delta\delta_{\text{pole}} = -2.5$ at -60 °C).^[5, 17] Since the upfield shifts of the fullerene signals are induced mostly by the shielding effect of the porphyrin macrocycle, this trend indicates that included C₇₀ adopts a side-on conformation with respect to the two zinc porphyrins, which possibly maximizes the host–guest π interaction.^[5, 7b] With **1-RhMe** as host, C₇₀ upon inclusion showed a similar change in spectral profile at 25 °C ($\Delta\delta_{\text{equator}} = -3.6$, $\Delta\delta_{\text{pole}} = -3.0$).^[18] However, on lowering the temperature to -60 °C, the shielding effect became slightly but definitely more pronounced for the carbon atoms at the pole than for those on the equator ($\Delta\delta_{\text{equator}} = -3.9$, $\Delta\delta_{\text{pole}} = -4.1$), which suggests that an end-on orientation is preferred for included C₇₀ at low temperatures.^[19]

Variable-temperature (VT) ¹³C NMR spectroscopy is informative of the dynamics of the complexation of fullerenes with cyclic dimers of metalloporphyrins.^[5] For example, a 1:2 mixture of **1-Zn** and ¹³C-enriched C₆₀ at -60 °C in [D₈]toluene showed two singlet ¹³C NMR signals at $\delta = 139.7$ and 142.9 arising from included and free C₆₀ molecules, respectively (Figure 3a). On elevation of the temperature, the signals coalesced at 20 °C as a result of exchange of C₆₀ faster than the NMR timescale. When ¹³C-enriched C₇₀ was the guest ([**1-Zn**]/[C₇₀] = 1:2), a similar coalescence signature was observed at a higher temperature (60 °C), as the K_{assoc} value for C₇₀ is 31 times larger than that for C₆₀. In sharp contrast, although the K_{assoc} value is almost comparable to that for the **1-Zn**/C₇₀

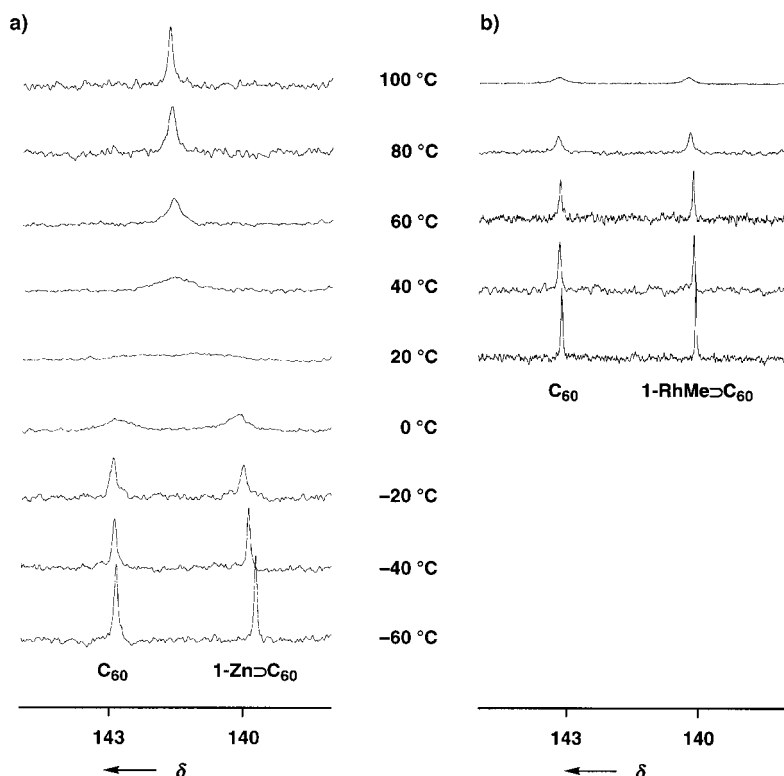


Figure 3. VT ^{13}C NMR profiles of ^{13}C -enriched C_{60} in the presence of 0.5 equiv of **1-Zn** (a) and **1-RhMe** (b) in $[\text{D}_8]\text{toluene}$.

system (Figure 2), the **1-RhMe**/ C_{60} (1:2) system did not show such a coalescence phenomenon even at 100 °C (Figure 3b). The same was true of the **1-RhMe**/ C_{70} system. Since the rate constant of dissociation k_{dissoc} is much smaller than that of association k_{assoc} ($K_{\text{assoc}} = k_{\text{assoc}}/k_{\text{dissoc}} \gg 1$), the above coalescence profiles should reflect the magnitude of k_{dissoc} rather than k_{assoc} . From the differences in resonance frequency between the free and included fullerenes,^[20] the k_{dissoc} values for **1-Zn** $\supset$ C_{60} and **1-Zn** $\supset$ C_{70} at the coalescence temperatures were estimated to be 450 (20 °C) and 310 s^{-1} ^[21] (60 °C), respectively.^[22] The absence of coalescence for the **1-RhMe** fullerene systems indicates that **1-RhMe** $\supset$ fullerenes dissociate much less frequently than **1-Zn** $\supset$ fullerenes. Together with the fact that rhodium(III) porphyrins can form ethene π complexes,^[23] the very low dissociation activities of **1-RhMe** $\supset$ fullerenes suggest some sort of bonding interaction between the central rhodium(III) ions of the host and the included fullerenes.

By taking advantage of the tunable affinity of the host molecule toward fullerenes, choice of appropriate central metal ions of the host allows simple separation of C_{70} from a mixture of C_{60} and C_{70} . For example, a $\text{C}_{60}/\text{C}_{70}$ mixture containing 65 % of C_{70} was mixed with **2-Zn** ([fullerenes]/[**2-Zn**] = 10) in benzene,^[24] and the inclusion complexes were isolated by column chromatography on alumina, and then treated with 4,4'-bipyridine to extract the included fullerenes from the cavity. According to HPLC analysis on Buckyprep with toluene as eluent, the extract contained almost pure C_{70} (> 99 %). Even from a $\text{C}_{60}/\text{C}_{70}$ mixture with a much lower C_{70} content such as 20 %, an extract highly enriched in C_{70} (91 %) was again obtained.

In conclusion, we have demonstrated a remarkable effect of the central metal ions on the interaction of metalloporphyrin cyclic dimers with fullerenes. In particular, the extremely high association constants ($\sim 10^8 \text{ M}^{-1}$)^[25] and low dissociation activities of the **1-RhMe**/fullerene systems should allow construction of more complex supramolecular architectures based on fullerenes. Further studies along this line together with an investigation of electronic and magnetic properties of such multiwalled π -electron supramolecular systems are now in progress.

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- higher than those of **1**-Zn ($1.4 \times 10^4 \text{ M}^{-1}$) and **1**-Co ($7.2 \times 10^4 \text{ M}^{-1}$) under the same conditions.
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- [15] ^{13}C NMR ($\text{CDCl}_3/\text{CS}_2$ 1:1): C_{70} (equator to pole) at 25°C : $\delta = 130.4$, 144.9, 147.6, 146.9, 150.1; at -60°C : $\delta = 130.0$, 144.5, 147.2, 146.5, 149.7; $\text{C}_{70}/\textbf{1}$ -Zn (1:2) at 25°C : $\delta = 126.6$ ($\Delta\delta = -3.8$), 141.3 (-3.6), 144.5 (-3.1), 144.2 (-2.7), 147.7 (-2.4); at -60°C : $\delta = 125.9$ ($\Delta\delta = -4.1$), 140.7 (-3.8), 143.9 (-3.3), 143.7 (-2.8), 147.2 (-2.5).
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Photoelectrochemistry with Controlled DNA-Cross-Linked CdS Nanoparticle Arrays**

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Electronics based on DNA has been the subject of extensive recent research activities that address the conductivity features of double-stranded (ds) DNA,^[1–7] the use of ds-DNA as a template for the construction of nanowires,^[8] and the employment of metal nanoparticles cross-linked by DNA

as single-electron charging devices.^[9, 10] The optical properties of DNA-cross-linked Au nanoparticles were recently studied and applied for DNA sensing,^[11, 12] and nanoarchitectures of DNA/Au nanoparticles were assembled.^[13] The electronic transduction of DNA sensing and, in particular, amplified DNA analyses were recently studied by using electrochemical measurements^[14–23] or microgravimetry^[16] with a quartz-crystal microbalance. Direct electrochemical detection of DNA was achieved by monitoring the electrochemical response of DNA^[14–16] or by the incorporation of redox-labels into ds-DNA.^[17–19] The amplified detection of DNA was accomplished by the use of biocatalytic conjugates^[20, 21] and the application of labeled liposomes^[22, 23] or nanoparticles.^[24, 25]

Herein we describe the novel architecture of double-stranded DNA-cross-linked CdS nanoparticle arrays on electrode supports and the structurally controlled generation of photocurrents upon irradiation of these arrays. The electrostatic binding of $[\text{Ru}(\text{NH}_3)_6]^{3+}$ to the ds-DNA units provides tunneling routes for the conduction-band electrons and thus results in enhanced photocurrents. Besides the unique and novel photoelectrochemical features of the systems, the assemblies provide a new means for the optical fluorescence and electronic (photoelectrochemical) transduction of DNA-sensing events.

CdS nanoparticles ($2.6 \pm 0.4 \text{ nm}$) were functionalized with thiolated oligonucleotide **1** or **2**. These two oligonucleotides are complementary to the 5'- and 3'-ends of the target DNA **3**. The size of the CdS nanoparticles was determined from HR-transmission electron microscopy (TEM) images (average of 150 particles). Using the absorption spectra of the CdS nanoparticles ($\lambda_{\text{max}} = 405 \text{ nm}$) and the Brus equation^[26] gave a similar particle size. We estimate that about 20–24 oligonucleotide units are associated with each CdS nanoparticle (see *Experimental Section* for details). Figure 1 shows the stepwise assembly of the DNA-cross-linked CdS particles on an Au electrode. The oligonucleotide **1** was assembled on the Au electrode ($2.3 \times 10^{-11} \text{ mol cm}^{-2}$) and then treated with the analyte **3** to yield the ds system. Subsequent interaction of the surface with the **2**-functionalized CdS resulted in the binding of the CdS nanoparticles to the surface. Further alternating interaction of the interface with a solution containing the **1**-functionalized CdS nanoparticles (1 mg mL^{-1}) pretreated with **3** ($1 \times 10^{-6} \text{ M}$) and with a solution containing **2**-functionalized CdS nanoparticles resulted in an array with a controlled number of CdS nanoparticle generations. The buildup of the DNA-cross-linked CdS nanoparticle array was monitored by microgravimetry with a quartz-crystal microbalance (Figure 2A).

From the frequency changes observed upon the buildup of the first generation of CdS nanoparticles, and knowing their dimensions, we estimate the surface coverage to be about 1.6×10^{12} particles per square centimeter. This value corresponds to around 15% of a densely packed particle layer. The negative charge associated with the nucleic acid functionalized nanoparticles probably prevents the formation of a dense particle configuration. The DNA-cross-linked CdS nanoparticle arrays were also assembled on glass supports by using an aminopropylsiloxane-functionalized glass that was treated with ϵ -maleimidocaproic *N*-hydroxysuccinimide ester^[24, 25] as a base interface for the covalent linkage of **1** and the organization of the nanoparticle systems. Figure 2B shows

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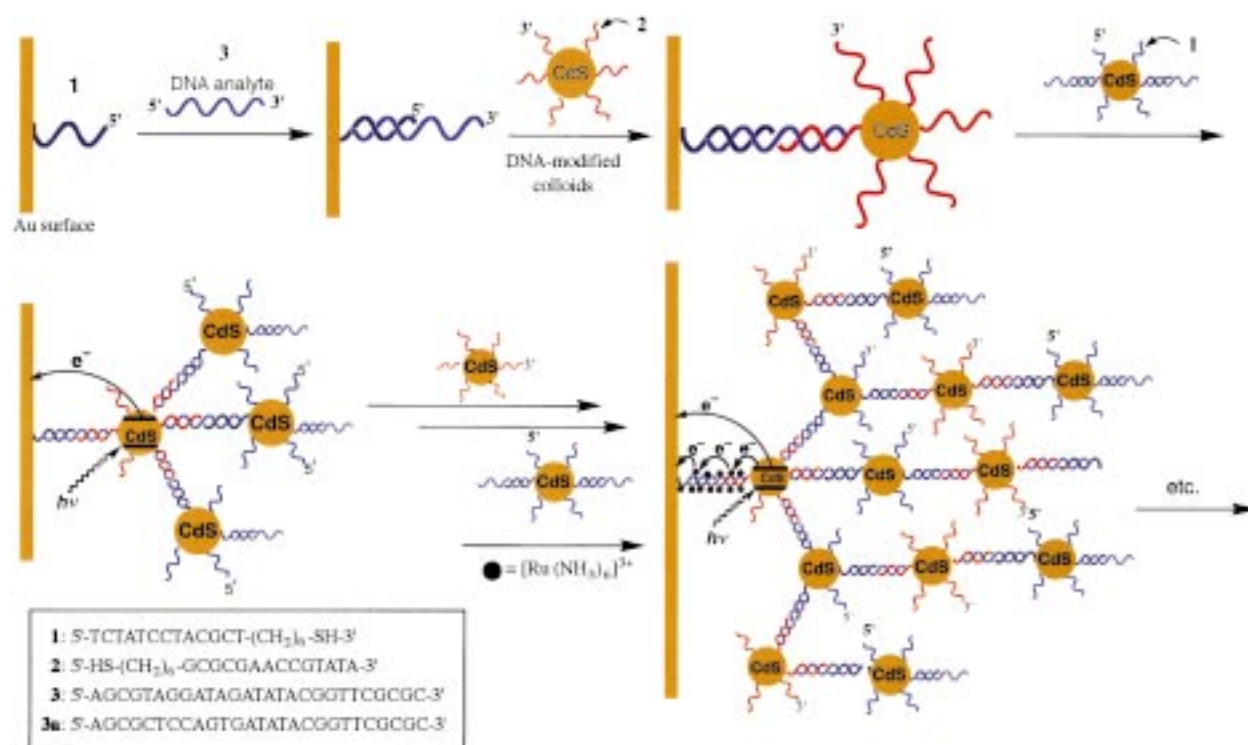


Figure 1. The organization of oligonucleotide/DNA-cross-linked arrays of CdS nanoparticles and the photoelectrochemical response of the nano-architectures.

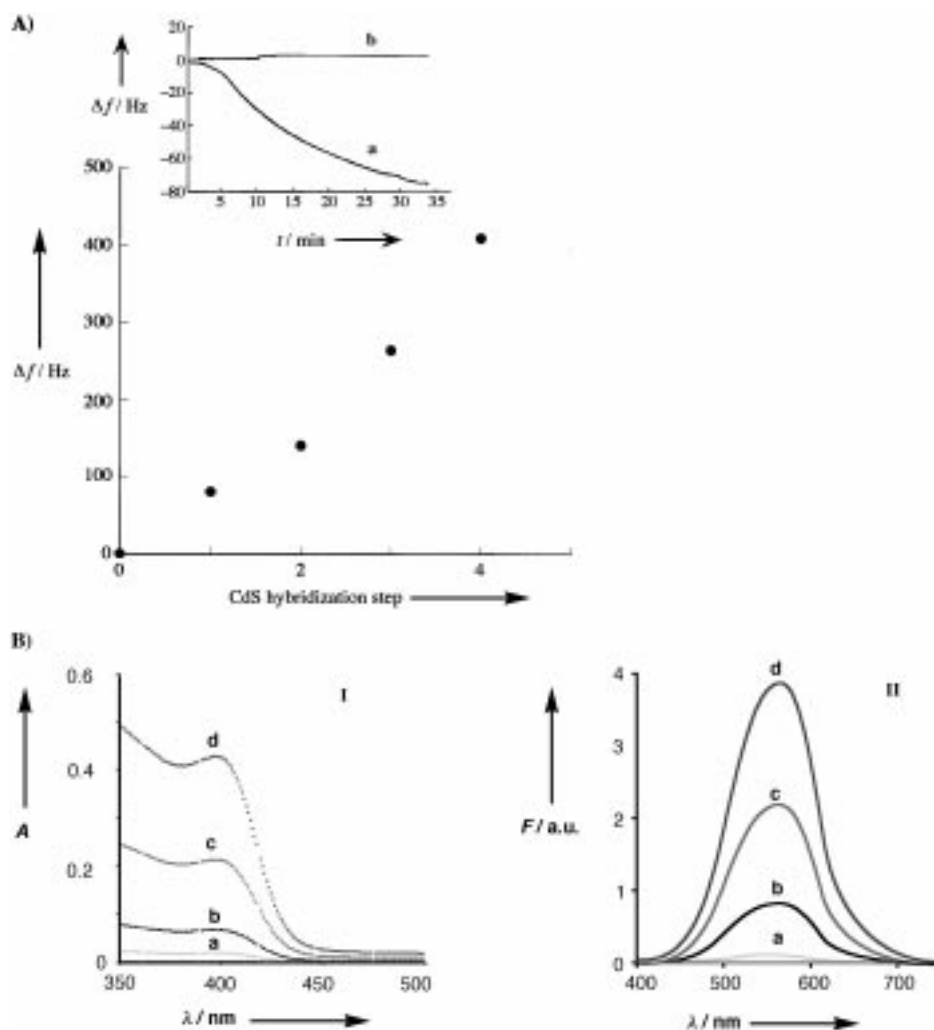


Figure 2. A) The frequency change of an Au/quartz crystal in air (9 MHz, AT-cut) upon the assembly of oligonucleotide/DNA-cross-linked CdS nanoparticle layers. The first layer was assembled by the reaction of the 1-functionalized electrode with 3 (1×10^{-6} M) and then with the 2-modified CdS nanoparticles. The other layers were constructed by the alternating treatment of the surface with a solution of 3 (1×10^{-6} M) containing the 1-modified CdS nanoparticles, and a solution of 2-functionalized CdS-nanoparticles. Inset: Kinetics of association of the first generation of the 2-functionalized CdS nanoparticles with a) The 1-modified Au/quartz interface that was hybridized with 2 (1×10^{-6} M) and then allowed to interact with 2-functionalized CdS nanoparticles (1 mg mL^{-1}); b) the 1-modified interface was hybridized with 3a and then treated with 2-functionalized CdS nanoparticles. B) Absorbance spectra (I) and fluorescence spectra (II) of layered oligonucleotide/DNA-cross-linked CdS nanoparticle arrays: a) to d) correspond to one to four CdS nanoparticle layers; $\lambda_{\text{ex}} = 405 \text{ nm}$ for fluorescence spectra.

the absorbance and fluorescence spectra of the DNA-cross-linked CdS-nanoparticle arrays. The intensities of the absorbance and fluorescence spectra increase as the number of generations of cross-linked CdS particles increases. The large Stokes shift observed in the fluorescence spectra suggests that the emission originates from surface traps. In fact, the preparation of the CdS quantum dots involves the generation of an excess of Cd^{2+} surface sites to enable the association of the nucleic acid. These sites probably act as surface traps.

Figure 3 A shows the photocurrent action spectra upon the excitation of arrays that consist of different numbers of CdS nanoparticle generations which are associated with the

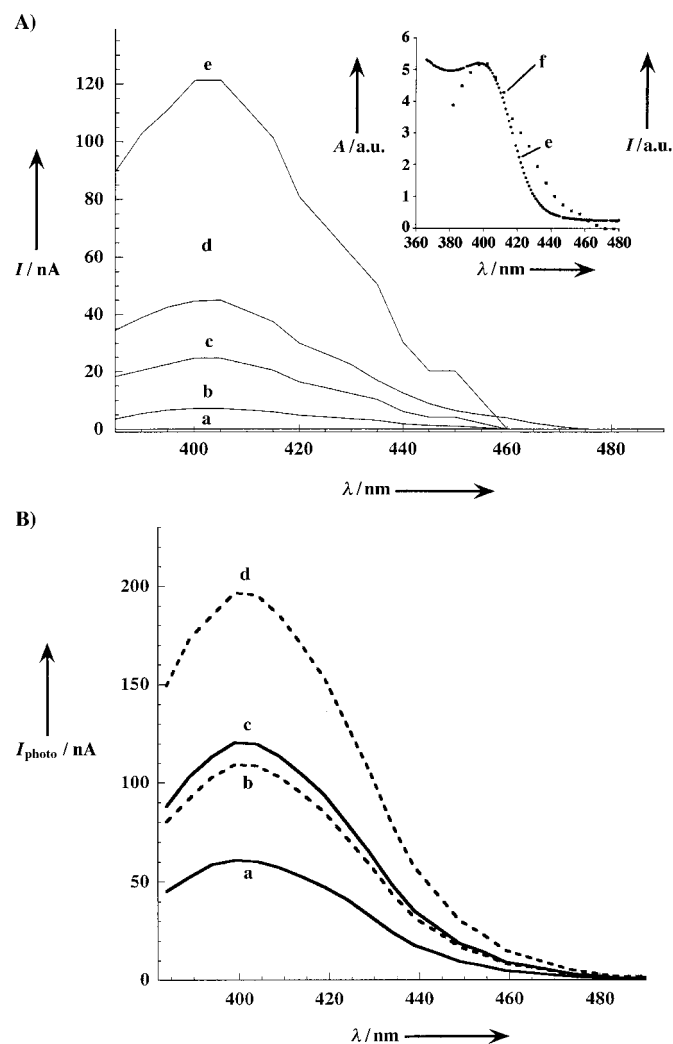


Figure 3. A) Photocurrent action spectra of an Au electrode that is associated with controlled numbers of layers of oligonucleotide/DNA-cross-linked CdS nanoparticles: a) Prior to the deposition of CdS nanoparticles. b) to e) One to four oligonucleotide/DNA-cross-linked CdS nanoparticle layers. Inset: Comparison of the photocurrent action spectrum of a four-layer CdS nanoparticle array (e) with the absorption spectrum (f) of the array. B) Photocurrent action spectra of two-layer (a) and four-layer (c) oligonucleotide-cross-linked CdS nanoparticle arrays. Two-layer (b) and four-layer (d) oligonucleotide/DNA-cross-linked CdS nanoparticle arrays in the presence of $[\text{Ru}(\text{NH}_3)_6]^{3+}$ ($5 \times 10^{-6} \text{ M}$). All photocurrent spectra were recorded under argon in 0.1 M KCl with triethanolamine ($2 \times 10^{-2} \text{ M}$) as sacrificial electron donor. The area of illuminated electrode corresponds to 1 cm^2 . The photocurrent spectra were normalized with respect to the wavelength dependence of the light intensity.

electrode in the presence of triethanolamine ($2 \times 10^{-2} \text{ M}$) as a sacrificial electron donor. The photocurrent follows the absorbance spectrum of the CdS nanoparticles (Figure 3 A, inset), and it increases with increasing number of generations of cross-linked particles. As we use a sacrificial electron donor as hole scavenger, we attribute the resulting photocurrent to the injection of conduction-band electrons into the electrode. The photocurrent can be switched "on" and "off" by pulsed irradiation of the arrays. The mechanism of photocurrent generation probably involves the photoejection of conduction-band electrons of CdS particles in contact with or at tunneling distances from the electrode (cf. Figure 1). This suggests, however, that some of the cross-linked nanoparticles do not participate in the development of the photocurrent. To assist the generation of the photocurrent by inactive CdS particles, the arrays were treated with $[\text{Ru}(\text{NH}_3)_6]^{3+}$ ($5 \times 10^{-6} \text{ M}$), which binds electrostatically to the DNA.^[27] The transition metal complex ($E^\circ = -0.16 \text{ V}$ vs SCE) acts as an electron acceptor for the conduction-band electrons ($E_{\text{CB}}^\circ < -0.9 \text{ V}$ vs SCE), and could thus mediate electron transfer from inactive CdS particles to the electrode.

Figure 3 B shows the photocurrents that are generated by the DNA-cross-linked CdS arrays that contain two and four generations of nanoparticles in the absence and presence of $[\text{Ru}(\text{NH}_3)_6]^{3+}$, respectively. In the presence of $[\text{Ru}(\text{NH}_3)_6]^{3+}$ the photocurrent is about twofold higher, and this implies that the DNA units act as a template for the electron-acceptor units that mediate electron transfer to the electrode (Figure 1). However, increasing the $[\text{Ru}(\text{NH}_3)_6]^{3+}$ concentration to $5 \times 10^{-4} \text{ M}$ adversely affects the photocurrent, which decreases to values below those observed for the CdS arrays without the electron acceptor. This result is reasonable, since at high bulk concentrations of $[\text{Ru}(\text{NH}_3)_6]^{3+}$, diffusional electron-transfer quenching of the semiconductor nanoparticles occurs. This process traps the conduction-band electrons and thus prevents even the direct electron photoejection process.

The photocurrents generated by the DNA-cross-linked array can be used for the quantitative detection of DNA. Figure 4 shows the photocurrents of a two-layer DNA-cross-linked nanoparticle array upon the formation of a third generation of CdS nanoparticles in the presence of 2-functionalized CdS at different concentrations of **3**. As the concentration of **3** increases, enhanced photocurrents are observed owing to greater coverage of the electrode by the third generation of semiconductor nanoparticles. In all of the systems described in the present study, no photocurrents are observed upon interaction of the 1-functionalized electrode with the **1**- or 2-functionalized nanoparticles or on attempting to cross-link the nanoparticle arrays with **3a**. Hence, no nonspecific binding of the CdS nanoparticles to the transducers is observed, and the photocurrents are specific to the cross-linking process involving the target DNA **3**.

In conclusion, we have demonstrated the novel generation of photocurrents in controlled DNA-cross-linked semiconductor nanoparticle arrays. We revealed that the DNA cross-linking units act as a template for the association of $[\text{Ru}(\text{NH}_3)_6]^{3+}$ and the electrical wiring of the semiconductor with the electrode support. Other electron acceptors, and

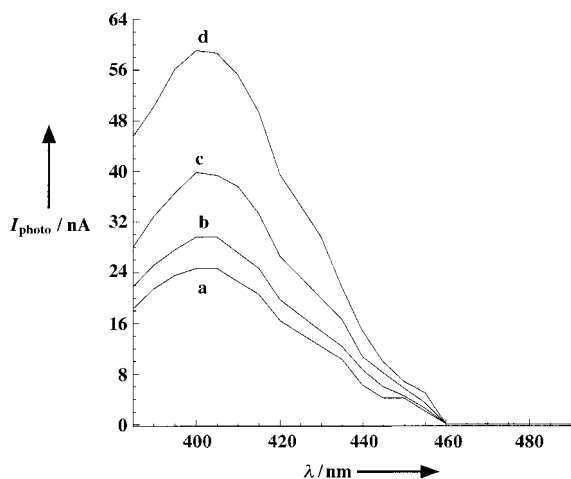


Figure 4. Sensing of the DNA 3 by means of the photocurrent response of the arrays. a) A two-layer oligonucleotide/DNA-cross-linked CdS array. b) Upon treatment of the two-layer cross-linked array with 3 (1×10^{-9} M) in the presence of 2-functionalized CdS. c) Upon treatment of the two-layer cross-linked array with 3 (1×10^{-8} M) in the presence of 2-functionalized CdS. d) Upon treatment of the two-layer cross-linked array with 3 (1×10^{-7} M) in the presence of 2-functionalized CdS. Photocurrent spectra were recorded under the conditions specified in the caption of Figure 3.

specifically intercalators, could improve the electrical contact of the semiconductor particles with the electrode. The unique photophysical and photoelectrochemical properties of the semiconductor nanoparticles pave the way for new DNA sensors and electronic devices.

Experimental Section

Preparation of oligonucleotide-functionalized CdS nanoparticles: An AOT/*n*-heptane water-in-oil microemulsion was prepared by the solubilization of 2 mL of distilled water in 100 mL *n*-heptane in the presence of 7.0 g of AOT surfactant, dioctyl sulfosuccinate, sodium salt. The resulting mixture was separated into 60 mL and 40 mL reverse-micelle sub-volumes. Aqueous solutions of Cd(ClO₄)₄ (0.24 mL, 1 M) and Na₂S (0.16 mL, 1.0 M) were added to the 60 mL and 40 mL subvolumes of reverse micelles, respectively. After stirring the two subvolumes for 1 h, they were united and stirred under argon for 1 h to yield the CdS nanoparticles. To the resulting mixture were added aqueous solutions of 2-aminoethanethiol (cystamine; 0.17 mL, 0.32 M) and 2-sulfanyethane sulfonic acid (0.33 mL, 0.32 M), and the mixture was stirred for 24 h under Ar. The resulting mixture was evaporated under vacuum and the residue was successively washed with pyridine, *n*-heptane, acetone, and methanol to yield the cystamine/thioethanesulfonate-capped, water-soluble CdS nanoparticles.

The resulting CdS nanoparticles (1 mg mL^{-1}) were treated with the respective thiolated oligonucleotide ($40\text{--}50 \text{ OD mL}^{-1}$), and the mixture was stirred for 24 h at room temperature under Ar. To the resulting mixture were added the appropriate salts to generate a 0.24 M NaCl and 0.1 M phosphate buffer solution (pH 7.4). The mixture was dialyzed for 48 h against 0.2 M NaCl and 0.1 M phosphate buffer (pH 7.4) containing 0.01 % sodium azide. The resulting oligonucleotide-functionalized CdS nanoparticles exhibited high stability in the form of an aqueous suspension. The CdS nanoparticles could be isolated in the solid state by flash evaporation, and could be re-suspended in water for further experiments.

Characterization of CdS nanoparticles: To estimate the average number of oligonucleotide units associated with each CdS particle, a suspension of CdS nanoparticles was treated with the thiolated fluorescein-labeled oligonucleotide 5'-HS(CH₂)₆-GCGCGAACCGTA(T-fluorescein)A-3', as described above. The resulting fluorescein-labeled, oligonucleotide-functionalized CdS (1 mg mL^{-1} , 200 μL) was treated for 2 h with DNase I (Amersham Pharmacia; 20 units at 37 °C in 40 mM tris HCl, pH 7.5, in the presence of 6 mM of MgCl₂). The resulting mixture was centrifuged, and the

fluorescence of the fluorescence label in the supernatant solution was determined.

Independently, the capped CdS nanoparticles (1 mg) were heated for 2 h at 400 °C in an oven and then dissolved in perchloric acid. The content of Cd²⁺ in the sample was determined by atomic absorption. From the known amount of Cd²⁺ in the sample, the size of the CdS nanoparticles, the density of CdS, and the amount of fluorescence label released from the particles, we estimate that about 20–24 oligonucleotides are associated with each CdS particle.

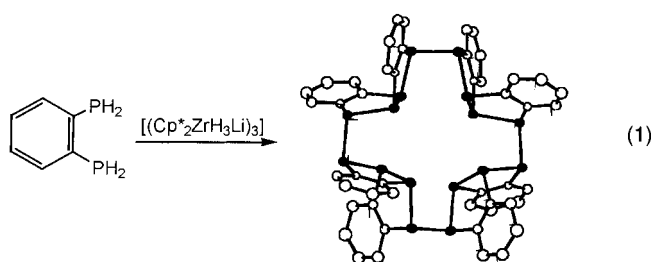
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The Main Group Macrocycle $[(\text{PCH}_2\text{CH}_2\text{PAlMe}_2)_2]_4 \cdot 4[\text{AlMe}_3]^*$

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Recent reviews in the fields of main group,^[1] organo-metallic,^[2] solid-state,^[3] and organo-phosphorus chemistry^[4] have reflected the multidisciplinary interest in compounds containing phosphorus. While organo-phosphorus ligands are ubiquitous in transition metal chemistry, the catenation of phosphorus atoms in organophosphanes and related polyphosphorus anions has drawn attention from inorganic and solid-state chemists.^[1, 3] The work of Scherer, Driess, Fenske, and others^[2, 5, 6] concerning the studies of substituent-free phosphorus-metal complexes,^[7] is one example where studies have crossed these disciplinary lines. These disciplinary boundaries have been further eroded with the studies of phosphanide and phosphanediyl clusters reported by the research groups of Fenske^[8–11] and Driess.^[12–14] While these systems employ phosphorus atoms to link metals in complex clusters, we have targeted systems in which chains of phosphorus atoms act as metal-linking units. In targeting such systems we first sought a convenient route to organo-polyphosphanes as previously known syntheses were arduous.^[15, 16] To this end, we developed a catalyst for the dehydrocoupling of primary phosphanes to organopolyphosphanes.^[17] In a recent demonstration of such catalysis, we employed the catalyst precursor $[(\text{Cp}^*\text{ZrH}_3\text{Li})_3]$ to produce the macrocyclic P_{16} ring compound $(\text{C}_6\text{H}_4\text{P}_2)_8$ [Eq. (1)].^[18, 19]



Herein we report, the catalytic synthesis of the organo-tetraphosphane $(\text{PCH}_2\text{CH}_2\text{PH})_2$ (**1**) and employ it to prepare the unique $\text{P}_{16}-\text{Al}_{12}$ compound, $[(\text{PCH}_2\text{CH}_2\text{PAlMe}_2)_2]_4 \cdot 4[\text{AlMe}_3]$ **3**. This species employs four P_4 chains to link eight aluminum centers, forming Al_2P_3 rings in a unique macrocyclic structure comprised of solely main group elements (see Scheme 1).

The quantitative catalytic dehydrocoupling of the primary bidentate phosphane $\text{PH}_2\text{CH}_2\text{CH}_2\text{PH}_2$, using the catalyst precursor $[(\text{Cp}^*\text{ZrH}_3\text{Li})_3]$ proceeds smoothly at room temperature over a three day period to afford the colorless product **1**. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of **1** consists of two

resonances at $\delta = -22.5$ and -65.4 , each showing second-order coupling. Simulation of the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum shows that it is consistent with an $\text{AA}'\text{BB}'$ pattern with one and two bond P–P coupling constants of -237 Hz, -186 Hz and 20 Hz respectively. This data is in good agreement to that reported for **1**, previously prepared by Baudler et al. in 30–55 % via two different reductive coupling strategies.^[15, 16] Recrystallization of **1** from hexane at -35°C afforded colorless X-ray quality crystals. An X-ray diffraction study of **1** confirmed the formulation as the product of the dehydrocoupling of two molecules of the starting diphosphane, that is $(\text{PCH}_2\text{CH}_2\text{PH})_2$ (Figure 1).^[20] This molecule

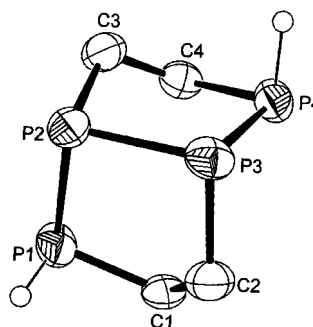


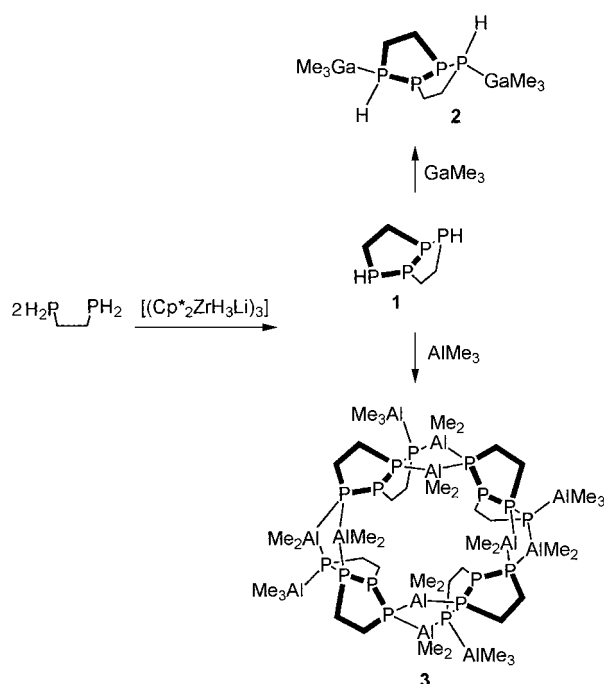
Figure 1. ORTEP drawing of **1**, thermal ellipsoids are set at the 50 % level. Carbon-bound hydrogen atoms are omitted for clarity. P1–P2 2.1928(14), P2–P3 2.2217(14), P3–P4 2.2063(14); P1–P2–P3 97.22(5), P4–P3–P2 96.96(5).

comprises two interlinked five-membered rings, in which one phosphorus atom of each of two diphosphane fragments forms P–P bonds with the two phosphorus atoms of the other diphosphane moiety. This results in a chain of four phosphorus atoms where the terminal phosphorus atoms retain a single proton. The average P–P bond length in **1** is 2.2069(14) Å while the P–P–P angles average 97.09(5)°. The two five-membered rings are approximately orthogonal, the angle between the mean P_3C_2 planes is 94.9(1)°. This constrained orientation directs the terminal protons in essentially orthogonal directions, the torsion angles about the H–P–P–P–H chain average 88.9°. This geometry of **1** is analogous to one quarter of the previously reported macrocycle $(\text{C}_6\text{H}_4\text{P}_2)_8$.^[18]

The catalytic formation of **1** provides convenient access to a corner-type molecular building block containing a P_4 chain. In attempts to employ **1** to link metal centers, reactions of **1** with $[\text{MMe}_3]$ ($\text{M} = \text{Ga}, \text{Al}$) were undertaken (Scheme 1). The reaction of **1** with $[\text{GaMe}_3]$ in hexane resulted in the formation of a highly unstable species **2**. This short-lived species exhibited a ^{31}P NMR spectrum showing signals at $\delta = -19.4$ and -65.1 . The downfield resonance appears similar to that observed for **1** while the upfield resonance has increased multiplicity suggesting coordination to Ga and the formulation $[(\text{PCH}_2\text{CH}_2\text{PH})\text{GaMe}_3]_2$ (**2**). The rapid degradation of this product with gas evolution (presumably methane) and the deposition of an insoluble white material, precluded further characterization of **2**. The nature of the subsequent P–Ga product(s) remains unknown, despite repeated attempts to obtain pure, crystalline material.

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Scheme 1.

In contrast, addition of excess $[\text{AlMe}_3]$ to a solution of **1** does not give a reaction at 25°C . However, heating a solution of **1** with excess $[\text{AlMe}_3]$ in hexane to 80°C for 1 week in a sealed reaction vessel gives a white solid **3** in 64% yield. Recrystallization of **3** from a 1:1 mixture of THF and hexane at -35°C yielded colorless cubic crystals. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the crystalline **3** showed four broad resonances at $\delta = 1.9, -50.9, -67.1$, and -88.8 . The ^1H NMR spectrum of **3** showed four distinct resonances attributable to aluminum bound methyl groups. While these data infer P–Al interactions, neither of the NMR spectra provided substantial structural information. This prompted an X-ray crystallographic study which confirmed the formulation of **3** as $[\{(\text{PCH}_2\text{CH}_2\text{PAI}(\text{Me}_2)_2)_4\} \cdot 4[\text{AlMe}_3]]$ (Figure 2).^[20] This centrosymmetric macrocyclic compound comprises four P_4C_4 units

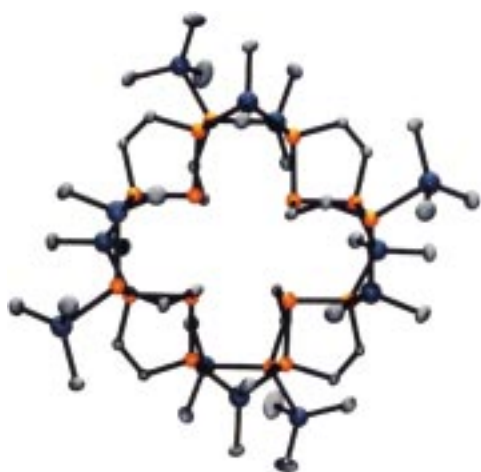


Figure 2. ORTEP drawing of **3**, the thermal ellipsoids are set at 20%. Hydrogen atoms are omitted for clarity. Phosphorus atoms are depicted in orange, aluminum in blue, and carbon in gray.

that are bridged by two AlMe_2 units. One of the Al centers bridges the terminal P atoms of two adjacent P_4C_4 units. The second Al center is bound to the terminal phosphorous of one P_4 unit and to a central P atom of the second P_4 moiety, giving five-membered P_3Al_2 rings. The result is four such rings linked by P units (Figure 3). The bridging Al–P bonds average

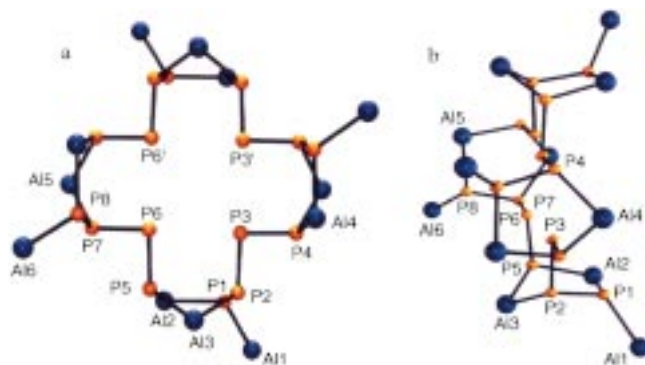


Figure 3. ORTEP drawings of the heteroatom core of **3**. Views a) and b) are approximately orthogonal. Phosphorus atoms are depicted in orange, aluminum in blue. Selected distances [$\text{\AA}$] and angles [$^\circ$] Al1–P1 2.576(4), Al2–P5 2.471(4), Al2–P1 2.484(4), Al3–P5 2.458(4), Al3–P2 2.477(4), Al4–P4 2.469(4), Al4–P8' 2.495(4), Al5–P4' 2.459(4), Al5–P7 2.502(4), Al6–P8 2.595(4), P1–P2 2.195(4), P2–P3 2.246(3), P3–P4 2.224(3), P5–P6 2.224(3), P6–P7 2.252(3), P7–P8 2.192(4); P5–Al2–P1 99.25(13), P5–Al3–P2 89.46(12), P4–Al4–P8' 98.94(14), P4'–Al5–P7 87.88(12), P2–P1–Al2 105.24(14), P2–P1–Al1 117.44(15), Al2–P1–Al1 116.44(14), P1–P2–P3 98.76(13), P1–P2–Al3 110.73(13), P3–P2–Al3 116.21(13), P4–P3–P2 92.86(12), P3–P4–Al5' 115.28(14), P3–P4–Al4 106.66(14), Al5–P4–Al4 106.49(14), P6–P5–Al3 115.44(14), P6–P5–Al2 106.37(14), Al3–P5–Al2 106.57(13), P5–P6–P7 92.69(12), P8–P7–P6 98.85(13), P8–P7–Al5 111.17(14), P6–P7–Al5 115.97(13), P7–P8–Al4' 104.46(13), P7–P8–Al6 119.84(15), Al4'–P8–Al6 116.48(14), Al3–P8–Al2 106.49(14).

2.477(5) $\text{\AA}$ while the P–P bonds range from 2.192(4) $\text{\AA}$ to 2.252(3) $\text{\AA}$. The angles at Al within the P_3Al_2 rings range from $89.46(12)$ to $99.25(13)^\circ$ while the corresponding angles at phosphorous span the range from $105.24(14)$ to $110.73(13)^\circ$. One of the P atoms of each P_3Al_2 ring also binds an additional equivalent of $[\text{AlMe}_3]$ with an average terminal Al–P bond of 2.586(4) $\text{\AA}$. The view of **3** in Figure 3a shows the main group macrocycle within the molecule. The dimensions of the depicted central cavity of this molecule are indicated by the P3–P6, P3–P3', and P6–P6' distances of 3.655(5), 5.071(5), and 5.016(5) $\text{\AA}$, respectively. The side view of **3** (Figure 3b) shows the P_3Al_2 rings are puckered (maximum deviation from the mean plane of 0.35 $\text{\AA}$). In addition the adjacent pairs of P_3Al_2 rings are approximately perpendicular, with the angles between the mean P_3Al_2 planes being 90.6 and 91.2° .

In conclusion, we have described the catalytic synthesis of the organotetraphosphane **1**, which reacts with $[\text{AlMe}_3]$ to give the main group macrocycle **3**. This species represents a rare, if not unprecedented example of a compound in which polyphosphorus chains linking metal atoms in a macrocyclic array. As this approach provides entry to compounds of cross-disciplinary interest, we are continuing to develop the chemistry of both catalytically generated organopolyphosphanes and their metal derivatives.

Experimental Section

1: [(Cp)₂ZrH₃Li]₃^[19] (0.1 g, 0.27 mmol) was dissolved in THF (3 mL), PH₂CH₂CH₂PH₂ (1.0 g, 10.87 mmol) was added dropwise to the stirred, colorless solution which became green, then aquamarine, and finally blue, over a period of 30 min. The reaction was stirred for 72 h, until it became colorless. Solvent was removed in vacuo, leaving a white solid which was dissolved in hexane, filtered, and placed in a freezer (−35 °C). Colorless, X-ray quality crystals (0.86 g, 87 % yield) precipitated from solution, over 24 h. ¹H NMR (C₆D₆): δ = 3.65 (dt, 2H, ¹J_{PH} = 330, ³J_{HH} = 10 Hz), 2.43 (m, 2H), 1.87 (m, 2H), 1.14 (m, 2H), 0.74 (m, 2H); ¹³C{¹H} NMR (C₆D₆): δ = 38.36, 30.66; ³¹P NMR (C₆D₆): δ = −22.5 (P₁: ¹J_{P1,P1} = −237, ¹J_{P1,P0} = −186, ²J_{P1,P0} = 20 Hz), −65.4 (P₀: ¹J_{P1,P1} = −237, ¹J_{P1,P0} = −186, ²J_{P1,P0} = 20 Hz); elemental analysis (%) calcd for P₄C₄H₁₀: C 26.39, H 5.54; found: C 26.18, H 5.42.

2: A 10 % by weight solution of [GaMe₃] in hexane (378 mg, 0.33 mmol) was added to a vial containing **1** (30 mg, 0.16 mmol), with stirring. A very fine white precipitate was evident in the clear colorless solution after 10 min. An aliquot of the reaction mixture was used immediately for ³¹P NMR spectroscopic characterization. This compound rapidly degraded on standing. ³¹P NMR (C₆D₆): δ = −19.4 (m), −65.1 (m).

3: A 2 M hexane solution of [AlMe₃] (0.14 mL, 0.28 mmol) was quickly added to a stirred toluene (1 mL) solution of **1** (20 mg, 0.11 mmol). The reaction mixture was heated to 80 °C in a sealed reaction vessel for 1 week, during which time the solution turned a very pale orange. Solvent was removed in vacuo, and the resulting white solid was dissolved in a 1:1 mixture of THF and hexane, and placed in a freezer (−35 °C) until clear, colorless, cubic crystals of **3** precipitated from solution in 64 % yield. ¹H NMR (C₇D₈): δ = 2.3 (brs, 2H), 1.8 (brs, 2H), 1.2 (brs, 3H), 1.1 (brs, 2H), 0.8 (brs, 3H), 0.6 (brs, 2H), −0.2 (brs, 3H), −0.3 (9H), −0.7 (brs, 3H); ³¹P NMR (C₆D₆): δ = 1.9 (brm), −50.9 (brm), −67.1 (brm) −88.8 (brm); elemental analysis (%) calcd for C₁₁H₂₉P₄Al₃: C 36.08, H 7.98; found: C 35.88, H 7.78.

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- [20] Diffraction experiments were performed on a Siemens SMART System CCD diffractometer and solved with the SHELX-TL software package. Crystal data for **1**: space group: *P* $\bar{1}$, *a* = 6.6064(1), *b* = 6.6258(2), *c* = 10.6067(3) Å, *α* = 80.624(2), *β* = 74.3540(10), *γ* = 67.241(2)°, *V* = 411.373(18) Å³, *Z* = 2, data/parameters: 1331/81, *R* = 0.0549, *R*_w = 0.1355, GOF = 1.014. Crystal data for **3**: space group: *C*2/*c*, *a* = 26.7605(2), *b* = 18.0602(3), *c* = 23.085 (3) Å, *β* = 98.04(1)°, *V* = 11047.4(2) Å³, *Z* = 8, data/parameters: 6497/326, *R* = 0.0996, *R*_w = 0.2875, GOF = 1.130. 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-152132 and CCDC-152133. 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).

Experimental and Theoretical Observations of Aromaticity in Heterocyclic XAl₃[−] (X = Si, Ge, Sn, Pb) Systems**

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The concept of aromaticity may seem foreign for metallic systems. After all, aromaticity usually refers to cyclic, planar, or conjugated organic molecules which possess (4*n* + 2) *π* electrons and have a specific chemical and structural stability. Nevertheless, aromaticity has been extended to include

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heterosystems^[1–3] and organometallic compounds.^[4–6] In particular, Robinson and co-workers have synthesized organometallic compounds that contain a cyclic Ga_3 group stabilized by three large organic ligands.^[4] However, aromaticity has never been considered in pure all-metal species. We recently reported experimental and theoretical evidence of aromaticity in an all-metal system, the Al_4^{2-} dianion in a series of bimetallic and ionic clusters MAl_4^- ($\text{M} = \text{Li}, \text{Na}, \text{or Cu}$).^[7] The Al_4^{2-} dianion, both as an isolated species and in the bimetallic molecules (MAl_4^-), is square planar and possesses two delocalized π electrons, thus conforming to the structural criterion and the $(4n+2)$ electron-counting rule for aromaticity. The delocalization of the two π electrons is critical for the planar structure and aromaticity of Al_4^{2-} . Herein we explore the possibility of aromaticity in a series of heterosystems, XAl_3^- ($\text{X} = \text{Si}, \text{Ge}, \text{Sn}, \text{and Pb}$), which are isoelectronic with Al_4^{2-} . All the XAl_3^- species have two lowest singlet isomers: a four-membered heterocyclic structure (C_{2v}) and a pyramidal structure (C_{3v}). The heterocyclic structure is aromatic, with two delocalized π electrons, analogous to Al_4^{2-} . The substitution of one Al in Al_4^{2-} by Si, Ge, Sn, and Pb allowed us to investigate systematically how the delocalized π orbital, and thus aromaticity, affects the relative stabilities and properties of the heterocyclic and pyramidal structures.

The XAl_3^- anions were produced by laser vaporization of the respective alloy targets.^[8] The anionic species from the cluster source were analyzed using a time-of-flight mass spectrometer.^[9] The XAl_3^- anions of interest were selected and decelerated before being subjected to photodetachment. Photoelectron spectra of the four XAl_3^- species were taken at two detachment laser wavelengths (355 and 266 nm, Figure 1) by using a magnetic bottle type analyzer,^[9] and were calibrated with the known spectra of Cu^- . The photoelectron energy resolution was about 25 meV for 1-eV electrons. The spectra of the four species are similar, each with an intense threshold peak (X and A), followed by another intense peak (B) and a relatively weaker feature (C) only observed in the 266-nm spectra for $\text{X} = \text{Ge}, \text{Sn}, \text{and Pb}$, and also for $\text{X} = \text{Si}$ in both 266 and 355 nm spectra. Weak low-binding energy features seem to be present in the spectra of SiAl_3^- and GeAl_3^- . The X and A features overlapped heavily and were resolved only in the 355-nm spectrum of PbAl_3^- . Whereas the binding energies of the X and A features decrease from $\text{X} = \text{Si}$ to Pb , those of the B and C features increase, leading to the well-separated spectra of PbAl_3^- . The vertical detachment energies (VDEs) of the four spectral features measured from the peak maxima are listed in Table 1 and are compared to the values obtained from ab initio calculations.

We have found that combining photoelectron spectroscopy and ab initio calculations offers a particularly powerful approach to investigate the structure and bonding of novel molecular and cluster species.^[7, 8, 10, 11] To search for the global minima of XAl_3^- , we first performed ab initio calculations on a wide variety of singlet and triplet structures of SiAl_3^- by using three different and sophisticated theoretical methods.^[12, 13] For the heavier XAl_3^- species, we focused only on the two low-lying singlet structures (a C_{2v} cyclic and a C_{3v} pyramidal structure) initially obtained for SiAl_3^- . We found that the most stable structure for all four XAl_3^- species is the

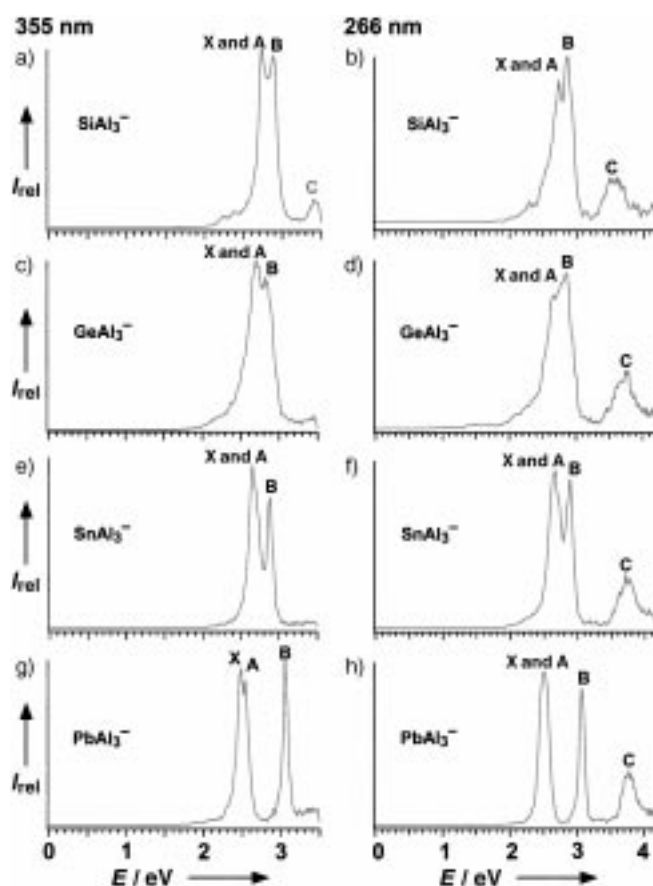


Figure 1. Photoelectron spectra at 355 nm (3.496 eV) of a) SiAl_3^- , c) GeAl_3^- , e) SnAl_3^- , and g) PbAl_3^- , and at 266 nm (4.661 eV) of b) SiAl_3^- , d) GeAl_3^- , f) SnAl_3^- , and h) PbAl_3^- . The spectra are plotted in order of increasing electron-binding energies.

Table 1. Experimental and theoretical vertical detachment energies (VDE) in eV for SiAl_3^- , GeAl_3^- , SnAl_3^- , and PbAl_3^- .

Exp. Features	Exp. VDE	MO	C_{2v} VDE ^[a]	MO	C_{3v} VDE ^[a]
SiAl_3^-					
X&A	2.73 ± 0.08	$4a_1$	2.64 (0.86)	$2e$	2.48 (0.86)
		$1b_1$	2.70 (0.86)	$3a$	2.72 (0.86)
B	2.88 ± 0.05	$2b_2$	2.82 (0.86)	$2a_1$	4.64 (0.80)
C	3.54 ± 0.10	$3a_1$	3.33 (0.86)		
GeAl_3^-					
X&A	2.70 ± 0.09	$4a_1$	2.61 (0.87)	$2e$	2.46 (0.86)
		$1b_1$	2.65 (0.86)	$3a$	2.56 (0.86)
B	2.83 ± 0.08	$2b_2$	2.81 (0.86)	$2a_1$	4.66 (0.79)
C	3.65 ± 0.18	$3a_1$	3.43 (0.86)		
SnAl_3^-					
X	2.66 ± 0.04	$1b_1$	2.47 (0.86)	$2e$	2.24 (0.86)
A	2.70 ± 0.04	$4a_1$	2.51 (0.86)	$3a_1$	2.43 (0.86)
B	2.88 ± 0.02	$2b_2$	2.71 (0.86)	$2a_1$	5.10 (0.74)
C	3.72 ± 0.06	$3a_1$	3.63 (0.85)		
PbAl_3^-					
X	2.484 ± 0.020	$1b_1$	2.36 (0.86)	$2e$	2.11 (0.86)
A	2.538 ± 0.020	$4a_1$	2.41 (0.87)	$3a_1$	2.33 (0.86)
B	3.054 ± 0.010	$2b_2$	2.61 (0.86)	$2a_1$	5.79 (0.00)
C	3.76 ± 0.06	$3a_1$	3.74 (0.85)		

[a] The theoretical VDEs were calculated at the OVGF/6-311 + G(2df) or OVGF/4s4p2d1 f levels of theory. The numbers in the parentheses indicate the pole strength, which characterizes the validity of the one-electron detachment picture. The ionization processes from the $1b_1$ and $4a_1$ orbitals are too close in energy, and their order cannot be definitely established in our calculations.

C_{2v} cyclic structure (Figure 2a, 2c, 2e, and 2g). The C_{3v} pyramidal structure is a low-lying isomer for all XAl_3^- species (Figure 2b, 2d, 2f, and 2h). The optimized geometries, vibrational frequencies, and relative energies agreed well at

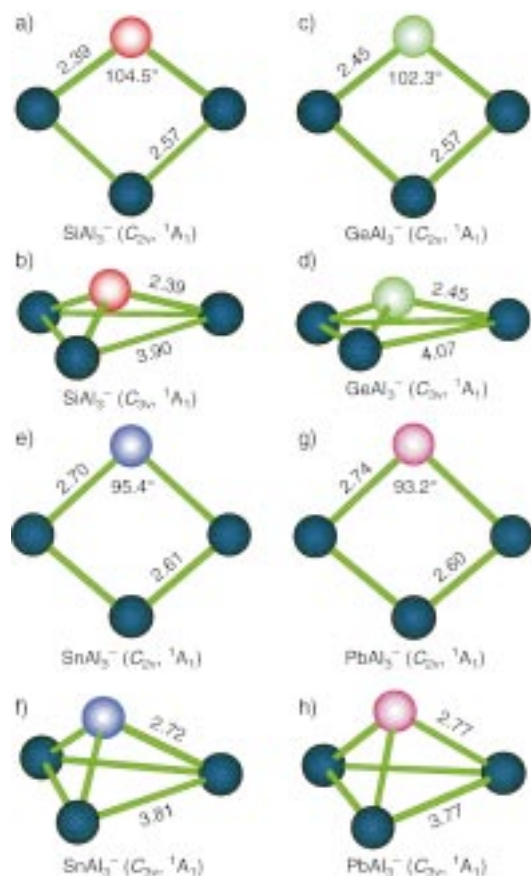


Figure 2. Optimized structures of XAl_3^- at the CCSD(T)/6-311 + G* and CCSD4s4p1d level of theory. Bond lengths are given in Å. a) Cyclic planar $SiAl_3^-$ (C_{2v} , $^1A_1$), b) pyramidal $SiAl_3^-$ (C_{3v} , $^1A_1$), c) cyclic planar $GeAl_3^-$ (C_{2v} , $^1A_1$), d) pyramidal $GeAl_3^-$ (C_{3v} , $^1A_1$), e) cyclic planar $SnAl_3^-$ (C_{2v} , $^1A_1$), f) pyramidal $SnAl_3^-$ (C_{3v} , $^1A_1$), g) cyclic planar $PbAl_3^-$ (C_{2v} , $^1A_1$), and h) pyramidal $PbAl_3^-$ (C_{3v} , $^1A_1$).

the three levels of theory used in this work for all four XAl_3^- species. At our highest level of theory, the global minimum C_{2v} cyclic structure is more stable than the C_{3v} pyramidal structure by 14.7, 18.4, 29.2, and 33.4 kcal mol $^{-1}$ for $X = Si, Ge, Sn,$ and Pb , respectively.

Theoretical calculations of the four lowest-lying vertical one-electron detachment processes for the cyclic and pyramidal species are compared with the experimental VDEs in Table 1. Excellent agreement was obtained for all four anions between the predicted VDEs of the C_{2v} cyclic structures and the experimental spectra, whereas the predicted VDEs of the low-lying pyramidal isomers do not agree with the experimental data. The highest occupied molecular orbital (HOMO) of the C_{3v} isomer consists of two degenerate orbitals (2e), which have lower VDEs than those of the HOMO of the C_{2v} cyclic structure. The photoelectron spectra of $SiAl_3^-$ and $GeAl_3^-$ (Figure 1) both exhibited lower binding energy features, which suggests a significant population of the C_{3v} isomer. Similar lower binding-energy features seemed to also

exist in the spectra of $SnAl_3^-$ and $PbAl_3^-$, but they are weakened significantly along the $SiAl_3^- \rightarrow GaAl_3^- \rightarrow SnAl_3^- \rightarrow PbAl_3^-$ series. This observation is in complete agreement with the results of our ab initio calculations, which showed that the relative energy of the C_{3v} isomer steadily increased along the same direction. Both this observation and the excellent agreement between the calculated spectra of the cyclic structures and the experimental spectra provide conclusive evidence for the cyclic global minima structures of the XAl_3^- species.

The stability of the C_{2v} cyclic structure relative to the pyramidal structure is related to the $1b_1$ orbital, HOMO-1 in $SiAl_3^-$ and $GeAl_3^-$, and HOMO in $SnAl_3^-$ and $PbAl_3^-$ (Figure 3). Clearly the $1b_1$ orbital is a delocalized π orbital.

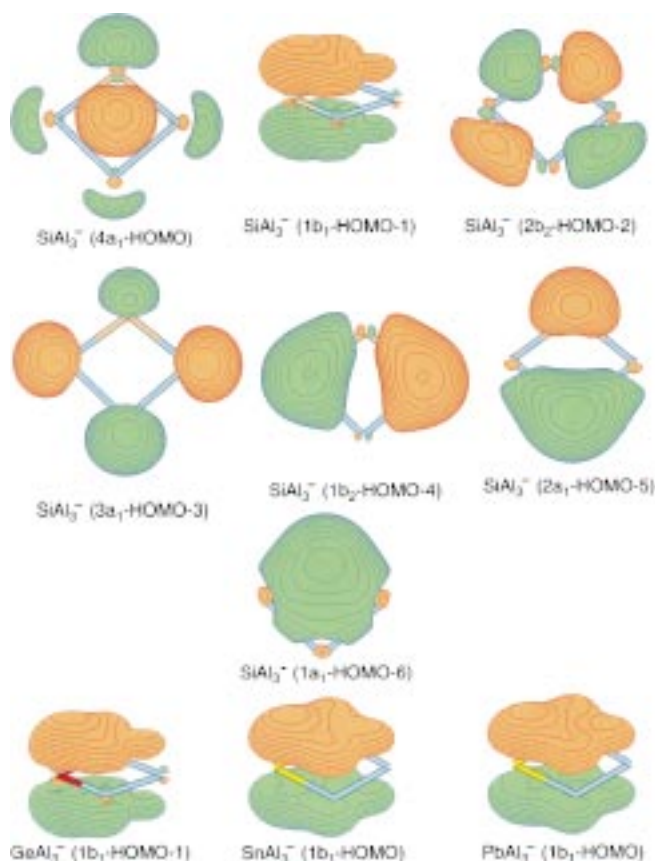


Figure 3. Molecular orbital pictures^[15] of cyclic planar $SiAl_3^-$, showing the highest occupied molecular orbital (HOMO, $4a_1$) down to the sixth valence molecular orbital from the HOMO (HOMO-6, $1a_1$), and the delocalized π orbitals ($1b_1$) of $GeAl_3^-$, $SnAl_3^-$, and $PbAl_3^-$.

However, in $SiAl_3^-$ the electron density of the $1b_1$ orbital is heavily concentrated at the Si site. When Si is substituted by the more metallic Ge, Sn, or Pb atoms, the $1b_1$ molecular orbital steadily expands towards the terminal Al atom (Figure 3). Consequently, the stability of the cyclic isomer is enhanced relative to the pyramidal structure. In our previous study of the lighter CA_3^- species,^[14] we found that the pyramidal isomer was the only minimum. The instability of the CA_3^- planar cyclic isomer is a result of the complete localization of the two π electrons on the C atom, because it is much more electronegative than Al. The series of the XAl_3^-

species thus provide unequivocal evidence that the delocalization of the π electrons is responsible for the C_{2v} cyclic structure, rendering the more metallic heterosystems aromatic. Schaefer and co-workers^[16] recently performed theoretical studies on model heterocyclic three-membered ring systems related to the Ga_3 organometallic compounds and concluded that these systems were indeed also aromatic.

Herein we extended the concept of aromaticity to the heterocyclic four-membered ring all-metal systems, XAl_3^- . We showed systematically the importance of the delocalization of the π electrons for the stability of the cyclic aromatic structure. Metallic systems can be aromatic when they are composed of heteroatoms, provided that the heteroatoms have similar electronegativities to the rest of atoms of the ring. However, if the heteroatoms differ substantially in their electronegativities, such as C in CAI_3^- ,^[14] the cyclic aromatic structure is no longer a minimum.

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Template-Directed Synthesis of a [2]Rotaxane by the Clipping under Thermodynamic Control of a Crown Ether Like Macrocycle Around a Dialkylammonium Ion**

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Andrew J. P. White, and David J. Williams*

New synthetic procedures for preparing rotaxanes^[1] are appearing in the current literature^[2] with ever-increasing regularity as a result of the attention^[3] these mechanically interlocked molecules^[4] are receiving because of their rapidly growing promise as molecular switches for developing devices^[5] on the mesoscale and as linear motor-molecules for constructing artificial molecular machinery^[6] on the nanoscale. One of the simplest recognition motifs that produces pseudorotaxanes,^[7] complexes that are often the precursors of catenanes and rotaxanes, is the binding^[8] of dialkylammonium ions with suitably large macrocycles, for example, dibenzo[24]crown-8. Although this motif has so far yielded rotaxanes by both the threading-followed-by-stoppering^[9] and slippage^[10] approaches, until now no rotaxanes based on the dialkylammonium ion have been synthesized using a clipping^[11] protocol. Here, we report the template-directed synthesis^[4c, 12] of a [2]rotaxane by a clipping approach under thermodynamic control and the subsequent conversion of the dynamic products into a kinetically stable [2]rotaxane which

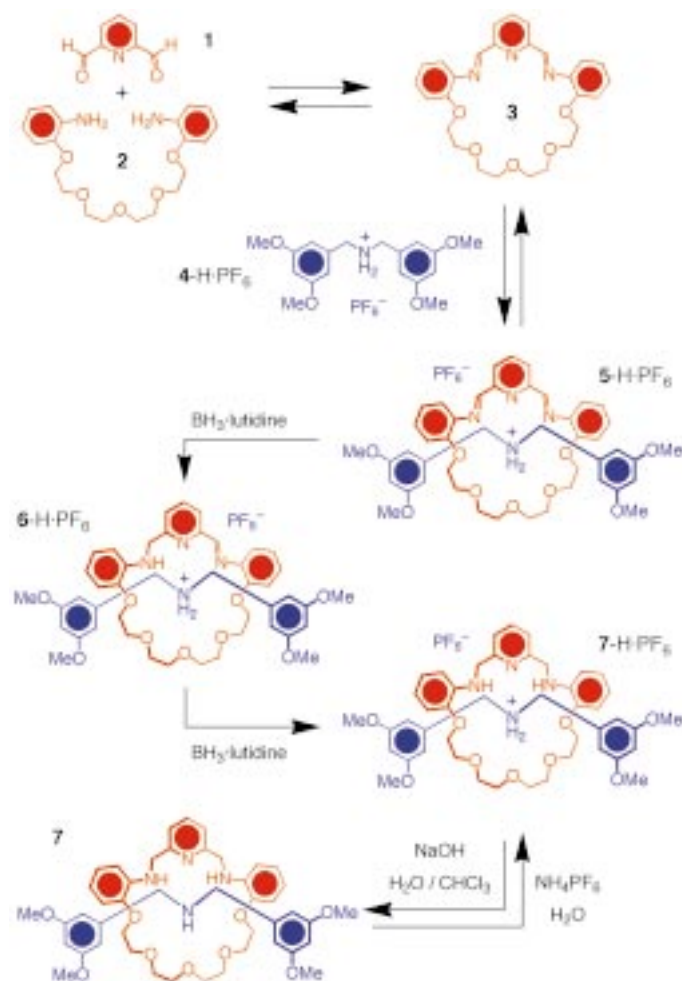
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has been isolated and characterized as a neutral as well as a charged compound.

Thermodynamic approaches have become popular methods^[13–16] of choice for the synthesis of catenanes and rotaxanes. Common dynamic (reversible) reactions exploited in these syntheses include metal–ligand exchanges,^[13] olefin metatheses,^[14] opening and closing of disulfide linkages,^[15] and imine formation^[16] from mixtures of aldehydes and amines. Imine formation has not yet been reported for the preparation of rotaxanes by the clipping approach even though macrocycles bearing imino groups can possess crown ether like constitutions suitable for binding^[17] guest molecules and ions. We reasoned (Scheme 1) that the macrocycle with a



Scheme 1. Synthesis of the [2]rotaxane 7-H·PF₆ by the clipping of dialdehyde **1** and diamine **2** around the dialkylammonium ion 4-H⁺, followed by reduction of the imino bonds.

[24]crown-8 constitution formed by the condensation of 2,6-pyridinedicarboxaldehyde^[18] (**1**) and tetraethyleneglycol bis(2-aminophenyl)ether^[19] (**2**) would be suitable for encircling the templating NH₂⁺ center of a dialkylammonium ion and, provided bulky stoppers terminated the axle-like components, then a rotaxane incorporating a macrocyclic diimine surrounding a dumbbell-shaped template would be the ultimate outcome of the equilibrium-controlled reaction.

An equilibrated, equimolar (20 mM) mixture of **1** and **2** in CD₃CN gave (after 24 h) a ¹H NMR spectrum (Figure 1 a) in which broad peaks appear that are indicative of an inter-

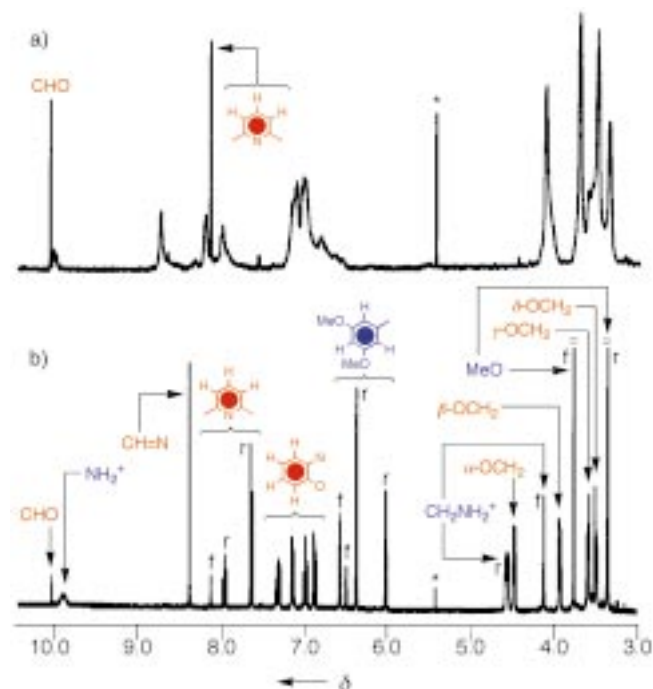


Figure 1. ¹H NMR spectra (360 MHz, CD₃CN, 298 K) of a) a 1:1 mixture (20 mM) of **1** and **2**, and b) a 1:1:1 mixture (20 mM) of **1**, **2**, and 4-H·PF₆. The descriptors “r” and “f” refer to signals representing protons in the rotaxane (namely, in 5-H·PF₆) and in free states, respectively. The signal labeled with an asterisk represents residual CH₂Cl₂.

conversion, which is on the order of the NMR timescale at 360 MHz, between imino groups, water, and aldehyde/amino groups. Presumably, the spectrum reflects a mixture of [1+1] (namely, **3**) and higher-order macrocyclic homologues, as well as related acyclic oligomers, all with the potential for displaying *syn/anti* isomerism about their C=N bonds. Addition of bis(3,5-dimethoxybenzyl)ammonium hexafluorophosphate (4-H·PF₆) has a dramatic effect on the composition of the equilibrium mixture. Equilibrium is established within only 4 min, and sharp resonances appear in the ¹H NMR spectrum (Figure 1 b) for the [2]rotaxane 5-H·PF₆, in addition to equally sharp resonances for the dumbbell-shaped compound 4-H·PF₆ and broad resonances for the free cyclic and acyclic species that are undergoing exchange with each other on the ¹H NMR timescale. The nature of these resonances suggests that the [2]rotaxane 5-H·PF₆ is thermodynamically stable yet interconverts slowly to its free components on the ¹H NMR timescale at 360 MHz, and that this added stability relative to that of the unthreaded species is a result of [N⁺–H⋯X] (X = O or N) hydrogen bonding and, possibly, also aromatic interactions between the macrocyclic and dumbbell-shaped components of 5-H·PF₆. Integration of the signals associated with the [2]rotaxane 5-H·PF₆ and those arising from the dumbbell-shaped compound 4-H·PF₆ led to an association constant (*K*_a) for the formation of 5-H·PF₆ of about 300 L mol^{–1} if it is assumed^[20] that there is an equal

amount of free macrocycle **3** present in the equilibrated mixture. This value of K_a is comparable with those obtained^[21, 22] for the associations of dibenzylammonium hexafluorophosphate with either dibenzo[24]crown-8 or *asym*-dibenzo[24]crown-8 in CD₃CN. FAB mass spectrometric analysis confirmed the stoichiometry of the complex by the presence of a very intense base peak at m/z 793 corresponding to $[5-H]^+$. These observations suggest that **3** displays a similar binding character of the dialkylammonium ion to that exhibited^[21] by the corresponding dibenzo[24]crown-8 macrocycles, and that the self-assembly^[23] of $5-H \cdot PF_6$ is a template-directed^[12] process.^[24]

The [2]rotaxane $5-H \cdot PF_6$ is kinetically labile as a result of the presence of hydrolyzable imino groups in this compound. These groups can be reduced to the corresponding amino functions to introduce kinetic stability into the rotaxane's structure. We have found that the borane·2,6-lutidine complex^[16b] is an efficient reducing agent for this process. We monitored the reaction between the equilibrated mixture of the dialdehyde **1**, the diamine **2**, and the dialkylammonium salt $4-H \cdot PF_6$, in the presence of a slight excess of the BH₃·lutidine complex in CD₃CN, and observed (Figure 2) the

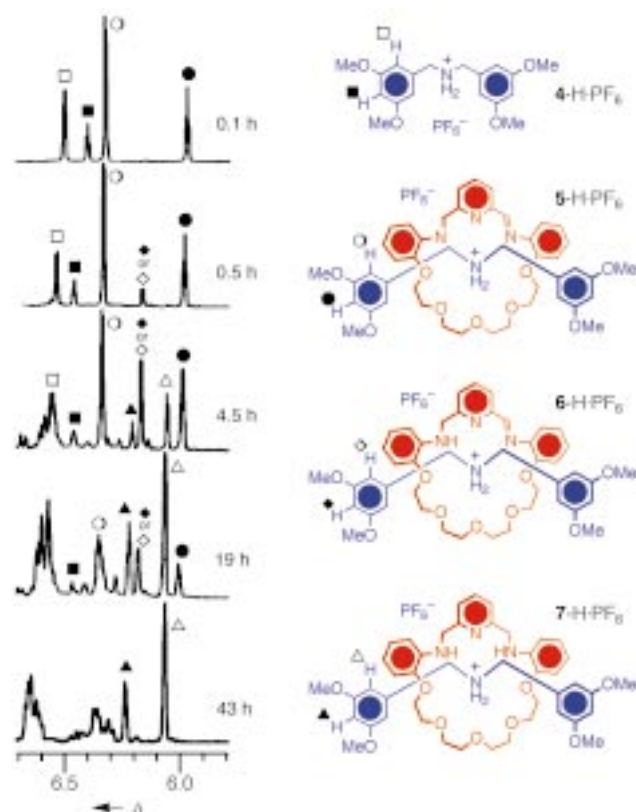


Figure 2. Partial ¹H NMR spectra (360 MHz, CD₃CN, 298 K) displaying the signals of the protons on the dimethoxybenzyl units in $4-H \cdot PF_6$ (□/■), $5-H \cdot PF_6$ (○/●), $6-H \cdot PF_6$ (◇/◆), and $7-H \cdot PF_6$ (△/▲) during reduction of the imino groups of $5-H \cdot PF_6$ with BH₃·2,6-lutidine.

gradual consumption of $5-H \cdot PF_6$, the initial appearance and subsequent disappearance of the monoreduced rotaxane $6-H \cdot PF_6$, and, ultimately, the appearance of the fully reduced rotaxane $7-H \cdot PF_6$. Interestingly, the signals for the dumbbell-shaped component $4-H \cdot PF_6$ also were observed to disappear

gradually. This observation implies that the reduction of the imino groups in the rotaxanes $5-H \cdot PF_6$ and $6-H \cdot PF_6$ is faster than the corresponding reductions in the free macrocycles (such as **3**) and in linear oligomeric species. The formation of $7-H \cdot PF_6$ results in the equilibrium between the threaded and unthreaded macrocycles producing more $5-H \cdot PF_6$ and $6-H \cdot PF_6$ until, eventually, all of the dialkylammonium salt and macrocyclic precursors are converted into the kinetically stable [2]rotaxane $7-H \cdot PF_6$. The reason for the faster rate of reduction of the imino groups in the rotaxanes—even though they are much more sterically inaccessible—compared to the unthreaded macrocyclic and acyclic species is believed to reside in the fact that the protonated amino groups in $5-H \cdot PF_6$ and $6-H \cdot PF_6$ provide a weakly acidic environment for the catalysis of the addition of BH to imine bonds. Hydrolysis of the B–N bonds formed upon reduction of the imino groups, to yield the aniline-like amino groups, is presumably effected by the water formed by the condensation of **1** and **2**. The free-base [2]rotaxane **7** was isolated in 70 % yield after a workup that included washing with aqueous NaOH and chromatography of the residue on SiO₂ (1 % Et₃N in MeOH). The X-ray crystal structure^[25, 26] of **7** reveals (Figure 3) the formation of a [2]rotaxane in which the

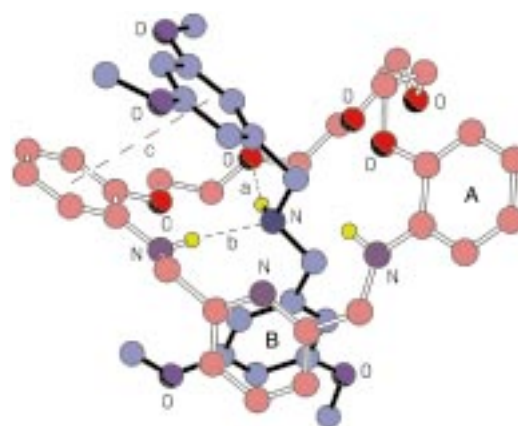


Figure 3. Ball-and-stick representation of the solid-state structure of the neutral [2]rotaxane **7**. Hydrogen-bonding geometries [N⋯X], [H⋯X] [Å], [N–H⋯X] [°]: a: 3.24, 2.35, 169 and b: 3.02, 2.13, 169. The centroid⋯centroid and mean interplanar separations [Å] are c: 4.01, 3.69; the rings are inclined by about 12°.

dumbbell-shaped component is threaded through the central cavity of the triaza crown ether. The co-conformation is stabilized by N–H⋯O and N–H⋯N hydrogen bonds between 1) the central amino group of the dumbbell-shaped component and one of the β-ether oxygen atoms of the macrocycle (interaction a) and 2) one of the aminophenol NH groups of the aza crown ether macrocycle and the nitrogen atom of the thread (interaction b). These interactions are supplemented by a π–π stacking interaction between one of the 3,5-dimethoxyphenyl rings of the thread and one of the aminophenol rings of the aza crown ether (interaction c). The only inter[2]rotaxane interactions of note are C–H⋯π interactions between centrosymmetrically related pairs of molecules, which involve, in each case, the *ortho* hydrogen

atom of ring A (*syn* to the amino group) in one molecule, and ring B of the thread of the other [$\text{H} \cdots \pi$ 2.79 Å, $\text{C}-\text{H} \cdots \pi$ 148°].

The [2]rotaxane **7** was converted into its hexafluorophosphate salt **7-H**·PF₆ by washing a solution of **7** in CH₂Cl₂ with saturated aqueous NH₄PF₆; this protonation procedure relies on the enhanced basicity of amino groups^[27] in rotaxane structures relative to those in free amines. The interlocked nature of the components of **7-H**·PF₆ was confirmed by its ¹H NMR spectrum, which displays peaks associated with the dumbbell and wheel-shaped components in a 1:1 ratio, and by its FAB mass spectrum, which displays a very intense base peak at *m/z* 797 corresponding to **[7-H]⁺**. A single-crystal X-ray analysis^[26, 28] of **7-H**·PF₆ shows (Figure 4) it to have a

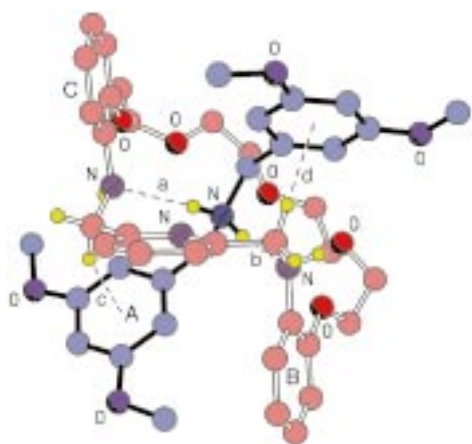


Figure 4. Ball-and-stick representation of the solid-state structure of the cationic [2]rotaxane **7-H⁺**. Hydrogen-bonding geometries [$\text{N} \cdots \text{N}$], [$\text{H} \cdots \text{N}$] [Å], [$\text{N}-\text{H} \cdots \text{N}$] [°]: a: 3.05, 2.18, 163 and b: 3.10, 2.24, 159. The $\text{H} \cdots \pi$ distances [Å] and $\text{C}-\text{H} \cdots \pi$ angles [°] are c: 2.82, 144 and d: 2.80, 142.

[2]rotaxane structure that is distinctly different from that of its neutral counterpart **7**. The structure of **7-H**·PF₆ is nearly symmetric, with a molecular *C*₂ axis passing through the pyridyl nitrogen atom of the triaza crown ether macrocycle and the NH₂⁺ center of the cationic thread. The conformations of both the thread and macrocyclic components are distinctly different from those observed for **7**. In **7-H**·PF₆ there are rotations of approximately 39° about both of the pyridyl-CH₂ bonds, with the geometries about the adjacent CH₂-NH bonds both being *gauche*. These rotations are in contrast to torsional twists in **7** of about 50 and 111° about the pyridyl-CH₂ bonds, and *anti* geometries for their adjacent CH₂-NH linkages. The torsional twists about the CH₂-aryl bonds in the cationic dumbbell component are around 70 and 74°, whereas the equivalent twists in the neutral species are about 72 and 36°, respectively. In **7-H**·PF₆ stabilization is achieved by a combination of $\text{N}^+-\text{H} \cdots \text{N}$ and $\text{C}-\text{H} \cdots \pi$ interactions (a–d in Figure 4). The [2]rotaxanes are loosely linked to their *C_i*-related counterparts to form sheets by π – π -stacking interactions between rings A and A', B and B', and C and C'; the centroid $\cdots$ centroid and mean interplanar separations are 3.95 and 3.52, 4.36 and 3.57, and 4.15 and 3.35 Å, respectively.

The synthesis of the [2]rotaxane **5-H**·PF₆ is an example of a clipping of a macrocycle under thermodynamic control in which the reaction that forms the macrocyclic component appears to be catalyzed by the presence of the dumbbell-shaped component. Moreover, the reduction of the macrocyclic component to yield **7-H**·PF₆ is a good example of template-directed, covalent capture of a self-assembled intermediate under kinetic control.^[29, 30] This two-step synthesis is reminiscent of enzymatic catalysis^[31] as well as catalysis^[32] using synthetic enzyme mimics, inasmuch as there is an initial recognition process—in this instance, the binding of **4-H**·PF₆ with an acyclic form of **3**—that leads to a preorganization of the substrate into a conformation suitable for reaction (in this case, the formation of **5-H**·PF₆) and a lowering of the activation energy barrier for the final reaction—in this instance, by the acid catalysis resulting from the presence of the NH₂⁺ center.

Currently, we are investigating the scope of our new protocol, in addition to extending its application to the template-directed synthesis^[12] of catenanes and other rotaxanes.

Experimental Section

A solution of **1** (123 mg, 0.91 mmol), **2** (343 mg, 0.91 mmol), and **4-H**·PF₆ (422 mg, 0.91 mmol) in MeCN was stirred for 5 min at ambient temperature. Evaporation of the solvent yielded a pale-yellow solid. **[5-H**·PF₆]: ¹H NMR (CD₃CN, 360 MHz, 298 K): δ = 3.36 (s, 12H), 3.49–3.51 (m, 4H), 3.58–3.61 (m, 4H), 3.92–3.95 (m, 4H), 4.47–4.50 (m, 4H), 4.55–4.60 (m, 4H), 6.05 (t, *J* = 2.2 Hz, 2H), 6.40 (d, *J* = 2.2 Hz, 4H), 6.91 (dd, *J* = 1.6, 7.6 Hz, 2H), 7.02 (dt, *J* = 1.0, 7.6 Hz, 2H), 7.17 (dd, *J* = 1.0, 8.3 Hz, 2H), 7.35 (dt, *J* = 1.6, 8.3 Hz, 2H), 7.67 (d, *J* = 7.8 Hz, 2H), 8.00 (t, *J* = 7.8 Hz, 1H), 8.43 (s, 2H), 9.95 (brs, 2H); MS (FAB): *m/z* (%): 793 (100) **[5-H]⁺**, 476 (10) **[3-H]⁺**. A portion of this solid (100 mg, 0.11 mmol) was dissolved in MeCN and an excess of BH₃·2,6-lutidine complex (65 mg, 0.54 mmol) was added. The mixture was stirred for 2 days and then the solvent was evaporated. The residue was partitioned between 1M NaOH and CHCl₃ and then the aqueous layer was extracted several times with CHCl₃. The organic extracts were then dried (MgSO₄) and the solvent was evaporated. The residue was purified by column chromatography (SiO₂: MeOH/Et₃N, 99/1) to yield **7** as a white solid (60 mg, 70%). ¹H NMR (CD₃CN, 360 MHz, 298 K): δ = 2.70 (brs, 1H), 3.28 (br, 4H), 3.36 (brs, 8H), 3.51 (brs, 4H), 3.55 (s, 12H), 3.99–4.01 (m, 4H), 4.22 (brs, 4H), 6.07 (brt, 2H), 6.19 (brs, 2H), 6.50 (brd, 4H), 6.56 (dt, *J* = 1.6, 7.7 Hz, 2H), 6.68–6.72 (m, 4H), 6.79 (dt, *J* = 1.2, 7.6 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H); ¹³C NMR (CDCl₃, 90 MHz, 298 K): δ = 50.3, 53.1, 55.1, 67.5, 70.2, 70.6, 70.8, 98.6, 106.5, 109.8, 114.4, 116.1, 122.3, 136.4, 138.3, 146.1, 149.3, 158.1, 160.0; MS (FAB): *m/z* (%): 797 (100) **[7-H]⁺**, 480 (7) **[macrocycle-H]⁺**, 318 (4) **[4-H]⁺**. Single crystals, suitable for X-ray crystallography, of this free-base rotaxane were obtained by liquid diffusion of *i*Pr₂O into a solution of **7** in CH₂Cl₂, followed by slow evaporation. A portion of **7** (30 mg, 38 μmol) was dissolved in CH₂Cl₂ (1 mL) and washed with saturated NH₄PF₆ (1 mL). The organic phase was separated, the aqueous phase extracted with CH₂Cl₂ (3 × 1 mL) and then the combined organic extracts were dried (MgSO₄) and evaporated to dryness to yield **4-H**·PF₆ as a white solid (34 mg, 95%). ¹H NMR (CDCl₃, 360 MHz, 298 K): δ = 3.37 (s, 12H), 3.74–3.78 (m, 8H), 3.79–3.80 (m, 4H), 4.00–4.02 (m, 4H), 4.14–4.16 (m, 4H), 4.26 (brs, 2H), 4.50–4.54 (m, 4H), 6.07 (d, *J* = 2.2 Hz, 4H), 6.24 (t, *J* = 2.2 Hz, 2H), 6.36–6.38 (m, 2H), 6.63–6.74 (m, 6H), 7.27 (d, *J* = 7.7 Hz, 2H), 7.76 (t, *J* = 7.7 Hz, 1H), 8.97 (brs, 2H); ¹³C NMR (CDCl₃, 90 MHz, 298 K): δ = 49.6, 53.5, 55.8, 68.5, 71.5, 72.0, 72.3, 101.7, 107.8, 111.3, 113.2, 120.3, 122.3, 124.2, 135.2, 137.9, 147.7, 159.0, 162.0 (1 aryl C missing/overlapping); MS (FAB): *m/z* (%): 797 (100) **[7-H]⁺**. Single crystals, suitable for X-ray crystallography, of this protonated rotaxane were obtained by liquid diffusion of hexane into a solution of **7-H**·PF₆ in Me₂CO.

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- [25] Crystal data for **7**: $C_{45}H_{50}N_4O_9$, $M_r = 796.9$, triclinic, $P\bar{1}$ (no. 2), $a = 9.993(1)$, $b = 13.063(1)$, $c = 16.382(1)$ Å, $\alpha = 95.90(1)$, $\beta = 90.81(1)$, $\gamma = 92.45(1)^\circ$, $V = 2124.8(2)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.246$ g cm⁻³, $\mu(\text{Cu}_{K\alpha}) = 7.07$ cm⁻¹, $T = 293$ K, colorless platy needles; 6291 independent measured reflections, F^2 refinement, $R_1 = 0.048$, $wR_2 = 0.125$, 5221 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$], $2\theta \leq 120^\circ$, 556 parameters.
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nos. CCDC-156104 (7) and -156105 (7-H · PF₆). 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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Precipitons—Functional Protecting Groups to Facilitate Product Separation: Applications in Isoxazoline Synthesis

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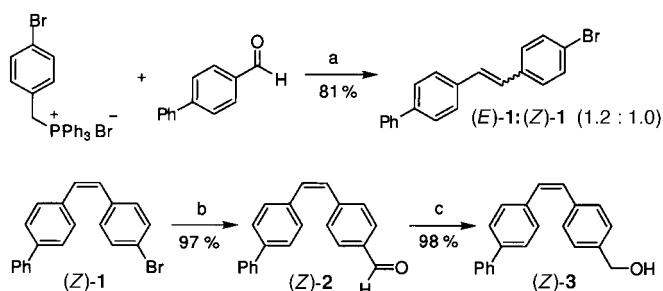
Dedicated to Prof. Dr. Ronald Breslow
on the occasion of his 70th birthday symposium

Automated solid-phase organic synthesis (SPOS) has emerged as an important tool in organic synthesis and medicinal chemistry.^[1] One of the advantages of SPOS is that the technique allows a large excess of reagents or co-reactants to be employed to ensure that a reaction reaches completion, and these reaction components can then be easily separated from resin-bound products by simple filtration. Although the insoluble nature of the resin is an advantage at the purification stage, it is often a liability at the reaction stage. For example, heterogeneous reaction conditions can complicate monitoring the progress of a reaction by classical methods, and tedious optimization of reaction protocols is sometimes required to obtain good yields in solid-phase reactions. In response to these limitations several research groups have introduced alternatives to SPOS. The new methods (fluorous synthesis,^[2] soluble polymer-supported organic synthesis

(SPSOS),^[3] dendrimer-supported organic synthesis,^[4] and new approaches to acid-base-induced isolation^[5]) begin with a step in which reactant molecules are attached to “phase-tags”,^[2b] which are molecular fragments that have special physical properties that facilitate product isolation. These alternatives to solid-phase synthesis share two features: they allow reactions to be carried out under homogeneous conditions, and, after the reaction stage, the product can be isolated by a phase-transfer event (precipitation or liquid–liquid partition) that is induced by the addition of a solvent or by the addition of new co-solutes or reactants.

We envisioned a separation process enabled by a change in solubility that would be caused *not* by a change in solvent or environment, but by structural isomerization of an ancillary portion of the desired product. We define a “precipiton” as a group of atoms (molecular fragment) that is purposefully attached to a reactant molecule and can be isomerized after the reaction to facilitate precipitation or phase transfer of the attached product. One class of precipitons would include molecular fragments that can exist in two isomeric forms: one form freely soluble in a given organic solvent and the other form quite insoluble in that solvent. A product attached to such a molecular fragment could be isolated directly from a reaction mixture by isomerization of the ancillary group to generate the insoluble isomer of the product. The precipitated product would then be isolated by filtration or centrifugation. In the ideal example of this concept of controlled changes in solubility, only products or reagents labeled with the precipiton group would precipitate. Therefore, as in SPOS, excess reagents and co-reactants that might be required to provide good reaction efficiency could be easily removed by filtration.

Our search for such precipitons began with a study of stilbene analogues because *cis*-stilbenes can be more soluble than *trans*-stilbenes.^[6, 7] The biphenyl-derived alkenes (*Z*)-**3** and (*E*)-**3** were prepared by a Wittig reaction (Scheme 1).



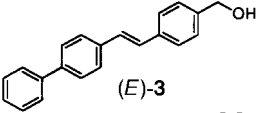
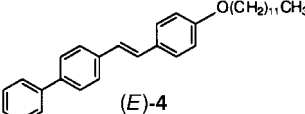
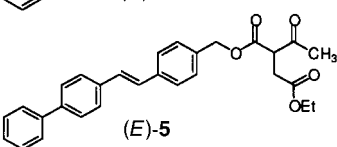
Scheme 1. Synthesis of precipiton (*Z*)-**3**. a) KHMDS, THF, –78 °C, 81%; b) 1. *t*BuLi, THF, –78 °C; 2. DMF, –78 → 0 °C, 97%; c) NaBH₄, EtOH, 0 °C, 98%. KHMDS = potassium 1,1,1,3,3,3-hexamethyldisilazane.

Alkene (*Z*)-**3** was freely soluble (saturated solutions exceeded 0.2 M) in common organic solvents such as EtOAc, THF, Et₂O, CH₂Cl₂, CHCl₃, and C₆H₅CH₃. The solubility of (*E*)-**3** in the same solvents were determined by UV/Vis spectroscopic analysis of saturated solutions.^[7, 8] Isomer (*E*)-**3** was virtually insoluble in all solvents examined (Table 1, entry 1). We prepared dodecyl ether (*E*)-**4** and β-ketoester (*E*)-**5** and measured their solubilities in common organic solvents by the same methods used for (*E*)-**3** (Table 1, entries 2 and 3) to assess the effect that attached productlike groups might have

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Table 1. Solubilities of precipitons (*E*)-3, (*E*)-4, and (*E*)-5 in common organic solvents.

Compound	EtOAc	Solubility [mg mL ⁻¹ /mm]				Hexanes
		THF	Et ₂ O	MeOH		
 (<i>E</i>)-3	0.8/2.9	4.0/14	0.4/1.3	0.2/0.7	0.0/0.0	0.0/0.0
 (<i>E</i>)-4	< 0.1 / < 0.2	1.3/3.0	0.1/0.2	0.0/0.0	0.0/0.0	0.0/0.0
 (<i>E</i>)-5	> 11 / > 24	> 13 / > 29	2.9/6.4	0.7/1.6	0.1/0.2	0.1/0.2

on the solubility of the precipiton. The dodecyl group had no measurable effect on the solubility of the *E* isomer, but the β -ketoester functionality increased the solubility of the *E* isomer in EtOAc and THF. Fortunately, regardless of the nature of the appended fragment, the *E* isomers remained virtually insoluble in Et₂O, hexanes, and MeOH.

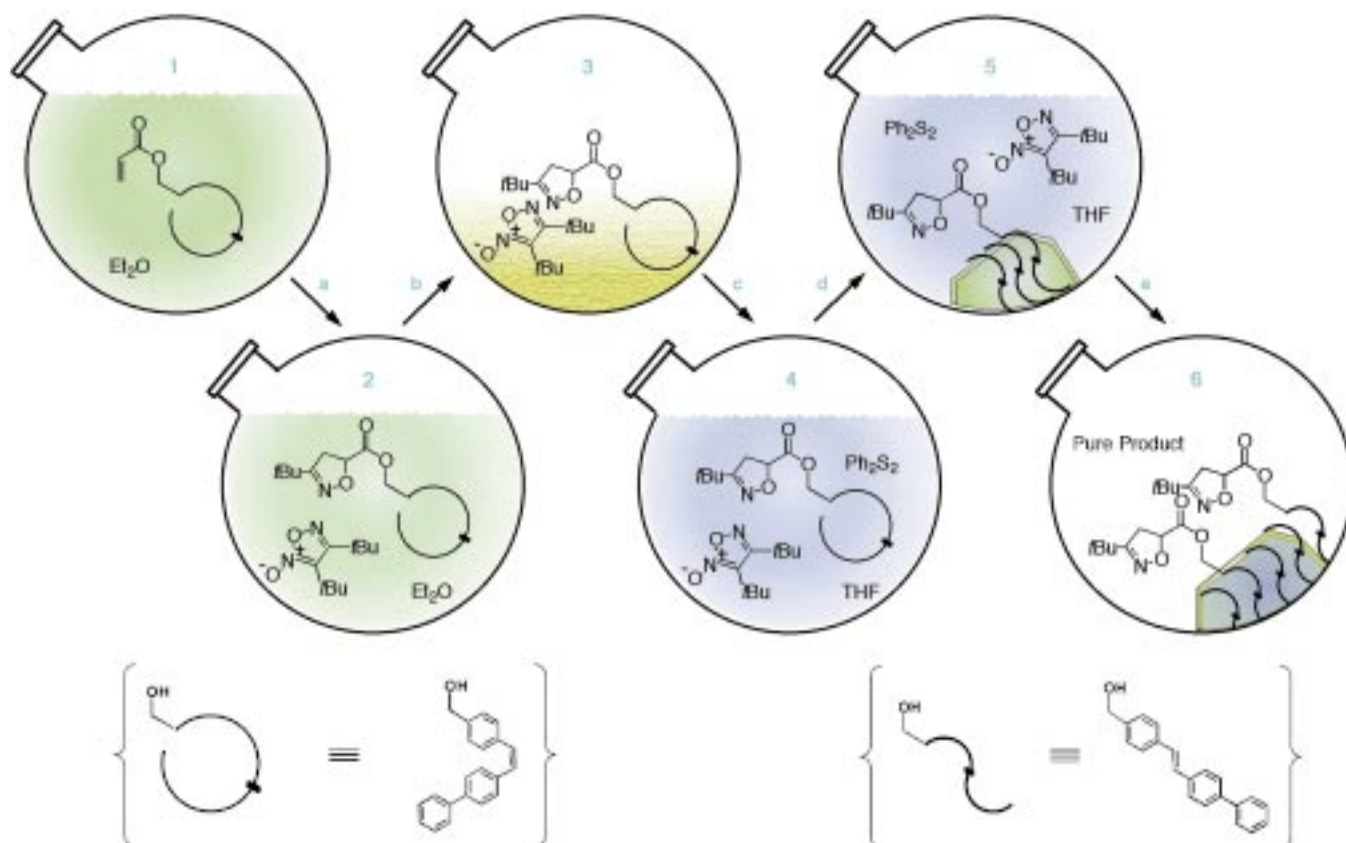
Before using auxiliary groups similar to **3** for isolating products we examined several isomerization conditions that might effect the conversion of the high solubility (*Z*) form of **3** into the low solubility (*E*) form. Photochemical methods (with and without sensitization^[9]) were examined, but these meth-

ods were not satisfactory because the reactions were slow and side products arose. However, the use of diphenyl disulfide^[10] in THF at reflux (18 h) or iodine with benzoyl peroxide^[11] under illumination by a sunlamp (1 h) were very effective and afforded excellent yields of precipitated product.

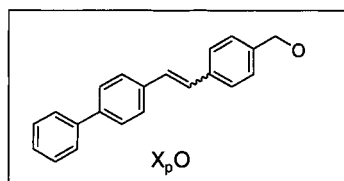
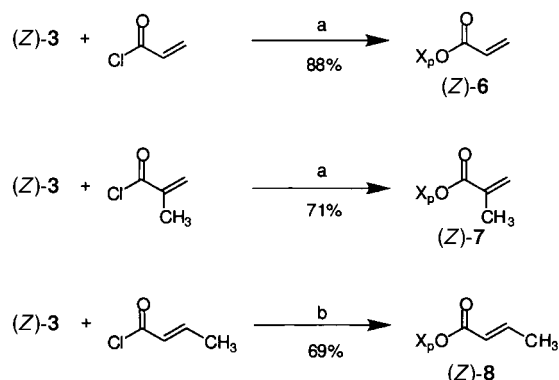
To evaluate the effectiveness of our method we prepared a family of Δ^2 -isoxazolines. Usually these compounds are generated by [3+2] cycloaddition reactions between alkenes and nitrile oxides.^[12–14] Furoxans, formed by dimerization of nitrile oxides, are troublesome by-products of such cycloadditions. Canonical methods require puri-

fication of the desired isoxazoline products by flash chromatography to remove this by-product. The problem is exacerbated when an excess of the nitrile oxide is required. Solid-phase^[15] and fluorous^[16] techniques for isolation of the nitrile oxide cycloaddition product have been developed in efforts to simplify removal of the furoxan.

We hypothesized that the precipiton approach to product isolation would allow nitrile oxide cycloaddition products to be separated from reaction by-products (Scheme 2). To test this hypothesis, several alkenoates were attached to precipiton (*Z*)-**3** by an ester linkage (Scheme 3) and subjected to



Scheme 2. Illustration of the “precipiton” process for isoxazoline isolation. a) A solution of *tert*-butylnitrile oxide is added to an ethereal solution of acrylate (*Z*)-**4**. b) The Et₂O is removed to afford a crude residue. c) The crude residue is diluted with THF and one equivalent of diphenyl disulfide is added. d) The solution is heated at reflux to cause isomerization and product precipitation. e) The THF is removed and the solid is washed with hexanes, Et₂O, or methanol to afford clean solid.



Scheme 3. Synthesis of alkene substrates for cycloaddition with nitrile oxide. a) TEA, CH_2Cl_2 , 0°C ; b) Pyridine, CH_2Cl_2 , 0°C .

cycloaddition with nitrile oxides in diethyl ether. The nitrile oxides were generated by the method of Christl and Huisgen.^[14] The iminoyl chloride precursors to the nitrile oxides were prepared from the appropriate hydroxylamines.^[17] After the reaction, the reaction mixture was washed with water and the volatile components were removed. The precipiton approach allowed pure isoxazolines to be isolated from this crude product. To accomplish this the residue was dissolved in THF and *Z/E* isomerization of the precipiton auxiliary was induced by adding diphenyl disulfide and heating the solution. The solvent was removed after isomerization, the crude residue was washed with Et_2O , MeOH, or hexanes to remove any by-products, and the sparingly soluble pure product was isolated by filtration. The desired products were attached to the *trans*-precipiton and hence they were nearly insoluble in these solvents, and all by-products (including the furoxan) could be removed during this trituration.

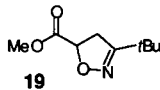
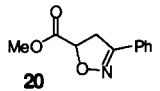
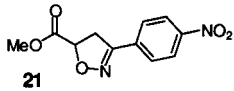
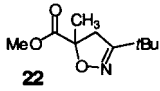
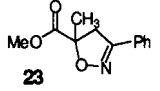
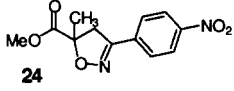
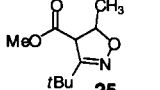
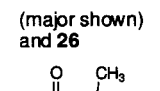
Precipiton-bound isoxazolines were isolated in good yields and high purity (Table 2). As expected, two regioisomers were observed in the cycloadditions of crotonate (*Z*)-8 with either *tert*-butylnitrile oxide or benzonitrile oxide (Table 2, entries 7

Table 2. The use of the precipiton method in nitrile oxide cycloaddition reactions.

Entry	Alkene	Nitrile oxide	Major product	Minor product	Yield [%]	Regioselectivity ^[a]
1	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}_2$ (<i>Z</i>)-6	$t\text{Bu}-\text{C}\equiv\text{N}-\text{N}^+\text{O}^-$	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{N}-t\text{Bu})-\text{CH}_2$ (<i>E</i>)-9		88	
2	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}_2$ (<i>Z</i>)-6	$\text{Ph}-\text{C}\equiv\text{N}-\text{N}^+\text{O}^-$	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{N}-\text{Ph})-\text{CH}_2$ (<i>E</i>)-10		81	
3	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}_2$ (<i>Z</i>)-6	$\text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{C}\equiv\text{N}-\text{N}^+\text{O}^-$	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{N}-\text{C}_6\text{H}_4\text{NO}_2)-\text{CH}_2$ (<i>E</i>)-11		90	
4	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)=\text{CH}_2$ (<i>Z</i>)-7	$t\text{Bu}-\text{C}\equiv\text{N}-\text{N}^+\text{O}^-$	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{CH}(\text{N}-t\text{Bu})$ (<i>E</i>)-12		74	
5	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)=\text{CH}_2$ (<i>Z</i>)-7	$\text{Ph}-\text{C}\equiv\text{N}-\text{N}^+\text{O}^-$	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{CH}(\text{N}-\text{Ph})$ (<i>E</i>)-13		74	
6	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)=\text{CH}_2$ (<i>Z</i>)-7	$\text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{C}\equiv\text{N}-\text{N}^+\text{O}^-$	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{CH}(\text{N}-\text{C}_6\text{H}_4\text{NO}_2)$ (<i>E</i>)-14		87	
7	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{CH}_3$ (<i>Z</i>)-8	$t\text{Bu}-\text{C}\equiv\text{N}-\text{N}^+\text{O}^-$	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{CH}(\text{N}-t\text{Bu})$ (<i>E</i>)-15	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{CH}(\text{N}-t\text{Bu})$ (<i>E</i>)-16	75	5:1
8	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{CH}_3$ (<i>Z</i>)-8	$\text{Ph}-\text{C}\equiv\text{N}-\text{N}^+\text{O}^-$	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{CH}(\text{N}-\text{Ph})$ (<i>E</i>)-17	$\text{X}_p\text{O}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{CH}(\text{N}-\text{Ph})$ (<i>E</i>)-18	74	13:3 ^[b]

[a] Regioselectivity was determined by comparison of the ^1H NMR data for these products with data for the reported methyl esters. [b] Both diastereomers of the major regioisomer were observed.

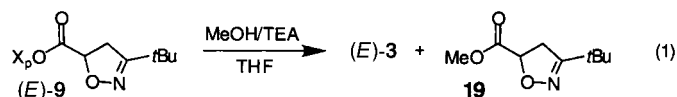
Table 3. Cleavage of the precipiton auxiliary from the isoxazolines.

Entry	Starting material	Yield of (<i>E</i>)-3 [%]	Isoxazoline product	Yield [%]	Purity ^[a]
1	(<i>E</i>)-9	84		90	95
2	(<i>E</i>)-10	87		79	95
3	(<i>E</i>)-11	88		79	91
4	(<i>E</i>)-12	84		73	95
5	(<i>E</i>)-13	88		74	95
6	(<i>E</i>)-14	89		82	95
7	(<i>E</i>)-15, (<i>E</i>)-16	89	 (major shown) and 26	73	88
8	(<i>E</i>)-17, (<i>E</i>)-18	92	 (major shown) and 28	84	95

[a] The only impurity detected by NMR spectroscopy was a small amount of (*E*)-3. The amount of this contaminant was usually less than 5% and was determined by NMR analysis.

and 8), and in the case of benzonitrile oxide both diastereomers of the major regioisomer were observed. All of the products were fully characterized and obtained in greater than 95% purity as determined by ¹H NMR spectroscopy.

The *trans*-precipiton-bound products are sufficiently soluble in THF to allow cleavage of the precipiton from the products by methanolytic transesterification in THF by methanol/triethylamine (MeOH/TEA) [Eq. (1)].^[4a] After re-



moval of the volatile components from the reaction mixture, the desired methyl esters were separated from the insoluble benzyl alcohol precipiton (*E*)-3 by extraction with Et₂O or MeOH. Removal of solvents from the extract afforded methyl ester isoxazolines **19**–**28** in good yields and purities (Table 3). The purity was determined by ¹H NMR spectroscopy. The only detectable impurity was alcohol (*E*)-3 (typically present in < 5%). Some epimerization at the carbon atom adjacent to the ester functionality occurred during methanolysis of the isoxazo-

line mixtures (*E*)-15/(*E*)-16 and (*E*)-17/(*E*)-18, and this resulted in mixtures of diastereomers (Table 3, entries 7 and 8).

These experiments demonstrate a promising new approach to product isolation. Control of the solubility properties in this initial class of precipitons was achieved by isomerization from the soluble *Z* form of a biphenyl stilbene analogue to the insoluble *E* form. Significant features of this approach are: 1) it allows reactions to be performed under homogenous conditions; 2) the reactions may be monitored by standard methods; 3) loading capacities for this precipiton phase tag are high (3–4 mmol g^{−1}); 4) very little solvent is used during the isolation stage of the synthesis; 5) the process can be applied to large- or small-scale syntheses; and 6) the process may be automated. Reactions using this strategy have been conducted on a 5–600 milligram scale and the method could well be used to produce kilogram quantities of material. These stilbene-based precipitons are being evaluated for use with other reactions. It is not yet possible to efficiently regenerate the high-solubility form of the precipiton. We are examining more cost-effective approaches to this class of precipitons and the development of precipitons that can be recycled.

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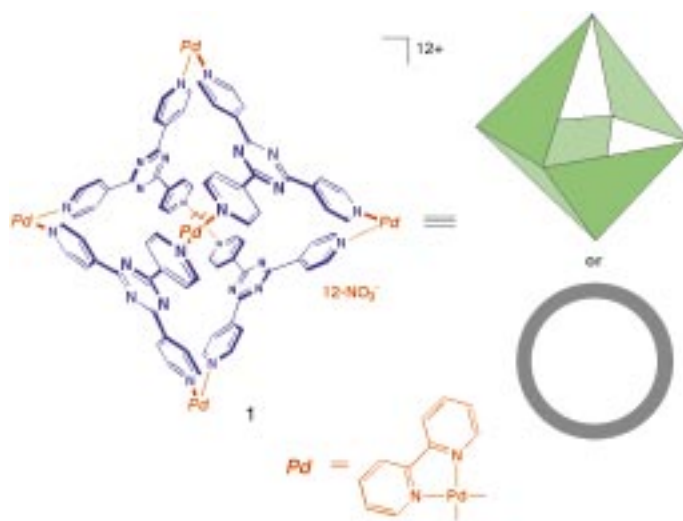
Probing Guest Geometry and Dynamics through Host–Guest Interactions**

Takahiro Kusakawa, Michito Yoshizawa, and Makoto Fujita*

Conformational freedom of molecules is restricted when they are enclathrated within the limited interior space of hollow compounds.^[1] Analysis of the inclusion geometry of guest molecules is important because molecules in a specific

geometry or aggregation are expected to show unique properties and reactivities which do not appear when they are in solution. The restricted conformations are in general analyzed by observing guest molecules themselves. On the other hand, information on the geometry of guests can be read out by the spectroscopic analysis of host frameworks provided the host and the guest communicate with each other through subtle host–guest interactions. Several reports have dealt with the conformational analysis of guests by the observation of host frameworks.^[2, 3] However, the observed spectra of the hosts are often not sufficiently simple to analyze details.

Coordination nanocage **1** has recently been shown to strongly bind a variety of neutral substrates within its nanosized cavity.^[4] As a result of the high symmetry of cage



1 (T_d) the twelve pyridine rings in **1** are all equivalent, and the NMR spectrum of the empty cage displays only a set of pyridine protons at $\delta = 9.47$ (PyH^a) and 8.92 (PyH^b) (Figure 1a). When the cage accommodates guest molecule(s) with lower symmetry the T_d symmetry of the cage is desymmetrized and the symmetry of the entity follows that of the guest(s) if the cage and the guest(s) strongly interact. For example, if the guest has C_1 symmetry then 48 pyridine protons of **1** become inequivalent and, in principle, 48 independent pyridine protons should be observed in the ¹H NMR spectrum. Scheme 1 summarizes the relationship between the guest symmetry and the maximum number of pyridine protons which should appear in the NMR spectra. Thus, an analysis of the symmetry of the cage probes how guests are accommodated in the cavity. We show in the following discussions some examples of probing the guest geometry by NMR analysis of the host symmetry, where all predicted structures have been confirmed by X-ray analyses. The analysis of the symmetry by NMR spectroscopic analysis also elucidates the dynamic motion of included guests.

The 1:2 complexation of cage **1** with 4,4'-dimethoxydibenzoyl (**2a**) provides a fine example. The 1:2 inclusion complex (**2a**)₂ ⊂ **1** was easily prepared by mixing a solution of **2a** in hexane (saturated, 1 mL) and a solution of **1** in D₂O (5.3 mM, 2 mL), and stirring the mixture at 80 °C for 0.5 h. After

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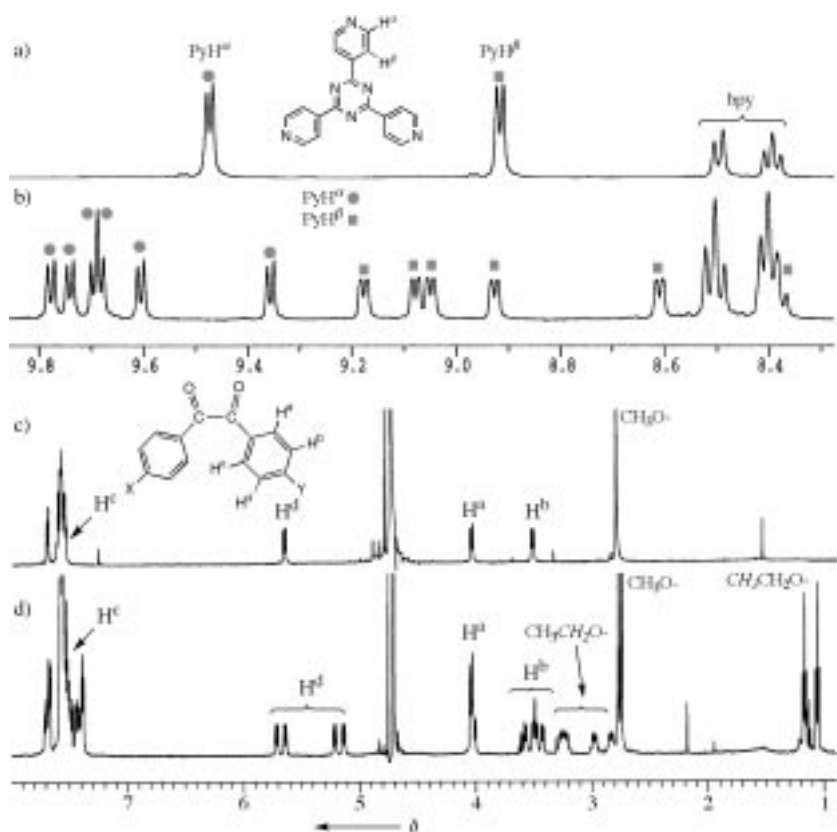
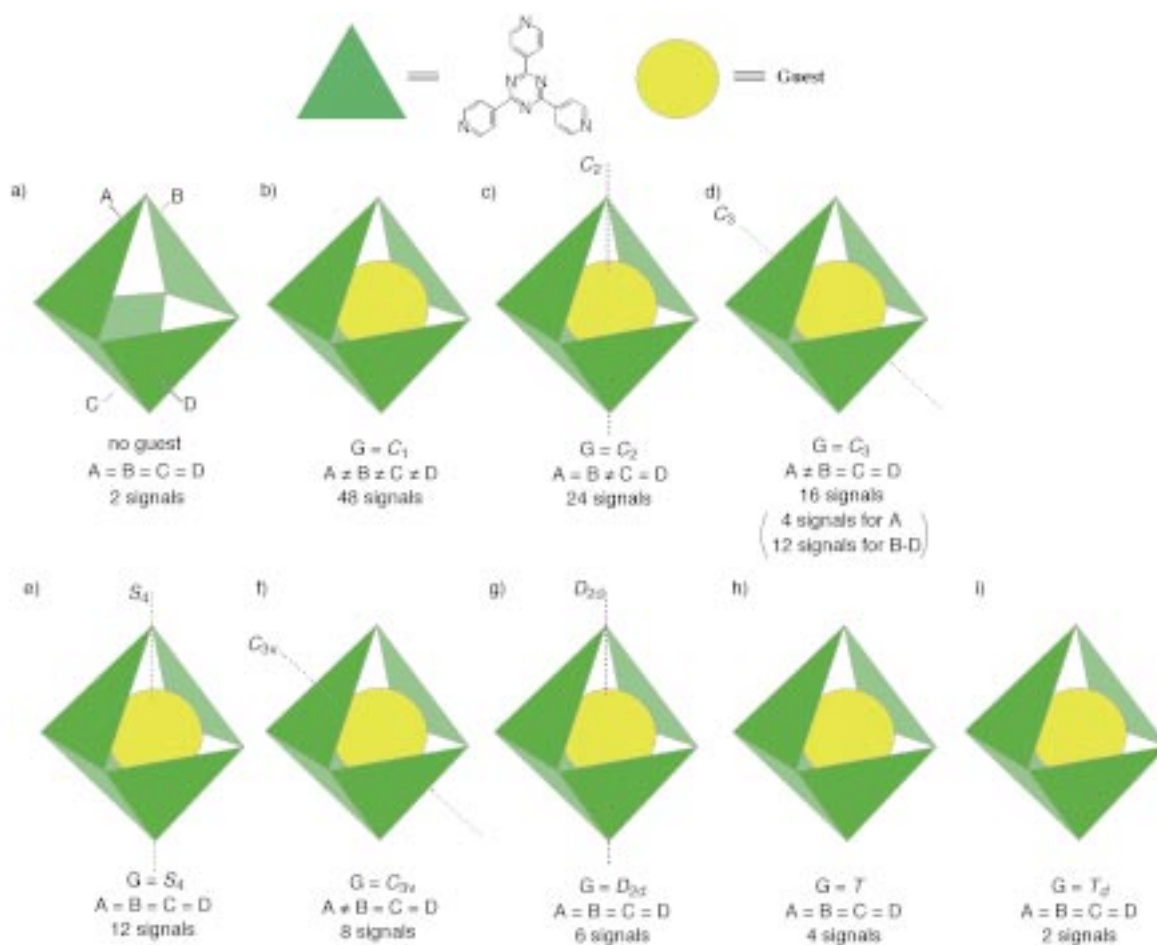
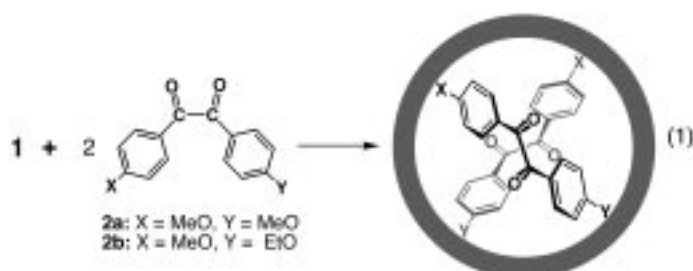


Figure 1. ^1H NMR observations of the enclathration of **2a** in nanocage **1**. a) Empty **1**. b) and c) $(2a)_2 \cdot 1$. d) $(2b)_2 \cdot 1$.

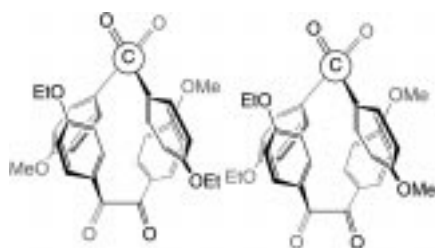


Scheme 1. The relationships between the guest symmetry and the maximum number of pyridine protons that should appear in the NMR spectra.

complexation was complete, the pyridine protons of the host were split into six pairs: six PyH^{α} protons at $\delta = 9.35\text{--}9.8$ and six PyH^{β} protons at $\delta = 8.35\text{--}9.2$ (Figure 1b). This observation suggested the desymmetrization of the host into an S_4 symmetric entity with 12 inequivalent protons on each ligand (see case e of Scheme 1 where ligands A–D are all equivalent but each ligand possesses no symmetry element). The S_4 symmetry can originate from a specific orientation of two guest molecules in the cavity and will be generated only if they aggregate orthogonally and adopt a chiral, twisted conformation with opposite screw senses [Eq. (1)].^[5]



The S_4 orientation of the guests was also supported by the guest signals in the ^1H NMR spectrum. A tight contact of the two guest molecules was shown by NOEs (1.2–18.4%) between the methoxy protons and other aromatic protons. These interactions must be intermolecular because the corresponding NOEs were not observed in the NMR spectrum of free **2** in CDCl_3 . The twisted conformation of **2** was consistent with the observation of four different chemical shifts for the four aromatic protons on the phenylene groups (Figure 1c). The observation of the chirality of each guest demonstrated that two conformations of enclathrated **2a** were completely frozen at room temperature, while those of free **2a** are in rapid equilibrium in solution. With the asymmetric substituted analogue **2b**, a diastereomeric pair (see below) was observed in a 1:1 ratio (Figure 1d).



The proposed orientation of **2a** was confirmed by an X-ray analysis (Figure 2). As expected, two molecules were packed orthogonally and each of them adopted a twisted conformation with a dihedral angle (ψ) of $80.6\text{--}80.8^\circ$ between the two carbonyl groups. This angle is considerably smaller than that of dibenzoyl in its crystal structure ($\psi = 124.6^\circ$),^[6] but very close to that of an optimized conformation ($\psi = -83.27^\circ$).^[7] Thus, each guest adopts its optimal geometry without influence from crystal-packing effects.

The dynamics of the guest were studied using variable temperature NMR spectroscopy. Upon heating the sample,

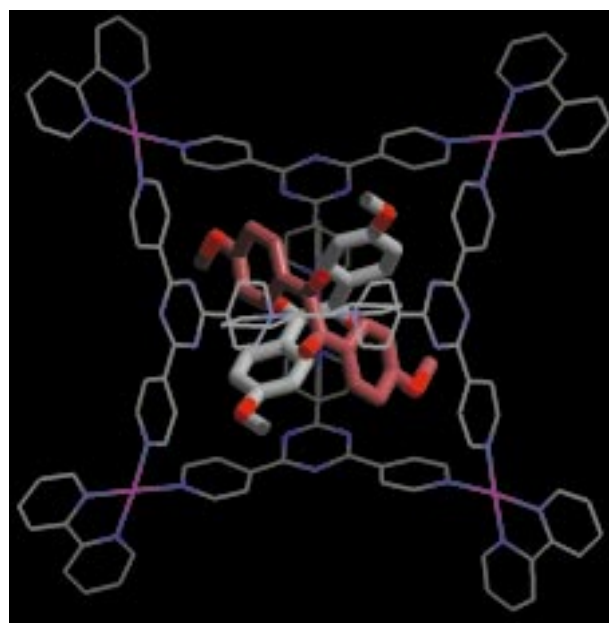
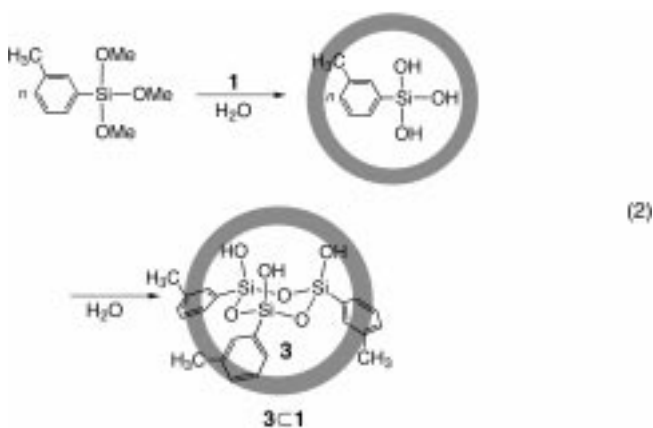


Figure 2. Crystal structure of $(\mathbf{2a})_2 \cdot \mathbf{1}$.

the signals for the PyH^{α} and PyH^{β} protons coalesced at 343 K into a broad pair of signals around $\delta = 9.6$ and 9.0, respectively. Since the average chemical shifts of the pyridine protons did not change significantly, the coalescence of the signals can be explained by the rapid P/M interconversion of the guest to give the apparent T_d -symmetric environment of the host.

The enclathration of a cyclic siloxane trimer (**3**) with C_{3v} symmetry was also studied. This guest molecule was synthesized in situ within the cavity of **1** by a hydrolysis of trimethoxy(*m*-tolyl)silane followed by condensation [Eq. (2)].^[8] Eight pyridine signals were observed in the



aromatic region of the ^1H NMR spectrum for cage **1**, which is in good agreement with C_{3v} symmetry (see case f in Scheme 1). Thus, the observed ^1H NMR spectrum suggests one C_{3v} -symmetrized ligand (A) and three C_{2v} -symmetrized ligands (B). Ligand A gave a pair of doublets (H^{a} and H^{b} ; 6H integral for each) while ligand B gave three pairs of doublets (H^{c} and H^{d} , H^{e} and H^{f} , and H^{g} and H^{h} ; 2H integral for each, Figure 3). Indeed, the spectrum of guest **3** was consistent with

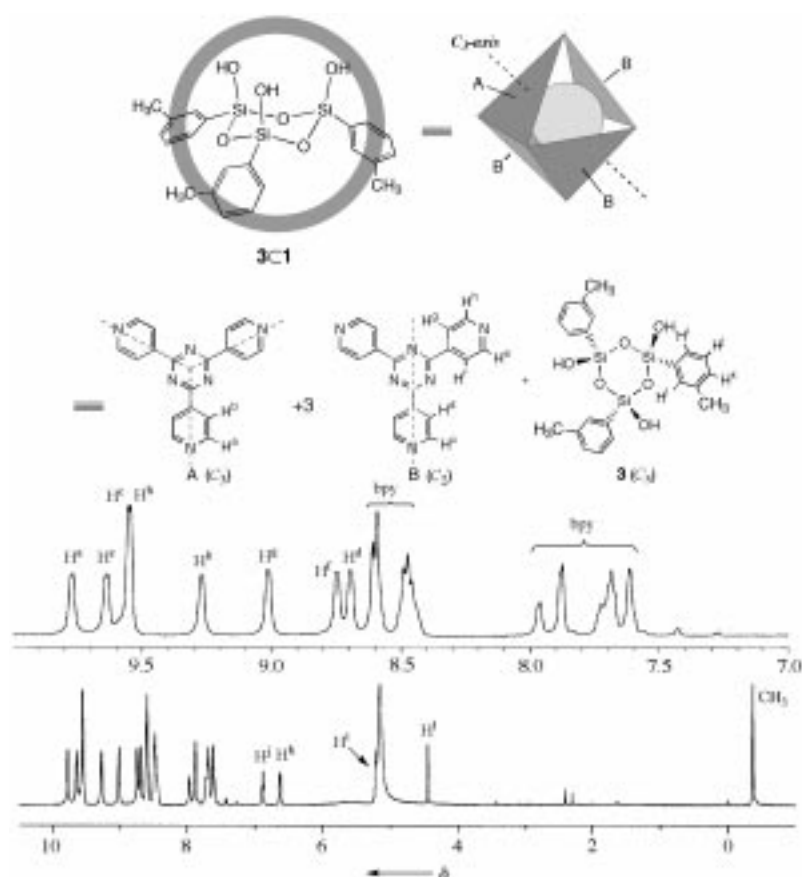


Figure 3. ^1H NMR spectra of **3** $\subset$ **1** at 278 K.

the strong binding of **3** in the cavity: highly upfield-shifted methyl protons at $\delta = -0.37$ and aromatic protons at $\delta = 6.88$, 6.63, 5.21, and 4.45 were observed.

The C_{3v} inclusion geometry was also evident from an X-ray analysis (Figure 4). A C_3 -axis passes through both the host and the guest frameworks as expected. The all-*cis* configuration of **3** with respect to an almost planar six-membered siloxane ring was confirmed. The guest conformation in the solid structure is in fact C_3 (not C_{3v}) as a consequence of the presence of asymmetric *m*-tolyl groups. Thus, the observation of C_{3v} symmetry for the host framework probes the rapid flipping of *m*-tolyl groups in solution which gives an apparent C_{3v} structure. While guest **3** is frozen or allowed to only spin around the C_{3v} axis at room temperature, its motion becomes random at elevated temperatures. The host signals coalesced at 313 K in variable-temperature NMR measurements (Figure 5), which showed that the guest turned around rapidly within the cage above this temperature.

The present study has shown that the specific conformation and orientation of guest molecules in cage-like host **1** can be predicted in a dynamic fashion by analyzing not the guest but the host framework as a result of the simple, highly symmetric structure of **1**. The facile probe of guest information by this method will make possible the design of new properties and reactivities of molecules.^[9]

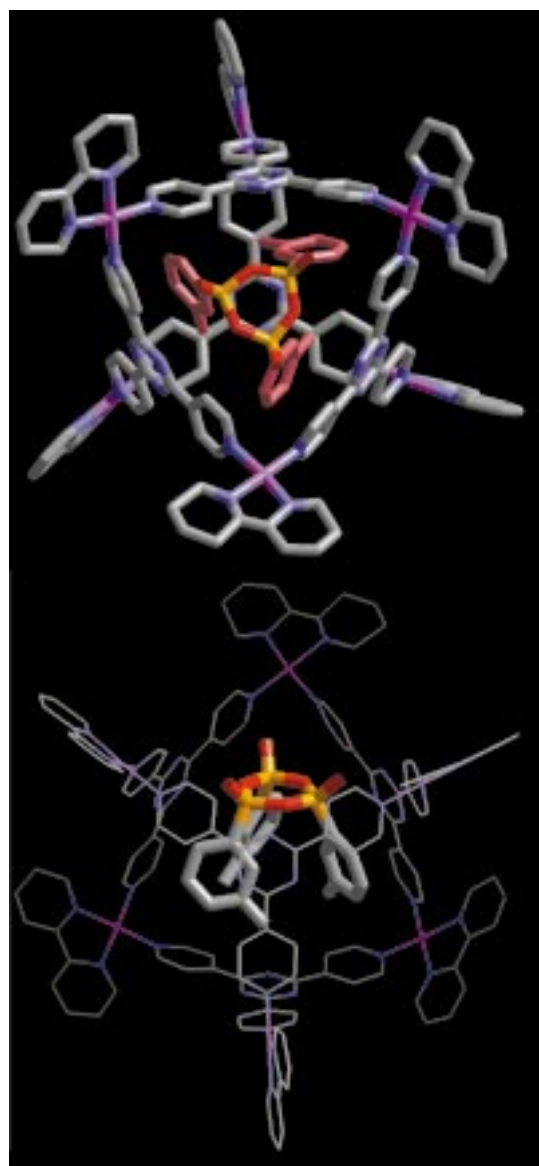


Figure 4. The top and side views of the $\mathbf{3} \subset \mathbf{1}$.

Experimental Section

Typical procedure: A suspension of **2a** (61.1 mg, 0.226 mmol) in hexane (1 mL) was stirred with a solution of **1** in D₂O (7.5 mM, 1.5 mL) for 0.5 h. The two phases were then separated. Analysis of the aqueous phase by NMR spectroscopy showed the stoichiometric formation of (**2a**)₂ ⋅ **1**. The aqueous solution was condensed to give (**2a**)₂ ⋅ **1** as a pale yellow powder (44.5 mg) in 97% yield.

(2a)₂: 1: ¹H NMR (500 MHz, D₂O, 300 K, TMS as external standard): δ = 9.78 (d, *J* = 6.0 Hz, 4H, PyH^α), 9.74 (d, *J* = 5.9 Hz, 4H, PyH^α), 9.74 (d, *J* = 5.9 Hz, 4H, PyH^α), 9.61 (d, *J* = 5.4 Hz, 4H, PyH^α), 9.36 (d, *J* = 6.0 Hz, 4H, PyH^α), 9.18 (d, *J* = 6.0 Hz, 4H, PyH^β), 9.08 (d, *J* = 5.9 Hz, 4H, PyH^β), 9.05 (d, *J* = 5.9 Hz, 4H, PyH^β), 8.93 (d, *J* = 5.9 Hz, 4H, PyH^β), 8.61 (d, *J* = 5.4 Hz, 4H, PyH^β), 8.50 (t, *J* = 8.6 Hz, 12H, bpy), 8.40 (t, *J* = 8.4 Hz, 12H, bpy), 8.37 (d, *J* = 6.0 Hz, 4H, PyH^β), 7.7–7.5 (m, 28H, 24H for bpy, 4H for diketone ArH), 5.66 (d, *J* = 8.9 Hz, 4H, diketone ArH), 4.05 (d, *J* = 8.9 Hz, 4H, diketone ArH), 3.52 (d, *J* = 8.8 Hz, 4H, diketone ArH), 2.80 (s, 12H, diketone CH₃O-); ¹³C NMR (125 MHz, D₂O, 300 K): δ = 193.0 (s, diketone CO), 169.6 (s, triazine), 169.5 (s, triazine), 169.3 (s, triazine), 163.0 (s, diketone), 157.14 (s, bpy), 157.08 (s, bpy), 153.5 (d, py), 153.3 (d, py), 153.2 (d, py), 153.0 (d, py), 152.9 (d, py), 152.8 (d, py), 150.6 (d, bpy), 150.4

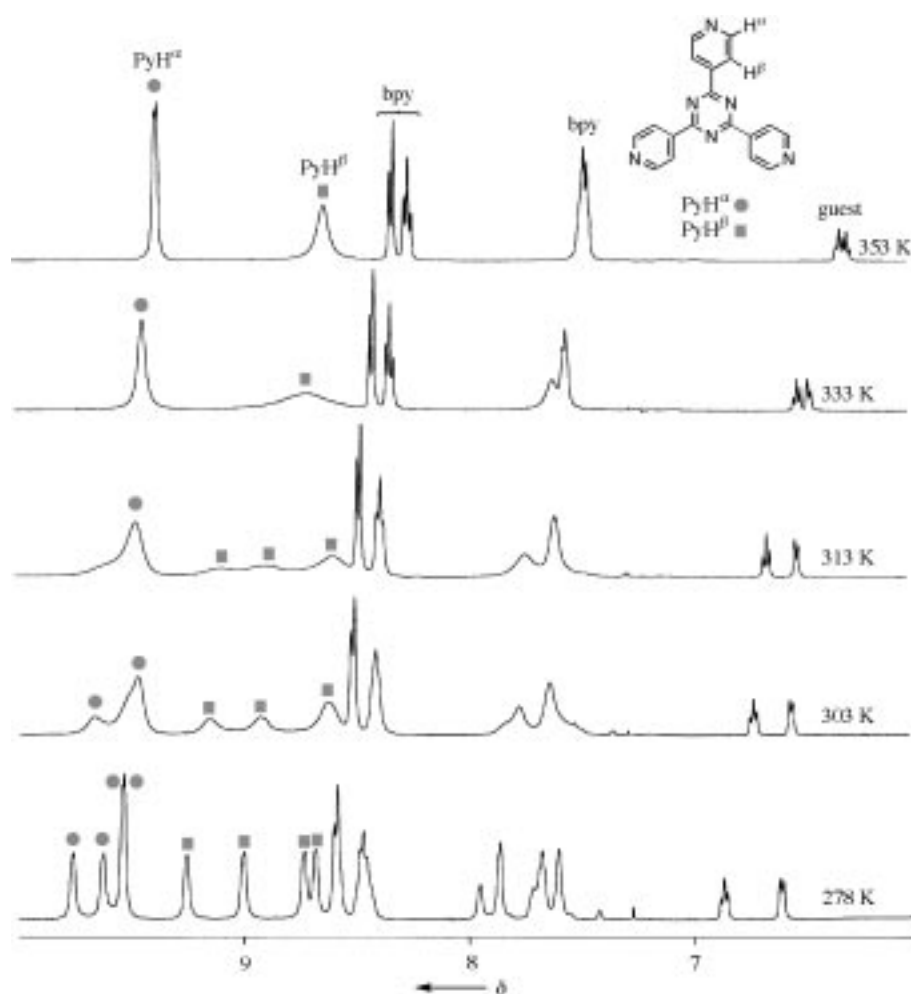


Figure 5. Variable-temperature ^1H NMR spectra of **3** in D_2O . PyH^a and PyH^b protons are marked with a circle (●) and a square (■). The coalescence at 313 K indicates the random movement of the guest above this temperature, which results in the loss of the apparent C_{3v} symmetry of the cage.

(d, py), 150.3 (d, py), 146.3 (s, py), 145.3 (s, py), 145.0 (s, py), 143.3 (d, bpy), 143.2 (d, bpy), 132.3 (d, diketone Ar), 132.3 (d, diketone Ar), 129.7 (d, diketone Ar), 128.5 (d, py, bpy), 127.8 (d, py), 127.6 (d, py), 126.5 (d, py), 126.2 (d, py), 124.9 (d, bpy), 124.8 (d, bpy), 124.1 (s, diketone Ar), 120.4 (s, diketone Ar), 107.4 (d, diketone Ar), 56.5 (q, diketone CH_3O).

An aqueous solution of $(\mathbf{2a})_2 \cdot \mathbf{1}$ (7.5 mm, 0.5 mL) was allowed to stand at ambient temperature for a few days to give single crystals of $(\mathbf{2a})_2 \cdot \mathbf{1}$. A pale yellow crystal was selected under ambient conditions, attached to the tip of a glass fiber, and transferred to a Bruker SMART CCD diffractometer. Crystal data for $(\mathbf{2a})_2 \cdot \mathbf{1}$: $\text{C}_{164}\text{H}_{124}\text{N}_{48}\text{O}_{44}\text{Pd}_6$, $M_r = 4109.51$, crystal dimensions $0.50 \times 0.50 \times 0.50 \text{ mm}^3$, tetragonal space group $P4_32_12$ (no. 96), $a = b = 29.535(3)$, $c = 31.351(4) \text{ \AA}$, $V = 27349(5) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 0.998 \text{ g cm}^{-3}$, $F(000) = 8288$, radiation, $\lambda(\text{MoK}\alpha) = 0.71073 \text{ \AA}$, $T = 298 \text{ K}$, reflections collected/unique $88739/12358$ ($R_{\text{int}} = 0.0615$). The structure was solved by direct methods (SHELXL-97) and refined by full-matrix least-squares methods on F^2 with 865 parameters. $R_1 = 0.1080$ ($I > 2\sigma(I)$), $wR_2 = 0.2809$, GOF 2.151; max./min. residual density $1.000/-0.655 \text{ e \AA}^{-3}$. Further refinement was unsuccessful because of the high degree of disorder of the counterions and water molecules.

Preparation of **3** **1**: *m*-Tolyltrimethoxysilane (17.9 mg; $8.45 \times 10^{-2} \text{ mmol}$, 5 equiv) was suspended in a solution of **1** (60.3 mg; $16.9 \times 10^{-3} \text{ mmol}$, 6.5 mm) in H_2O (2.6 mL) at 100°C and the mixture was stirred at the same temperature for 1 h. After the mixture was cooled down to room temperature, the solution was filtered, and evaporated to dryness. The crude product was purified by crystallization from H_2O to give **3** **1** as a pale yellow powder (61.5 mg; $15.3 \times 10^{-3} \text{ mmol}$) in 90% yield. Physical data of **3** **1**: m.p. $> 300^\circ\text{C}$; ^1H NMR (500 MHz, D_2O , 278 K, TMS as

external standard): $\delta = 9.77$ (d, 6H, PyH^a), 9.63 (d, 6H, PyH^c), 9.55 (d, 12H, PyH^{cb}), 9.27 (d, 6H, PyH^b), 9.02 (d, 6H, PyH^d), 8.75 (d, 6H, PyH^f), 8.70 (brs, 6H, PyH^d), 8.61 (d, 12H, bpy), 8.48 (t, 12H, bpy), 7.9–7.8 (m, 3H, bpy), 7.87 (m, 6H, bpy), 7.68–7.72 (m, 9H, bpy), 7.61 (m, 6H, bpy), 6.88 (t, $J = 7.0 \text{ Hz}$, 3H, ArH), 6.63 (d, $J = 7.0 \text{ Hz}$, 3H, ArH), 5.21 (d, $J = 7.0 \text{ Hz}$, 3H, ArH), 4.45 (s, 3H, ArH), -0.37 (s, 18H, CH_3); ^{13}C NMR (125 MHz, D_2O , 278 K, TMS as external standard): $\delta = 169.8$ (s), 169.4 (s), 168.3 (s), 156.7 (s), 152.9 (d), 152.4 (d), 152.2 (d), 151.7 (d), 150.3 (d), 150.1 (d), 146.1 (s), 145.9 (s), 142.8 (d), 134.4 (s), 132.9 (d), 130.4 (d), 130.2 (d), 129.3 (s), 128.0 (d), 127.7 (d), 127.1 (d), 126.9 (d), 126.5 (d), 126.2 (d), 124.6 (d), 18.5 (q, CH_3); ^{29}Si NMR (99 MHz, D_2O , 278 K, TMS as external standard): $\delta = -63.9$; IR (KBr, cm^{-1}): 3400 (brs), 3030 (brs), 1603, 1576, 1520, 1375, 1313, 1249, 1032 (O–Si–O), 958, 869, 826, 802, 771, 744, 722, 701, 641, 520, 458; elemental analysis (%) calcd for $\text{C}_{153}\text{H}_{120}\text{O}_{42}\text{N}_{48}\text{Pd}_6\text{Si}_3 \cdot 16\text{H}_2\text{O}$: C 42.60, H 3.55, N 15.58; found: C 42.77, H 3.44, N 15.35.

An aqueous solution of **3** **1** ($16.9 \times 10^{-2} \text{ mmol}$, 2.6 mL) was allowed to stand at ambient temperature for a few days to give single crystal of **3** **1**. A colorless crystal was selected under ambient conditions, attached to the tip of a glass fiber, and transferred to a Bruker SMART CCD diffractometer. Crystal data for **3** **1**: $\text{C}_{153}\text{H}_{120}\text{N}_{48}\text{O}_{42}\text{Pd}_6\text{Si}_3$, $M_r = 4025.64$, crystal dimensions $0.40 \times 0.20 \times 0.20 \text{ mm}^3$, trigonal space group $P\bar{3}c1$ (no. 165), $a = b = 27.6231(9)$, $c = 34.1541(17) \text{ \AA}$, $V = 22569.3(15) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.185 \text{ g cm}^{-3}$, $F(000) = 8112$, radiation, $\lambda(\text{MoK}\alpha) = 0.71073 \text{ \AA}$, $T = 105 \text{ K}$, reflections collected/unique $70124/6814$ ($R_{\text{int}} = 0.0568$). The structure was solved by direct methods (SHELXL-97) and refined by full-matrix least-squares methods on F^2 with 667 parameters. $R_1 = 0.1307$ ($I > 2\sigma(I)$), $wR_2 = 0.3578$, GOF 3.012; max./min. residual density $2.250/-0.874 \text{ e \AA}^{-3}$. Owing to the high degree of disorder of the counterions and water molecules, further refinement was unsuccessful. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-155770 ($(\mathbf{2a})_2 \cdot \mathbf{1}$) and CCDC-155771 (**3** **1**). 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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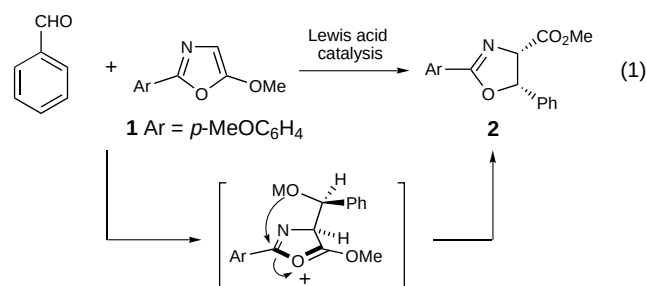
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Chiral Salen–Aluminum Complexes as Catalysts for Enantioselective Aldol Reactions of Aldehydes and 5-Alkoxyoxazoles: An Efficient Approach to the Asymmetric Synthesis of *syn* and *anti* β -Hydroxy- α -amino Acid Derivatives**

David A. Evans,* Jacob M. Janey, Nabi Magomedov, and Jason S. Tedrow

The stereoselective synthesis of α -amino- β -hydroxy acids is a topic of ongoing interest as these structures are found in numerous peptide-based natural products including the vancomycin antibiotics.^[1] The stereoselective synthesis of *trans*-5-substituted 2-oxazoline-4-carboxylates has been reported using an aldol reaction between aldehydes and methyl isocyanoacetate,^[2] and the enantioselective version of this reaction has subsequently been developed by Ito and Hayashi et al.^[3] A related aldol addition/acyl transfer process wherein 5-methoxyoxazole **1** functions as the glycine enolate synthon has been described by Suga and Ibata et al. [Eq. (1)].^[4] In



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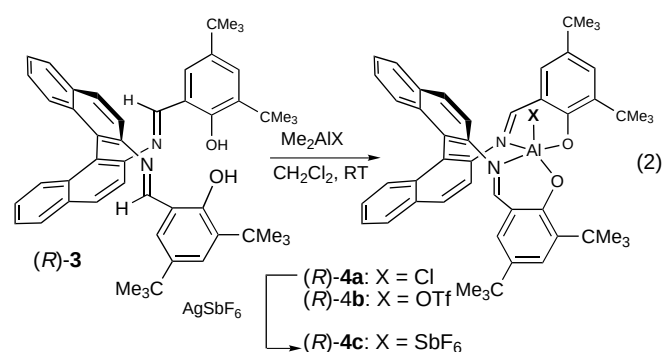
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contrast to the Hayashi–Ito reaction, this addition affords the more versatile *cis*-2-oxazoline-4-carboxylates **2**. These substrates may be cleanly isomerized to their *trans* counterparts, thus providing access to both α -amino- β -hydroxy acid diastereomers from the same reaction sequence.

In the current rendition, the Suga–Ibata reaction [Eq. (1)] is mediated by an uncharacterized metal complex derived from trimethylaluminum and (*R*)- or (*S*)-BINOL. This chiral complex affords *cis*-**2** with good diastereoselection (4:1–20:1) but variable enantioselectivities. As described, this reaction suffers from high catalyst loading (30 %), long reaction times, and the requirement of excess aldehyde to drive the reactions to completion.^[4] Here we describe the synthesis and characterization of the chiral aluminum complexes (*R*)-**4** and their use in the catalysis of this *cis*-diastereoselective aldol reaction with enantioselectivities in excess of 90 % for a range of aromatic aldehydes.

Chiral aluminum complex (*R*)-**4a** was prepared in quantitative yield by reaction of the enantiomerically pure diamino-biphenyl-derived ligand^[5] (*R*)-**3** with dimethylaluminum chloride [Eq. (2); CH₂Cl₂, 25 °C]. Complex (*R*)-**4a** was



isolated as a yellow, bench-stable amorphous solid. The structure of *rac*-**4a** was determined by X-ray crystallography.^[6] The complex exhibits a distorted trigonal bipyramidal geometry with the chlorine atom located in the equatorial plane (Figure 1). The dihedral angle between the two naphthyl planes is 62°, creating a chiral environment around the aluminum metal center. The corresponding triflate complex (*R*)-**4b** was prepared by the reaction of (*R*)-**3** with dimethylaluminum triflate^[7] (CH₂Cl₂, 0→25 °C) in 94 % yield. The structure of *rac*-**4b** was also determined by X-ray analysis. In contrast to the aluminum chloride complex *rac*-**4a**, the triflate complex *rac*-**4b** crystallized as the diaqua aluminum complex *rac*-**5**, and exhibited a distorted octahedral geometry with two *cis* water molecules coordinated to the metal center (Figure 1). According to the triflate–aluminum distance of 4.5 Å the triflate anion is fully dissociated. Inspection of the X-ray structure of *rac*-**5** indicates that the (*R*)-**3** ligand is bound to the aluminum center of (*R*)-**4b** in a Δ -*cis*- β configuration.^[8]

Initial experiments revealed that [Al(OH₂)₂]{(*R*)-**3**}[OTf] (**5**) (20 mol %) catalyzes the reaction of oxazole **1** with benzaldehyde (1.2 equiv, CH₂Cl₂, 3 Å MS, 25 °C, 20 h) to furnish (4*S*,5*S*)-oxazoline **2** in 98 % *ee* and with high diastereoselection (93:7 *dr*) favoring *cis*-**2**. However, catalyst turn-

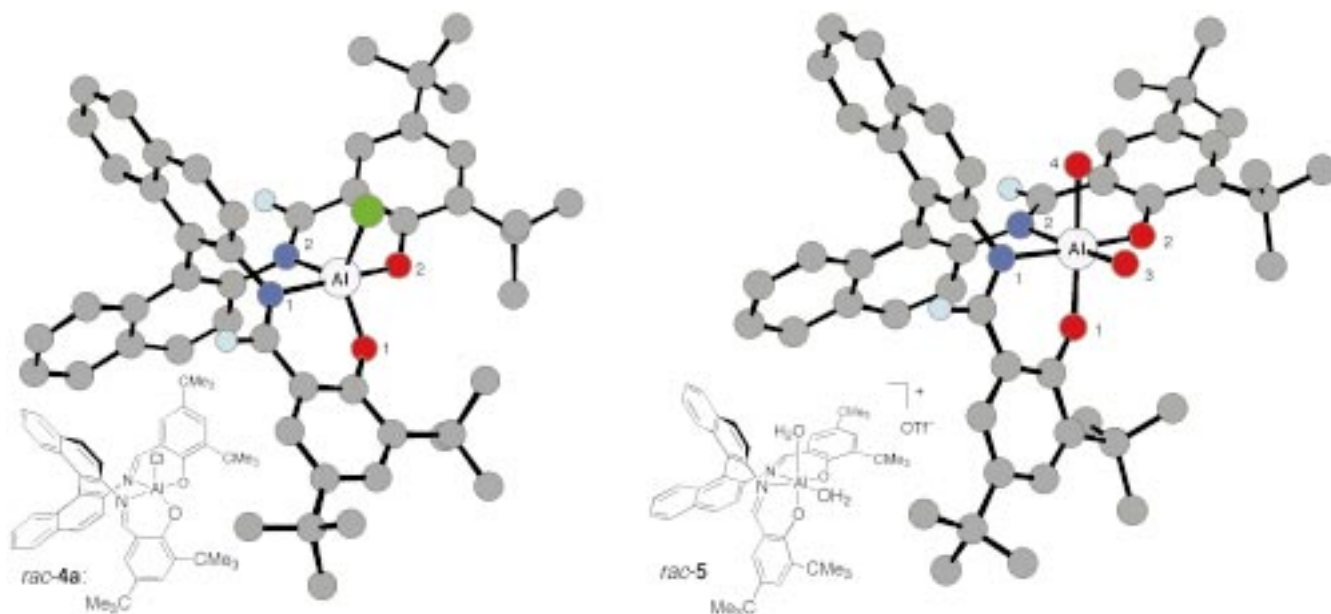


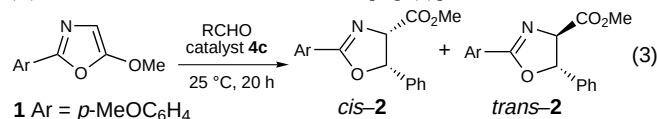
Figure 1. X-ray structure of chiral aluminum complexes *rac-4a* and *rac-5*. The dissociated triflate counterion is not illustrated in *rac-5*.

over appeared to be a problem as the reaction proceeded to only 60% conversion. While the aluminum chloride complex (*R*)-**4a** was not catalytically active, activation by AgSbF₆ provides a highly reactive species, presumably the cationic complex (*R*)-**4c**. Reaction of oxazole **1** with benzaldehyde in the presence of 20 mol % of (*R*)-**4c** afforded oxazoline **2** with good conversion (80%; 20 h) and the same enantio- and diastereoselection (93:7 *dr*, 98% *ee*). The same reaction performed in the absence of molecular sieves afforded similar stereoselectivity, but decreased conversion (60%). In subsequent experiments it was established that the problem of low conversion was not due to product inhibition.

Solvent effects were next investigated in an attempt to improve catalyst turnover. In general, poorly coordinating solvents provide higher conversions than reactions conducted in THF or acetonitrile [Table 1, Eq. (3)]. Ultimately, toluene was found to be the optimal solvent affording oxazoline **2** (80% conversion, 95:5 *dr*, 99% *ee*) in the presence of only 10 mol % of (*R*)-**4c**. It is noteworthy that asymmetric induction and reaction diastereoselection are virtually solvent insensitive.

A salt additive sharply increases the catalyst efficiency (Table 1). For example, the reaction of **1** with 1.2 equiv of benzaldehyde (PhMe, 3 Å MS, 25 °C, 5 mol % of (*R*)-**4c**) furnishes oxazoline **2** in 99% yield with excellent stereoselectivity (95:5 *dr*, 99% *ee*) when conducted in the presence of 20 mol % of LiClO₄. The same reaction performed in the absence of any additive proceeds with only 35% conversion. Low conversion (40%) is also observed when lithium perchlorate is replaced with 20 mol % of tetramethylammonium perchlorate. The latter experiments suggest that a hard cation such as Li⁺ (or Na⁺) might serve to promote the breakdown of the proposed aluminum–alkoxide aldolate intermediate [Eq. (1)]. A practical extension of this effect was made by utilizing Na₂SO₄ as both additive and drying agent. This reaction may be readily scaled up. Thus, on a one-gram scale, reaction of oxazole **1** and benzaldehyde (1M in toluene,

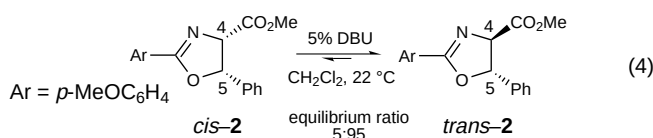
Table 1. Enantioselective reaction of **1** with PhCHO catalyzed by complex (*R*)-**4c**. Assessment of reaction variables [Eq. (3)]



Solvent ^[a]	Additive ^[b]	mol % 4c	conv. [%]	<i>dr</i> ^[c]	<i>ee</i> [%] ^[c]
MeCN	none	20	10	97:3	99
THF	none	20	19	95:5	98
CH ₂ Cl ₂	none	10	50	95:5	98
MeC ₆ H ₅	none	10	80	95:5	99
MeC ₆ H ₅	none	5	34	95:5	99
MeC ₆ H ₅	LiClO ₄	5	94	95:5	99
MeC ₆ H ₅	Me ₄ NClO ₄	5	42	95:5	99
MeC ₆ H ₅	Na ₂ SO ₄ ^[d]	1	96	96:4	99
MeC ₆ H ₅	NaBPh ₄	5	94	95:5	99

[a] The reaction was carried out in the indicated solvent at room temperature in the presence of crushed 3 Å molecular sieves (200 mg for 0.4 mmol **1**). [b] The indicated additive was used in 20 mol %. [c] *cis:trans* ratio and enantiomeric excess (*cis-2*) determined by HPLC (Chiralcel AD). [d] Use of molecular sieves replaced by additive on 1-g scale reaction.

1 g Na₂SO₄, 25 °C, 20 h) with 1 mol % of (*R*)-**4c** furnished the desired *cis-2* in 92% yield (96% conversion, 96:4 *dr*, 99% *ee*). In addition, *cis-2* (>99% *ee*) was epimerized to *trans-2* by treatment with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (*cis:trans* 5:95, >99% *ee*) [Eq. (4)]. The absolute configuration of the known (4*S*,5*S*)-*cis-2* was readily determined by its optical rotation.^[4] This experiment also establishes that the sample of (4*R*,5*S*)-*trans-2*



obtained by epimerization has the same absolute configuration as the minor aldol reaction product [Eq. (3)].

The scope of the reaction was explored using the optimized conditions described in the preceding paragraph (PhMe, 20% LiClO₄, 3 Å MS, 25 °C, 20 h; Table 2). A wide range of aromatic aldehydes were found to be excellent substrates. The reactions of densely functionalized benzaldehydes containing both electron withdrawing and donating substituents afford oxazoline adducts (**8c**, **9a–c**, and **10**) in high yield (90–100%) and good stereoselection (74:26–96:4 *dr*, 92–98% *ee*). Furfural affords oxazoline **12** with good stereoselection (77:23 *dr*, 96% *ee*), but in moderate yield (58%). We speculate that the longer reaction times necessary for higher conversion lead to epimerization of the *cis*-oxazoline **12** to the *trans* isomer (6:94 *dr*, 68% *ee trans*; 20 h). The absolute configurations of the above products were assigned by analogy to the known *cis*-oxazoline **2**. Surprisingly, aliphatic aldehydes, such as dihydrocinnamaldehyde and cyclohexane carbaldehyde, were found to be unreactive under the standard reaction conditions.

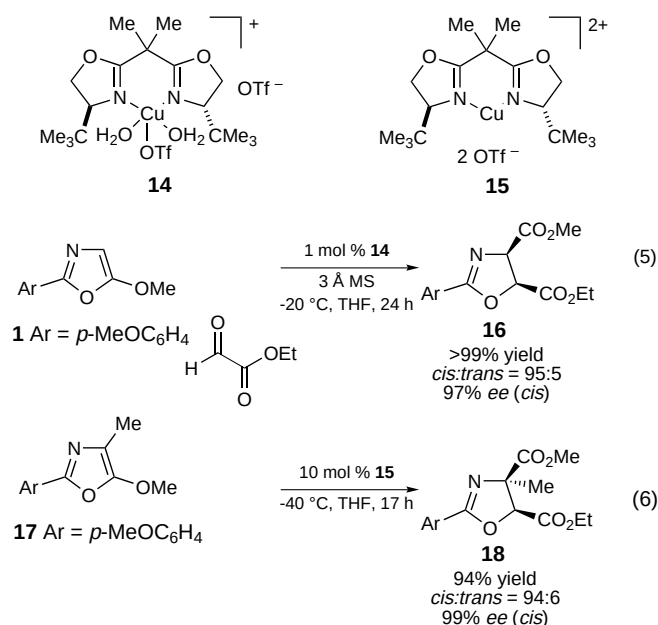
This reaction is not limited to catalysis by aluminum-derived Lewis acids. We have found that Cu^{II}-bis(oxazoline) complexes are efficient catalysts for chelating aldehydes. For example, the reaction between oxazole **1** and ethyl glyoxylate, mediated by [Cu(OTf)(OH₂)₂[(*S,S*)-*t*Bu-box]](OTf) (**14**) (1 mol %, THF, 3 Å MS, –20 °C, 24 h) afforded adduct **16** in quantitative yield and excellent stereoselectivity (95:5 *dr*, 97% *ee*) [Eq. (5)].^[9] Furthermore, 4-methyl substituted oxazole **17** reacts in an analogous fashion with ethyl glyoxylate in the presence of **15** (10 mol %, THF, –40 °C, 17 h) to provide a 94% yield of oxazoline **18** (94:6 *dr*, 99% *ee*) [Eq. (6)]. The absolute configuration of the cycloadduct^[10] is consistent with the previously proposed model for asymmetric induction with Cu^{II}-bis(oxazoline) and glyoxylate esters.^[9, 11] The observed stereochemistry may be rationalized by assuming an aldol-like addition of the nucleophilic oxazole to the Lewis acid-activated aldehyde.

Based upon the published X-ray structure of complex **14**,^[12] semiempirical calculations (PM3) were employed to model the complex between ethyl glyoxylate and **15**. For simplicity,

Table 2. Enantioselective reaction of aldehydes with oxazole **1** catalyzed by chiral aluminum complex (*R*)-**4c** [Eq. (3)].

Aldehyde		mol % 4c	Yield (%) ^[a]	<i>dr</i> ^[b]	<i>ee</i> [%] (product) ^[c]
	X = H	5	99	95:5	99 (2)
	X = F	10	98	96:4	> 99 (6a)
	X = NO ₂	5	99	88:12	97 (6b)
	X = CN	5	96	83:17	95 ^[d] (6c)
	X = COOMe	5	98	93:7	> 99 (6d)
	X = OPh	10	89	96:4	> 99 (6e)
	X = OAc	5	95	96:4	> 99 (6f)
	X = Me	5	96	92:8	96 (6g)
	X = Ph	5	100	96:4	99 (6h)
	X = Cl	5	93	90:10	99 (7a)
	X = NO ₂	5	99	73:27	91 (7b)
	X = OMe	5	95	93:7	99 (7c)
	X = Me	5	98	95:5	98 (7d)
	X = Cl, Y = H	5	96	> 99:1	> 99 (8a)
	X = NO ₂ , Y = H	5	93	93:7	> 99 (8b)
	X = Br, Y = OMe	5	98	96:4	95 (8c)
	X = Me, Y = H	5	86	> 99:1	> 99 (8d)
	X = Cl, Y = H	5	96	> 99:1	> 99 (8d)
	X = F, Y = Cl	5	100	89:11	98 (9a)
	X = OMe, Y = Br	5	90	91:9	98 (9b)
	X = Cl, Y = NO ₂	5	99	74:26	92 (9c)
		5	96	90:10	98 (10)
	1-Naphthyl	10	97	96:4	> 99 (11a)
	2-Naphthyl	10	98	96:4	> 99 (11b)
		10	58	77:23	96 (12)
		10	98	90:10	98 (13)

[a] Yield of isolated product. [b] *cis:trans* ratio determined by ¹H NMR or HPLC. [c] Enantiomeric excess of the *cis* isomer determined by HPLC (Chiralcel AD). [d] Enantiomeric excess determined by ¹H NMR with BINOL as a shift reagent.



the triflate counterions were omitted from the calculations. As shown in Figure 2, the *Re* face of the bound glyoxalate is screened by the ligand's *tert*-butyl substituent, leaving the *Si* face accessible to nucleophile approach.



Figure 2. PM3 model of the **15**–glyoxalate complex.

Experimental Section

(R)-4a: To an oven-dried round-bottom flask containing a magnetic stir bar was added **(R)-3**^[13] (1.96 g, 2.74 mmol). The flask was charged with 20 mL of CH_2Cl_2 and cooled to 0°C . Neat Me_2AlCl (255 μL , 2.74 mmol) was slowly added to the stirred solution with a syringe over 3 minutes. The red reaction mixture was allowed to warm to room temperature and stirred overnight (15 h). It was then concentrated in vacuo to give an orange glass. Hexane (20 mL) was added and the solvent was removed in vacuo to afford the product **(R)-4a** as a bright yellow amorphous solid (2.13 g, 2.74 mmol, $>99\%$ yield). Analytical data for **(R)-4a**: m.p. $234\text{--}236^\circ\text{C}$; $[\alpha]_D^{25} = -977^\circ$ ($c = 0.66$, CHCl_3); IR (CH_2Cl_2): $\tilde{\nu} = 2964, 1615, 1584, 1540, 1471, 1179 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3) $\delta = 8.43$ (s, 1 H), 8.22 (s, 1 H), 8.09 (d, $J = 8.0 \text{ Hz}$, 1 H), 8.01 (d, $J = 8.0 \text{ Hz}$, 1 H), 7.95–7.90 (m, 2 H), 7.79 (d, $J = 7.5 \text{ Hz}$, 1 H), 7.60 (s, 1 H), 7.54–7.47 (m, 3 H), 7.34 (t, $J = 7.5 \text{ Hz}$, 1 H), 7.31–7.25 (m, 2 H), 7.21 (d, $J = 7.5 \text{ Hz}$, 1 H), 7.10 (d, $J = 8.5 \text{ Hz}$, 1 H), 7.02 (s, 1 H), 6.94 (s, 1 H), 1.53 (s, 9 H), 1.49 (s, 9 H), 1.26 (s, 18 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 173.9, 170.0, 165.5, 161.8, 145.1, 144.9, 141.8, 141.3, 139.6, 138.8, 133.4, 132.8, 132.7, 132.4, 132.3, 131.7, 130.5, 129.6, 128.8, 128.5, 128.0, 127.9, 127.2, 126.9, 126.7, 126.3, 126.0, 125.7, 125.2, 119.2, 118.4, 35.7, 34.2, 31.8, 31.4, 31.3,$

30.0, 29.7, 22.9, 14.4; HR-MS (FAB): m/z calcd for $\text{C}_{50}\text{H}_{54}\text{AlN}_2\text{O}_2$: 741.4001 $[M - \text{Cl}]^+$, found: 741.3980.

8a: A dry, round-bottom flask equipped with a magnetic stirrer was charged with **(R)-4a** (15.5 mg, 0.020 mmol; 0.050 equiv), oxazole **1** (82 mg, 0.40 mmol; 1 equiv), AgSbF_6 (7.6 mg, 0.022 mmol; 0.055 equiv), LiClO_4 (8.5 mg, 0.08 mmol; 0.20 equiv), and powdered 3 Å molecular sieves (200 mg). To this mixture was added toluene (2 mL), followed by addition of 2-chlorobenzaldehyde (54 μL , 0.48 mmol; 1.2 equiv) with a syringe. After stirring at room temperature for 20 h, the reaction mixture was filtered through a short plug of silica gel and eluted with diethyl ether. After concentration in vacuo, the product was purified by flash chromatography on silica gel and eluted with 30% EtOAc in hexanes to afford **8a** as a thick, colorless oil (133 mg, 0.38 mmol, 96%). ^1H NMR analysis of the unpurified product showed no *trans* product. Chiral analysis by HPLC (Chiralpak AD, *i*PrOH/hexanes (20:80), flow rate 0.7 mL min^{-1} , 254 nm; $t_r = 17.1$ (minor *cis* product), 27.1 (major *cis* product)) gave the isomeric composition of the product: $>99:1 \text{ dr}$, $>99\%$ ee. Analytical data for **8a**: $[\alpha]_D^{25} = +362^\circ$ ($c = 1.64$, CHCl_3); IR (CHCl_3): 3018, 1746, 1647, 1610, 1514, 1258, 1218, 1172, 1088, 1030, 992, 842 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) $\delta = 8.04$ (d, $J = 8.5 \text{ Hz}$, 2 H), 7.46–7.43 (m, 1 H), 7.40–7.36 (m, 1 H), 7.28–7.24 (m, 2 H), 6.97 (d, $J = 8.5 \text{ Hz}$, 2 H), 6.24 (d, $J = 10.5 \text{ Hz}$, 1 H), 5.36 (d, $J = 10.5 \text{ Hz}$, 1 H), 3.88 (s, 3 H), 3.23 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 169.6, 166.6, 162.9, 134.4, 132.4, 130.7, 129.7, 129.2, 127.4, 127.0, 119.4, 114.1, 80.2, 72.8, 55.6, 51.8$; HR-MS (EI): m/z calcd for $\text{C}_{18}\text{H}_{16}\text{ClNO}_4$: 345.0768 $[M]^+$, found: 345.0774; satisfactory elemental analysis was obtained.

Crystal data for **rac-4a** ($\text{C}_{52}\text{H}_{61}\text{AlClN}_2\text{O}_3$):^[14] crystal dimensions $0.15 \times 0.2 \times 0.2 \text{ mm}^3$, triclinic, space group *P1*, $a = 12.1105(8)$, $b = 15.4529(10)$, $c = 16.5387(11) \text{ Å}$, $\beta = 108^\circ$; $V = 2559.9(3) \text{ Å}^3$, $\rho = 1.070 \text{ mg mm}^{-3}$; Siemens SMART CCD diffractometer, $1.49 < \theta < 27.85^\circ$, MoK_α radiation, $\lambda = 0.71073 \text{ Å}$, $\theta/2\theta$ -scans, $T = 293(2) \text{ K}$; of 16249 measured reflections, 10558 were independent and 10558 were observed with $I > 2\sigma(I)$, $-14 \leq h \leq 13$, $-19 \leq k \leq 20$, $-21 \leq l \leq 14$; $R = 0.0599$, $wR = 0.1720$, GOF = 0.968 for 565 parameters, $\Delta\rho_{\text{max}} = 0.715 \text{ e Å}^{-3}$.

Crystal data for **rac-5** ($\text{C}_{68}\text{H}_{98}\text{AlF}_3\text{N}_2\text{O}_{10}\text{S}_2$):^[14] crystal dimensions $0.2 \times 0.3 \times 0.5 \text{ mm}^3$, triclinic, space group *P1*, $a = 13.8209(9)$, $b = 15.3143(9)$, $c = 18.6786(11) \text{ Å}$, $\beta = 84^\circ$; $V = 3857.7(4) \text{ Å}^3$, $\rho = 1.077 \text{ mg mm}^{-3}$; Siemens SMART CCD diffractometer, $1.11 < \theta < 22.50^\circ$, MoK_α radiation, $\lambda = 0.71073 \text{ Å}$, $\theta/2\theta$ -scans, $T = 293(2) \text{ K}$; of 17719 measured reflections, 10033 were independent and 10033 were observed with $I > 2\sigma(I)$, $-14 \leq h \leq 14$, $-16 \leq k \leq 10$, $-19 \leq l \leq 20$; $R = 0.0713$, $wR = 0.2287$, GOF = 1.192 for 785 parameters, $\Delta\rho_{\text{max}} = 0.826 \text{ e Å}^{-3}$.

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- [14] The structures were solved by direct methods (SHELXTL Plus) and developed by least squares refinement against $|F^2|$ (SHELXL93). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-157312 (*rac*-**4a**) and CCDC-157313 (*rac*-**5**). 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).

Fluorescent Fingerprinting of Molecular Recognition Landscapes**

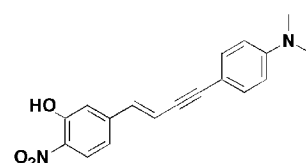
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Within the last decade, the number of molecules examined per experiment has dramatically increased. This advance now allows molecular matter to be screened on an unprecedented scale, and has, for a large part, allowed the completion of expansive projects, such as the sequencing of the genomes of over 30 organisms.^[1] The next advance lies in putting these advances in a *popular* format, thereby extending a common medium for molecular information. While technologies, such as DNA microarraying,^[2] begin to reach this level, by accessing up to 10⁶ different molecular recognition events, considerable hurdles exist before these and related multidimensional technologies can identify a single molecular component in array of materials with similar structural and/or biophysical features.

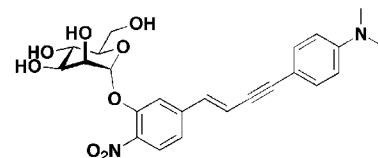
Multidimensional screening has become possible as a result of the development of: 1) spatially addressable microarrays,^[2] 2) more responsive sensing elements (i.e., single molecule spectroscopy),^[3] 3) molecular encoding,^[4] 4) "molecular noses"^[5] and/or 5) microrobotics.^[6] Currently, a significant portion of these advances employ fluorescence spectroscopy.

For a large part, fluorescent methodologies are based on monitoring steady-state fluorescent probes (i.e., compounds whose rigid structural backbone provides a maximum fluorescence with minimal wavelength dependency). In contrast, the SENSI-like fluorophore (**1**), in which rotation about six bonds is possible, has numerous conformations both in the ground and excited states.^[7] Each conformation presents a different extent of conjugation, and therefore, increases the information density expressed within this probe's absorption and emission spectra. The complex photophysics of this system^[8] provide information density far greater than that of traditional rigid fluorophores (e.g., fluorescein and rhodamine).

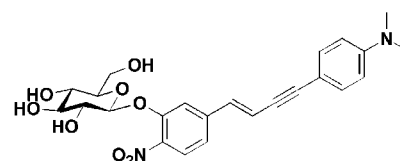
The restriction of the space about **1** upon contact with, or approach to, the surface of another molecule or group of molecules can alter access to various charge transfer states or conformers, thereby reducing the net photophysical response.^[8] This information provides a rich medium to differentiate molecular recognition events. Herein, we illustrate how this tool can be used to distinguish low-affinity molecular recognition events. A typical class of carbohydrate–protein interactions is used as a model system.



SENSI 1



2



3

Agglutinins from *Lens culinaris* (LCA),^[9] *Galanthus nivalis* (GNL),^[10] and *Pisum sativum* (PSA)^[11] share a common recognition of α -mannosides,^[12] but have no affinity towards β -glucosides. Lectins LCA and PSA are homodimeric proteins consisting of an α and β chain, they are 91 % homologous and have comparable three-dimensional structures. Like other legume lectins two large antiparallel β -sheets stretch out over the whole dimer and one calcium and one manganese atom lie in the vicinity of the carbohydrate recognition site.^[9, 11] Dimeric complexes of LCA and PSA contain four possible carbohydrate binding sites.

In contrast to LCA and PSA, the tetrameric GNL agglutinin belongs to the super-family of α -D-mannose-specific plant-bulb lectins known to be potent inhibitors of retroviruses. The crystal structure of this lectin complexed with methyl α -D-mannose reveals a novel β -sheet polypeptide fold having threefold symmetry. Three antiparallel four-strand β -sheets, each with a conserved mannose-binding site, are arranged as a 12-strand β -barrel. Pairs of monomers form stable dimers through C-terminal strand exchange. The hybrid β -sheets so formed are the sites for high-affinity mannose binding at or on the dimer interface. Occupancy observed at corresponding sites in other β -sheets suggests that there could be twelve binding sites per tetramer.^[10]

A series of carbohydrate ligands was prepared by attaching the phenolic group in **1** to the anomeric center of a given carbohydrate.^[12] Using this connection, carbohydrates representing active-binding α -mannoside **2**^[12] and nonbinding β -glucoside **3** were prepared using a previously described phase-transfer method.^[7] Even using the maximum sensitivity of our spectrometer,^[13] fluorescence arising from aqueous solutions of **1–3** could not be resolved from the background when examined over an excitation range from $\lambda_a = 350$ to 450 nm and emission range from $\lambda_e = 480$ to 600 nm.^[13] Fluorescence from the label **1** became detectable only after mixing with a lectin.

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As presented in the upper right corner of Figure 1 a, only mixtures containing **2** and a lectin fluoresced upon excitation at $\lambda_a = 370$ nm. By using a conventional two-dimensional

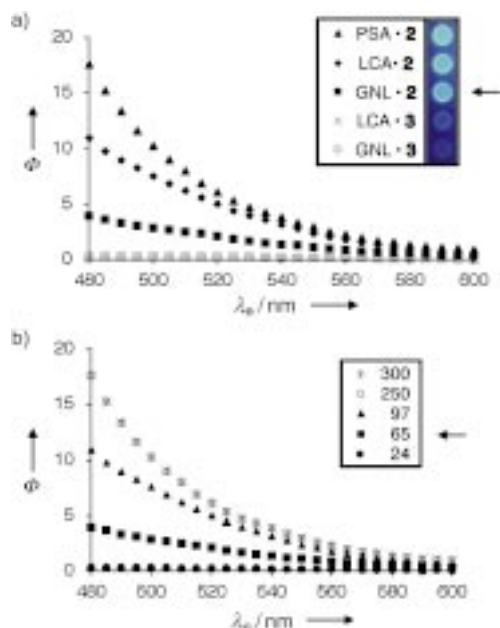


Figure 1. Fluorescence emission spectra from the complex of the conjugated carbohydrates **2** and **3** with lectins PSA, LCA, and GNL. Spectra provided are given by plotting intensity (Φ) versus emission wavelength (λ_e) at a given excitation wavelength ($\lambda_a = 370$ nm). a) Incubation of lectin at 300 μ M with carbohydrate at 200 μ M. The upper right section shows which wells fluoresce. The relative intensity is given by $\text{PSA} \cdot \mathbf{2} > \text{LCA} \cdot \mathbf{2} > \text{GNL} \cdot \mathbf{2} \gg \text{LCA} \cdot \mathbf{3} \sim \text{GNL} \cdot \mathbf{3}$. b) Titration of 200 μ M of **2** with PSA. the spectral information found in (a) can be reproduced by using the same spectral settings and altering the concentration of PSA from 24 to 300 μ M in a stepwise manner. Note that spectra highlighted by arrows (i.e., 300 μ M of GNL with 200 μ M **2** and 65 μ M of PSA with 200 μ M **2**) are nearly indistinguishable.

approach, we would conclude that lectins PSA, LCA, and GNL bind to **2** and not to **3**. Each of these interactions could then be identified by plotting fluorescence intensity (Φ) versus emission wavelength (λ_e), as illustrated by the five spectra displayed in Figure 1 a. For this method to be valid, one must certify that the observed effects can not be produced by alteration of the stoichiometry of the complex. As seen in Figure 1 b, a comparable series of spectra were produced by mixing **2** with PSA. Comparing the trials in Figure 1 highlighted by arrows, the fluorescence arising from incubating 65 μ M PSA with 200 μ M **2** is nearly indistinguishable from that of **2** with 300 μ M GNL (squares in Figure 1 b and Figure 1 a, respectively).

Advantageously, the response from **1** was dependent on the choice of both excitation and emission wavelength. Data was collected in a three-dimensional manner and plotted in projection or contour (Figure 2). These topographies illustrate a simple means to fluorescently “landscape” molecular recognition. The addition of LCA and PSA to **2** resulted in comparable responses (Figure 2 a–c), displaying only modest alteration in the fluorescence intensity observed around an excitation at $\lambda_a = 410$ nm and emission at $\lambda_e = 505$ nm.^[14] The structurally different lectin GNL bound to **2**, presented a

different topology (Figure 2 d), including a second maximum at $\lambda_a = 413$ nm and $\lambda_e = 490$ nm. Landscapes arising from mannoside **2** (Figure 2 b–d) differ from those obtained with the nonbinding carbohydrate **3** (Figure 2 e, f). Nonspecific multiple binding site interactions with **3** were easily distinguished by examining the relative fluorescence in the region between $\lambda_a = 420$ nm and 440 nm (excitation) and $\lambda_e = 520$ nm and 570 nm (emission).

As illustrated by comparison of Figure 2 b or 2 c with 2 d, landscapes from ligand **2** served to resolve PSA or LCA from GNL. On the other hand, landscapes generated under identical conditions with the nonspecific binding **3** did not distinguish between the two classes of agglutinins (Figure 2 e and 2 f) because the structure of these landscapes was inconsistent, deviating by up to 40 % at each data point even after repeated measurements. While this discrepancy primarily arose from the increased background associated with the reduced fluorescence intensity (Figure 2 h), other nonspecific interactions (i.e., mixing **1–3** with bovine serum albumin, BSA) gave comparable inconsistent data sets.^[15]

Most importantly, this three-dimensional method provides a means to distinguish recognition events from stoichiometric effects. As illustrated, the spectrum obtained for **2** with 300 μ M GNL is comparable to that generated by adding 65 μ M PSA (arrows in Figure 1). This is, however, not the case when examined three-dimensionally. While the landscape of **2** obtained with 65 μ M PSA (Figure 2 g) is less intense than that observed at 300 μ M (Figure 2 b), its structure and contours remains intact. Even at reduced concentrations this landscaping still serves to distinguish the PSA (Figure 2 g) from GNL (Figure 2 d).

The combination of a nonrigid fluorescence probe **1** and three-dimensional fluorescence spectroscopy provides an efficient means to differentiate subtle structural attributes resulting from molecular interactions. This method was able to distinguish low-affinity protein–carbohydrate interactions ($K_d \sim 10$ –50 μ M). The ease and technical simplicity of this method suggest a practical means to increase the reliability of affinity matrixes, and illustrate a potent tool for characterizing (or landscaping) a wide-range of biological and chemical processes (e.g. drug screening, characterization of chemical purity, and resolution of mixtures).

In pharmaceutical drug screening low-affinity interactions in the range between 10 μ M and 100 μ M K_d are currently extremely difficult to measure. As conjugates of **1** and various different classes of ligands including carbohydrates and lipids become discernable, this method will become an increasingly powerful tool for both primary and secondary assays. As seen here, it is not the affinity but the “fingerprint” of molecular recognition which is vital in selecting compounds for cellular and in vivo testing and for establishing structure–activity relationships for follow up bioinformatics, molecular modeling, and/or rational drug design.

Experimental Section

Samples of carbohydrate–lectin mixtures were prepared by adding a DMSO stock solution (20.6 mM) of either **2** or **3** to the appropriate lectins (200 μ L, Sigma) in $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$ (18 mM), CaCl_2 (10 mM), MnCl_2 (10 mM), NaCl (1 mM), pH 7.2, such that the final carbohydrate and lectin

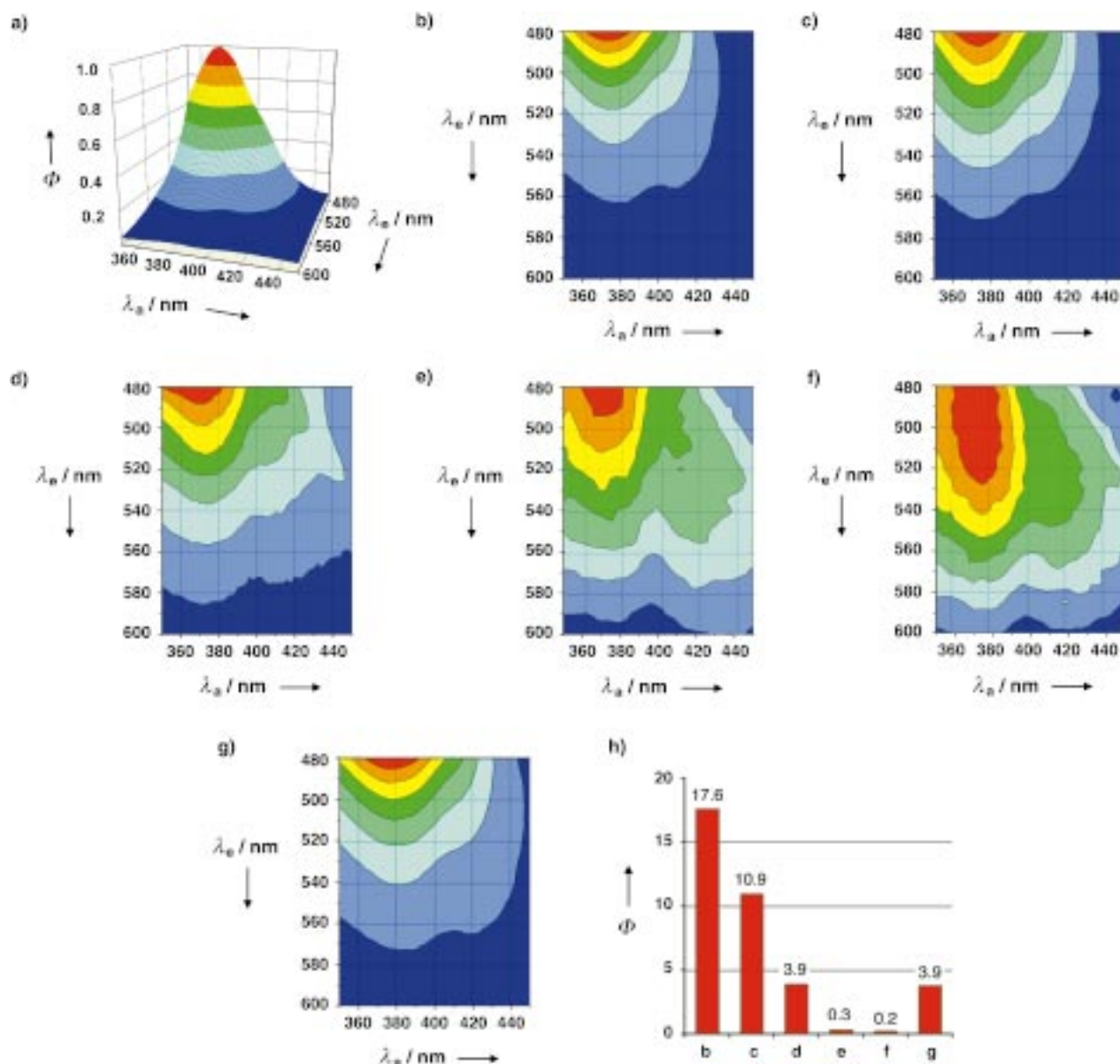


Figure 2. Fingerprint landscapes of the interactions between carbohydrate ligands **2** and **3** and lectins PSA, LCA, and GNL are given by plotting the fluorescent intensity (Φ) against excitation wavelength (λ_a) and emission wavelength (λ_e). [a] three-dimensional diagram, b) contour diagram.] The fluorescence intensity (Φ) is color-coded: 1.0–0.875 (red), 0.875–0.750 (orange), 0.750–0.625 (yellow), 0.625–0.500 (green), 0.500–0.375 (light green), 0.375–0.250 (aqua), 0.250–0.125 (blue) and 0.125–0 (purple); a) and b) 200 μM **2** with 300 μM PSA, c) 200 μM **2** with 300 μM LCA, d) 200 μM **2** with 300 μM GNL, e) 200 μM **3** with 300 μM LCA, f) 200 μM **3** with 300 μM GNL, g) 200 μM **2** with 65 μM PSA, h) (Φ) observed in (a)–(g) for $\lambda_a = 370$ nm and $\lambda_e = 480$ nm.

concentration was 200 and 300 μM , respectively. These solutions were filtered through a 0.2 μm syringe filter (Millipore) and then transferred to a quartz cuvette (160 μL).

Fluorescence measurements were made in photon-counting mode^[13] at 25 °C using magic-angle collection and emission and excitation bandwidths set to 8 nm. The fluorescence intensity for each measurement was standardized against a sample of 5-carboxytetramethylrhodamine. Topologies were collected in three dimensions by monitoring the fluorescence intensity with respect to variance of both excitation and emission wavelengths. Excitation was collected at 2 nm increments of λ_a from 350 to 450 nm with variance of the emission over 5 nm increments of λ_e from 480 to 600 nm. Topologies were then algorithmically corrected using two-pass trinomial smoothing, processed, and displayed graphically.^[16]

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- [12] Each lectin (GNL, LCA, and PSA) recognizes α -mannopyranosides with affinities ranging from 5–100 μ M. This includes carbohydrates fused to colorimetric or fluorescent probes through their anomeric center. Typically, the addition of these labels reduces the net affinity of the carbohydrate ligand by an order of magnitude. Based on this assumption, the stoichiometry of lectin to **2** would ensure that at least 80% of the carbohydrate ligand is bound to the lectin hosts.
- [13] Fluorescence measurements were collected on a SLM 8100C Fluorometer equipped with a JD-590 photomultiplier and a 450 W Xenon Arc lamp (SLM Instruments).
- [14] This difference arose from the structural attributes of these complexes and not from the association or aggregation kinetics of the given complexes. This was verified in that topologies identical to that shown in Figure 2 were also obtained after repeating the measurements after reducing the lectin concentration by 15%.
- [15] BSA does recognize either carbohydrate and therefore serves as a measure of nonspecific interactions. That the fluorescence response from **3** was from nonspecific interactions was further established by comparison with BSA; landscapes generated from addition of **3** either to LCA or BSA were strikingly similar. This result further supports that the fluorescence enhancement with **2** originates, in part, because of docking of the carbohydrate domain in or near the binding pocket of the lectin.
- [16] Smoothing was performed using the trinomial algorithm provided within the software package v1995 accompanying the SLM-8100 series 2 spectrometer. The raw data was then processed in Excel97 (Microsoft) and plotted using Origin 5 (Microcal).

Direct Observation of Surface-Controlled Self-Assembly of Coordination Cages by Using AFM as a Molecular Ruler**

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The development of nanotechnology requires miniaturizing complex systems as well as addressing problems at the molecular level.^[1] The challenge of overcoming the present limits in routine microfabrication technology in order to reach the nanometer scale requires new methodologies for assembling three-dimensional structures in a controlled fashion directly on solid supports.^[2]

In the last few years self-assembly has proven to be a viable alternative to covalent synthesis for the construction of many types of molecular architectures. The desired compounds are formed quantitatively by simply mixing the programmed components under thermodynamic control.^[3] Unlike covalent synthesis, self-assembly is a reversible process. This is a very attractive feature because it allows the system to self-repair possible structural deficiencies. Of the self-assembly protocols developed so far, metal-directed self-assembly is particularly appealing as a result of the large number of different structural motifs and bond energies that are available through coordination chemistry.^[3a] Until now, the self-assembly approach has mainly been limited to solution chemistry, with very few attempts made to use it directly on surfaces.^[4]

Molecular containers represent a very interesting class of compounds^[5] as a consequence of their ability to encapsulate ions and neutral molecules. These structures can in principle be addressed individually in a confined environment.^[6] Furthermore they are large enough to be detected by scanning force microscopy (SFM).^[7] We previously reported the self-assembly of cavitand-based coordination cages formed in solution^[8] and the immobilization of covalent container

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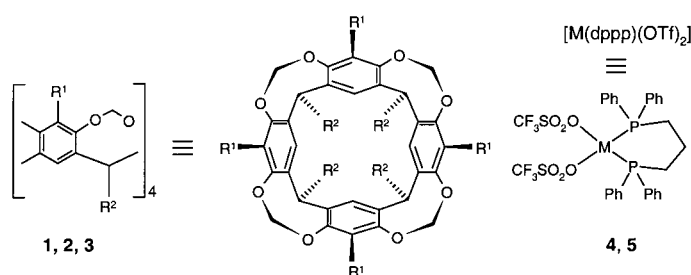
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

molecules on gold.^[9] Herein we show a straightforward way to generate coordination cages directly on surfaces by using self-assembled monolayers (SAMs) as molecular platforms. When combined with microcontact-printed (μ CP) surfaces this approach allows the direct measurement of the formation of such assemblies on gold without any assumption of parameters.

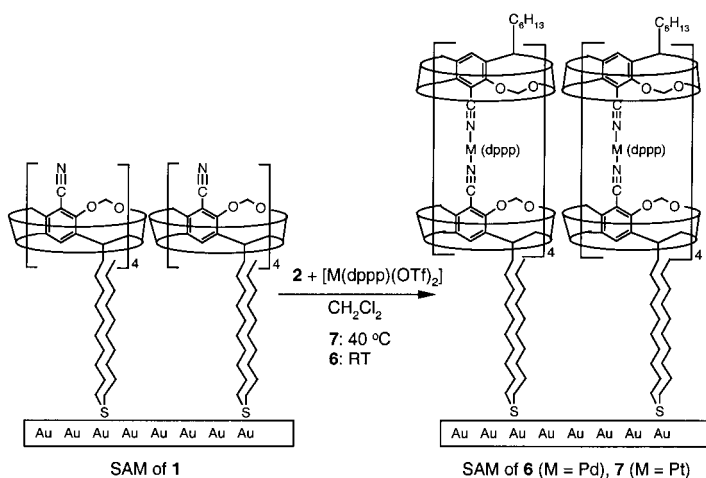
Monolayers of **1** were prepared by adsorption at 60 °C from a solution of EtOH/ CHCl_3 (3/1, $c = 0.1 \text{ mM}$) for at least 12 h.^[10] The layers obtained were used to perform the metal-induced capping reactions. Monolayers of cage **6** were assembled by soaking SAMs of **1** in a solution of **2** and **4** in CH_2Cl_2 . SAMs of **7** were prepared in the same way using compounds **2** and **5** (Scheme 1).



- 1: $\text{R}^1 = \text{CN}$ $\text{R}^2 = \text{C}_{11}\text{H}_{22}\text{-S-C}_{10}\text{H}_{21}$
 2: $\text{R}^1 = \text{CN}$ $\text{R}^2 = \text{C}_6\text{H}_{13}$
 3: $\text{R}^1 = \text{H}$ $\text{R}^2 = \text{C}_{11}\text{H}_{22}\text{-S-C}_{10}\text{H}_{21}$
 4: $\text{M} = \text{Pt}$
 5: $\text{M} = \text{Pd}$

Scheme 1. The molecular building blocks: Cavitands **1** and **2** form the upper and the lower halves of the cages, compounds **4** and **5** are the metal complexes which direct the assembly. dppp = 1,3-bis(diphenylphosphanyl)propane; Tf = F_3CSO_2 .

Solution experiments have shown that different R^2 substituents do not bias the outcome of the self-assembly toward the formation of a cage. Under the reported conditions, formation of homocages of **2** occurs in solution, while cages of **6** or **7** form on the surface of the SAM (Scheme 2).



Scheme 2. Representation of the self-assembly reaction that leads to the formation of cages on a SAM.

The formation of cages **6** and **7** on SAMs of **1** was proven by contact-angle measurements, electrochemistry, X-ray photoelectron spectroscopy (XPS), and atomic force microscopy (AFM). The slight variations in the values of the contact angles observed for SAMs of **1**, **6**, and **7**, respectively, indicate that the order of the SAMs after assembly of the cages is maintained (Table 1), which is in accord with previous results

Table 1. Results obtained from electrochemical and contact-angle measurements.

SAM	$Q_{\text{ml}}^{\text{[a]}}$ [$\mu\text{F cm}^{-2}$]	$R_{\text{ml}}^{\text{[b]}}$ [$10^3 \Omega$]	$i_{\text{HET}}^{\text{[c]}}$ [μA]	$\Theta_{\text{adv}}^{\text{[d]}}$ [$^\circ$]	$\Theta_{\text{rec}}^{\text{[d]}}$ [$^\circ$]
1	2.3 ± 0.3	348	0.20 ± 0.05	89 ± 2	50 ± 2
3	2.5 ± 0.3	180	0.50 ± 0.05	105 ± 2	81 ± 2
6	2.0 ± 0.2	634	0.13 ± 0.03	95 ± 2	42 ± 2
7	1.9 ± 0.2	532	0.10 ± 0.03	88 ± 2	53 ± 2

[a] Capacitance of the monolayer measured by cyclic voltammetry (CV) in the absence of a redox couple. [b] Resistance of the monolayer measured by electrochemical impedance spectroscopy (EIS). [c] Heterogeneous electron transfer (HET) measured in the presence of a redox couple. [d] Contact angles (advancing (adv) and receding (rec)) of a water droplet on the monolayer surface.

from similar monolayers.^[9] The value of the capacitance Q_{ml} (ml = monolayer), as measured by cyclic voltammetry (CV),^[11] of about $2.3 \mu\text{F cm}^{-2}$ for monolayers of adsorbate **1** is almost the same as that of well-packed monolayers of equal thickness, such as SAMs of cavitands ($1.5\text{--}2.5 \mu\text{F cm}^{-2}$).^[10a]

The respective values of the capacitance decrease after the metal-induced assembly of the cages (Table 1), which indicates there is an increase of the effective thickness (d_{ml})^[12] of the SAMs, and is consistent with cage formation on the surface. Heterogeneous electron transfer (HET)^[13] and electrochemical impedance spectroscopy (EIS)^[14] show a decrease in the intensity of the current and an increase of the resistance in SAMs of **6** and **7**. These data, which are in agreement with the previous results, are consistent with the results found by CV.^[15c] In agreement with the electrochemistry results, XPS measurements on SAMs of **6** and **7** reveal the presence of all the elements expected from the molecular structure (Table 2).^[15]

A series of control experiments were performed to prove that self-assembly of the cages occurs on the surface of the SAMs through metal coordination. The cage capping on the

Table 2. Results from the XPS elemental analysis.

Peak	SAM of 1		SAM of 6		SAM of 7	
	Measured [%]	Calcd [%]	Measured [%]	Calcd [%]	Measured [%]	Calcd [%]
C-1s	84.4	87.9	74.4	75.2	74.1	75.2
O-1s	11.0	6.1	13.9	10.3	14.4	10.3
N-1s	3.1	3.0	2.6	2.1	2.8	2.1
S-2p	2.3	3.0	4.6	3.1	3.4	3.1
Pd-3d	–	–	n.o. ^[a]	1.0	–	–
Pt-4f	–	–	–	–	0.5	1.0
P-2p	–	–	2.6	2.1	2.4	2.1
F-1s	–	–	5.1	6.1	4.5	6.1

[a] Values of Pd for cage **6** could not be obtained (n.o.) because of the overlapping proximity of the much more intense Au signal of the substrate.

SAM of cavitand **3** left the monolayer unchanged, as proven by electrochemistry measurements; this occurs since **3** cannot coordinate metals because it lacks nitrile functionalities. A second control experiment consisted of the treatment of the SAM of **6** with triethylamine, which is able to shift the equilibrium towards the formation of $[M(dppp)-(NEt_3)_2](OTf)_2$ plus cavitand **1**.^[8] The complete disassembly of the cages on the SAM was monitored by electrochemistry, and the results were in full agreement with the expectations (Table 3).

Table 3. Electrochemical analyses of control experiments.^[a]

SAM	Q_{ml} [$\mu F cm^{-2}$]	i_{HET} [μA]	R_{ml} [$10^3 \Omega$]
3	2.5 ± 0.20	0.50 ± 0.05	180
3 +metal complex	2.8 ± 0.20	0.53 ± 0.05	150
6	2.1 ± 0.20	0.08 ± 0.02	650
6 +Et ₃ N	2.3 ± 0.20	0.17 ± 0.02	350

[a] See the footnotes in Table 1 for an explanation of the represented quantities.

The formation of the molecular cages was monitored directly by atomic force microscopy (AFM). For this purpose microcontact-printed templates were created using standard soft lithography methods.^[16] These templates showed the presence of very regular features over large areas (Figure 1). By means of wet-etching,^[16] grooves exposing bare gold were formed with an arbitrary depth (6.9 nm).^[17] In this way we obtained a sample in which stripes with a lower height correspond to areas of bare gold, and stripes with a higher topographic profile which are covered by the SAM of 11-sulfanylundecanol.^[18] After deposition of a monolayer of cavitand **1** on the bare gold grooves, AFM was used to directly measure changes in the depth of the modified grooves (4.3 nm). The height difference of 2.6 nm (Figure 1 A and B) is consistent with the formation of a monolayer of **1**. Formation of the molecular cages on the printed layers was performed using the same procedure as for the full mono-

layers. A total difference of 4.2 nm was measured after assembly of the cages (Figure 1 C), a value which is consistent with the calculated dimensions of the assembly. The self-assembly of the cages was monitored by comparing the relative height differences.

The attractiveness of this very simple method is the possibility to track changes at a nanometer level directly.^[19] Unlike other techniques that measure thickness (for example, ellipsometry, electrochemistry), AFM does not make use of parameters (for example, dielectric constant, refractive index of the SAM) that are approximations because of the difficulty of measuring them. The presence of an internal fixed height reference—namely, the grooves in the microcontact-printed substrates—allows statistical analysis to be performed on thickness variations of the adsorbed organic layer. All heights recorded by AFM were plotted against the *z*-axis and showed that the measured heights follow a Gaussian distribution, thus allowing an estimation of the statistical error.^[20] In this way AFM can be used as a “molecular ruler” to measure the thickness of monolayers.^[21]

The insertion of sulfides into SAMs of thiols has been recently investigated in our group.^[22] We prepared a SAM where single cavitands could be detected far apart from each other by AFM to study the formation of the coordination cages individually. Insertion of cavitand **1** into a monolayer of sulfanylundecanol was achieved by soaking SAMs of thiol into a 0.1 mM solution of **1** in ethanol for one hour. Under these experimental conditions an average of 20–25 molecules per μm^2 were inserted into the SAM.^[23] Extensive washing with large amounts of solvents ensured the removal of all physisorbed material. AFM experiments and profile analysis showed the presence of individual round entities which were protruding from the flat monolayer.^[24] A height profile analysis revealed that these entities all had the expected size of approximately 2 nm.^[25] The formation of the cages **6** and **7** by the addition of **2** and **4** or **5**, respectively, was performed on these samples as described above for the full monolayers. AFM analysis on the new samples revealed the presence of two different types of features: 1) individual dots with heights

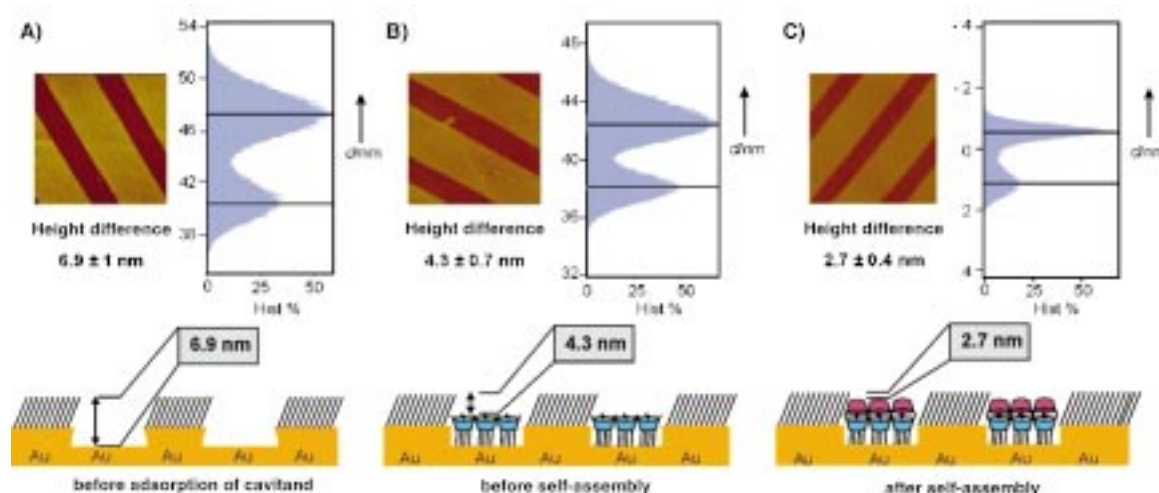


Figure 1. Self-assembly of coordination cages on μ -CP-modified substrates. The grooves on the substrates were obtained by first printing and subsequently wet-etching procedures. The AFM picture, the corresponding histogram, and a schematic representation of the surface is shown for each.

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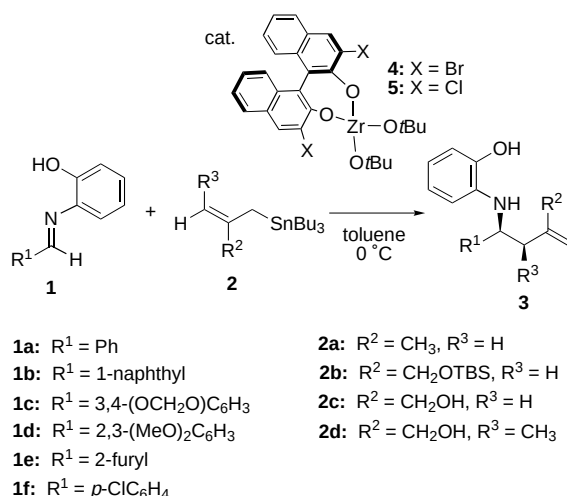
Highly Enantioselective Allylation of Imines with a Chiral Zirconium Catalyst**

Thomas Gastner, Haruro Ishitani, Ryo Akiyama, and Shū Kobayashi*

Over the past several years, powerful asymmetric catalytic variants for many basic synthetic reactions have been developed,^[1] and in this large and fast-expanding area of chemistry, several chiral Lewis acids have been successfully used as catalysts.^[2] Although highly effective methods that follow this approach for the catalytic asymmetric alkylation of carbonyl compounds have been reported,^[3] only very few examples are known for their aza analogues.^[4] In the case of imines, the Lewis acids are often deactivated or decomposed by the nitrogen atoms of the starting materials or products, and therefore, catalytic reactions are difficult to perform.

The synthesis of chiral homoallylic amines is of particular interest since they can be used as versatile synthetic intermediates and can be easily converted into many different functional groups.^[5] The first catalytic asymmetric allylation of imines was reported in 1998 by Yamamoto and co-workers using allyltributylstannane in the presence of a chiral π -allylpalladium complex.^[6] In 1999, Jørgensen and co-workers reported the catalytic asymmetric allylation of α -imino esters.^[7] In recent reports, we have demonstrated the extraordinary potential of zirconium(IV) as a metal center for the design of chiral Lewis acid catalysts that are suitable for the activation of bidentate imino compounds in an efficient way.^[8]

In this paper, the viability of this approach is illustrated by the allylation of imines **1** with allylstannanes **2** to afford the corresponding homoallylic amines **3** in good yields and with high stereoselectivities (Scheme 1).



Scheme 1. Catalytic asymmetric allylation of imines. TBS = *tert*-butyldimethylsilyl.

We first screened different BINOL derivatives and additives, and found that preparation of the catalyst in situ from Zr(O*t*Bu)₄ and an equimolar amount of (*R*)-3,3'-dibromo-1,1'-bi-2-naphthol ((*R*)-3,3'-Br₂BINOL) or (*R*)-3,3'-dichloro-1,1'-bi-2-naphthol ((*R*)-3,3'-Cl₂BINOL) in toluene gave the best results.^[9] Conversion of imine **1a** was carried out with stannanes **2a–c** (Table 1). The use of **2a** and **2b** resulted in

Table 1. Enantioselective allylation of imines with allylstannanes **2a–c**^[a].

Entry	Imine	Stannane	Yield [%]	ee [%]
1	1a	2a	74	55
2	1a	2b	74	54
3	1a	2c	86	83
4	1b	2c	91	68

[a] 10 mol % of catalyst **4** was used.

modest enantioselectivities,^[10] and reaction times up to 30 hours were required. A remarkable acceleration of the reaction rate and improved enantioselectivities were observed with stannane **2c** in which the alcohol functionality is unprotected.^[10] The reaction was completed within 2 hours, and an 86 % yield and an enantiomeric excess of 83 % were obtained. In an attempt to extend the scope of this reaction, allylstannane **2d**, with a methyl substituent at the C-3 position, has also been studied.^[11] As can be seen from Table 2, improved enantioselectivities and excellent *syn/anti* ratios were obtained. The absolute configuration of **3cd** (R¹ = 3,4-(OCH₂O)C₆H₃, R² = CH₂OH, R³ = CH₃) was determined to be 3*R*,4*S* by X-ray crystal structure analysis.^[12] Interestingly, nearly identical yields and asymmetric inductions were observed with catalysts **4** and **5**. However, catalyst **5**

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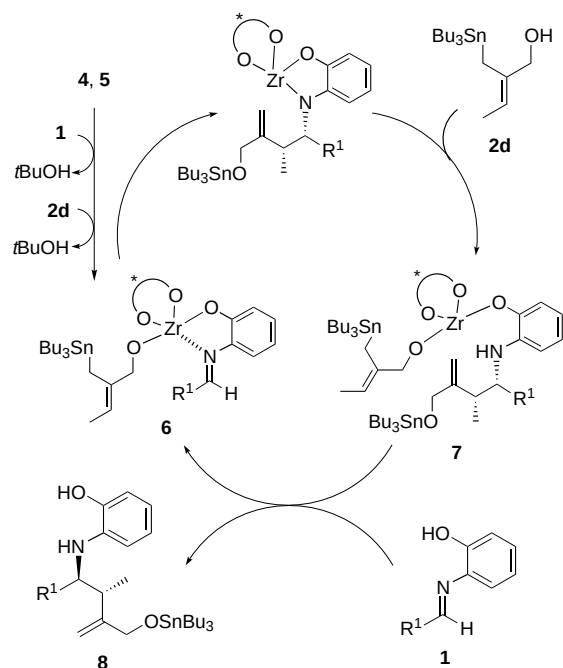
Table 2. Enantioselective allylation of imines with allylstannane **2d**.

Entry	Catalyst ^[a]	Imine	Yield [%] ^[b]	ee [%]
1	4	1a	84	93
2	4	1b	81	95
3	4	1c	72	91
4	4	1d	71	94
5	5	1e	76	92
6	4	1f	78	87

[a] 10 mol % of catalyst was used. [b] The *syn:anti* ratio was determined by NMR spectroscopic analysis to be >95:5 in all cases.

showed a beneficial effect on the yield in the reaction of **1e** (Table 2, entry 5).^[13]

The proposed catalytic cycle of this asymmetric reaction is shown in Scheme 2. The active catalyst is generated by the bonding of the alcohol functionalities of imine **1** and



Scheme 2. Proposed catalytic cycle. The asterisk represents the position of the BINOL derivative.

allylstannane **2d** to the zirconium center.^[14] In an intramolecular reaction, the allylstannane attacks the carbon–nitrogen double bond in an ene-like fashion, which leads to intermediate **7**.^[15] The product **8** is released from the zirconium center and the intermediate **6** is regenerated by bonding of **1** to the zirconium.

In addition, excellent results for the reaction of allylstannane **2c** were observed when the catalyst **4** or **5** was prepared in THF with addition of two equivalents of methanol as an additive (Table 3). After preparation of the catalyst, the THF was evaporated and the reaction was performed in toluene as described.^[16] This modified catalyst system resulted in significantly improved enantioselectivities. While the 83 % ee value in the reaction of **1a** with **2c** was improved to 96 % ee (Table 1, entry 3, and Table 3, entry 1), the 67 % ee value in

Table 3. Enantioselective allylation of imines with allylstannane **2c** with the use of a novel Zr catalyst prepared with methanol as an additive.

Entry	Catalyst ^[a]	Imine	Yield [%]	ee [%]
1	4	1a	77	96
2	5	1b	85	97
3	4	1c	84	99
4	4	1d	80	87
5	4	1e	68	96

[a] 10 mol % of catalyst was used.

the reaction of **1b** with **2c** with catalyst **5** was further improved to 97 % ee when the new catalyst system was used. Furthermore, a 99 % ee for the *syn* adduct (*syn:anti* > 95:5) was obtained in the reaction of **1a** with **2d**. Although NMR studies gave almost no valuable information on the structure of the new catalyst, it was revealed from control experiments that the use of water instead of methanol was also effective, and that even one equivalent of the additive was sufficient to get comparable results. We assume at this stage that the effect of the additive is to deoligomerize the less selective oligomeric catalyst structures; this would result in the formation of the desired active monomeric catalyst species.^[17]

In summary, we have developed a very efficient procedure to synthesize substituted homoallylic amines from imines in an asymmetric catalytic manner. High yields and high levels of diastereo- and enantioselectivity were obtained for all substrates. The expansion of this basic concept, which provides a convenient entry into various chiral building blocks, and further mechanistic studies to clarify the exact structure of the catalyst and the mechanism of the reaction are currently in progress.

Experimental Section

Representative experimental procedure for the reaction of imines **1** and allylstannanes **2**: (*R*)-3,3'-Br₂BINOL (0.13 mmol) was added to a solution of Zr(O*t*Bu)₄ (0.13 mmol) in toluene (5.0 mL). The solution was stirred for 1 h at room temperature and then cooled to 0 °C. Compounds **1a** (1.3 mmol) and **2d** (1.3 mmol) were successively added in toluene (2.5 mL each). The mixture was stirred for 12 h, quenched with a saturated aqueous solution of NaHCO₃, and extracted with diethyl ether. After a standard workup, the crude product was purified by column chromatography on silica gel to give the desired adduct. The diastereomer ratio was determined by NMR spectroscopic analysis, and the optical purity was determined by HPLC analysis with a chiral column.^[16]

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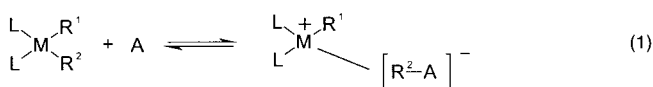
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- [13] For the effect of the hydroxyamino moiety of imines and for deprotection of this moiety of the product to form the free amino group, see ref. [8a].
- [14] In NMR spectroscopic experiments, we were able to show that an allyl alcohol, as a model compound, was bonded to the zirconium center of the catalyst. From this observation, it is assumed that bonding of allylstannane **2c** to the zirconium leads to a better-organized transition state and, therefore, to higher enantioselectivities and even accelerated reaction rates. When equimolar amounts of **4** and **2d** were mixed and imine **1a** was then added after 1 h, no formation of the product was observed. An allyltransfer from tin to zirconium is likely to be the reason for this observation (A. L. Costa, M. G. Piazza, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Am. Chem. Soc.* **1993**, *115*, 7001–7002). Also from the product formed when **2d** is the substrate, we can rule out the idea that an allyltransfer from zirconium to imine is the actual reaction pathway.
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Noncoordinating Dendrimer Polyanions: Cocatalysts for the Metallocene-Catalyzed Olefin Polymerization

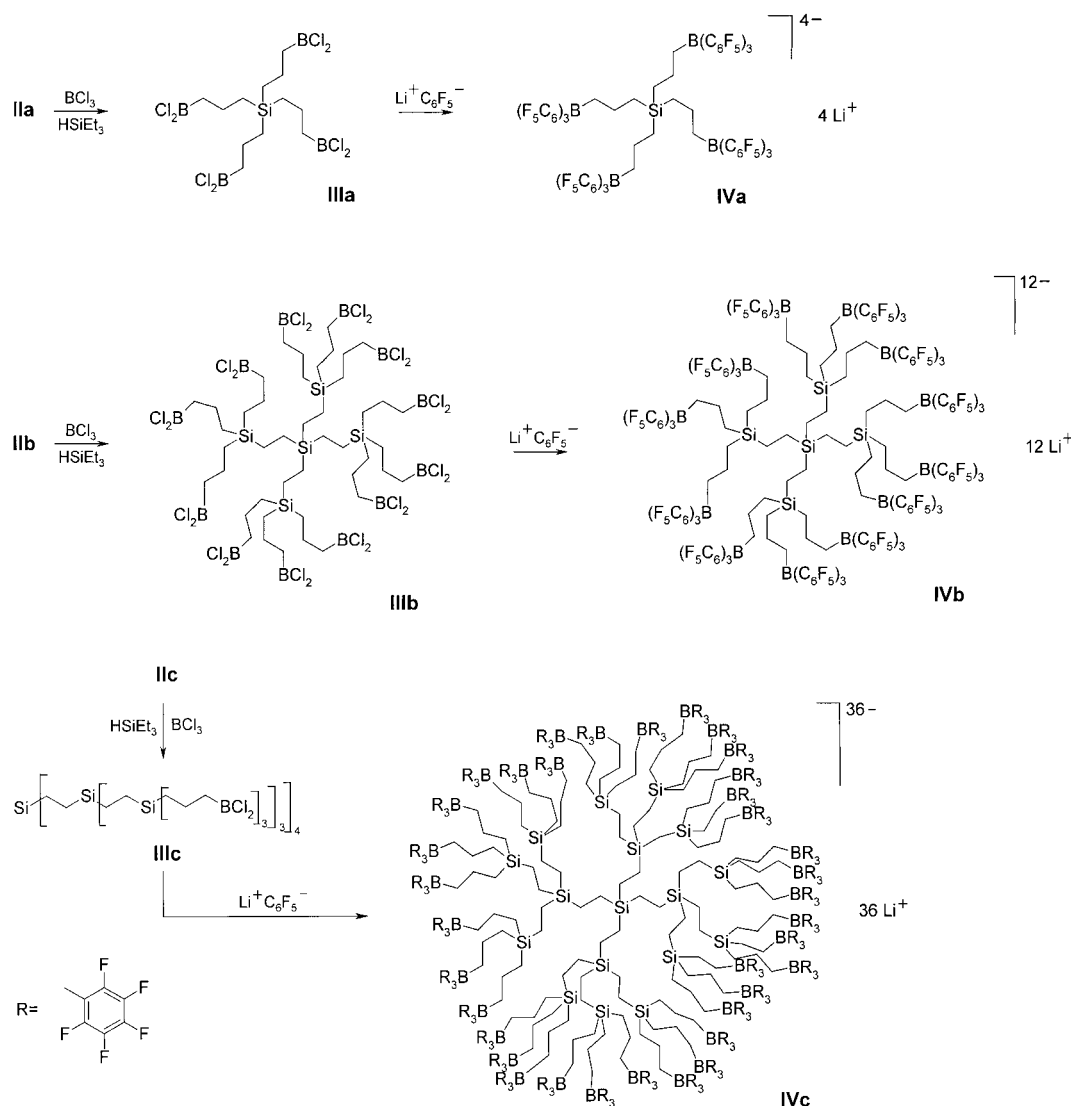
Michael Mager,* Sigurd Becke, Heike Windisch, and Uwe Denninger

The metallocene-catalyzed polymerization of nonpolar monomers (in particular α olefins) allows the production of polymers with new architectures and properties.^[1] In addition, because of their high activity, metallocene catalyst systems are used in very small amounts and can be left in the product, simplifying the polymer work up. During the polymerization the activated metallocene complex is present as a cation $[L_2MR^1]^+$ that is stabilized by an noncoordinating anion $[R^2A]^-$.^[2, 3] This contact ion pair can be formed by treating a neutral metallocene with an activating cocatalyst that can abstract a ligand from the metallocene [Eq. (1)]. To date the

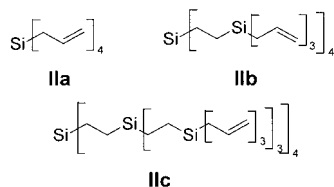


most important industrial examples of such cocatalysts have been methylaluminoxane (MAO),^[4, 5] a condensation product prepared from $AlMe_3$ and water, which has a complex structure, and the perfluorophenylborane $B(C_6F_5)_3$.^[3g, 6, 7] The interaction within the ion pair $[L_2MR^1]^+[R^2A]^-$ for a given ligand system L has an important influence on the catalytic properties such as activity, life time of the active species, chain-termination and chain-transfer reactions, and regio- and stereoregularity.^[3wx, 8] Thus there is increased interest in the synthesis of new, noncoordinating anions that are less nucleophilic; this can be achieved by the extensive delocalization of the negative charge^[9] or steric shielding^[3x, 10]. Tris(perfluorobiphenyl)alkylborates,^[11] (perfluoroaryl)fluoroaluminates,^[12] and triorganosilyl-substituted tetrakis(perfluorophenyl)borates^[13] are examples of anions which, in addition to a delocalization of the charge, are sterically more demanding than $[R^2B(C_6F_5)_3]^-$. We wished to study the polymerization properties of metallocene–cation–anion pairs in which the anion is extremely sterically demanding; dendrimers, defined, highly branched, and highly functionalized, space-filling molecules have not been used in this context before.^[14] Carbosilane dendrimers appeared to be particularly suitable in that the Si–C bond is basically chemically inert and thus side reactions (such as degradation of the dendrimer) during synthesis or the polymerization are unlikely.^[15] The new polyanionic carbosilanes **IVa–c** are the first noncoordinating polyanions to be based on dendrimers. The construction of the Si–C framework was by means of alternating hydrosilation and Grignard reactions starting from tetravinylsilane, followed by hydroboration of the resulting allylsilyl dendrimer

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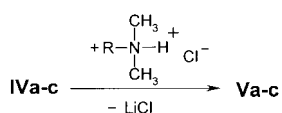

 Scheme 1. The synthesis of the polyanionic carbosilane dendrimers **IVa–c**.

with dichloroborane and arylation with pentafluorophenyllithium (Scheme 1). The divergent synthesis of the carbosilane skeleton has been described many times before and gives the allylsilane dendrimers **IIa–c** (Scheme 2) in high yield.^[15] By


 Scheme 2. The carbosilane dendrimers **IIa–c** with 4, 12, and 36 allyl groups, respectively.

hydroboration with HBCl_2 , prepared in situ from BCl_3 and HSiEt_3 , at -60°C ^[16] the polyalkyldichloroboranes **IIIa–c** are produced as colorless oils or waxes (Scheme 1). These products hydrolyze rapidly in air. The hydroboration is quantitative and regioselective (because of the influence of the silicon atom the hydroboration of the corresponding

vinylsilyl dendrimers is no longer regioselective and a large amount of the α -addition product $\text{SiCH}(\text{BCl}_2)\text{CH}_3$ is formed). In the $^{11}\text{B}\{^1\text{H}\}$ NMR spectrum resonance signals corresponding to **IIIa–c** are found at $\delta = 63.1$, 63.1 , and 62.2 , respectively, which corresponds well to the expected value ($\text{C}_3\text{H}_7\text{BCl}_2$, $\delta = 62.3$ ^[17]). Through the reaction of **IIIa–c** with pentafluorophenyllithium, the lithium salts of the anionic polyborates **IVa–c** are formed (Scheme 1). For this reaction a suspension of pentafluorophenyllithium is prepared in situ by transmetalation of bromopentafluorobenzene with $n\text{BuLi}$ at -70°C ^[18] and the polyalkyldichloroborane **III** was then added at a temperature below -65°C (exothermic reaction). At higher temperature the pentafluorophenyllithium formed can decompose. The lithium salts **IVa–c** are only sparingly soluble in standard solvents. Treatment of the lithium salts with N,N -dimethylaniliniumhydrochloride (**IVa, b**) or N,N -dimethylundecylammoniumchloride (**IVc**) affords the soluble ammonium salts **Va–c** (Scheme 3), which can be isolated from the reaction mixture by extraction with CH_2Cl_2 and characterized by NMR spectroscopy. In the $^{11}\text{B}\{^1\text{H}\}$ NMR



IVa,b, Va,b: R=C₆H₅
IVc, Vc: R=C₁₁H₂₃

Scheme 3. Reactions of IVa, b with *N,N*-dimethylaniliniumhydrochloride and of IVc with *N,N*-dimethylundecylammoniumchloride to give Va, b, and Vc, respectively.

The structure of the polyborates Va–c is further confirmed by ¹⁹F{¹H} NMR spectroscopy: these spectra show resonance signals for the aromatic *o*-, *m*-, and *p* fluorine atoms in the expected region and in the ratio of 2:2:1 (Table 1).

Table 1. ¹¹B{¹H} and ¹⁹F{¹H} NMR spectroscopic data for Va–c.

Compound	δ(¹¹ B{ ¹ H}) ^[a]	δ(¹⁹ F{ ¹ H}) ^[b]
Va	–13.4 (s)	–133.0 –165.4 –168.4
Vb	–13.2 (s)	–132.5 –165.4 –168.2
Vc	–13.9 (s)	–127.5 –160.6 –163.0
[C ₆ H ₅ N(CH ₃) ₂ H] ⁺ [B(C ₆ F ₅) ₄] ⁻ [c]	–16.3 (s)	
Li ⁺ [B(C ₆ F ₅) ₄] ⁻ [d]		–131.6 –164.2 –167.9
B(C ₆ F ₅) ₃ [d]		–128.7 –144.3 –160.6

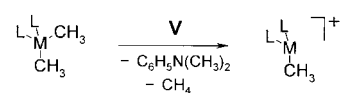
[a] Measurements in CD₂Cl₂; external standard BF₃OEt₂. [b] Measurement of Va and Vb in CD₂Cl₂, Vc in CDCl₃; results for Li⁺[B(C₆F₅)₄]⁻ in Et₂O and for B(C₆F₅)₃ in pentane from ref. [27]; external standard CFCl₃. [c] For preparation see ref. [26]. [d] For preparation see ref. [18].

The stable ammonium salts Va–c were prepared for the first time and tested in catalysis. Va and Vb are among the most active cocatalysts of the type [RB(C₆F₅)₃]⁻ (R = alkyl), described so far.^[6, 9b] The dimethylzirconocenes bis(indenyl)-dimethylzirconium (Ia), bis(cyclopentadienyl)dimethylzirconium (Ib), and *rac*-ethylenebis(1-indenyl)dimethylzirconium (Id) react with Va–c by abstracting a methyl group thus generating catalytically active metallocene cations (Scheme 4). These reactions do not lead to degradation of the polyborates and thus no deactivation of the catalyst is observed.^[3d, 19, 20] The metallocene dichloride *rac*-dimethylsilylbis(1-indenyl)dichlorozirconium (Ic) and *rac*-ethylenebis(4,5,6,7-tetrahydro-1-indenyl)dichlorozirconium (Ie) were

Table 2. Polymerization of ethene (E), propene (P), ethene/propene (E/P) and ethene/1-hexene (E/H) with Ia–e and Va–c.

Entry	Metallocene/cocatalyst	Monomer	Metallocene [μmol]	Zr:B	<i>t</i> [min]	<i>T</i> [°C]	<i>p</i> [bar]	Yield [g]	Activity ^[a] [g mol ⁻¹ h ⁻¹]
1	[(Ind) ₂ ZrMe ₂] Ia/Va	E	5.0	1:1	15	40	1.1	2.0	1.6 × 10 ⁶
2	[(Ind) ₂ ZrMe ₂] Ia/Vb ^[b]	E	5.0	5:6	15	40	1.1	2.1	1.7 × 10 ⁶
3	[(Ind) ₂ ZrMe ₂] Ia/Vc	E	10.0	1:2	10	40	1.1	1.6	9.6 × 10 ⁵
4	[Cp ₂ ZrMe ₂] Ib/Va	E	1.0	1:2	20	60	6.0	36.6	1.1 × 10 ⁸
5	[Me ₂ Si(Ind) ₂ ZrCl ₂] Ic ^[c] /Va	P	5.0	1:2	30	40	1.1	4.4 ^[d]	1.8 × 10 ⁶ [e]
6	[Et(Ind) ₂ ZrMe ₂] Id/Va	E/H	1.0	1:2	30	20	1.1	5.4	1.1 × 10 ⁷
7	[Et(H ₄ -Ind) ₂ ZrCl ₂] Ie ^[d] /Vb	E/P	1.0	1:3	40	40	4.0	70.1	1.1 × 10 ⁸ [e]

[a] Activity = mass(polymer) [g] × 6 × 10⁷ mol (metallocene) [μmol⁻¹] × time [min⁻¹]; solvent: toluene. [b] Standard solution in CH₂Cl₂. [c] Ic was alkylated in situ with [Al(C₂H₅)₃] (Zr:Al = 1:2) then activated with Va. [d] Isotactic polypropylene with 92.9% isotacticity (NMR). [e] Solvent: *n*-hexane. [f] Ie was alkylated in situ with triisobutylaluminum (Zr:Al = 1:360) and then activated with Vb.



Scheme 4. Activation of metallocenes with Va–c.

alkylated in situ with aluminumalkyl compounds then activated with Va or Vb. To investigate the cocatalytic properties of the polyborates Va–c ethene, propene, as well as ethene/propene and ethene/1-hexene mixtures were polymerized in the presence of the metallocenes Ia–e (Table 2). Al*i*Bu₃ was added as a scavenger to remove disruptive impurities (e.g., traces of water). All the catalyst systems tested showed high activity that could be increased significantly further by increasing the (ethene) pressure from 1.1 bar to 4 or 6 bar.^[3x, 9a, 10] Although polymerization experiments with cationic metallocenes are usually carried out in toluene,^[3g–x] this solvent is in fact unsuitable for industrial polymerizations.^[21] With Va and Vb however, high polymerization activities are achieved in aliphatic solvents such as *n*-hexane. A further advantage of the new catalysts based on dendrimer anions is their high stability during the polymerization.^[22] In the copolymerization of ethene and propene no decrease in activity was observed after 40 mins. The new polyborates could prove to be particularly interesting if employed for bulk and gas-phase polymerization.^[23] The dendrimers described here are the first examples of effective polyanionic cocatalysts for the metallocene-catalyzed polymerization of olefins.

Experimental Section

All procedures were carried out under argon or in vacuum, the solvents were dried by standard methods and distilled under argon before use. Tetraallylsilane IIa was prepared from SiCl₄ and allylmagnesiumchloride.^[24] Si[(CH₂)₂SiCl₃]₄ from the hydrosilylation of tetravinyldisilane with HSiCl₃ and Si[(CH₂)₂Si[(CH₂)₂SiCl₃]₃]₄ followed by further treatment with vinylmagnesiumbromide and HSiCl₃.^[25] The preparation of carbosilane dendrimers with allyl end groups is known.^[24] and Si[(CH₂)₂Si(C₃H₅)₃]₄ (IIb) and Si[(CH₂)₂Si[(CH₂)₂Si(C₃H₅)₃]₃]₄ (IIc) were obtained by the corresponding reaction with allylmagnesiumchloride.

IIa: At –65 °C BCl₃ (23.5 g, 0.2 mol) was condensed into a flask with a gas inlet, reflux condenser, and internal thermometer, and a mixture of HSiEt₃ (23.3 g, 0.2 mol) and IIa (9.6 g, 0.05 mol) was slowly added dropwise. After the end of the addition the reaction mixture was warmed to room temperature and the volatiles (mainly ClSiEt₃) were removed under vacuum, first at room temperature and then at a bath temperature of 40 °C. The product was obtained as a colorless runny oil. ¹H NMR (CDCl₃): δ = 0.5 (m, 2H, SiCH₂), 1.6 (m, 4H, (CH₂)₂BCl₂); ¹³C{¹H} NMR (CDCl₃): δ =

15.4 (SiCH₃), 20.0 (SiCH₂CH₂), 34.2 (Cl₂BCH₂); ¹B{¹H} NMR (CDCl₃): δ = 63.1.

Va: *n*BuLi (6.35 mL, 10.1 mmol; 1.6 M in hexane) was added dropwise over 20 min to a solution of C₆F₅Br (2.5 g, 10.1 mmol) in hexane (60 mL) at –70 °C. The resulting suspension was stirred for 2 h at –70 °C. Then a solution of **IIIa** (445 mg, 0.85 mmol) in hexane (5 mL) was added dropwise over 5 min, and the reaction mixture was warmed to room temperature over 3 h and stirred over night. A solution of [C₆H₅N(CH₃)₂H]⁺Cl[–] (536 mg, 3.4 mmol) in CH₂Cl₂ (20 mL) was then added and the mixture stirred over night. After removal of the volatiles in vacuum the residue was extracted with CH₂Cl₂ (40 mL), filtered through kieselguhr, and the colorless filtrate evaporated to dryness under vacuum. After washing with hexane (2x20 mL) the product was obtained as a colorless wax. ¹B{¹H} NMR (CD₂Cl₂): δ = –13.4; ¹⁹F{¹H} NMR δ = –133.0 (m, 2F, *o*-F), –165.4 (m, 1F, *p*-F), –168.4 (m, 2F, *m*-F).

IIIb: As described for **IIIa** a mixture of HSiEt₃ (23.3 g, 0.2 mol) and **IIb** (12.4 g, 166 mmol) was slowly added dropwise to BCl₃ (23.5 g, 0.2 mol) at –65 °C. After the addition was complete the mixture was warmed to room temperature and stirred over night. Following work up as for **IIIa** the product was isolated as a colorless oil that partially crystallized on the walls of the flask. ¹H NMR (CD₂Cl₂): δ = 0.4 (m, 4H, Si-C^aH₂-C^bH₂-Si), 0.5 (m, 6H, Si-C^aH₂), 1.6 (m, 12H, C^aH₂-C^bH₂-BCl₂); ¹³C{¹H} NMR (CD₂Cl₂): δ = 3.3 (Si-C^aH₂), 4.8 (Si-C^bH₂), 15.1 (Si-C^aH₂), 20.1 (Si-C^bH₂), 34.4 (br. s, Cl₂B-C^bH₂); ¹¹B{¹H} NMR (CD₂Cl₂): δ = 63.1.

Vb: *n*BuLi (6.35 mL, 10.1 mmol; 1.6 M in hexane) was added dropwise within 20 min to a solution of C₆F₅Br (2.5 g, 10.1 mmol) in hexane (60 mL) at –70 °C. The resulting suspension was stirred at –70 °C for 2 h. Then a solution of **IIIb** (487 mg, 0.28 mmol) in hexane (5 mL) was added dropwise over 5 min, the reaction mixture was then slowly warmed to room temperature over 3 h and stirred over night. Following the addition of [C₆H₅N(CH₃)₂H]⁺Cl[–] (536 mg, 3.4 mmol) in CH₂Cl₂ (20 mL), the solution was stirred over night, and the volatiles were removed in vacuum. After the addition of CH₂Cl₂ (40 mL), the solution was filtered through kieselguhr and the colorless filtrate evaporated to dryness under vacuum. After washing with hexane (2x20 mL) the product was obtained as a colorless wax. ¹B{¹H} NMR (CD₂Cl₂): δ = –13.2; ¹⁹F{¹H} NMR: δ = –132.7 (m, 2F, *o*-F), –165.4 (m, 1F, *p*-F), –168.2 (m, 2F, *m*-F).

IIIc: As described for **IIIa** a mixture of HSiEt₃ (16 mL, 11.6 g; 100.2 mmol) and **IIc** (6.1 g, 2.5 mmol) was added dropwise to BCl₃ (8.5 mL, 11.5 g; 97.7 mmol) at –70 °C so that the temperature never rose above –60 °C. After the addition (ca. 1.5 h) the reaction mixture was stirred at –70 °C for a further 30 min then warmed to room temperature and stirred for a further 15 h. To remove a small amount of pyrophoric, highly volatile components the mixture was purged with argon (bubbler with dilute NaOH) for 2 h. Finally the remaining volatiles were removed under vacuum while the reaction mixture was slowly warmed to 40 °C. The product was obtained as a colorless wax. ¹B{¹H} NMR (CDCl₃): δ = 62.2.

Vc: *n*BuLi (12.7 mL, 1.6 M in hexane; 20.2 mmol) was added dropwise to a stirred solution of C₆F₅Br (5.0 g, 20.2 mmol) in hexane (120 mL) at –70 °C. The reaction mixture was stirred for a further 2 h at this temperature. **IIIc** (1.0 g, 0.2 mmol) in toluene (10 mL) was added dropwise, the reaction mixture was warmed to room temperature over 3 h, and was then stirred for a further 60 h. After the addition of *N,N*-dimethylundecylammonium-chloride (1.6 g, 6.7 mmol) in CH₂Cl₂ (40 mL) and stirring for 20 h at room temperature the volatiles were removed under vacuum, and the residue was extracted with CH₂Cl₂ (40 mL) and filtered through kieselguhr. The filtrate was evaporated to dryness under vacuum giving the product as a pale yellow wax. ¹B{¹H} NMR (CDCl₃): δ = –13.9; ¹⁹F{¹H} NMR: δ = –127.5 (m, 2F, *o*-F), –160.6 (m, 1F, *p*-F), –163.0 (m, 2F, *m*-F).

Polymerizations: The solvent (toluene or hexane), triisobutylaluminum, and the metallocene catalyst (standard solution in toluene) were placed in either a 1.4 L steel autoclave (Table 2, entries 4 and 7) or a 250 mL glass reactor (Table 2, entries 1–3, 5, 6). For the copolymerization reaction the comonomer was also placed in the reactor (entry 6: 1-hexene 5 mL; entry 7: propene 50 g). The reactor was equilibrated at the reaction temperature and ethene (propene for entry 5) introduced to the required pressure. The polymerization was started by the addition of a standard solution from **Va**, **Vb**, or **Vc** in toluene or CH₂Cl₂. Ethene (propene for entry 5) was continuously introduced and a constant pressure was maintained. The polymerization was terminated with methanol, the precipitated

polymer collected by filtration, washed with methanol, and dried in a vacuum oven.

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- [21] Aliphatic hydrocarbons are usually used as the polymerization medium for industrial Ziegler–Natta polymerization in solution or slurry. Compared to toluene aliphatic hydrocarbons offer advantages in the isolation of the polymer (separation, purification, drying).
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- [23] For bulk and gas-phase polymerization homogeneous metallocene catalysts are usually used immobilized on a support (e.g., silica gel). To date there are only a few examples of supported, MAO-free metallocene catalysts with noncoordinating anions (supported metallocene catalysts; see for example, *Metalorganic Catalysts for Synthesis and Polymerisation* (Ed.: W. Kaminsky), Springer, New York, **1999**, pp. 307–431). In the polyborates of the type **Va–c** the noncoordinating anions are fixed to a “dendrimer surface”. Dendrimers have various advantages over standard supports: defined molecular size, monodispersed particle-size distribution, an easily accessible surface, and a controllable number of catalytic centers.
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The First Barium–Carborate Complex: Synthesis and Structural Investigation**

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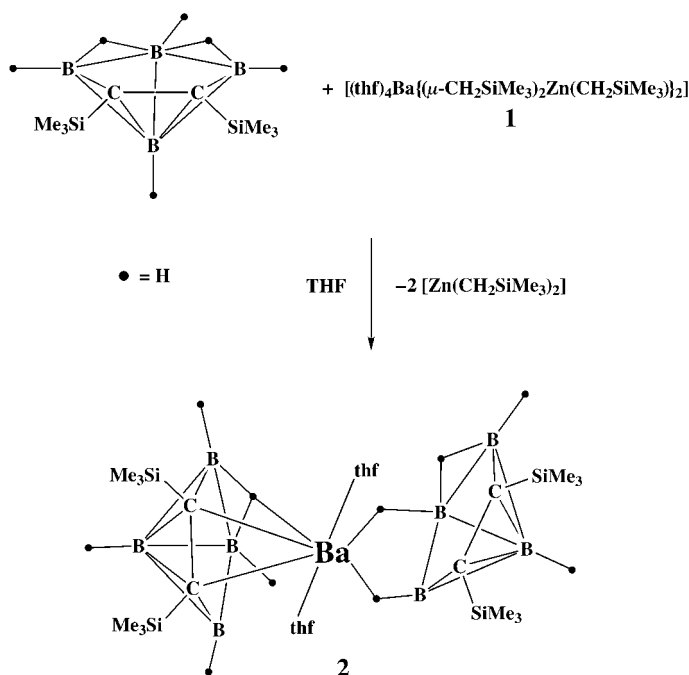
Of all the metallaboranes the Group 1 compounds are some of the most often encountered, in that they are common starting materials in the syntheses of higher order heterobor-

ane clusters. Although, there is no evidence as to the role of the Group 1 metal in their reactions with other metal reagents, it has generally been assumed that they do not play an active role.^[1] The Group 1 metallacarboranes are also the most common precursors in the syntheses of the p-, d-, and f-block metallacarboranes. There seems to be a more direct metal involvement with the smaller, C_2B_4 cages.^[1c,d] For example, the structure of the dilithium compound shows that one [(tmeda)Li] unit (tmeda = *N,N,N',N'*-tetramethylethylenediamine) occupies the apical position above the C_2B_3 face of the carborane, with the other solvated Li atom being *exopolyhedrally* bound through two B–H bridges.^[2] While assignment to a *closo*-carborane is consistent with both the structure and the cage electron pair count of eight, it is not apparent that the [(tmeda)Li]⁺ ion is in any way isolobal with a B–H group; the apical position might simply be that favored by electrostatic interactions. The compound could alternatively be described as a half-sandwich lithium complex in which the *nido*-carborane dianion is η^5 -bonded to the capping Li atom. The structures of several Group 1 compounds in the C_2B_4 - and C_4B_8 -carborane systems have been reported.^[1c,d,3] Structural information available on the Group 2 metal complexed boranes is not plentiful, and, with several notable exceptions, seems to be limited to the two smallest members of that group, beryllium and magnesium.^[4–7] In contrast to the boranes, there have been a number of reports on the Group 2 metallacarboranes,^[3] one reason being that a carbon plus a Group 2 element combination is isoelectronic with two boron atoms. This isoelectronic relationship led Popp and Hawthorne to explore the syntheses and properties of the beryllacarboranes in MC_2B_9 cage systems.^[8,9] While the structures of the beryllacarboranes could not be determined, the heavier Group 2 metals form structurally known metallacarboranes with the *nido*-[7,9- $C_2B_{10}H_{12}$]²⁻ ligand.^[10,11] The 1,1,1,1-(CH₃CN)₄-*closo*-1,2,4- $CaC_2B_{10}H_{12}$ was the first structurally characterized Group 2 metallacarborane. The Ca ion, which is coordinated by four CH₃CN molecules, resides above the C_2B_4 face of the carborane. A similar reaction with SrI₂ produced the novel polymeric strontium carborane, [1,1,1-(CH₃CN)₃-*closo*-1,2,4-SrC₂B₁₀H₁₂]_n, whose structure shows a cage geometry similar to that of the calcium carborane, except that one of the solvating CH₃CN molecules is replaced by a set of Sr–H–X bridge bonds to a neighboring carborane, where X can be a boron atom on the lower belt of the carborane and a carbon atom on its C_2B_4 upper ring.^[11] However, the magnesacarboranes were limited to the 2,3- C_2B_4 and 2,4- C_2B_4 cage systems. The reactions of their mono- and dianions with various magnesium reagents have been studied by Hosmane and co-workers and showed that contrasting results can be obtained from slight changes in the carborane and magnesium reagents.^[12,13] Nonetheless, there have been no reports on similar carborane complexation with the heaviest Group 2 metal, barium. Here we report the first barium half-sandwich complex of any carborane and/or borane cage systems of which we are aware. The reaction of tetrakis(tetrahydrofuran)barium bis[tris(trimethylsilylmethyl)zincate]^[14] (**1**) with 2,3-bis(trimethylsilyl)-2,3-dicarba-*nido*-hexaborane in THF yields nearly quantitatively barium bis(carborate) **2** (Scheme 1). Only one of the trimethylsilylmethyl groups of

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Scheme 1. Synthesis of barium bis(carborate) **2** by metalation of **1** with barium bis[tris(trimethylsilylmethyl)zincate] in THF.

the zincate is active in this metalation reaction. The resulting bis(trimethylsilylmethyl)zinc neither reacts with the carborane nor with **2**.

The molecular structure of dimeric **2** is shown in Figure 1. Each barium atom shows a coordination number of nine (Figure 2). The Ba–O bond lengths of approximately 274 pm lie in the expected region. Furthermore, two carborate ligands are bonded through hydride bridges with Ba–H distances of approximately 290 pm; these bridges were refined isotropically and can be interpreted as three-center Ba–H–B. A third carborate ligand is coordinated with Ba–C distances of 316 pm and the bridging hydrogen atom (Ba1–H356 293(4) pm). This situation corresponds to a four-center BaHB₂ bond. In the highly ionic solvated Ba(BH₄)₂ the boranate anions coordinate through three H atoms to the alkaline earth metal thus forming three-center Ba–H–B bonds.^[15] The Ba–C distances are similar to those of the barium bis[tris(trimethylsilylmethyl)zincates]^[14] (**1**), in which bridging trimethylsilylmethyl moieties between barium and zinc were found. The Ba–C distances of substituted barocenes vary between 290 and 300 pm.^[16] This coordination of the carborate to the barium center is quite different to that observed for the carborate complexes of magnesium and calcium.^[10–13] In the magnesacarborane complex the metal center bonds to the hydride substituents but not to the carbon atoms. With the doubly deprotonated carborane ligands the metal centers show shorter contacts to the boron than to the carbon atoms. In **2** very long Ba–B bonds are observed due to the coordination geometry about the metal center. Nevertheless, the baracarborane **2** is the first metallacarborane of the heaviest Group 2 metal.

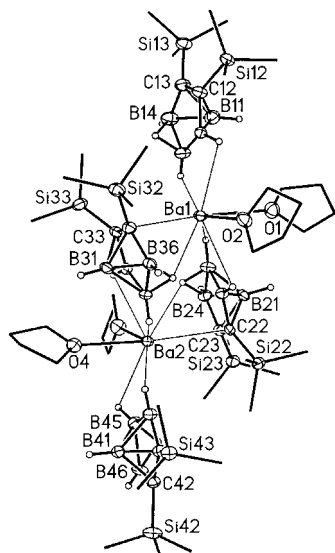


Figure 1. Molecular structure of barium bis(carborate) **2**. The ellipsoids of heavier atoms represent a probability of 40%. The boron-bonded hydrogen atoms are drawn with arbitrary radii.

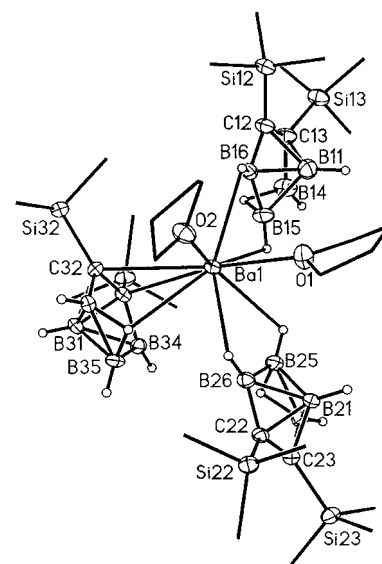


Figure 2. The coordination sphere of the barium center in **2**. The numbering of the H atoms corresponds to that of the respective boron atoms (H356 denotes the H atom that bridges the B atoms B35 and B36). Selected bond lengths [pm]: Ba1–O1 276.7(4), Ba1–O2 273.7(3), Ba1–C32 318.8(5), Ba1–C33 311.3(5), Ba1–H15 287(4), Ba1–H16 282(4), Ba1–H25 279(4), Ba1–H26 288(4), Ba1–H356 290(4).

dination of the carborate to the barium center is quite different to that observed for the carborate complexes of magnesium and calcium.^[10–13] In the magnesacarborane complex the metal center bonds to the hydride substituents but not to the carbon atoms. With the doubly deprotonated carborane ligands the metal centers show shorter contacts to the boron than to the carbon atoms. In **2** very long Ba–B bonds are observed due to the coordination geometry about the metal center. Nevertheless, the baracarborane **2** is the first metallacarborane of the heaviest Group 2 metal.

Experimental Section

All manipulations were carried out in an anhydrous argon atmosphere. The solvents were thoroughly dried and distilled under argon.

2: Bis(trimethylsilyl)-2,3-dicarba-*nido*-hexaborane (1.29 g, 5.88 mmol) was added dropwise to a solution of **1** (2.64 g, 2.44 mmol) in THF (15 mL). The solution was stirred at room temperature for several hours. Then all volatile materials were removed at room temperature under reduced pressure. The colorless residue was dissolved in toluene (10 mL). Cooling to -20°C afforded the precipitation of colorless crystalline **2** (0.73 g, 1.78 mmol; 73 %); m.p. 185°C (decomp). ^1H NMR ($[\text{D}_8]\text{THF}$): $\delta = 0.19$ (s, 18H; SiMe₃), 1.78 (4H; THF), 3.63 (4H; THF); $^{13}\text{C}\{^1\text{H}\}$ NMR ($[\text{D}_8]\text{THF}$): $\delta = 2.52$ (s; SiMe₃), 25.47 (s; THF), 67.43 (s; THF), 111.15 (br.s; SiCB); ^{11}B NMR ($[\text{D}_8]\text{THF}$): $\delta = -50.26$ (s, br., 1B, $^1J(^{11}\text{B}, ^1\text{H})$ unresolved; BH_{apical}), -1.28 (br.s, 1B, $^1J(^{11}\text{B}, ^1\text{H})$ unresolved; BH_{basal}); $^{29}\text{Si}\{^1\text{H}\}$ NMR ($[\text{D}_8]\text{THF}$): $\delta = -7.20$; IR (Nujol, KBr): $\tilde{\nu} = 2589$ sh, 2579 s, 2556 sh, 2545 sh, 2535 sh, 2501 m, 2445 s, 2424 s, 2378 m, 1944 m, 1927 m, 1872 m, 1496 m, 1472 m, 1459 m, 1447 m, 1404 s, 1369 m, 1343 m, 1250 s, 1205 m, 1182 s, 1162 sh, 1073 m, 1035 s, 998 m, 987 m, 961 m, 931 s, 858 s, 841 sh, 834 vs, 753 s, 683 s, 664 sh, 626 m, 590 m, 524 m, 479 m, 413 s, 386 s, 373 cm^{-1} ; elemental analysis (%) calcd for C₂₄H₆₃B₈BaO₂Si₄ (718.912): C 40.10, H 8.69; found: C 38.04, H 8.47. X-ray structure determination:^[17] Siemens P4 diffractometer with CCD imaging plate, 193 K, monoclinic, $P2_1/n$, $a = 2100.8(5)$, $b = 1886.5(5)$, $c = 2188.2(6)$ pm, $\beta = 111.893(5)^{\circ}$, $Z = 4$, 12938 symmetry-independent reflec-

tions, 783 parameters, $wR2(F^2) = 0.081$, $R1$ (7545 data with $I > 2\sigma(I)$) = 0.039. All non-hydrogen atoms were refined anisotropically, the B-bonded hydrogen atoms isotropically. All other H atoms were considered with the riding model.

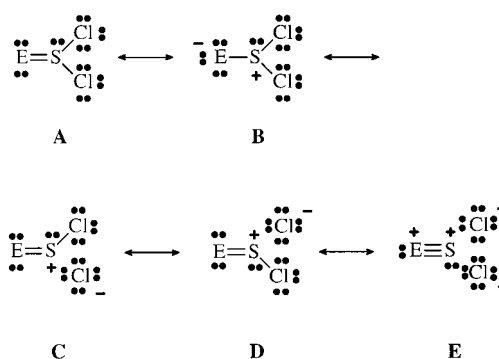
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NSCl₂[−]: Thiazyl Dichloride—An Aza Analogue of Thionyl Dichloride**

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Formally, the NSCl₂[−] ion can be regarded as the isoelectronic aza analogue of thionyl dichloride (OSCl₂) with sulfur in the oxidation state +IV. OSCI₂ represents a highly polarized electron-rich species with a strong S–O bond and two labile S–Cl bonds (Scheme 1). Exchanging the oxygen



Scheme 1. VB representation of OSCI₂ and NSCl₂[−] (E = O, N[−]).

atom for an N[−] ion should result in S–Cl bonds which are further destabilized, and a strong N–S bond with a large amount of π character (bond order between 2 and 3).

The NSCl₂[−] ion belongs to a new class of very labile ternary anions NSX₂[−] (X = halogen) of which, to the best of our knowledge, no representative containing the “naked” anion has been structurally characterized^[1] or synthesized in high yield. Most compounds containing the NSX₂ unit are stabilized by covalent interaction of the N atom with either a metal center, for example, [Hg(NSF₂)₂]^[2–4] or organic groups as in RNNSCl₂ (R = R'C, R''SO₂, C₆F₅, etc.).^[5]

First we undertook a theoretical study of the acceptor properties of the Cl[−] ion and the thermodynamics of NSCl. Ab initio (CCSD(T)) and density functional (B3LYP) calculations indicate a barrier-free attack of the Cl[−] ion at the NSCl molecule resulting in the formation of the highly polarized NSCl₂[−] ion. This reaction represents an exothermic Lewis acid Lewis base reaction with an estimated molar enthalpy ΔH_{298} of $-124.6 \text{ kJ mol}^{-1}$ and a charge transfer Q_{CT} of 0.385 e

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[†] X-ray investigation

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(B3LYP/6-311+G(3df)).^[6] Therefore, it was our idea to start the synthesis of NSCl₂[−] from NSCl and Cl[−] donors with bulky cations in polar solvents.

An easily accessible source for generating NSCl is the trimer (NSCl)₃. The chemistry of (NSCl)₃ shows a great diversity and has been investigated intensively. It has been known for a long time that the (NSCl)₃/NSCl equilibrium [Eq. (1)] strongly determines the chemistry of (NSCl)₃ and



NSCl in solution.^[7] On the basis of ¹⁴N NMR spectroscopy studies Passmore et al. estimated the thermodynamic quantities of the (NSCl)₃/NSCl equilibrium (1) in solution to be $\Delta H^\circ = 65 \pm 13 \text{ kJ mol}^{-1}$ and $\Delta S^\circ = 206 \pm 20 \text{ J mol}^{-1} \text{ K}^{-1}$.^[8] Moreover, they concluded that both the forward and reverse reactions are kinetically very hindered. Impurities were assumed to “facilitate” the monomerization of the trimer. The influence of Cl[−], NH₄⁺, and Cl₂ on the equilibrium has been investigated and, as a result, these compounds were ruled out as “facilitating agents” for the monomerization. The conclusion concerning the influence of the Cl[−] ion is in contrast to our computational results, and indeed, upon adding a solution of (NSCl)₃/NSCl in CH₂Cl₂ to a solution of Ph₄PCl in CH₂Cl₂ an immediate reaction occurs as demonstrated by ¹⁴N NMR spectroscopic studies [Eq. (2), Table 1].



Table 1. ¹⁴N NMR chemical shifts (δ) and line widths (Δν^{1/2}).^[a]

Species		δ	Δν ^{1/2} [Hz]
[Ph ₄ P] ⁺ [NSCl ₂] [−]	¹⁴ N	+ 153	140
[Ph ₄ P] ⁺ [NSCl ₂] [−]	¹⁵ N	+ 148	–
[Ph ₄ P] ⁺ [NSCl ₂] [−]	¹⁵ N MAS ^[d]	+ 147	–
[Ph ₃ BzP] ⁺ [NSCl ₂] [−] ^[b]	¹⁴ N	+ 153	140
[(Ph ₃ PN) ₂ SCI] ⁺ [NSCl ₂] [−]	¹⁴ N	+ 153	140
(NSCl) ₃ ^[c]	¹⁴ N	– 263	260
NSCl ^[c]	¹⁴ N	+ 329	80

[a] Chemical shift values are reported relative to neat nitromethane, solvent: CH₂Cl₂. [b] Bz = benzyl. [c] See Passmore et al.^[8]; δ (in CCl₄) = – 264 ((NSCl)₃), + 352 (NSCl); δ (in SO₂) = – 259 ((NSCl)₃), + 19 (ClNSCl⁺), + 196 (NSF), + 202(NS⁺), + 323 (NSCl). [d] MAS = magic angle spinning.

Table 2. Experimental and calculated Raman and IR data.

Compound ^[a]				$\tilde{\nu}_{\text{exp}}$ [cm ^{−1}] ^[b]			
Assignment			$\tilde{\nu}_{\text{calcd}}$ [cm ^{−1}]				
NSF ₂ [−]	OSF ₂	OSCl ₂	NSCl ₂ [−]				
IR	IR	IR	IR	Raman	for C _s NSCl ₂ [−]		B3LYP/6-311+G(3df) ^[c,d]
1368	1333	1251	1338 (s)	1339 [10] ^[e]	ν ₁ (A')	ν(SN)	1405 (96) [116] ^[f]
500 (br)	808	492	302 (m)	308 [2]	ν ₂ (A')	ν _s (SCI)	304 (48) [9]
500 (br)	748	455	293 (m)	293 [2]	ν ₃ (A'')	ν _{as} (SCI)	300 (155) [1]
325 (br)	530	344	220 (m)	222 [4]	ν ₃ (A')	δ _s (NSCl ₂)	210 (16) [15]
325 (br)	390	284	–	160 [3]	ν ₆ (A'')	δ _{as} (NSCl ₂)	164 (84) [11]
–	410	194	–	–	ν ₄ (A')	δ(ClSCI)	69 (0.2) [11]

[a] Taken from refs. [1] and [9]; with [(Me₂N)₃S]⁺ as counter ion of NSF₂[−]. [b] cf. (NSCl)₃ (IR: $\tilde{\nu}$ = 1017(vs), 698(ms), 621(w), 514(m), 493(m), 385(m), 320(m) cm^{−1}).^[31] [c] Unscaled frequencies; IR intensities [kmol^{−1}] in round brackets, Raman activities [Å⁴amu^{−1}] in square brackets. [d] CCSD(T)/6-311+(2d): $\tilde{\nu}$ = 1310, 295, 311, 211, 169, 64 cm^{−1}. [e] cf. SN⁺: ν₁(Σ_g) = 1434 cm^{−1}.^[9] [f] Besides ν₁ there is a good agreement between experiment and theory. A similar large difference was found for the ν(S–N) in NSCl: B3LYP/6-311+G(3df): ν₁(S–N) = 1386(51) [41], ν₂(SCI) 406(128) [10], ν₃(N–S–Cl, bending) 268(14) [15]; exp.: NSCl (IR): $\tilde{\nu}$ = 1324(s), 415(m), 272(m) cm^{−1}).^[32]

Within seconds of adding the Ph₄PCl solution the dark green (NSCl)₃/NSCl solution turned bright yellow. After 24 h only one ¹⁴N resonance signal was detected (δ = + 153) which can be assigned to the NSCl₂[−] ion. This resonance lies between those of NSCl δ = + 329 and (NSCl)₃ δ = – 263. The solution Raman spectrum showed a new very strong band at 1343 cm^{−1} assigned to the stretching mode of the S–N moiety. After removing the solvent a pale yellow solid was isolated, the Raman spectrum of which was consistent with pure [Ph₄P]⁺[NSCl₂][−]. By comparison to the theoretically obtained data five new normal modes could be assigned to the C_s symmetric NSCl₂[−] ion (Table 2).^[9] Compared to monomeric NSCl (ν₁ = 1323 cm^{−1}) the wave number of the S–N stretching mode (ν₁ = 1339 cm^{−1}) is increased indicating a shorter S–N bond. The normal modes ν₃ and ν₆ represent the symmetric and antisymmetric deformation vibrations of the entire NSCl₂[−] ion. The ν₂ and ν₅ motions can be described as the symmetric and antisymmetric stretch of the SCl₂ units, and ν₄ represents a deformation of the SCl₂ moiety. It is interesting to compare the IR/Raman data of the isoelectronic pair NSF₂[−] and OSF₂ as well as OSCI₂ and NSCl₂[−].^[1, 9, 10] Both NSX₂[−] ions show a higher wave number for ν₁ than the OS analogue whereas the S–X (X = Cl, F) stretching modes appear at lower wave numbers.

Using [Me₄N]Cl, which is only very sparingly soluble in CH₂Cl₂, instead of [Ph₄P]Cl results in a slow conversion of the white [Me₄N]Cl suspension into a pale yellow precipitate. This pale yellow precipitate was found to be pure [Me₄N][NSCl₂], regardless of the reaction stoichiometry ([Me₄N]Cl: NSCl = 1:1, 1:2, and 1:3). This result was confirmed by C,H,N analysis, Raman spectroscopy, and X-ray powder diffraction experiments.^[11] When an excess of NSCl was used, unreacted NSCl/(NSCl)₃ remained in solution in accord with the stoichiometry. The NSCl₂[−] ion with [(Ph₃PN)₂SCI]⁺^[12] was also found as a side product (yield 10 %) in the reaction of Ph₃PNSiMe₃ with NSCl in a 1:3 ratio. The reaction of (NSCl)₃ with Ph₃PNSiMe₃ is very complex and depending on the reaction conditions different products are formed.^[13]

To date, no structural data for a compound containing a “naked” NSX₂[−] ion (X = halogen) have been published. In [Hg(NSF₂)₂], the NSF₂ group is covalently attached to the Hg atom (*d*(N–S) = 1.439 Å).^[4b] The single-crystal X-ray study of [(Ph₃PN)₂SCI]⁺[NSCl₂][−] revealed a slightly distorted C_s

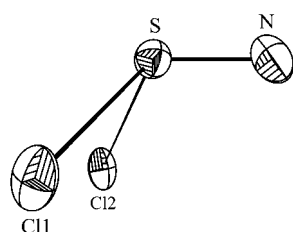


Figure 1. ORTEP drawing of the NSCl_2^- ion in the $[(\text{Ph}_3\text{PN})_2\text{SCl}]^+$ salt. Thermal ellipsoids set at the 25% probability level at 200 K.

shows a relatively small Cl-S-Cl angle (93.3°) and a large N-S-Cl angle (112.8°) which is a consequence of the repulsive interaction between the S-N π bonds and the S-Cl σ bonds.

Table 3. Experimentally and theoretically obtained structural data of NSCl_2^- .

	$[(\text{Ph}_3\text{PN})_2\text{SCl}][\text{NSCl}_2]$	B3LYP 6-311+G(3df) ^[a]	CCSD(T) 6-311+G(3df) ^[a]
S-N [Å]	1.436(6)	1.445	1.456
S-Cl [Å]	2.423(2), 2.427(2)	2.487	2.453
$\angle$ N-S-Cl [$^\circ$]	112.76(19), 113.8(3)	114.4	113.9
$\angle$ Cl-S-Cl [$^\circ$]	93.26(8)	102.4	99.9

[a] It should be emphasized that the computation was carried out for a single, isolated (gas-phase) anion in C_s symmetry. There may well be significant differences between gas-phase and solid-state data because of lattice effects. See also ref. [33].

The intriguing structural features of NSCl_2^- can be rationalized by a qualitative valence bond (VB) consideration (Scheme 1). Canonical Lewis structures of types **A**–**E** are easily anticipated. In the structure **A**, the sulfur atom has expanded its valence shell to use d atomic orbitals (d-AO) to form an electron-pair π bond to either the oxygen or nitrogen atom. However, because natural atomic populations of the d_{xy} -, d_{xz} -, and d_{yz} -AOs are so small,^[20] Lewis structures with an expanded valence-shell (such as **A**) would be expected to make very minor contributions to the ground-state resonance scheme.^[21, 22] The calculated natural atomic population (NAO) net charges are $Q_S = +1.01$ e on sulfur, $Q_N = -0.79$ e on nitrogen, and $Q_{Cl} = -0.61$ e on both the chlorine atoms. These partial charges and the calculated bond orders ($\text{BO}(\text{NS}) = 2.21$, $\text{BO}(\text{SCI}) = 0.23$; cf. $\text{BO}(\text{SN}, \text{SN}^+) = 2.76$, $\text{BO}(\text{SN}, \text{NSCl}) = 2.16$, $\text{BO}(\text{SCI}, \text{NSCl}) = 0.45$, $\text{BO}(\text{SCI}, \text{OSCl}_2) = 0.74$, $\text{BO}(\text{SO}, \text{OSCl}_2) = 0.98$)^[23] support the conclusion that resonance structures **C**–**E** are the primary structures for NSCl_2^- .^[24] This is in accord with the short S–N bond and the long S–Cl bonds. For OSCl_2 a larger SCI bond order is estimated indicating that structure **E** is less important. Moreover, formal charge consideration for OSCl_2 indicate that the resonance structures **B**–**D** are the primary canonical Lewis structures.^[25] Hence, the difference between the primary resonance scheme of OSCl_2 and NSCl_2^- is the weight of structure **B** in the resonance scheme for OSCl_2 and the weight of structure **E** in the resonance scheme of NSCl_2^- . The NBO analysis of NSCl_2^- corresponds to structure **E**. As indicated by an investigation of the noncovalent effects,^[26]

symmetric anion (Figure 1) with a very short S–N bond ($d(\text{S–N}) = 1.436$ Å, cf. 1.416 in $\text{NSF}_3(\text{g})$,^[14] 1.444 in $\text{OSCl}_2(\text{g})$,^[15] 1.446 in $\text{NSF}(\text{g})$,^[16] 1.450 in $\text{NSCl}(\text{g})$,^[17] 1.42 in $\text{SN}^+(\text{s})$ ^[18]) and two loosely bound chlorine atoms $d(\text{S–Cl}) = 2.423$ Å, cf. 2.014 in $\text{SCI}_2(\text{g})$,^[19] 2.076 in $\text{OSCl}_2(\text{g})$,^[15] 2.161 in $\text{NSCl}(\text{g})$,^[17] Table 3). NSCl_2^-

there is a significant interaction of the lone pairs (p-LP, localized in p-AOs) on both chlorine atoms with the two unoccupied, antibonding π^* orbitals of the S–N triple bond. This intramolecular p-LP(Cl) $\rightarrow \pi^*(\text{N–S})$ donor–acceptor interaction (hyperconjugation) describes the rather long S–Cl bond^[27] and corresponds to resonance between structures **C** $\leftrightarrow$ **D** $\leftrightarrow$ **E**. According to the NBO analysis, each of these interactions will involve a concerted delocalization of the two chlorine electrons. As indicated by Harcourt the concerted two-electron delocalization could have a higher energy than has a concerted one-electron delocalization. If this is the case, then increased-valence structures will provide a better primary VB representation of the electronic structure.^[28]

Investigation of the molecular orbitals (MO) of C_s symmetric NSCl_2^- ion revealed two MOs with N–S π -bonding character, one MO for the π_x electrons and one for the π_y electrons which, however, are further delocalized over the SCI_2 moiety stabilizing the weak S–Cl σ bonds, (Figure 2).^[29] This can best be understood as the interaction of the π system

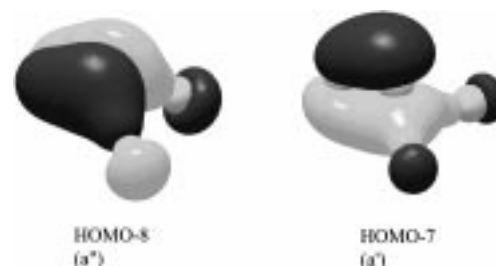


Figure 2. Delocalized bonding molecular orbitals of NSCl_2^- describing the S–N π and the weak S–Cl σ bonds.

of the SN^+ unit (S–N triple bond) with one lone pair of each Cl^- ion. For the system: $\text{NS}^+ + \text{Cl}^- + \text{Cl}^-$, the doubly occupied $3p_x(\text{Cl}^-)$ -AO overlaps in a σ manner with the singly occupied $3p_x(\text{S})$ -AO, and the doubly occupied $3p_y(\text{Cl}^-)$ -AO also overlaps in a σ manner with the singly occupied $3p_y(\text{S})$ -AO. The $3p_x(\text{S})$ - and $3p_y(\text{S})$ -AOs also overlap in a π_x and a π_y manner with the singly occupied $2p_x(\text{N})$ - and $2p_y(\text{N})$ -AOs, respectively. Therefore two 4-electron 3-center bonding units arise, with fractional S–Cl1 and S–Cl2 σ bonding, and fractional S–N π_x and π_y bonding.^[28, 30] It is interesting to note that the resulting bonding MOs are composed of mostly p-AOs (on N, S and Cl; no d orbitals) whereas the nonbonding MOs are stabilized by a small amount of d-AOs localized on the S atom.

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- $$\Delta_{q,q^*}E^{(2)} = -2 \frac{(\langle \varphi | h^F | \varphi^* \rangle)^2}{\epsilon_{q^*} - \epsilon_{\text{GF}}} \quad (3)$$
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A Homoleptic Carbene–Lithium Complex**

Robert Fränkel, Christine Birg, Ulrich Kernbach, Tassilo Habereeder, Heinrich Nöth, and Wolf P. Fehlhammer*

The coordination chemistry of N-heterocyclic carbenes was given great impetus by the isolation of stable, free species by Arduengo.^[1] Since then carbene complexes of nearly all the metals of the periodic table have been synthesized and studied in detail.^[2, 3] As strongly nucleophilic two-electron donors the N,N-carbenes even form stable complexes with metals that normally show no tendency for π back-donation. Thus, a few years ago, Arduengo et al. were able to prepare a series of carbene complexes from the elements of Group 2.^[4] However, to date there are very few examples of carbene complexes with Group 1 metals;^[5–8] this is surprising as for the formation of “free” carbenes from the corresponding formamidine and imidazolium salts, even by the ammonia method of Herrmann et al.,^[9] alkali metal containing bases such as KO^tBu , NaH , or lithiumdiisopropylamide are used in stoichiometric amounts as deprotonating agents. Thus, knowledge of the interactions between carbenes and alkali metals is essential for the understanding of the reactivity and properties of these complexes in solution.

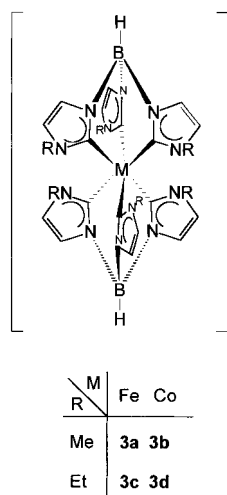
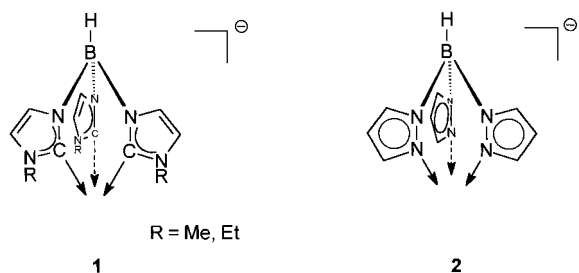
In 1995 we were able to synthesize, for the first time, an Fe^{III} complex of the monoanionic, tridentate hydrotris(3-methyl-

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[+] X-ray analysis

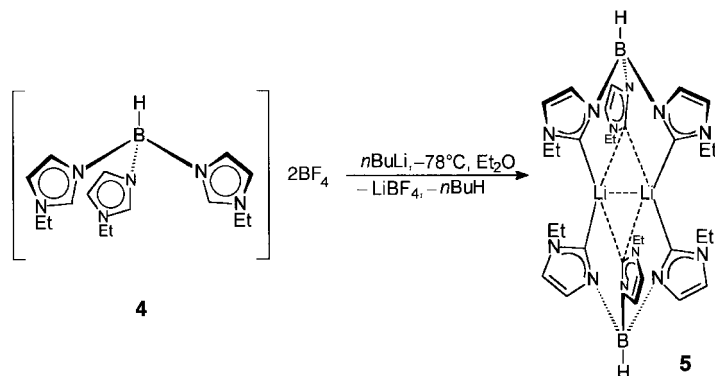
[**] Homoleptic carbene complexes part 10. This work was supported by the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, and by the Studienstiftung des Deutschen Volkes. Part 9 ref. [14].

imidazolin-2-ylidene)borate carbene ligand (**1**; TRIS^{Me}),^[10] which has a topology analogous to that of the known tris(pyrazolyl)borate (**2**; Tp)^[11] of Trofimenko.



Further Fe^{III}, Co^{III}^[12] (**3**), and Re^{VII} complexes^[13] with this ligand, as well as the corresponding ethyl derivate hydrotris(3-ethylimidazolin-2-ylidene)-borate (TRIS^{Et}), were reported recently. In the synthesis of these compounds the “free” monoanionic carbenes (TRIS^R), formed in situ from the corresponding hydrotris(3-alkylimidazolium)borate tetrafluoroborates by deprotonation with *n*BuLi, were treated directly with the corresponding metallic precursor. We have always assumed that these syntheses proceed

via saltlike lithium carbene intermediates. Recently we have concentrated on isolating such intermediates, whereby the possible uses of the TRIS^R ligands should be considerably broadened as *n*BuLi residues in the “in situ reaction mixture” frequently led to undesired side reactions. Deprotonation experiments with less aggressive amides (NaN(SiMe₃)₂) or oxo bases (KO^tBu) resulted in substitution reactions at the boron center, just as in the preparation of the bidentate bis(3-alkylimidazolin-2-ylidene)dihydroborate ligands^[14] reported recently. However, no reaction occurred in a two-phase system with NaH and a catalytic amount of KO^tBu. On the other hand if **4**, suspended in diethylether, is deprotonated with *n*BuLi at -78°C then LiTRIS^{Et} (**5**) precipitates in high yield, together with LiBF₄, [Eq. (1)]; thus it is easily separated



from excess base and can be reacted further in polar solvents.

The isolated almost colorless material is extremely moisture sensitive and decomposes slowly at room temperature turning yellow even under an inert atmosphere. At -30°C , however, the substance can be kept for months without losing any of its reactivity.

Single crystals of the hexacarbene dilithium complex **5**, suitable for X-ray diffraction, were obtained by cooling a saturated diethyl ether solution to -30°C .^[15] The most surprising feature in the molecular structure of **5** is the unusual solvent-free complexation of each lithium atom by four carbene carbon atoms (Figure 1).^[16, 17] This arrangement

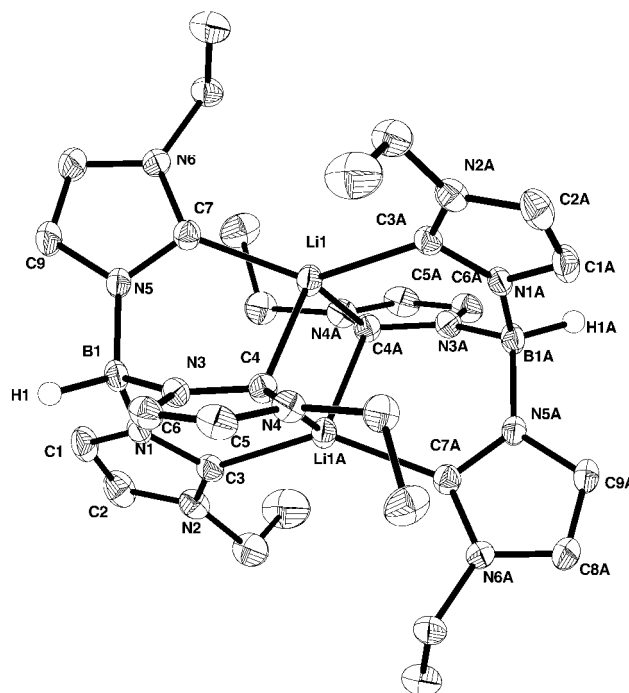
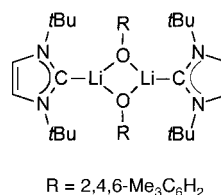
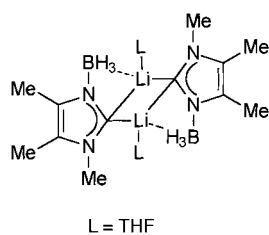
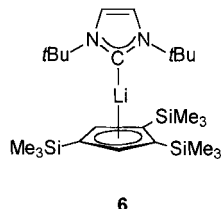


Figure 1. Molecular structure of **5** (for clarity the carbon-bound hydrogen atoms are omitted). The thermal ellipsoids are set at the 30% level. Selected bond lengths [Å] and angles [°]: N-C(carbene) 1.361(3)–1.370(3), (C=C)-N 1.373(3)–1.388(3), C=C 1.331(4)–1.336(4), N-B 1.545(3)–1.553(4); N-C(carbene)-N 103.7(2)–103.8(2), C7-Li1-C3A 140.3(2), C7-Li1-C4 92.7(2), C4A-Li1-C4 111.8(2), Li1-C4-Li1A 68.2(2), N-B-N 110.4(2)–111.6(2).

comes about by the terminal binding to the lithium centers of two carbon atoms (C3 (C3A), C7 (C7A)) from each hydrotris(3-ethylimidazolin-2-ylidene)borate anion while the third carbene carbon atoms (C4, C4A) adopt a bridging mode of coordination. At $68.2(2)^\circ$ the Li1-C4-Li1A angle in the central Li₂C₂ four-membered ring is very similar to the corresponding angle ($67.4(1)^\circ$) in the phenyl-bridged dimer $[\{\text{Li}(\text{Ph})\text{tmeda}\}_2]$.^[18, 19] The LiC₄ coordination geometry is highly twisted forming a tetrahedron that is “flattened on one side”: the C4A-Li1-C4 angle of $111.8(2)^\circ$ approaches the ideal tetrahedral angle, the C7-Li1-C4 angle ($92.7(2)^\circ$) is compressed, and the C3A-Li1-C7 angle ($140.3(2)^\circ$) is greatly expanded. The planes of the bridging rings are almost perpendicular

(93.8°) to the plane determined by Li1, C4, (C4A), and Li1A. The Li–C bonds to the terminal carbene atoms are 2.138(4) and 2.147(4) Å and thus resemble those in 1,2,4-tris(trimethylsilyl)cyclopentadienyl-[1,3-di(*tert*-butyl)imidazolin-2-ylidene]lithium (**6**; 2.155(4) Å).^[6] In aryllithium compounds the terminal Li–C bonds are usually around this length.^[20, 21] The two bonds to the bridging carbon atoms C4 (C4A) are



significantly longer (2.201(4) and 2.311(4) Å, respectively) and of strikingly different length to each other. In the carbene-bridged dimeric [3-borane-(1,4,5-trimethylimidazolin-2-ylidene)]lithium (**7**) the Li–μ-C bonds (2.169(5) and 2.339(5) Å) vary even more.^[8]

Arduengo and Tamm have investigated the structural influence of the Lewis acid Li⁺ on a neutral N,N-heterocyclic carbene. The comparison of the free and coordinated carbene in **8** shows that neither the N–C(carbene) bond lengths nor the N–C(carbene)–N angle are influenced by the Li cation.^[5a, 22] However, on coordination to a transition metal both opening of the N–C–N angle from 101–102° to 103–105° and a slight shortening of the N–C(carbene) bond compared to that in the free N-heterocyclic carbene have been discussed.^[1, 2] The comparison of **5** (103.7(2)–103.8(2)°; 1.361(3)–1.370(3) Å) with the hexacarbene complex **3** that we have studied by X-ray diffraction^[10, 12] (104.5(4)–106.1(4)°; 1.345(6)–1.378(6) Å) shows that the differences here lie within 3σ; nor do other bond lengths, for example, those in the ring, show significant differences between **5** and the hexacarbene transition metal complexes **3**. However, there are significant differences when the data are compared to those of the crystal structure of the trisimidazolium salt **4**.^[23–26]

In the ¹H NMR spectrum of **5** ([D₃]acetonitrile) the resonance signals arising from the ring protons appear as two doublets at δ = 6.91 and 7.05 and are thus shifted significantly to higher field than the corresponding resonances in **4** (δ = 7.55 and 7.83). The signal arising from the acidic H atom at C2 in **4** (δ = 8.86) has disappeared.

In the room-temperature ¹³C NMR spectrum the resonance signal for the carbene carbon atom is missing. This effect can be attributed to signal broadening as a result of the exchange

processes commonly observed in organolithium complexes. A low-temperature measurement could not shed any more light on this problem. In the spectrum recorded at 65 °C for a concentrated sample however, the averaged signal for the C2 carbon atom was observed in the expected region (δ = 191.8). The solutions show no decomposition even after several weeks at 0 °C, an observation that Arduengo^[27] also made for free carbenes.^[6, 7]

Experimental Section

5: Under Argon a suspension of **4**^[12] (500 mg, 1.06 mmol) in diethyl ether (5.0 mL) at –78 °C was treated with a solution of *n*BuLi in hexane (1.6 M, 3.17 mmol; 1.98 mL). The reaction mixture was stirred for 2 h and at the same time allowed to warm slowly to room temperature. The almost colorless solid, a mixture of **5** and LiBF₄, was collected on a D4-sinter. Extraction of the solid with diethyl ether (3 × 10 mL), concentration of the solution to about half the original volume, and cooling to –30 °C afforded pure **5** as colorless prismlike crystals. ¹H NMR (400 MHz, CD₃CN, 25 °C): δ = 1.38 (q, 18H; CH₃), 4.00 (t, 12H; CH₂), 6.91 (d, 6H; CH), 7.05 (d, 6H; CH); ¹³C NMR (68 MHz, CD₃CN, 65 °C): δ = 15.7 (CH₃), 41.7 (CH₂), 119.0 (CH), 128.3 (CH), 191.8 (C2); ⁷Li NMR (155 MHz, CD₃CN, 25 °C): δ = 2.56 (s); IR (KBr): ν̄ = 3064, 2982 (C–H), 2479 (B–H), 1560, 1543, 1146 cm^{–1}.

The solid mixture of **5** and LiBF₄ collected by filtration (see above) is completely soluble in THF and can be used in this form for the preparation of metal complexes.^[12]

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Domino Hydroformylation/Knoevenagel/Hydrogenation Reactions**

Bernhard Breit* and Stephan K. Zahn

Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

Efficient synthetic transformations are those forming new carbon–carbon bonds with complete control of chemo-, regio-, and stereoselectivity.^[1] Reactions in accord with the criteria of atom economy are particularly useful.^[2] In this context, the industrially important hydroformylation of olefins would be an ideal transformation if selectivity, in particular stereoselectivity, could be controlled.^[3] We recently devised one solution to this problem by making more efficient use of substrate control with the aid of a substrate-bound catalyst-directing group.^[4]

Although the hydroformylation of a carbon–carbon double bond introduces the preparatively useful aldehyde functionality, in terms of synthetic efficiency the reaction suffers from the fact that it provides only a one carbon chain elongation. One way to overcome this deficiency could be to incorporate this reaction as a key step in a domino-type process.^[5, 6] In this context we recently developed a domino hydroformylation/Wittig olefination protocol.^[7] In an extension of this study we herein report on the first domino hydroformylation/Knoevenagel reaction/hydrogenation process of acyclic olefinic substrates, which occurs with concomitant control of regio- and stereoselectivity and, additionally, provides useful building blocks for polyketide synthesis.

When the methallyl *ortho*-diphenylphosphanylbenzoate ($\pm$)-**1** was subjected to hydroformylation conditions in the presence of 1.5 equivalents of dimethylmalonate and 0.3 equivalents of piperidinium acetate (Scheme 1), the substituted malonate ($\pm$)-**2** could be isolated in satisfactory yield and with good diastereoselectivity (*syn/anti* 96:4, Table 1, entry 6). Malonate ($\pm$)-**2** is obviously the final product of a sequential domino hydroformylation/Knoevenagel reaction/

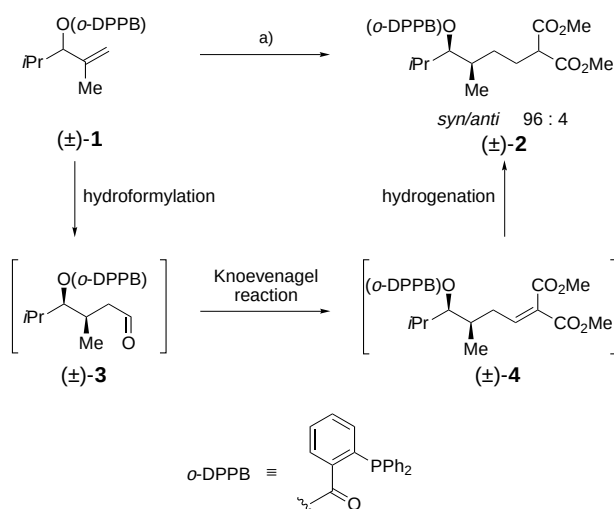
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Table 1. Optimization of reaction conditions for the domino hydroformylation/Knoevenagel reaction/hydrogenation cascade of methallyl alcohol derivative ($\pm$)-**1** with dimethylmalonate.

Entry	Equiv malonate	Rh Cat.	Base/equiv	<i>T</i> [°C]	Yield ^[a] [%]	d.r. ^[b] (<i>syn/anti</i>)
1	1.0	[RhH(CO)(PPh ₃) ₃]	piperidine/0.5	70	20	96:4
2	1.0	[RhH(CO)(PPh ₃) ₃]	piperidine/0.5	90	36	96:4
3	1.0	[{Rh(cod)Cl} ₂] ^[c]	piperidine/0.5	90	42	96:4
4	1.0	[Rh(CO) ₂ (acac)]/4 P(OPh) ₃	piperidine/0.5	90	41	96:4
5	1.0	[RhH(CO)(PPh ₃) ₃]	pyridine/0.5	90	0	—
6	1.5	[RhH(CO)(PPh ₃) ₃]	piperidiniumacetate/0.3	90	51	96:4

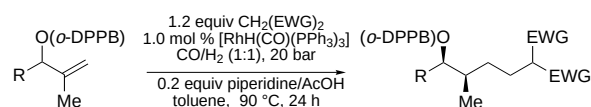
[a] Determined after workup and purification by column chromatography. [b] Determined through NMR spectroscopic analysis of the crude product. [c] cod = cycloocta-1,5-diene.



Scheme 1. Domino hydroformylation/Knoevenagel reaction/hydrogenation process [($\pm$)-**1** $\rightarrow$ ($\pm$)-**2**] and proposed mechanism. a) CH₂(CO₂Me)₂, 1.0 mol % Rh cat., 20 bar CO/H₂ (1:1), amine base, toluene, Δ , 24 h.

hydrogenation cascade. As we have shown previously, diastereoselectivity in the course of the hydroformylation reaction is controlled by the substrate-bound catalyst-directing *o*-DPPB.^[8] The yield and stereoselectivity of this new transition metal catalyzed domino process are basically independent from the rhodium-catalyst precursor that is used (Table 1, entries 2–4), but they depend strongly on the nature of the amine base employed (Table 1, entries 2, 5, 6). While pyridine was completely unsuccessful, the best result was obtained with catalytic amounts of piperidinium acetate.^[9] Hence, this new domino process allows in a single operational step the formation of two carbon–carbon single bonds under almost neutral reaction conditions and simultaneously introduces the synthetically useful malonate functionality. Additionally, a new stereogenic center is formed with excellent levels of acyclic stereocontrol.

In addition to malonates, β -ketoesters such as ethyl acetoacetate (Scheme 2; Table 2, entries 2, 5, 7, 8) could be

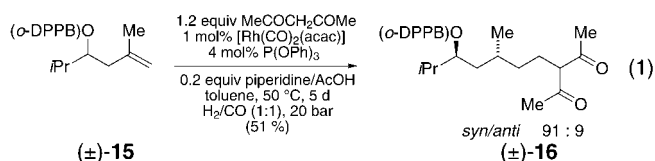


Scheme 2. Domino hydroformylation/Knoevenagel reaction/hydrogenation process. EWG = electron withdrawing group.

employed to give the corresponding domino products **5**, **9**, **12**, and **14** in generally better yields. Furthermore β -diketones undergo a similar cascade reaction to give the formally alkylated and saturated derivatives **6**, **10**, and **16** (Table 2, entries 3, 6, 9).

The reaction could be used for the construction of the *anti*–*syn* and the all-*anti* stereotriad sequences (Table 2, entries 7, 8), which are known to be central building blocks of polyketide natural products.^[13] In all the reactions 1,2-asymmetric induction was controlled during the hydroformylation step either by making use of the substrate-bound catalyst-directing *o*-DPPB group (entries 1–7),^[7, 8] or by substrate control through conformational constraints (entry 8).^[14]

The domino reaction could also be applied to a homo-methallyl *o*-DPPB ester ($\pm$)-**15** [Eq. (1); acac = acetylacetonate]. The substrate-bound catalyst-directing *o*-DPPB group al-



lowed the control of diastereoselectivity by making efficient use of 1,3-asymmetric induction.^[15] Thus, the functionalized β -diketone ($\pm$)-**16** was obtained in good yield and with good diastereoselectivity.

Additionally, a regioselective hydroformylation of a mono-substituted alkene with the BIPHEPHOS/rhodium catalyst^[16] could be employed as the key step in this domino process to give the linear β -ketoester **18** in good yield and with excellent regioselectivity [Eq. (2)].

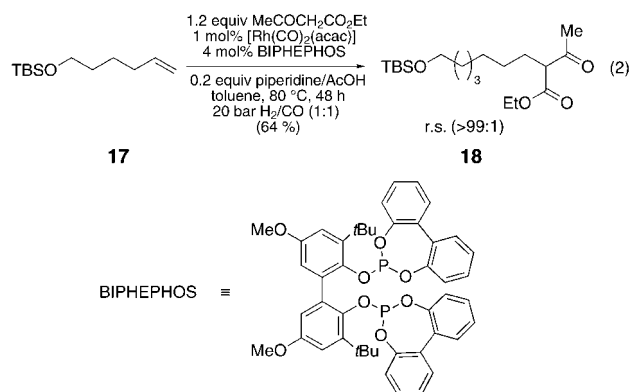


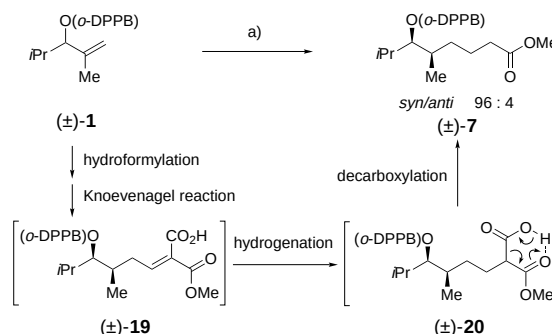
Table 2. Results of the regio- and stereoselective domino hydroformylation/Knoevenagel reaction/hydrogenation process.^[a]

Entry	Alkene ^[10]	CH ₂ (EWG) ₂	Product ^[11, 12]	Yield ^[b] [%]	d.r. ^[c] (<i>syn/anti</i>)
1		CH ₂ (CO ₂ Me) ₂		51	96:4
2		MeCOCH ₂ CO ₂ Et		71	96:4
3		MeCOCH ₂ COMe		52	96:4
4		HO ₂ CCH ₂ CO ₂ Me		41	96:4
5		MeCOCH ₂ CO ₂ Et		64	92:8
6		MeCOCH ₂ COMe		60	92:8
7		MeCOCH ₂ CO ₂ Et		55	96:4
8 ^[d]		MeCOCH ₂ CO ₂ Et		62	> 98:2
9 ^[e]		MeCOCH ₂ COMe		51	91:9
10 ^[e]		MeCOCH ₂ CO ₂ Et		64	> 99: < 1 ^[f]

[a] For a representative procedure, see the Experimental Section. TBS = *tert*-butyldimethylsilyl. [b] Determined after workup and purification by column chromatography. [c] Determined through NMR or GC analysis of the crude product. [d] Conditions: 1 mol % [Rh(CO)₂(acac)]/4 mol % P(OPh)₃, 0.2 equiv piperidine. [e] For detailed reaction conditions, see Equations (1) and (2). [f] Ratio of regioisomers (linear/branched).

When malonic acid monomethyl ester was used as the CH₂-acidic Knoevenagel component the monoester derivative (±)-7 was obtained as the sole product (Table 2, entry 4). Hence, the mechanism of this sequential transformation must involve four separate steps (Scheme 3). First, *o*-DPPB-directed stereoselective hydroformylation provides the aldehyde (±)-3,^[8] which should condense immediately with the malonic acid methyl ester to form the corresponding doubly acceptor-activated alkene derivative (±)-19. Rhodium-catalyzed hydrogenation of this alkene and subsequent decarboxylation conclude the sequence of events affording the isolable ester (±)-7.

Hence, the new sequential transformation described herein allows the formation of two carbon–carbon single bonds in a single operational step, with concomitant generation of a new



Scheme 3. Proposed mechanism of the domino hydroformylation/Knoevenagel reaction/hydrogenation/decarboxylation cascade ((±)-1 → (±)-7). a) 1.1 equiv HO₂CCH₂CO₂Me, 1.0 mol % [RhH(CO)(PPh₃)₃], 20 bar CO/H₂ (1:1), 0.1 equiv piperidine, 0.1 equiv AcOH, toluene, 90 °C, 24 h (41 %).

stereogenic center and with high levels of regio- and acyclic stereocontrol. Additionally, a synthetically useful β -dicarbonyl functionality is introduced.

Experimental Section

Compound ($\pm$)-**5**: ($\pm$)-**1** (402 mg, 1.0 mmol) and ethyl acetoacetate (156 mg, 1.2 mmol) were added sequentially to a solution of $[\text{RhH}(\text{CO})(\text{PPh}_3)_3]$ (9.2 mg, 1×10^{-2} mmol) in toluene (3 mL) at 20 °C (with exclusion of air and moisture). The solution was stirred for 5 min and then piperidine (17 mg, 0.2 mmol) and acetic acid (12 mg, 0.2 mmol) were added sequentially. The resulting solution was transferred by cannula (rinsed with 2 mL of toluene) into an evacuated and argon-filled stainless-steel autoclave. The autoclave was heated to 90 °C and pressurized with 20 bar H_2/CO (1:1). After stirring for 24 h at this temperature the autoclave was cooled rapidly to 20 °C and depressurized. The reaction solution was filtered through a small pad of silica with *tert*-butylmethylether (50 mL). After evaporation of the solvent, the crude product was analyzed by NMR spectroscopy to determine the diastereomeric ratio (*syn/anti* 96:4). Subsequent purification by column chromatography on silica with petroleum ether (40/60)/*tert*-butylmethylether (4:1) provided the β -ketoester ($\pm$)-**5** (390 mg, 71 %) as a highly viscous oil. ^1H NMR (500.130 MHz, CDCl_3 , 25 °C, TMS): δ = 0.77–0.87 (m, 9H), 1.05–1.10 (m, 1H), 1.24 (m_c, 3H), 1.69–1.92 (m, 5H), 2.15 [2.18] (s, 3H), 3.24 [3.30] (pt, J = 7.3 Hz, 1H), 4.11–4.21 (m, 2H), 4.81 (m_c, 1H), 6.91 (m_c, 1H), 7.25–7.31 (m, 10H), 7.38 (m_c, 2H), 8.08 (m_c, 1H); ^{13}C NMR (125.758 MHz, CDCl_3 , 25 °C): δ = 13.7 [13.8], 14.0, 18.2 [18.4], 19.1 [19.2], 25.6 [25.7], 28.7 [29.0], 29.5, 31.2 [31.4], 34.3, 56.6 [59.9], 61.2 [61.3], 81.5 [81.8], 128.1 (d, $^3J_{\text{C,P}}$ = 2.8 Hz), 128.4 (d, $^3J_{\text{C,P}}$ = 6.9 Hz, 2C), 128.4–128.5 (2C), 130.4, 131.8 (d, $^3J_{\text{C,P}}$ = 6.4 Hz), 133.7–134.3 (8C), 138.1–138.3 (2C), 140.9 (d, $^1J_{\text{C,P}}$ = 28.2 Hz) [141.0 (d, $^1J_{\text{C,P}}$ = 27.6 Hz)], 166.30 [166.32], 169.6 [169.7], 203.2 [203.3]; ^{31}P NMR (202.457 MHz, CDCl_3 , 25 °C, 85 % H_3PO_4): δ = –4.49 (s) [–4.51 (s)]; elemental analysis: calcd. (%) for $\text{C}_{33}\text{H}_{39}\text{O}_5\text{P}$: C 72.51, H 7.19; found C 72.62, H 7.34.

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- [11] All compounds were characterized by ^1H , ^{13}C , and ^{31}P NMR spectroscopy and elemental analysis. The β -diketones show keto–enol tautomerism. The ratios of the enolic form range from 32 % (Table 2, entry 3) to 56 % (Table 2, entries 6 and 9).
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Dialkenylation of Carbonyl Groups by Alkenyllithium Compounds: Formation of Cyclopentadiene Derivatives by the Reaction of 1,4-Dilithio-1,3-dienes with Ketones and Aldehydes**

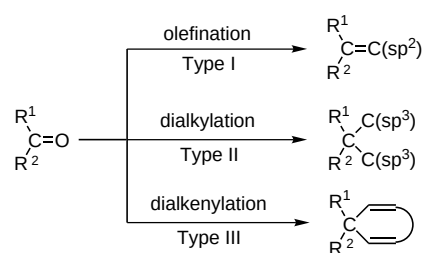
Zhenfeng Xi,* Qiuling Song, Jinglong Chen, Hairong Guan, and Pixu Li

The development of methodologies for carbon–carbon bond formation by deoxygenation of the $\text{C}=\text{O}$ moieties in carbonyl compounds has attracted much attention as a powerful synthetic strategy.^[1] In general, two types of C–C bond-forming reactions that involve the deoxygenation of C–O double bonds in carbonyl compounds are known (Scheme 1, Type I and Type II). Type I reactions give rise to a C–C double bond. The Wittig-type reactions,^[2] Tebbe's reagent or Grubbs' titanacycle,^[3] and the McMurry reaction^[4] have been utilized extensively to convert carbonyl compounds into alkenes. Type II reactions form two $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ bonds. Reetz's direct geminal dialkylation, which uses organotitanium reagents^[5] and AlMe_3 ,^[6] and direct geminal diallylation, which uses vanadium(II) species^[7] have been reported. We

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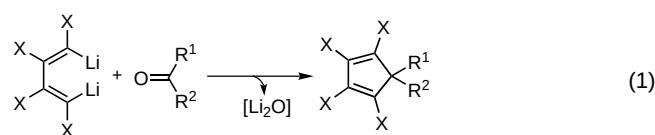
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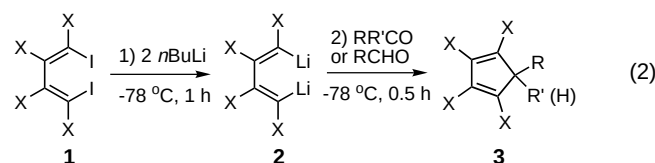
Scheme 1. Types of reactions for the formation of C–C bonds from C=O bonds.

recently described an AlCl_3 -mediated reaction of zirconacyclopentadienes with aldehydes to afford cyclopentadiene derivatives.^[8] Although the complete deoxygenation of the carbonyl group and the quaternization of its carbon atom can lead to useful methods for the formation of quaternary carbons or complex structures, such kinds of procedures are surprisingly rare, probably because reactions of ketones or aldehydes with reactive organometallic compounds, especially organolithium or Grignard reagents, normally result in alcohols.^[9]

We report herein a new reaction of ketones and aldehydes with organolithium compounds which involves the deoxygenation of the C=O moieties. Type III reactions (Scheme 1) form $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ bonds in the direct cyclodialkenylation of ketones and aldehydes with dilithium compounds to form cyclopentadiene derivatives ([Eq. (1)]; the substituents X are not necessarily identical).



The reaction of organomonolithium compounds, including alkyl- and alkenyllithium compounds, with carbonyl groups is normally straightforward, and gives alcohols after hydrolysis, or α -deprotonation products.^[9] However, when dialkenyllithium compounds (1,4-dilithio-1,3-diene derivatives **2** generated in situ from their corresponding diiodo compounds **1** and $n\text{BuLi}$ ^[10–12]) were treated with one equivalent of a ketone or an aldehyde at -78°C , cyclopentadiene derivatives **3** were formed within 1 h in high yields [Eq. (2)].



With this method, spiro compounds **3a** and **3b** were obtained from cyclohexanone in high yields (Table 1). The reactions of the lithium derivative of **1b** with 4-heptanone and benzophenone afforded tetrahydroindene derivatives **3c** and **3d**. Hexasubstituted cyclopentadienes **3e** and **3f** were isolated in good yields. Compounds **3c–f** were the only isomers

Table 1. Reactions of 1,4-dilithio-1,3-dienes with ketones and aldehydes.^[a]

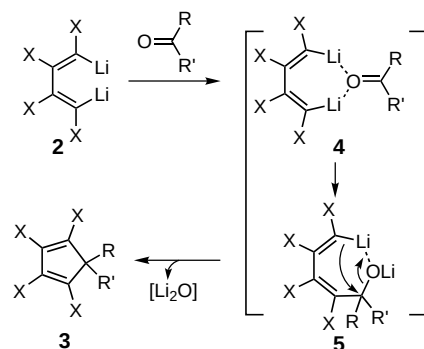
Entry	Diiodo compound	Ketone or aldehyde	Product	Yield [%] ^[b]
1				75
2				74 (3:1) ^[c]
3	1b			92
4	1b			75
5				72
6				67
7	1a	PhCHO		56
8	1a	PrCHO		53 (3:1) ^[c]
9	1b	PhCHO		70 (4:1) ^[c]

[a] Conditions: a molar ratio of 2:1 of $n\text{BuLi}$ and a diiodo compound in diethyl ether at -78°C for 1 h, then 1.1 equivalent of a ketone or an aldehyde at -78°C for 0.5 h. [b] Yields refer to isolated amounts after column chromatography. [c] Ratios of double-bond positional isomers; the minor isomer has an exocyclic double bond.

obtained from the reactions described in Table 1. However, in the case of benzophenone (Table 1, entries 4–6), hexamethyl phosphoramide (HMPA) was needed to achieve a complete reaction.

Similarly, aromatic and aliphatic aldehydes reacted with 1,4-dilithio-1,3-dienes to form pentasubstituted cyclopentadienes in good yields (Table 1, entries 7–9). Characterization data for **3g–i** are consistent with those previously reported.^[8] In most cases, the corresponding alcohols were not detected at all.

The interaction (or chelation) of the alkenyllithium moieties with the carbonyl group (e.g. **4**), although very weak, is proposed to be essential in this inter/intramolecular reaction (Scheme 2).^[13–17] One of the two alkenyllithium moieties



Scheme 2. Proposed reaction mechanism for the reaction between di-alkenyllithium compounds (e.g. **2**) and ketones or aldehydes.

reacts first with the carbonyl group to form **5**, which then undergoes an intramolecular attack by the remaining alkenyllithium moiety to give cyclopentadiene derivatives, with the concomitant release of lithium oxide. This result is in sharp contrast to the case of organomonolithium reactions with carbonyl groups, which usually afford alcohols after hydrolysis.^[9] The inter/intramolecular reaction, the chelation effect of the alkenyllithium moieties, and the formation of stable cyclopentadiene derivatives and of lithium oxide are assumed to be the driving forces in this novel reaction.

Experimental Section

¹H NMR and ¹³C NMR spectra were recorded at 300 MHz and 75 MHz, respectively. All spectra were measured in CDCl₃ at 25 °C, with TMS as internal reference.

Typical procedure: *n*BuLi (2.2 mmol, 1.6 M in hexane) was added to a solution of **1a** (1 mmol) in diethyl ether (5 mL) at –78 °C. The reaction mixture was then stirred at –78 °C for 1 h to generate **2a**, which was monitored by GC analysis or by TLC. After the addition of cyclohexanone (1.1 mmol) at –78 °C, the mixture was stirred at –78 °C for 0.5 h. The reaction mixture was quenched with HCl (3 N) and extracted with hexane. The extract was washed with NaHCO₃ and brine, and dried over MgSO₄. The solvent was evaporated in vacuo to give a brown oil, which was purified by column chromatography (silica gel, hexane) to afford **3a** as a colorless liquid (226 mg, 75 %). ¹H NMR: δ = 0.81–1.01 (m, 12H), 1.07–1.66 (m, 18H), 2.03–2.16 (m, 6H), 2.85 (t, *J* = 6.6 Hz, 1H), 5.20 (t, *J* = 6.4 Hz, 1H); ¹³C NMR: δ = 14.48, 14.77, 15.01, 15.20, 20.26, 22.09, 23.04, 23.45, 23.75, 24.31, 26.06, 27.04, 28.11, 29.12, 33.14, 35.64, 45.14, 50.88, 118.70, 135.91, 147.56, 149.44; HRMS calcd for C₂₂H₃₈: 302.2974; found: 302.2977.

3b: Colorless liquid, 3:1 mixture of positional double-bond isomers (201 mg, 74 %); ¹³C NMR (mixture): δ = 15.31, 15.32, 15.46, 21.29, 23.68, 23.97, 24.09, 24.29, 24.55, 25.26, 26.34, 26.90, 28.35, 30.34, 33.35, 37.41, 43.45, 47.49, 52.66, 66.81, 102.14, 115.63, 132.18, 133.18, 141.31, 147.81, 148.64, 148.76; HRMS calcd for C₂₀H₃₂: 272.2504; found: 272.2496.

3c: Colorless liquid (264 mg, 92 %); ¹H NMR: δ = 0.71–0.95 (m, 16H), 1.12–1.68 (m, 12H), 1.96 (t, *J* = 6.4 Hz, 4H), 2.40–2.48 (brs, 4H); ¹³C NMR: δ = 14.50, 15.16, 16.50, 21.74, 24.14, 28.24, 29.41, 38.12, 61.57, 136.63, 140.56.

3d: Sticky liquid (267 mg, 75 %); ¹H NMR: δ = 0.50–0.85 (m, 10H), 1.18–1.57 (m, 4H), 1.99 (t, *J* = 7.0 Hz, 4H), 2.30–2.36 (brs, 4H), 7.06–7.17 (m, 10H); ¹³C NMR: δ = 13.60, 20.84, 22.77, 23.55, 28.41, 71.45, 124.96, 126.88,

127.44, 136.17, 141.01, 144.69; HRMS calcd for C₂₇H₃₂: 356.2504; found: 356.2488.

3e: Colorless liquid (318 mg, 72 %); ¹H NMR: δ = 0.63–1.48 (m, 28H), 2.08 (t, *J* = 6.4 Hz, 4H), 2.25 (t, *J* = 7.8 Hz, 4H), 7.10–7.26 (m, 10H); ¹³C NMR: δ = 13.67, 14.08, 23.36, 26.18, 26.88, 29.45, 31.87, 32.46, 71.94, 125.97, 127.96, 128.48, 140.97, 141.98, 147.77; HRMS calcd for C₃₃H₄₆: 442.3600; found: 442.3616.

3f: Colorless liquid (238 mg, 67 %); ¹H NMR: δ = 0.64–1.28 (m, 14H), 1.63 (s, 3H), 1.85 (s, 3H), 2.11 (t, *J* = 8.4 Hz, 2H), 2.26 (t, *J* = 7.6 Hz, 2H), 7.08–7.25 (m, 10H); ¹³C NMR: δ = 11.15, 11.37, 13.64, 14.10, 23.22, 26.24, 26.94, 29.44, 32.17, 32.25, 71.66, 125.96, 128.04, 128.40, 135.72, 141.28, 142.25, 142.37, 147.88; HRMS calcd for C₂₇H₃₄: 358.2661; found: 358.2669.

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[Me₂C(η⁵-C₅H₄)₂Ru₂(CO)₄]-An Organometallic Thermo-Optical Switch**

Peter Burger*

Potential applications of molecular devices and molecular machines have generated an extended area of research within the realm of supramolecular chemistry.^[1, 2] Most of these systems are either based on organic units or incorporate inorganic coordination chemistry fragments.^[1, 2] Besides a report by Vollhardt and co-workers, to the best of our knowledge, there are no further publications in which organometallic complexes/transformations have been applied.^[3] In the latter system, reversible C–C, M–M, and M–C bond-cleavage steps were observed leading to a photochemical process, which can be thermally reversed. Recently, we have entered this area and have described a diruthenium system, in which a photochemical, albeit thermally irreversible rearrangement by Si–C bond cleavage was observed.^[4] Herein, we report on the CMe₂ bridged dicyclopentadienyl diruthenium complex [Me₂C(η⁵-C₅H₄)₂Ru₂(CO)₄] (**1a**) which is a fully reversible *organometallic thermo-optical switch*, that is, a photochromic system (Figure 1). When toluene

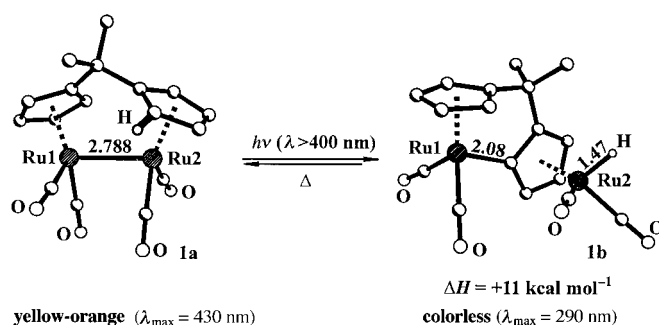


Figure 1. X-ray crystal structures of complexes **1a**, **b** (selected bond lengths [Å] are shown) and their photochemical and thermal interconversion.

or benzene solutions of complex **1a** are irradiated with a Hg medium-pressure lamp using a UV cutoff filter with $\lambda > 400 \text{ nm}$, the *quantitative* and *very efficient* rearrangement to complex **1b** shown in Figure 1 was observed.^[5] Both complexes **1a** and **1b** were fully characterized by one- and two-dimensional NMR spectroscopic methods and their structures unambiguously confirmed by single-crystal X-ray diffraction.^[6]

Based on known and estimated C–H, Ru–H, Ru–C, and Ru–Ru bond dissociation enthalpies^[3, 8–11] and the aforementioned results by Vollhardt and co-workers,^[3] we were suspi-

cious that the photochemical transformation led to the thermodynamically unfavorable product **1b**. Indeed, in a quite slow reaction, clean and quantitative conversion into the starting material **1a** was observed within 1 day when complex **1b** was heated to 140 °C in a [D₈]toluene solution (Figure 1). Interestingly, the thermal reaction also took place when neat (solid) **1b** was heated to 160 °C (see below). This result clearly indicated a higher free enthalpy of the rearranged photochemical product **1b** and established a sizable barrier for the reverse thermal reaction which enabled the isolation of **1b**.

Before we address the kinetic and thermodynamic aspects of the forward and backward transformations, it should be noted that the low-yield synthesis of compound **1a** was first reported by Bitterwolf et al.^[12] This group also studied the photochemistry of **1a** and isolated and crystallographically characterized the chloro substituted analogue of **1b**.^[12] As a result of the absence of a UV cutoff filter, however, these reactions were not found to be clean and secondary photochemical processes involving **1b**, initiated by UV light exposure, were observed. The use of a UV cutoff filter in the photolysis experiments is therefore crucial for a complete and quantitative photochemical conversion. It allowed us to preclude photochemical pathways for the reverse reaction, which is readily apparent in that the rearranged product **1b** is colorless ($\lambda_{\text{max}} = 290 \text{ nm}$) and displays no absorption band above 400 nm.

Insights into the thermodynamics of the Ru system **1a**, **b** stem from density functional theory (DFT) calculations^[13] for which the Becke–Perdew 86 (BP-86)^[14] and also the B3LYP^[15] functionals were used. The fully geometrically optimized structures for **1a**, **b** were characterized as stationary points and displayed only slight deviations from the X-ray crystal structures with either the B3LYP or the BP-86 optimized geometries. The calculated energy differences for **1a** and **1b** are 11.3 kcal mol^{−1} for the B3LYP functional and 10.5 kcal mol^{−1} with the BP-86 functional. In both cases and in full agreement with experiment, the photochemically rearranged product **1b** was calculated to be energetically less favorable than **1a**.

The theoretical results were later confirmed experimentally by differential scanning calorimetry (DSC) measurements for compound **1b**. The transformation **1b** → **1a** was found to be irreversible and the ¹H NMR spectrum of the product obtained in these experiments displayed the signals corresponding to the pure complex **1a**. In excellent agreement with the DFT calculations, we obtained an *exothermic* enthalpy change of −11.2 kcal mol^{−1} for this process. Noteworthy is that the thermal conversion is preceded by an endothermic melting process (m.p. 125 °C, $\Delta H_{\text{melt}} = 15.8 \text{ cal g}^{-1}$, 7.7 kcal mol^{−1}) of **1b**, which explains the aforementioned transformation of **1b** in the solid state.

In an attempt to gain insights into the mechanism(s) of the process presented in Figure 1, further information was sought. The transformation **1a** → **1b** is a dramatic rearrangement and includes C–H bond cleavage of the cyclopentadienyl C–H group *ortho* to the bridgehead carbon atom and rupture of the M–M bond, which is not maintained in the rearranged product **1b**. At first glance two primary, equally likely photochemical transients can be envisaged,^[18] these are

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a) the homolytic metal–metal bond cleavage product, that is, the 17 electron ruthenium-centered diradical, $[\text{Me}_2\text{C}-(\text{C}_5\text{H}_4)\text{Ru}^*(\text{CO})_2]_2$, for which there are ample precedents through the M–M bond homolysis in the unbridged complexes $[\{\text{CpM}^*(\text{CO})_n\}_2]$, where $\text{M}(\text{CO})_n = \text{Mo}(\text{CO})_3$, $\text{W}(\text{CO})_3$ and $\text{Fe}(\text{CO})_2$, $\text{Ru}(\text{CO})_2$.^[19–24] b) irradiation may lead to loss of a CO ligand to yield the unsaturated tricarbonyl intermediate $[\text{Me}_2\text{C}(\text{C}_5\text{H}_4)_2\text{Ru}_2(\text{CO})_3]$, observed in a matrix-isolation study by the groups of Bitterwolf and Rest.^[25] However, the latter study also clearly showed that a wavelength of <400 nm is required to induce CO loss. This is also in accordance with a wavelength selective study of the parent complex, $[\{\text{Cp}(\text{CO})_2\text{Ru}\}_2]$, for which the $17e^-$ configured radical, $[\text{CpRu}^*(\text{CO})_2]$, was proposed as the primary photochemical product if visible light was used.^[26]

Although we do not have conclusive mechanistic information for the photochemically initiated steps, we favor mechanism (a) in which the C–H bond activation step is preceded by the homolysis of the Ru–Ru bond. This view is supported by a bandpass restricted photolysis experiment of **1a** in the range 320–370 nm, which, along with decomposition products, gave negligible photochemical conversion into **1b**. Some additional experimental evidence was provided through a photolysis experiment of **1a** in toluene under one atmosphere of ^{13}C labeled CO. While the conversion from **1a** into **1b** was found to proceed with an essentially unchanged rate. By ^1H and ^{13}C NMR spectroscopy we could detect incorporation of the ^{13}C labeled CO group into both the starting material **1a** and the product **1b**. The CO ligand exchange in **1a** is in accordance with the well-documented small ligand-substitution barriers in $17e^-$ transients including the unbridged transient $[\text{CpRu}^*(\text{CO})_2]$.^[27] On the other hand, fast incorporation of the isotopically labeled CO ligand in **1a**, may also be assumed by trapping of the alternative transient $[\text{Me}_2\text{C}-(\text{C}_5\text{H}_4)_2\text{Ru}_2(\text{CO})_3]$ with ^{13}CO . Since the rearrangement rate **1a** $\rightarrow$ **1b** is apparently not retarded in the presence of CO and the thermal CO exchange process has been found to be significantly slower for **1a** and **1b**, this provides some support for the homolytic cleavage product $[\text{Me}_2\text{C}((\text{C}_5\text{H}_4)\text{Ru}^*(\text{CO})_2)_2]$ as the reactive transient. However, this conclusion should be treated with some care since the photochemical intermediate of the exchange process may not lie on the reaction coordinate for the transformation **1a** $\rightarrow$ **1b**.

In general, photochemically generated metal-centered radicals, $[\text{CpM}^*(\text{CO})_n]$, are extremely short-lived transients and recombine with nearly diffusion controlled rates.^[20–22, 27, 28] Hence, only sufficiently fast atom-abstraction reactions from suitable organic substrates (mostly organic halides) can compete with the radical recombination process.^[19, 22, 27] Recently, however, Wayland et al. have shown that persistent metal-centered porphyrin rhodium(II) complexes are capable of *intermolecular* homolytic C–H bond cleavage even in highly inert alkanes, such as methane.^[29, 30] Since the C–H bond activation step in **1a** was *intramolecular*, it might therefore compete with the recombination process of the diradical.

To shed further light on the transformation, we have investigated the reverse reaction (**1b** $\rightarrow$ **1a**) by ^1H NMR spectroscopy kinetic experiments. In the thermolysis study of

1b in $[\text{D}_8]$ toluene at 137°C , we observed a clean first-order dependence for the disappearance of **1b** ($R^2 = 0.997$ up to 4 half lives) with a rather long half life $\tau_{1/2} = 3.5$ h ($k_{\text{obs},410} = 5.5(1) \times 10^{-5} \text{ s}^{-1}$). Further support for an intramolecular process was evidenced through the observation of identical thermolysis rates when the concentration of complex **1b** was doubled in these experiments. Noteworthy is that we observed a rather significant 10-fold rate enhancement of the thermolysis process in the more polar solvent acetonitrile.

Subsequently, the kinetic parameters were established from an Eyring plot of the temperature-dependent rate constants, determined in the extended temperature range 119 – 164°C , which displayed an excellent linear correlation ($R^2 = 0.994$). While the derived enthalpy of activation $\Delta H^\ddagger = 36(1) \text{ kcal mol}^{-1}$ was within our expectations, we were surprised by the *positive* entropy of activation $\Delta S^\ddagger = +10 \text{ cal K}^{-1} \text{ mol}^{-1}$. Together with the enthalpy of activation, which is in the range of typical ruthenium–carbonyl bond-dissociation enthalpies, this hinted at CO ligand dissociation as the rate-determining step. To address this point, we determined the dependence of the rate constants on the CO concentration. The essentially linear plot ($R^2 = 0.990$) for the reciprocal observed rate constant, $1/k_{\text{obs}}$, versus $[\text{CO}]$ seemed to support this view. However, this was questioned by the kinetic isotope effect, $k_{\text{H}}/k_{\text{D}} = 2$, which we observed in the thermolysis experiment of the 95% deuterium enriched Ru–D compound **1b**[D₁]. Since a maximum isotope effect of four can be estimated for the Ru–H moiety based on its stretching frequency ($\tilde{\nu}(\text{Ru–H}) = 2030 \text{ cm}^{-1}$), in the infrared (IR) spectrum, this also suggested a significant breaking of the Ru–H bond in the rate-determining step and therefore provided strong arguments against simple Ru–CO bond dissociation as the rate-determining step. Furthermore, by comparison with dissociative CO substitution mechanisms in organometallic complexes, we anticipated a somewhat higher entropy of activation, that is $\Delta S^\ddagger \approx +15$ – $20 \text{ cal K}^{-1} \text{ mol}^{-1}$, if the rate-determining step were purely limited by CO dissociation.^[31] Nevertheless, it is certainly difficult to judge a reaction mechanism based on its entropy of activation. At present, we envisage several potential mechanistic alternatives, without further experimental (in particular thermogravimetry/mass spectrometry (TG/MS) and TG/IR measurements for **1b**) and theoretical results, we prefer not to propose a mechanism for the thermal transformation.

The overall photo-thermal equilibrium of **1a/1b** is the first example of a thermo-optical organometallic switch (photochromic system), based on reversible C–H bond breaking and making. We observed analogous rearrangement processes for the tricarbonyl molybdenum and tungsten systems $[\text{Me}_2\text{C}((\text{C}_5\text{H}_4)\text{M}(\text{CO})_3)_2]$, **2a-Mo** and **2a-W**.^[32] In contrast to the ruthenium complex **1b**, however, the reversed thermal reactions for **2b-Mo** and **2b-W** were significantly faster, which is emphasized in that the photolysis of the molybdenum **2a-Mo** complex had to be pursued at -60°C to slow down the thermal reaction of **2b-Mo**, which displays a low free enthalpy of activation, $\Delta G_{213}^\ddagger = 16 \text{ kcal mol}^{-1}$ ($\Delta G^\ddagger(\text{2b-W}) = 27 \text{ kcal mol}^{-1}$ at 60°C). Based on these results, it is anticipated that the thermo-optical switch properties for this class of systems can be adjusted by the proper choice of the metal and

ligands. Currently, we are studying the mechanistic steps in further detail by methods including time-resolved IR spectroscopy and are also investigating potential applications.

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- [5] Complex **1a** (212 mg, 0.437 mmol) was dissolved in toluene (80 mL) and the solution was transferred to a Teflon tap sealed (Pyrex) Schlenk tube. The tube was immersed in a vessel containing a 1M solution of NaNO₂ and placed 2 cm from a mercury medium-pressure lamp (125 HPKW, shielded by a Quartz jacket water cooling mantle) also immersed in the NaNO₂ solution. The orange toluene solution of **1a** was irradiated for ca. 4 h during which time the solution decolorized (sometimes faintly red solutions were observed in the photolysis). The reaction mixture was evaporated to dryness and the residue recrystallized from ether/pentane at –36 °C from which complex **1b** was obtained as colorless crystals. Isolated yield of complex **1b**: (satisfactory elemental analysis) >95% in several runs. Monitoring of the photolysis of **1a** in sealed NMR tubes showed that the photolysis was essentially quantitative.
- [6] Crystal data **1a**: Orange rectangular parallelepiped 0.5 × 0.5 × 0.2 mm, Monoclinic cell, space group *C2/c* (No. 15), *Z* = 8, *a* = 23.825(2), *b* = 12.566(2), *c* = 11.485(2) Å, β = 111.45(1)°, *V* = 3200.3(9) Å³, ρ_{calcd} = 2.011 g cm^{–3}. 3108 reflections collected, thereof 3035 independent; 3010 reflections with *I* > 0 used for structure solution and refinement. The refinement converged at final *R* values *R*(*I* > 2σ(*I*)) *I* > 0: *R*1 = 0.0234 and *wR*2 = 0.0594 for 264 parameters; residual electron density: 0.36, –0.56 e Å^{–3}. **1b**: Colorless rectangular parallelepiped 0.3 × 0.3 × 0.2 mm; triclinic cell, space group *P1* No. 2, *Z* = 2, *a* = 8.431(1), *b* = 9.659(1), *c* = 10.061(1) Å, α = 85.86(1), β = 85.10(1), γ = 85.63(1)°, *V* = 812.2(2) Å³, ρ_{calcd} = 1.981 g cm^{–3}. 3251 reflections collected, thereof 3049 independent; 3020 reflections with *I* > 0 used for structure solution and refinement. Final *R* values (264 parameters) with *I* > 0 of *R*(*I* > 2σ(*I*)): *R*1 = 0.0194 and *wR*2 = 0.0451; residual electron density: 0.34, –0.37 e Å^{–3}. Data collection: Siemens/Nicolet P4, Mo_{Kα} radiation (0.71073 Å); ω scan; 4° < 2θ < 52° at 205 K for **1a** and 170 K for **1b**. Intensities were corrected for Lorentz and polarization effects. Structure solution: Patterson method using the SHELXS-97 program package; refinement against *F*² with SHELXL-93.^[7] All non-hydrogen atoms were refined anisotropically; the hydrogen atoms positions were located in the difference Fourier map and refined isotropically. 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-147430 (**1a**) and CCDC-147431 (**1b**). 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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Hydrothermal Synthesis, Structure, and Magnetism of $[\text{Co}_2(\text{OH})\{1,2,3-(\text{O}_2\text{C})_3\text{C}_6\text{H}_3\}-(\text{H}_2\text{O})] \cdot \text{H}_2\text{O}$ and $[\text{Co}_2(\text{OH})\{1,2,3-(\text{O}_2\text{C})_3\text{C}_6\text{H}_3\}]:$ Magnetic Δ -Chains with Mixed Cobalt Geometries**

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Solvo- and hydrothermal syntheses have been used for many years to prepare oxide-based materials such as zeolites and phosphates.^[1] The use of these techniques for synthesizing coordination compounds with extended structures is also receiving increasing interest.^[2] Many of the coordination solids thus prepared have small and simple repeat units which come together to build complex symmetrical forms, and this makes these materials particularly esthetically pleasing. Incorporation of the structure-directing organic moiety into the extended structure offers the possibility of producing composite materials, an area of current interest in materials research. A guiding principle of our work is the attempt to express some aspect of the templating ligand's character in the product. For instance, we previously demonstrated the ability of benzene-1,3,5-tricarboxylate to impose threefold symmetry on a three-dimensional metal–ligand array.^[2] We now present the results of reactions with benzene-1,2,3-tricarboxylic acid. This ligand possesses polar and nonpolar regions, a property which we wish to exploit in the preparation of bulk materials which mirror this structural feature. By studying the effect of structure on function we hope to “engineer” specific properties into materials by the action of structure-directing ligands. Of particular interest to us is the exploration of magnetostructural correlations in these types of compound. Our methodology allows us to create a number of hitherto rare, but theoretically important, spin topologies,^[3] and here we report on the formation and properties of two compounds built on the Δ -chain structure. Lattices in which the spin carriers lie at the vertices of triangles are of interest because they provide examples of spin-frustrated materials when antiferromagnetic coupling is present. Of the possible chain-like arrangements of triangles, the Δ -chain (Figure 1a) is of particular theoretical interest,^[4] as it represents a section of the two-dimensional spin-frustrated Kagomé lattice^[5] and provides a rare example of a topologically frustrated one-dimensional system which, in the absence of interchain

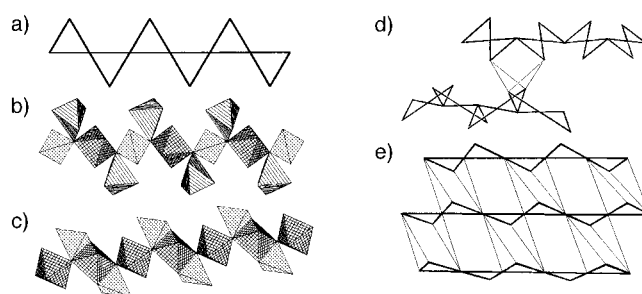


Figure 1. a) The idealized Δ -chain topology with a metal atom at each vertex. Polyhedral representation of a portion of a chain in b) **1** and c) **2**; octahedra are cross-hatched, trigonal bipyramids are striped, and tetrahedra have dotted faces. Topology of the superexchange-mediated magnetic lattice in d) **1** and e) **2**; a magnetic ion resides on each vertex, bold lines represent single-atom bridges, and narrow lines represent three-atom bridges.

couplings, cannot show magnetically ordered states.^[6] Here, in addition, the topological frustration should cause a large degeneracy in the ground state manifold, and at low temperatures unusual quantum spin liquid phases may be found. Whilst the Δ -chain topology has been the subject of extensive theoretical investigation prior to this work, only one real example^[4d,e] was known.

The hydrothermal reaction of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ with 1,2,3-benzenetricarboxylic acid hydrate and NaOH in the approximate ratio 2:1:4 at temperatures between 200 and 220 °C produces a mixture of dark bluish purple prismatic crystals of **1** and thin purple plates of **2**. The synthesis can be optimized to produce predominantly one compound or the other, so that single-phase material is obtained following purification. The X-ray crystal structures^[7] of **1** and **2** show them to have simple and closely related formulas, but extremely complex and entirely different structures. For **1** the asymmetric unit (Figure 2) consists of one ligand, three metal atoms, a μ_3 -OH group, and a terminal coordinated water molecule, as well as two (fractional occupancy) lattice water molecules. The material is built on a framework consisting of strips of corner-sharing $\text{Co}_3(\mu_3\text{-OH})$ triangles which have the Δ -chain topology (Figure 1b). Octahedral and tetrahedral cobalt sites alternate along the backbone of the chain, and pendant trigonal-bipyramidal cobalt sites are attached at each bridging hydroxide. The metal hydroxide strips run along the crystallographic *a* and *b* axes, and no atoms are shared between orthogonal chains. Co1 (octahedral) and Co2 (tetrahedral) have only minor deviations from idealized symmetry, whilst the geometry around Co3 is rather distorted; the two apical atoms are arranged in a nearly linear fashion, but there is significant distortion of the equatorial ligands. Bond lengths and angles for the cobalt ions and the ligand are all normal (Figure 2). Each oxygen atom of the ligand is coordinated to only one metal atom; O1, O2, and O3 are bonded to cobalt atoms which are part of one chain, while O4, O5, and O6 are bonded to an orthogonal chain. Two sites within the channels are occupied by water molecules (O9 and O10). The ligands do indeed arrange themselves so as to produce polar regions surrounding the cobalt hydroxide strips and nonpolar regions surrounding channels (Figure 3). There is no interaction between lattice water molecules and the bridging hydroxide

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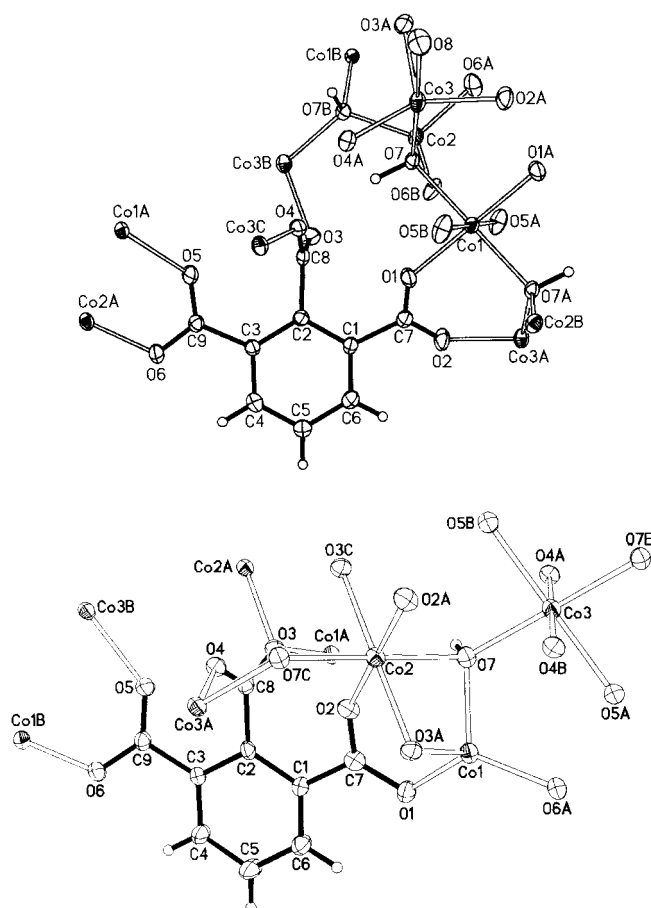


Figure 2. View of the ligand-metal environment in **1** (top) and **2** (bottom).

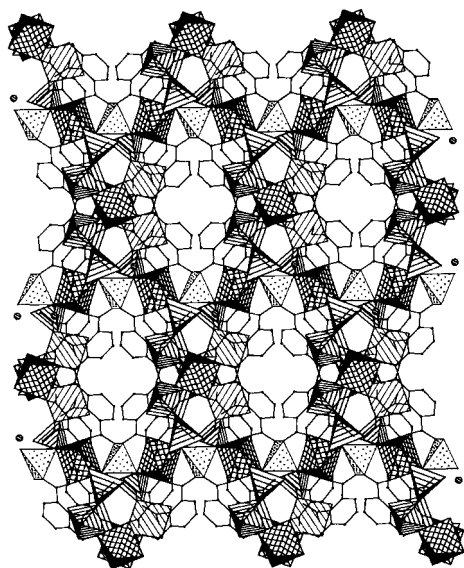
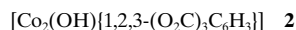
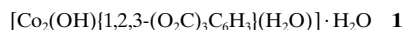


Figure 3. View down the crystallographic *a* axis of the packing in **1** showing the linking of polyhedra by the carboxylate ligands. Shading of polyhedra is as for Figure 1.

as we have observed in similar materials.^[21] The individual Δ -chains are linked to their four orthogonal nearest neighbors by OCO bridges between trigonal-bipyramidal cobalt ions. Two adjacent ions in one chain are both connected to two

similar ions on neighboring chains to give a pseudotetrahedral linkage (Figure 1d). Thus, an infinite three-dimensional lattice is created in which the metal ions form a relative of the pyrochlore^[8] structure, another topology in which topological spin frustration is possible.^[9]



The structure of **2** is also based on the Δ -chain structure in which the chains have backbones consisting of two crystallographically independent octahedral cobalt ions. Pendant tetrahedral cobalt ions are attached by μ_3 -OH groups (Figure 1c) and also to Co2 through a 1,1-bridging carboxylate. The conformation of the ligand and the arrangement of metal atoms around it in **2** is similar to that in **1** (Figure 2). The asymmetric unit contains one complete ligand in which five out of six oxygen atoms are nonbridging and bonded to only one metal center, while O3 bridges two metal atoms. Bond lengths and angles in **2** are all normal. The $\text{Co}_3(\text{OH})$ unit shows greater distortion than that in **1**, and the Co1-Co2 edge, which is triply bridged, is significantly shorter (2.906(2) vs. 3.419(2) and 3.666(1) Å). The ligand straddles adjacent chains and holds them together with 1,3-bridging carboxylate groups to form infinite layers (Figure 4). This forms further triangles

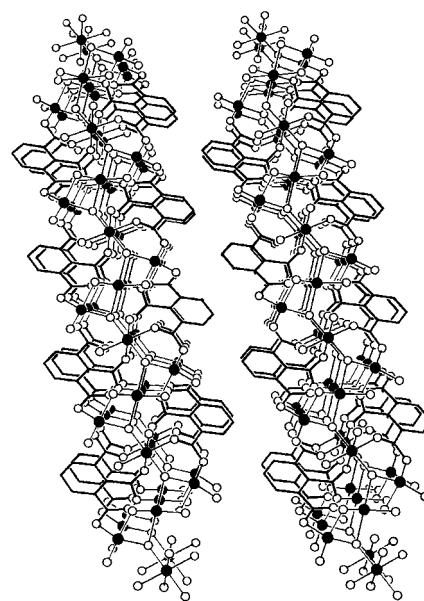


Figure 4. View down the crystallographic *b* axis showing the packing of layers in **2**.

that link individual Δ -chains to their two adjacent equivalents (Figure 1e). The cobalt atoms and the polar half of the ligand lie in the interior of the layer sandwiched between the nonpolar ligand regions. The ligands are arranged in such a way that the surface of the layers undulate. The grooves of adjacent layers fit quite tightly together, although we assume there are only weak interlayer interactions resulting from the nonpolar nature of the surfaces. The platelike shape of the crystals and their brittle character are good evidence for this.

Compounds **1** and **2** have similar nearest-neighbor interactions, but the 1,3-carboxylate bridges which link the next-nearest neighbors generate entirely different lattices, and therefore different superexchange topologies. Furthermore the triangles forming the chains in the two compounds deviate from equilateral by different amounts. At a simplistic level this might be expected to lead to different ratios between the three exchange interactions corresponding to the triangle's edges. For an idealized frustrated arrangement these should be equal, and deviation from equality is likely to lead to suppression of the frustration. A further complication is the possibility of orbital contributions to the susceptibility from the octahedral sites, particularly as the two compounds contain different proportions of sites with this geometry.

The magnetic susceptibility curve for **1** (Figure 5) resembles that expected for a simple paramagnet with the addition of a shoulder at approximately 4 K. Between 50 and 300 K, **1**

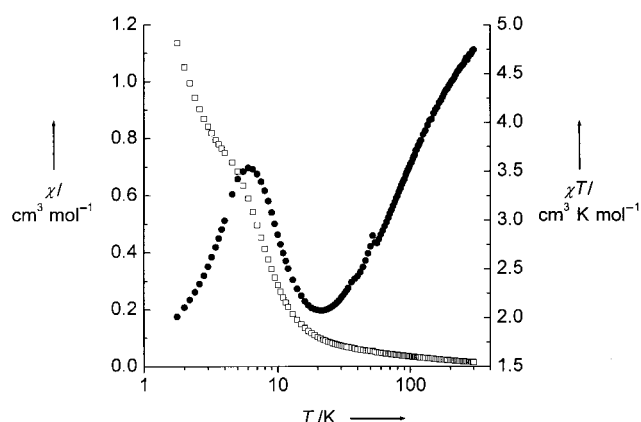


Figure 5. Plot of the susceptibility χ ($\square$) and χT ($\bullet$) for **1** derived from field cooled measurements at 100 G.

obeys the Curie–Weiss law, and the values of $C = 5.61 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$ and $\theta = -57 \text{ K}$ correspond to a high-temperature moment of $6.70 \mu_B$ per unit. As expected, this is slightly higher than the spin-only value resulting from the orbital contribution from the single octahedral Co^{II} ion in the formula unit. Plotting the product χT against T is also very informative. Down to 20 K this value decreases, confirming that the dominant exchange is antiferromagnetic; however, following a local minimum at 20 K, the value increases up to a local maximum at 5 K, before again decreasing. This is exactly the behavior predicted^[4d,e] for a Δ -chain. The Weiss constant is significantly larger than others we have measured for Co^{II} compounds which show long-range ordering at higher temperatures.^[2g] It is therefore significant that no sharp transition indicative of long-range order is observed, as this suggests that either spin frustration or a one-dimensional character as a result of weak interchain interactions may be important in **1**.

The magnetization of **2** shows a dramatic phase transition at approximately 40 K to a state with spontaneous magnetization (Figure 6). The sample obeys the Curie–Weiss law in the high-temperature paramagnetic regime, and fitting between 120 and 300 K yields values of $C = 5.44 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$ and $\theta = -27 \text{ K}$, characteristic of an overall antiferromagnetic interaction. The plot of χT shows a broad local minimum at

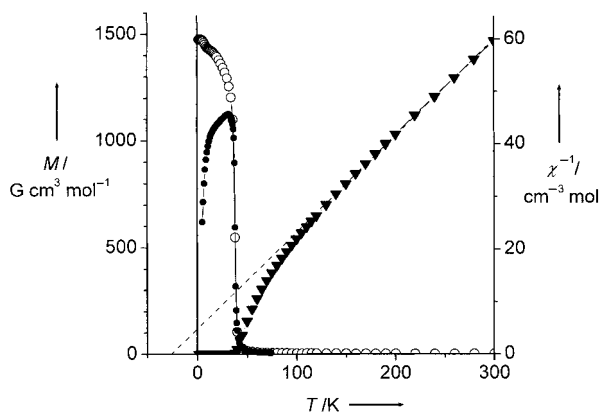


Figure 6. Graph of field cooled magnetization ($\square$), zero-field cooled magnetization ($\bullet$), and inverse susceptibility $1/\chi$ ($\blacktriangledown$) for **2** in a field of 100 G.

approximately 110 K. The combination of antiferromagnetic interactions and a large spontaneous magnetization indicated that the material is a ferrimagnet. This was confirmed by ac susceptibility measurements (Figure 7), in which the imaginary, “out-of-phase” component χ'' becomes nonzero below

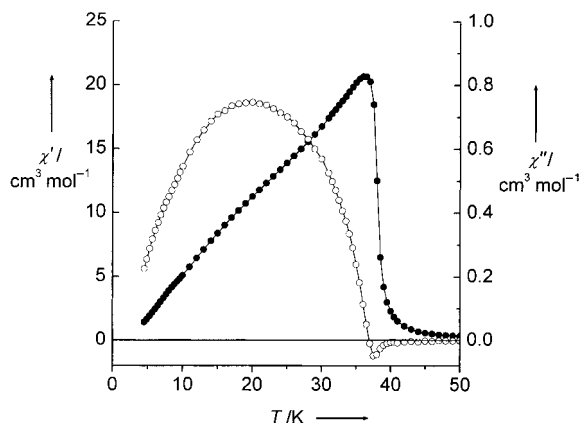


Figure 7. Real χ' ($\bullet$) and imaginary χ'' ($\circ$) components of the ac susceptibility of **2**.

T_c .^[10] Hysteresis measurements (Figure 8) in this ferrimagnetic state gave a saturation magnetization of $9700 \text{ G cm}^3 \text{ mol}^{-1}$ and revealed coercive fields of 250 and 1800 G at 25

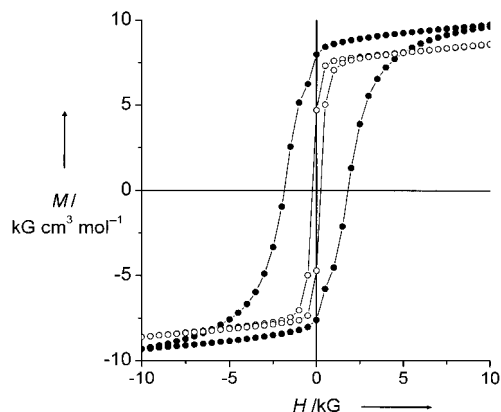


Figure 8. Hysteresis curve for **2** between $\pm 10 \text{ kG}$ at 5 K ($\bullet$) and 25 K ($\circ$).

and 5 K, respectively. The saturation magnetization appears to correspond to between 1/4 and 1/3 of that expected for a parallel (ferromagnetic) arrangement of spins. This suggests a complicated ground-state spin configuration.

It is remarkable that materials with such similar building blocks, that is, metal hydroxide chains, and arrangement of metal ions around the ligand, can have such different structures. In investigating the reactivity of this ligand we hoped to find that it would encourage the formation of low-dimensional structures, and this proved correct; both compounds contain one-dimensional metal–oxygen chains, and compound **2** has an overall two-dimensional structure. Both structures are made up of arrays of *A*-chains. In the case of **1** this gives rise to a completely new three-dimensional spin-frustrated topology with no magnetic ordering down to 2 K. Compound **2** also displays complex and unusual magnetism. In both cases we would ascribe the complexity of structure and magnetism to the presence of relatively low symmetry molecular components.

Experimental Section

1: In a typical experiment, 1,2,3-benzenetricarboxylic acid hydrate (0.110 g, 0.52 mmol) was dissolved in a solution of NaOH (0.085 g, 2.13 mmol) in H₂O (6 mL), and the resulting solution added to a solution of CoCl₂·6H₂O (0.250 g, 1.05 mmol) in 2 mL of water. The blue mixture was placed in a 23-mL Teflon-lined autoclave and heated at 220 °C for 16 h. The autoclave was cooled over a period of 4 h, and the product, which was a mixture of dark purple crystals of **1** and an approximately equal amount of **2**, was collected by filtration, washed with water, and dried in air. Pure product was obtained by manual separation. Final yield of **1**: 35 mg, 19% based on Co (total yield of crude product: 75 mg). Elemental analysis (%) calcd for C₉H₈O₉Co₂: C 28.60, H 2.13; found: C 28.65 H, 1.76.

2: The same procedure as for the preparation of compound **1** was followed, except that the autoclave was heated to 200 °C for 40 h. Yield: 90 mg, 52% based on Co. Elemental analysis (%) calcd for C₉H₄O₇Co₂: C 31.58, H 1.14; found: C 30.57, H 1.14.

Magnetization studies were performed with a Quantum Design MPMS SQUID magnetometer. The sample magnetizations were corrected for the intrinsic diamagnetic contributions by using Pascal's constants;^[11] $\chi_{\text{dia}} = -147 \times 10^{-6} \text{ cm}^3 \text{ mol}^{-1}$ for **1** and $-121 \times 10^{-6} \text{ cm}^3 \text{ mol}^{-1}$ for **2**.

Field cooled magnetization measurements on **1** were performed with applied fields of 10 and 100 G between 2 and 300 K. For **2**, field cooled magnetization measurements were recorded in a field of 100 G between 2 and 300 K. Subsequent field cooled and zero-field cooled measurements were recorded for the ordered phase, as well as hysteresis measurements at 5 and 25 K between -10000 and $+10000$ G. Dynamic ac susceptibility measurements were made between 4.5 and 50 K with a 1 G oscillating field (125 Hz) and no offset field.

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A Convenient Method for the Generation of a Disulfur Monoxide Equivalent and Its Reaction with Diazoalkanes to Yield Dithiirane 1-Oxides**

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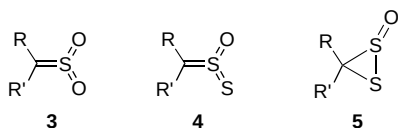
Dedicated to Professor Rolf Huisgen
on the occasion of his 80th birthday

Recently we found that thermal decomposition of tetra-thiolane 2,3-dioxide **1** (1-Ad = 1-adamantyl) generates disulfur monoxide S_2O , which was trapped with 2,3-dimethyl-1,3-butadiene to give the 3,6-dihydro-1,2-dithiin 1-oxide **2** in high

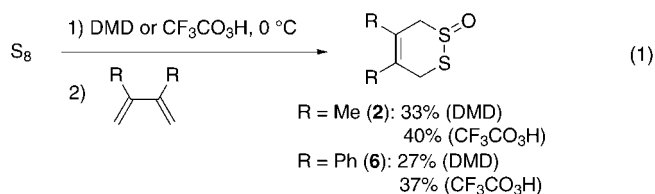


yield (ca. 90%).^[1] Up to now, the use of S_2O in organic chemistry has been limited to reactions with a few 1,3-butadienes.^[2] One reason for this is probably the troublesome methods for its generation; for example, pyrolysis of ethylene episulfide,^[2] electronic discharge of SO_2 ,^[3] and reactions of heavy metal oxides or sulfides with elemental sulfur at 250–400 °C or with gaseous $SOCl_2$ at 160 °C and 0.5 Torr.^[3]

Decomposition of oxides of elemental sulfur (S_8) is expected to be an alternative way to generate S_2O . Steudel et al. reported that S_nO ($n=6-8$) are isolable but decompose to SO_2 and sulfur in solution or to S_2O and S_{n-2} in vacuo.^[4-6] Here we report a convenient and inexpensive method for the generation of S_2O ^[7] and its reaction with typical 1,3-dipoles, namely, diazoalkanes. To our knowledge, there is no precedent for the reaction of diazoalkanes with S_2O , although reactions with SO_2 ,^[8] SO ,^[9] and thioketone S -oxides (sulfines) have been investigated.^[10] The reaction of diazoalkanes with SO_2 was claimed to give thioketone S,S -dioxides (sulfenes) **3**.^[8] If the reaction of diazoalkanes with S_2O takes place in a similar fashion, the formation of thiosulfenes **4** or their cyclic isomers, dithiirane 1-oxides **5**, is expected.

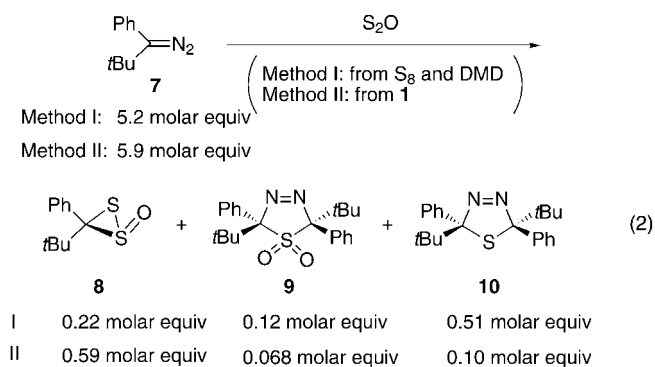


An equimolar amount of dimethyldioxirane (DMD)^[11] was added to a solution of elemental sulfur (S_8) in CH_2Cl_2 /benzene at 0 °C, and the solution was stirred for 1 h. The mixture contains S_8O as an S_2O precursor.^[7] Then, 2,3-dimethyl- or 2,3-diphenyl-1,3-butadiene (**11** and **3** molar equiv, respectively) was added, and the mixture was warmed to room temperature. Workup gave the adducts **2** and **6**^[2] in 33 and 27 % yield, respectively [Eq. (1)]. The use of excess DMD



did not improve the yields of the adducts because of the instability of higher oxides of S_8 .^[4d] When trifluoroperoxyacetic acid was employed as the oxidant in CH_2Cl_2 ,^[4b] the yields of **2** and **6** improved to 40 and 37 %, respectively. The above results indicate that 0.3–0.4 molar equiv of S_2O is available from equimolar amounts of S_8 and an oxidizing agent under these conditions.

We next examined reactions of diazoalkanes with S_2O generated in situ. Two methods were investigated: in method I, S_2O was generated from one molar equivalent of S_8 and DMD in CH_2Cl_2 /benzene or in CH_2Cl_2 , and in method II, from **1** in CH_2Cl_2 .^[1] The efficiency of the generation of S_2O by method I is 30 %, as mentioned above, and by method II, nearly 90%.^[1] The reaction of *tert*-butyl(phenyl)diazomethane **7** (5.2 molar equiv) with S_2O [Eq. (2); method I] gave

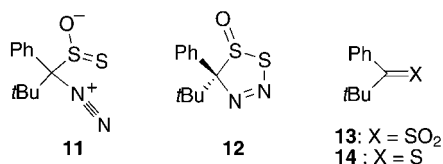


the expected dithiirane 1-oxide **8** (0.22 molar equiv based on S_8 and DMD) along with 1,3,4-thiadiazoline 1,1-dioxide **9**^[12] (0.12 molar equiv) and 1,3,4-thiadiazoline **10**^[12] (0.51 molar equiv). The configuration of **8** was determined to be $1R^*,3S^*$ from ^1H NMR spectroscopic data, and no other stereoisomer was obtained. The reaction of **7** (5.9 mol equiv) with S_2O by method II gave **8** in higher yield (0.59 molar equiv based on **1**) along with **9** and **10** in lower yields (0.068 and 0.10 molar equiv, respectively).

In the proposed mechanism for the reaction of Equation (2), three reactions take place independently. By analogy with reactions of diazoalkanes with SO_2 ,^[8] the reaction of **7** with S_2O would give an initial adduct **11** or **12**, although we

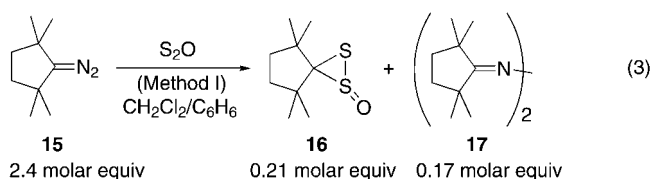
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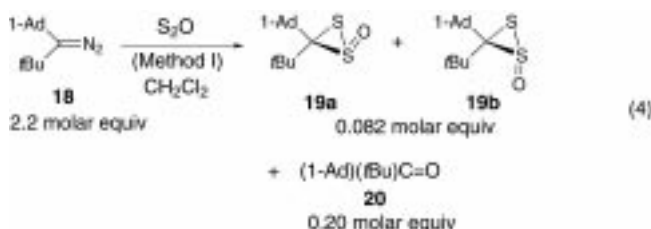


have no direct evidence for its formation. The extrusion of N₂ from the intermediate yields the dithiirane 1-oxide **8**. The formation of the 1,3,4-thiadiazoline 1,1-dioxide **9** implies the generation of sulfene **13** by reaction of **7** with SO₂, which undergoes a cycloaddition with **7** to give **9**.^[8] The SO₂ would be supplied by decomposition of higher oxides of S₈^[4d] or disproportionation of S₂O.^[1, 13] The 1,3,4-thiadiazoline **10** is a cycloadduct of the thioketone **14** and **7**.^[14] In fact, the thioketone **14**, prepared by a reported method,^[15] reacted with **7** quickly to give **10** in high yield. Since a separate experiment revealed that the reaction of **7** and elemental sulfur (S₈), which gives **14**, is sluggish under similar conditions,^[16] sulfur allotropes S_n that are more reactive than S₈ should be responsible for the formation of **14**.

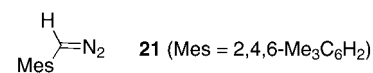
The reaction of a diazocyclopentane **15**^[17] (2.4 molar equiv) with S₂O (method I) yielded the spirodithiirane 1-oxide **16** (0.21 molar equiv) along with azine **17**^[17] (0.17 molar equiv) [Eq. (3)]. The formation of azines by reaction of diazoalkanes



with SO₂ is known.^[8, 18] The reaction of 1-adamantyl-*tert*-butyldiazomethane **18** with S₂O (method I) gave two stereoisomeric 1-oxides **19a** and **19b**,^[19] albeit in a low combined yield (0.082 molar equiv), probably for steric reasons, together with ketone **20** as the main product [Eq. (4)]. In these cases, products corresponding to **9** and **10** were not obtained.



Diphenyldiazomethane and monoaryl diazomethane **21** failed to react with S₂O (method I): diphenyldiazomethane gave a complex mixture, whereas **21** gave an alkene^[8, 18] ((*E*)- and (*Z*)-MesCH=CHMes,^[20] 5:1) together with an azine^[8, 18] ((MesCH=N)₂)^[21].



In summary, we have developed a convenient method for the generation of an S₂O equivalent by treatment of elemental sulfur with an oxidizing agent. The efficiency of generation was 30–40%. We also investigated the reaction of S₂O with diazoalkanes, which provides an alternative method for the preparation of dithiirane derivatives.^[22]

Experimental Section

Materials: elemental sulfur (S₈) was recrystallized from CS₂ before use. Dimethyldioxirane (DMD) was prepared as a solution in acetone.^[11]

General procedure for the generation of S₂O (method I) and the trapping reaction: DMD (0.10 M in acetone) was added to a solution of S₈ (80 mg, 0.31 mmol) in dichloromethane (10 mL) and benzene (2 mL) at 0 °C. After stirring at 0 °C for 1 h, a solution of a trapping reagent in dichloromethane was added. The mixture was warmed to room temperature, stirred for 1 h, and evaporated to dryness under reduced pressure. The yields of **2** and **6** were determined from ¹H NMR integral ratios with 9-acetylanthracene as internal standard.

Reaction of **7** with S₂O: Method I: 1) A solution of S₈ (32 mg, 0.124 mmol) in dichloromethane/benzene was treated with DMD (0.123 mmol), followed by addition of a solution of **7** (112 mg, 0.64 mmol, 5.2 equiv) in dichloromethane. Yields of **8**, **9**, and **10** were determined to be 0.027 (22% based on DMD), 0.0144, and 0.0624 mmol, respectively, by the ¹H NMR integral-ratio method with thioanisole as internal standard. 2) A solution of S₈ (70 mg, 0.27 mmol) in dichloromethane/benzene was treated with DMD (0.27 mmol), followed by addition of a solution of **7** (246 mg, 1.34 mmol, 4.9 equiv) in dichloromethane. The mixture was subjected to medium-pressure liquid chromatography (SiO₂, hexane/Et₂O 4/1) to give **8** (11 mg, 0.047 mmol, 17% based on DMD), **9** (71 mg, 0.185 mmol), and **10** (26 mg, 0.073 mmol). Method II: A solution of 5-(1-adamantyl)-5-(*tert*-butyl)tetra-thiolane (**22**)^[1, 23] (33 mg, 0.10 mmol) in dichloromethane (8 mL) was treated with DMD (0.40 mmol) at –20 °C. The mixture was stirred for 1.5 h at –20 °C and then the solvent was removed under reduced pressure. The residue was dissolved in a solution of **7** (106 mg, 0.595 mmol, 5.9 equiv) in dichloromethane (10 mL) at –20 °C, and then the mixture was warmed to room temperature. Yields of **8**, **9**, and **10** were determined to be 0.059 (59% based on **22**), 0.0068, and 0.0101 mmol, respectively, from the ¹H NMR integral ratios with thioanisole as internal standard.

8: Colorless crystals, m.p. 62–64 °C (dichloromethane/hexane). ¹H NMR (400 MHz, CDCl₃): δ = 1.02 (s, 9H), 7.37–7.50 (m, 5H); ¹³C NMR (100.6 MHz, CDCl₃): δ = 28.1, 38.4, 86.2, 127.8, 128.8, 133.2, 133.3; IR (KBr): ν̄ = 1118 cm^{–1} (S=O); elemental analysis (%) calcd for C₁₁H₁₄OS₂: C 58.36, H 6.23; found: C 58.16, H 6.26.

9: Pale yellow crystals, m.p. 189–192 °C (hexane). ¹H NMR (400 MHz, CDCl₃): δ = 1.06 (s, 18H), 7.31–7.47 (m, 6H), 7.54–7.56 (m, 4H); ¹³C NMR (100.6 MHz, CDCl₃): δ = 26.9, 42.1, 127.2, 127.5, 127.9, 128.6, 129.8, 133.4 (the signal of the thiadiazoline C atom seems to be superimposed on a signal for an sp² C atom); IR (KBr): ν̄ = 1304, 1136 cm^{–1} (SO₂); elemental analysis (%) calcd for C₂₂H₂₈N₂O₂S: C 68.72, H 7.34, N 7.29; found: C 68.69, H 7.39, N 7.33.

10: Colorless needles, m.p. 157–158 °C decomp (hexane). ¹H NMR (400 MHz, CDCl₃): δ = 0.81 (s, 18H), 7.22–7.32 (m, 6H), 7.60 (brd, *J* = 7.4 Hz, 4H); ¹³C NMR (100.6 MHz, CDCl₃): δ = 26.8 (CH₃), 41.3 (C), 124.4 (C), 127.06 (CH), 127.10 (CH), 128.2 (CH), 142.0 (C); elemental analysis (%) calcd for C₂₂H₂₈N₂S: C 74.95, H 8.01, N 7.95; found: C 75.32, H 8.06, N 8.04.

Reaction of **15** with S₂O (method I): A solution of S₈ (32.6 mg, 0.127 mmol) in dichloromethane/benzene was treated with DMD (0.111 mmol), followed by addition of a solution of **15** (40 mg, 0.265 mmol) in dichloromethane. The mixture was subjected to medium-pressure liquid chromatography (SiO₂, hexane/Et₂O 4/1) to give **16** (4.8 mg, 0.0235 mmol, 21% based on DMD) and **17** (5.4 mg, 0.195 mmol).

16: m.p. 81–83 °C (hexane). ¹H NMR (400 MHz, CDCl₃): δ = 0.72 (s, 3H), 1.04 (s, 3H), 1.18 (s, 3H), 1.56 (s, 3H), 1.70–1.90 (m, 3H), 2.04–2.11 (m, 1H); ¹³C NMR (100.6 MHz, CDCl₃): δ = 23.1, 28.5, 29.3, 30.9, 39.2, 41.7, 44.2, 48.0, 90.0; IR (KBr): ν̄ = 1123 cm⁻¹ (S=O); elemental analysis (%) calcd for C₉H₁₆OS₂: C 52.90, H 7.89; found: C 53.51, H 8.00.

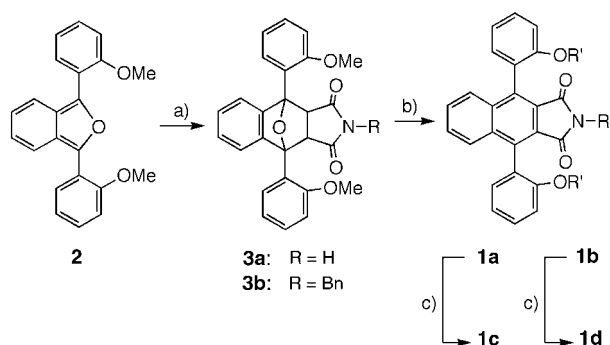
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Solid-State Isomerization of Atropodiastereomers: Effective Diastereoselection through Polymorphic Transformations**

Cathy Einhorn, André Durif, Marie-Thérèse Averbuch, and Jacques Einhorn*

Polymorphism is a fascinating phenomenon accompanied by a lot of strange manifestations.^[1] It is generally defined as the existence of a given compound in more than one crystalline form. In conformational polymorphs,^[2] a given molecular compound adopts different conformations in different polymorphs. But, at a molecular level, conformational changes may involve quite high energy barriers, allowing in some cases the isolation of separate stereoisomers (atropisomers) which do not interconvert rapidly in solution at room temperature, but do so if enough energy is supplied. Herein we report solid-state thermal isomerizations of compounds **1**, which present such a type of atropisomerism. These isomerizations have features reminiscent of polymorphic transformations, although not involving polymorphs in the usual sense of the word.^[3]

As depicted in Scheme 1, the synthesis of **1** has been achieved by Diels–Alder reactions between isobenzofuran **2** and maleimide or *N*-benzylmaleimide, giving adducts **3a** or **3b** in good yields. Their aromatization under strongly acidic conditions furnished **1a** and **1b** quantitatively. Demethylation of **1a** and **1b** gave diphenols **1c** and **1d** in high yields.



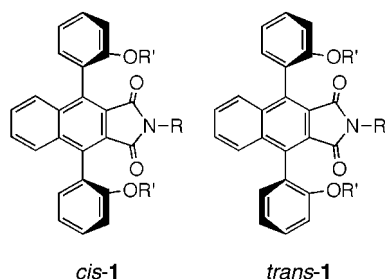
Scheme 1. Reagents, conditions, and yields: a) for **3a**: 1 equiv maleimide, toluene, RT, 6 h, 96%; for **3b**: 1 equiv *N*-benzylmaleimide, toluene, RT, 6 h, 81%; b) 6 equiv MeSO₃H, CH₂Cl₂, RT, 12 h, > 99% for **1a**, > 99% for **1b**; c) 3 equiv BBr₃, CH₂Cl₂, –78 °C to RT, 15 h, 98% for **1c**, 99% for **1d**. Full details can be found in the Supporting Information. RT = room temperature.

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

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- [7] A referee proposed that we examine the reaction of S₈O with trapping reagents, with regard to the mechanism of the reactions reported here. The reaction of S₈O, prepared by a reported method,^[4b] with 2,3-dimethyl-1,3-butadiene in dichloromethane at room temperature for 1 h gave **2** in only 1.4% yield, while that carried out under reflux gave **2** in 25% yield. At present we do not have direct evidence for the existence of free S₂O in solution, so that “S₂O” should be read as “S₂O equivalent” throughout this paper.
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a: R = H, R' = Me; **b:** R = Bn, R' = Me
c: R = H, R' = H; **d:** R = Bn, R' = H

For each compound of the series **1a–d**, the atropisomerization barrier was high enough to allow isolation of the diastereomeric *cis* and *trans* isomers. None of these showed noticeable interconversion in solution after one day at 20 °C. On the other hand, fast equilibration occurred in boiling toluene (b.p. 111 °C), leading, after two hours, to a 45:55 *cis:trans* ratio for **1a** and **1b** (Table 1, entries 1, 2 and 10), and

Table 1. Thermal isomerization of compounds **1a–d**.

Entry	Compound	Starting <i>cis:trans</i> ratio ^[a]	Isomerization conditions <i>T</i> [°C]/ <i>t</i> [h]	Final <i>cis:trans</i> ratio ^[a]
1	1a	100:0	111/2 ^[b]	45:55
2	1a	0:100	111/2 ^[b]	45:55
3	1a	100:0	111/2 ^[c]	98:2
4	1a	100:0	180/1 ^[c]	70:30
5	1a	100:0	180/15 ^[c]	10:90
6	1a	100:0	180/48 ^[c]	1:99
7	1a	0:100	180/48 ^[c]	0:100
8	1a	100:0	285/0.1 ^[d]	45:55
9	1a	0:100	285/0.1 ^[d]	45:55
10	1b	100:0	111/2 ^[b]	45:55
11	1b	45:55	180/48 ^[c]	5:95
12	1c	0:100	111/2 ^[b]	50:50
13	1c	50:50	180/48 ^[c]	95:5
14	1d	0:100	111/2 ^[b]	50:50
15	1d	40:60	180/48 ^[c]	ca. 100:0

[a] Determined by HPLC analysis. [b] Solution isomerization in refluxing toluene. [c] Heating in the solid state. [d] Complete melting of the sample, followed by fast cooling.

to a nearly 50:50 ratio for **1c** and **1d** (Table 1, entries 12 and 14). As both diastereomers of **1a** are crystalline solids with high melting points (> 250 °C), we have also investigated their isomerization in the solid state. When pure *cis*-**1a**, as a microcrystalline powder, was heated at 111 °C for two hours, small amounts of *trans*-**1a** formed but the diastereomeric ratio was far from that of the solution equilibrium. The isomerization rate increased as the temperature was raised: a *cis:trans* ratio of about 70:30 was obtained after one hour at 180 °C. More surprisingly, after 15 hours at 180 °C, the ratio was 10:90 in favor of the *trans* isomer, having overtaken the solution equilibrium ratio! Further heating at 180 °C for two days led to an almost complete isomerization of the sample (*cis:trans* 1:99) (Table 1, entries 3–6). During these experiments, no macroscopic changes of the sample, in particular no melting (even partial) were noticed. When similar experi-

ments were performed with solid *trans*-**1a**, no isomerization at all was noticed (Table 1, entry 7). Heating *cis*-**1a** or *trans*-**1a** up to complete melting (> 285 °C) and fast cooling of the samples gave the same ratio as that of the solution equilibrium (*cis:trans* 45:55) (Table 1, entries 8 and 9). A similar behavior was found with other compounds of the series: A 5:95 ratio was obtained after heating a 45:55 mixture of *cis*-**1b:trans**-**1b** in the solid state for two days at 180 °C (Table 1, entry 11). Under identical conditions, a 95:5 ratio in favor of the *cis* isomer was obtained for **1c**, and **1d** gave almost pure *cis* isomer (Table 1, entries 13 and 15).

On a Kofler hot bench “instantaneous” melting points of 250–252 °C for *cis*-**1a** and > 270 °C for *trans*-**1a** were obtained. For *trans*-**1a**, differential scanning calorimetry (DSC) gave sharp heat absorption at the melting point (281.4 °C) without any noticeable phase transition below this temperature. For *cis*-**1a** progressive heat absorption occurred within a large temperature interval, followed by a sharp peak with a maximum at 283.6 °C (Figure 1). These results suggest a solid

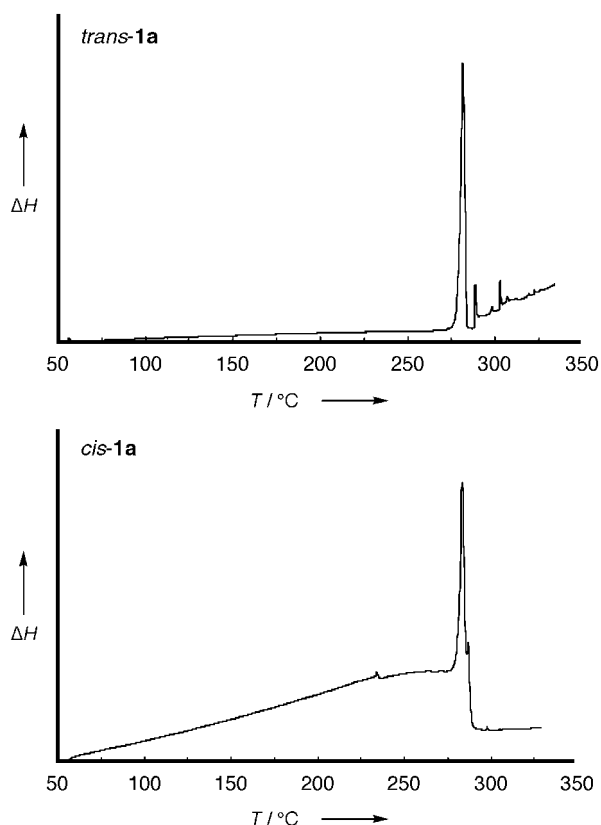


Figure 1. DSC heating thermograms of *trans*-**1a** and *cis*-**1a**. Heating rate 5 K min^{−1}.

-state transformation of *cis*-**1a**, yielding *trans*-**1a** in the same crystalline form as that obtained by room temperature crystallization of *trans*-**1a**, as confirmed by X-ray studies: Single-crystal X-ray diffraction analysis has been performed for both diastereomers of **1a**.^[7] The crystal of *trans*-**1a** was monoclinic (space group *P*2₁/*n*, *a* = 10.948(2), *b* = 8.269(3), *c* = 11.165(3) Å, β = 90.98(2)°, *V* = 1010.6(4) Å³, *Z* = 2). The enantiomers of *trans*-**1a** are statistically interchangeable at each molecular site of the lattice, by exchanging the position

of the fused benzene ring and that of the imide moiety. Compound *trans*-**1a** crystallized as a pseudoracemate or solid solution of enantiomers, a rather uncommon behavior of chiral compounds in the solid state (Figure 2a).^[8] The

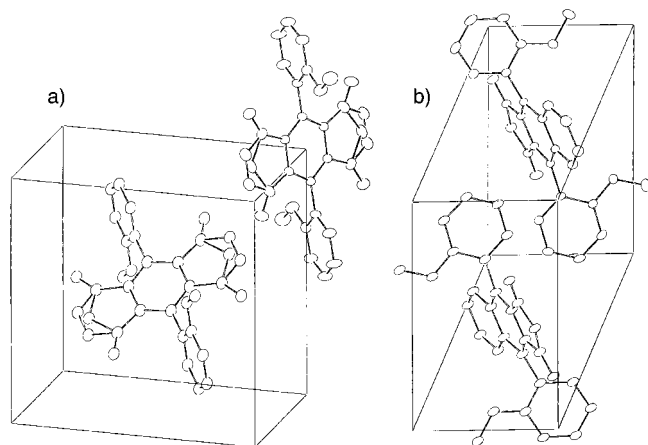


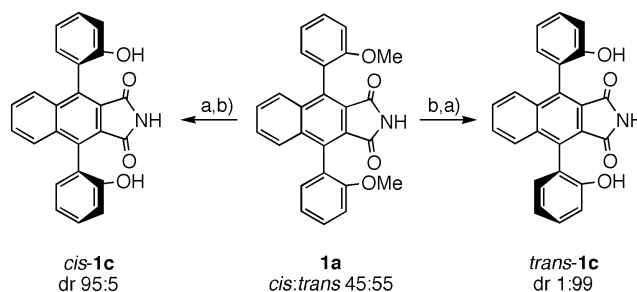
Figure 2. Crystal packing diagram of a) *trans*-**1a** and b) *cis*-**1a**. Hydrogen atoms have been omitted for clarity.

crystal of *cis*-**1a** was triclinic (space group $P\bar{1}$, $a = 9.136(4)$, $b = 11.029(5)$, $c = 10.368(5)$ Å, $\alpha = 100.37(2)$, $\beta = 111.79(2)$, $\gamma = 111.04(2)^\circ$, $V = 996.5(9)$ Å³, $Z = 2$; Figure 2b). A sample of polycrystalline *cis*-**1a**, heated for two days at 180 °C, was next submitted to X-ray powder diffraction. The diffraction pattern of this sample was identical to that of a simulation obtained from the single-crystal X-ray diffraction data of *trans*-**1a**.

The preceding results can be rationalized as follows. At room temperature, the diastereomeric *cis* and *trans* isomers are separate compounds, in solution and in the solid state. Each of them has its own physicochemical properties, in particular its own crystalline form. At higher temperatures, the isomers interconvert rapidly in solution. Therefore, their identity as separate compounds vanishes and they should then rather be considered as two conformers of a unique compound in conformational equilibrium. Consequently, at a temperature at which interconversion is fast in solution, crystalline *cis* and *trans* isomers can be considered as two conformational polymorphs of that unique compound. Two polymorphic forms having in general different stabilities, there will be a tendency of the metastable crystals to transform into the more stable ones.^[1] The consequence is that one crystalline form will disappear at the expense of the other, with, in the present case, concomitant selection of one conformer at the expense of the other. After cooling, the diastereomeric ratio of the macroscopic sample remains “frozen” at the point it had reached in the solid–solid transformation. In the melt, the ordering effect of the crystal lattice disappears and equilibration occurs very rapidly. Fast cooling “freezes” then the equilibrium reached in the melt.

An interesting point to be emphasized is that the same type of behavior has been found throughout the series **1a–d**, either the *cis* or the *trans* isomer being favored. Indeed, the driving forces that are operative in these solid-state isomer-

izations are related to crystal packing effects. These collective processes allow an efficient selection of stereoisomers which, otherwise, are obtained in nearly equal amounts by solution equilibration. As depicted in Scheme 2, either *cis*-**1c** or *trans*-**1c**, both in high diastereomeric purity, is obtained starting from an identical sample of **1a**, simply by carrying out solid-state isomerization *after* or *before* performing O-demethylation.



Scheme 2. Reagents and conditions: a) 3 equiv BBr₃, CH₂Cl₂, –78 °C to RT, 15 h; b) solid-state isomerization, 180 °C, 2 days.

As far as we know, this constitutes the first description of polymorphic transformations applied to a selection of atropisomers, which have such a long persistence in solution at room temperature.^[9] It could offer new opportunities for controlling the relative stereochemistry of two or more stereogenic axes—structural features found among various natural and synthetic compounds.

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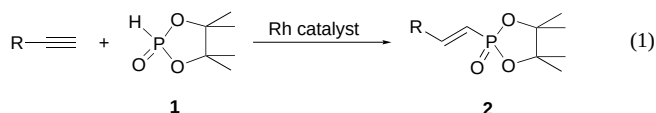
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- [7] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-149632 (*cis*-**1a**) and CCDC-149633 (*trans*-**1a**). 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] A solid-state polymorphic transformation of racemic 1,1'-binaphthyl with spontaneous appearance of optical activity has been described. See ref. [6c]. See also: R. B. Kress, E. N. Duesler, M. C. Etter, I. C. Paul, D. Y. Curtin, *J. Am. Chem. Soc.* **1980**, 102, 7709–7714. However, half-life for racemization of 1,1'-binaphthyl in solution is only about 2.5 h at 20 °C.

Rhodium-Catalyzed Hydrophosphorylation of Terminal Alkynes Leading to Highly Selective Formation of (*E*)-Alkenylphosphonates: Complete Reversal of Regioselectivity to the Palladium-Catalyzed Counterpart**

Chang-Qiu Zhao, Li-Biao Han,* Midori Goto, and Masato Tanaka*

Transition metal catalyzed addition reactions of heteroatom compounds across unsaturated carbon–carbon linkages are emerging rapidly as some of the most attractive, versatile, and clean methods for constructing carbon–heteroatom bonds.^[1] However, similar methodologies for phosphorus compounds, which play an important role in our daily life,

are limited.^[1f] All of the successful metal-catalyzed additions of P^V compounds so far reported have been conducted by employing palladium catalysts, usually at elevated temperatures.^[1f] Taking advantage of the exceptionally high reactivity of the five-membered cyclic hydrogen phosphonate **1**,^[2] we found the first successful rhodium-catalyzed hydrophosphorylation of alkynes, which affords high yields of the corresponding (*E*)-alkenylphosphonates **2** with excellent regio- and stereoselectivities [Eq. (1)]. The reaction readily



takes place even at room temperature with a complete regiochemical reversal to its palladium-catalyzed counterpart.^[3] Alkenylphosphonates, which are not readily accessible by conventional methods, are key intermediates for the preparation of the commercial antibacterial agent Fosfomycin and analogues.^[4] The synthetic and biological utilities of alkenylphosphonates are also well documented.^[5]

A mixture of **1** and one equivalent of phenylacetylene in toluene was stirred in the presence of [RhCl(PPh₃)₃] (3 mol %) at room temperature for 2 h to give a clear yellow solution, in which the corresponding product 2-phenyl-1-ethenylphosphonate (**2a**) was formed exclusively in 31 % yield. Its yield increased to 43 % after 24 h, but further extension to 48 h resulted in only a marginal increase. However, upon heating at 80 °C, the same mixture resumed the reaction to give a quantitative yield of **2a** after 1 h.

The solvent employed significantly influenced the progress of the reaction. In THF, the reaction kept proceeding smoothly, albeit slowly, to reach 97 % yield after 48 h at room temperature. When dichloromethane, acetonitrile, and in particular, acetone were used as the solvents, great enhancement of the reaction rate was realized. Hydrophosphorylation in acetone was complete after a few hours at room temperature and gave the adduct quantitatively.

Wilkinson-type complexes [RhX(PPh₃)₃] exhibited high catalytic activity. Other PPh₃-ligated Rh^I complexes such as [RhCl(CO)(PPh₃)₂] also formed **2a** in moderate yields at elevated temperatures. However, the phosphane-free rhodium complexes [[Rh(cod)Cl]₂] (cod = 1,5-cyclooctadiene) and [[Rh(CH₂=CH₂)₂Cl]₂] were inactive. The cationic rhodium complex [[Rh(cod)₂]⁺(OTf)[−] (Tf = CF₃SO₂), used either alone or in combination with PPh₃, also did not show catalytic activity.

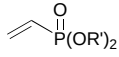
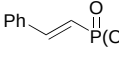
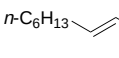
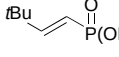
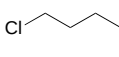
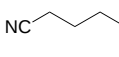
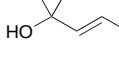
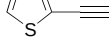
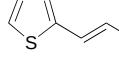
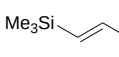
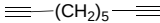
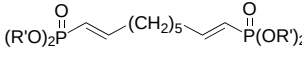
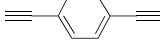
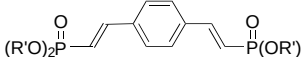
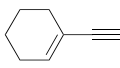
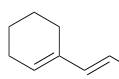
The rhodium-catalyzed hydrophosphorylation proved generally applicable to a variety of alkynes for synthesizing alkenylphosphonates at room temperature (Table 1).^[5, 6] Thus, the [RhBr(PPh₃)₃]-catalyzed reaction of unsubstituted acetylene (commercial acetylene gas from a cylinder was used without purification) efficiently proceeded in acetone to form the corresponding vinylphosphonate in a high yield. Substituted terminal alkynes, both aliphatic and aromatic, reacted as efficiently to afford *trans* adducts by the regioselective attack of the phosphorus center on the terminal carbon atom of the

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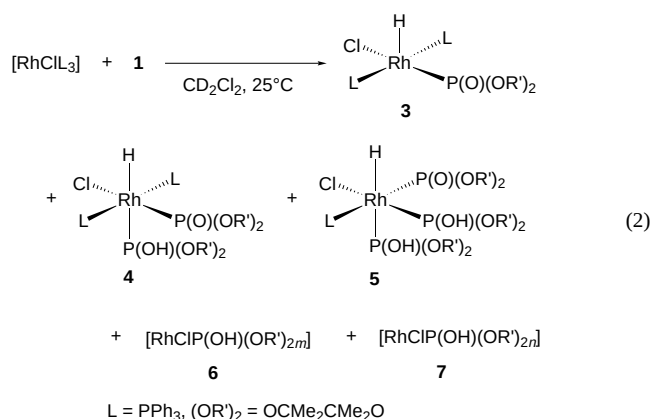
Table 1. Hydrophosphorylation of alkynes.^[a]

Alkyne	Adduct ^[b]	Yield [%] ^[c]
		81 ^[d]
Ph— 	Ph— 	93 (91)
<i>n</i> -C ₆ H ₁₃ — 	<i>n</i> -C ₆ H ₁₃ — 	95 (93)
<i>t</i> Bu— 	<i>t</i> Bu— 	79 (92)
Cl— 	Cl— 	89 (96)
NC— 	NC— 	95 (91)
HO— 	HO— 	82 (86)
		46 (75)
Me ₃ Si— 	Me ₃ Si— 	76 (98)
		93 (89)
		97 (87)
		92 (81)

[a] Run without optimization. Conditions A: an equimolar mixture of **1** and an alkyne in acetone (ca. 1 M), 1–2 mol % [RhBr(PPh₃)₃], 25 °C, 20 h. Conditions B: an equimolar mixture of **1** and an alkyne in toluene (0.5–1 M), 1–2 mol % [RhCl(PPh₃)₃], 100–110 °C, 2–6 h. ³¹P NMR spectroscopy revealed >98% selectivity in each reaction. [b] (OR')₂ = OCMe₂CMe₂O. [c] Yield obtained under conditions A after isolation by column chromatography on silica gel. The yield in parentheses was obtained under conditions B. [d] Performed under 1 atm acetylene gas.

triple bond. Functional groups such as chloro, cyano, hydroxy, thienyl, and silyl all tolerated the reaction conditions. 1-Ethynylcyclohexene selectively reacted at the triple bond to give the linear adduct; this proves the inertness of the internal olefinic bond.^[7]

Mechanistic studies revealed that oxidative addition of the H–P bond in **1** readily takes place.^[8] Thus, when [RhCl(PPh₃)₃] was treated at room temperature with **1** (3 equiv) in CD₂Cl₂, new signals attributable to Rh–H (*m*, *δ* = –8.0 to –10.1, –16.2 to –16.8) and Rh–P(O) (*δ* = 96 to 135) species emerged in the ¹H and ³¹P NMR spectra, respectively [Eq. (2)]. The starting rhodium complex disappeared after 22 h, and a yellow-orange solution formed. The ³¹P NMR spectrum suggested the formation of three P(O)-bound Rh^{III}–PPh₃ complexes **3**–**5**. The **3/4/5** ratio varied with the reaction time, and the change from the value of 1/2.5/0.31 after 3.5 h to 1/4.82/3.36 after 22 h is indicative of an equilibrium among these species (see below). The PPh₃-free rhodium complex **6**^[9] was also generated in a small amount. Since the ratio of these species depends on the conditions,



elaboration of the procedure allowed successful isolation of **3**–**5**.^[10] First, overnight stirring of a purple-colored suspension of [RhCl(PPh₃)₃] and **1** (Rh/**1** = 1/14) in acetone at room temperature resulted in a gradual color change to give a white suspension. Routine workup afforded **5** as a white solid (82% yield). Second, another reaction at room temperature starting with [[Rh(cod)Cl]₂], PPh₃, and **1** (Rh/PPh₃/**1** = 1/2/2) in dichloromethane generated **4** predominantly. Addition of pentane and refrigeration gave pale yellow crystalline **4** in 35% yield. Finally, heating a dilute solution of **4** in CH₂Cl₂ at 60 °C for 90 min resulted in dissociation of **1** to generate **3**,^[11, 12] which could be readily isolated as orange solid in 52% yield.

X-ray crystallography of **4** unambiguously confirmed the distorted octahedral structure (Figure 1).^[13] The short O3–O6 distance and the P2–O3 and P4–O6 distances are between the

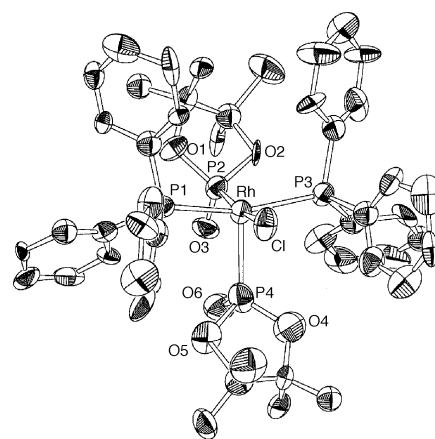
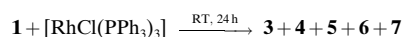


Figure 1. Molecular structure of complex **4**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: P1–Rh 2.38(1), P2–Rh 2.262(9), P4–Rh 2.467(10), Cl–Rh 2.436(8), P2–O3 1.56(2), P4–O6 1.59(2), O3–O6 2.45; Cl–Rh–P2 170.5(3); P1–Rh–P3 160.9(3), Cl–Rh–P4 95.7(3), Cl–Rh–P1 85.2(3), Cl–Rh–P3 86.0(3), P1–Rh–P2 92.6(4), P1–Rh–P4 99.2(4), P2–Rh–P3 93.3(4), P3–Rh–P4 98.5(4), O1–P2–O2 96(1), O4–P4–O5 95(1).

values reported for single and double bonds and suggest strong hydrogen bonds involving the two oxygen atoms.^[14, 15] The P4–Rh bond is longer than the P2–Rh bond, presumably due to the strong *trans* influence of the hydrido ligand as compared with Cl.^[16]

Interestingly, the distribution of rhodium species **3–7** generated is significantly dependent on the **1**/Rh ratio and the solvent.^[17] The distribution observed in the absence of the acetylene substrate (Table 2)^[18] indicates that a large excess of

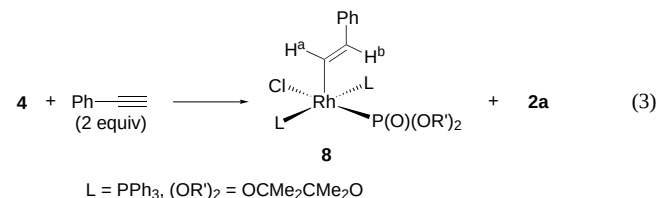
Table 2. Distribution of rhodium species **3–7** in the reaction of [RhCl(PPh₃)₃] with **1**.



1 /[RhCl(PPh ₃) ₃]	Solvent	3/4/5/6/7
3/1	acetone	10/57/16/17/0
17/1	acetone	0/0/40/60/0
3/1	toluene	15/28/47/10/0
17/1	toluene	0/0/7/36/57

1 suppresses coordination of PPh₃ and thus enhances the generation of PPh₃-free complexes **6** and **7**, which are inactive towards hydrophosphorylation. Note, however, that a considerable contribution of **5** is maintained even at higher **1**/Rh ratios (e.g., 17/1) in acetone but not in toluene. These results presumably are associated with the solvent effect observed in the catalytic reactions (see above).

The H–Rh bond in complex **4** was found to add across an acetylenic bond (hydorrhodation). For instance, when complex **4** (20.2 μmol) was treated with phenylacetylene (2 equiv) in [D₂]dichloromethane at room temperature, **4** was nearly completely consumed and about 14 μmol of alkenylrhodium complex **8**^[19] and 27 μmol of **2a** (by ¹H NMR spectroscopy) were formed after 20 h [Eq. (3)]. Subsequent heating of the

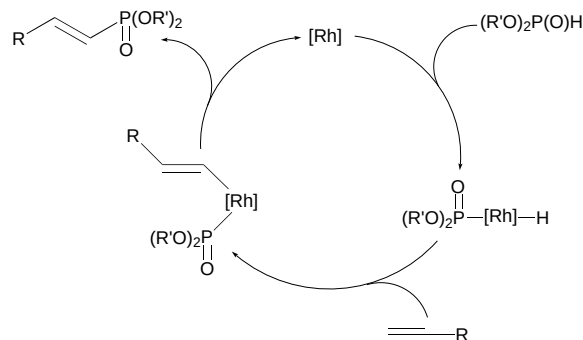


mixture at 50 °C for 4 h resulted in disappearance of **4** and **8** to give **2a** quantitatively. A similar but somewhat higher rate of consumption of **4** was observed in acetone. In toluene, most of **4** (ca. 93 %) remained unconverted, even after one day. Thus, the hydorrhodation process is also very much solvent-dependent, whereby acetone is far more favorable than toluene, which also conforms to the finding in the catalytic reactions.

Preliminary experiments revealed that **3** and **5** also react with phenylacetylene to form **8** and **2a**. On the basis of a competitive reaction with a mixture of **3**, **4**, and **5**, complex **5** appears to be most reactive.^[20] In contrast, PPh₃-free complexes **6** and **7**, which could be generated in situ by addition of **1** to [[RhCl(cod)]₂] (**1**/Rh = 3/1) in CD₂Cl₂,^[8b] did not add to phenylacetylene (25 °C, 23 h).

Even though we have not studied the details of the final product-forming step, we are now able to safely propose a

mechanism that accommodates the foregoing observations (Scheme 1). The significant solvent effect in the catalysis is most likely associated with the distribution and reactivity of the H–Rh species.



Scheme 1. Proposed catalytic cycle for the hydrophosphorylation of alkynes.

Experimental Section

Representative catalytic addition of **1**: Phenylacetylene (204 mg, 2.0 mmol), **1** (328 mg, 2.0 mmol), and [RhBr(PPh₃)₃] (38 mg, 2 mol %) were dissolved in 3 mL of degassed dry acetone under nitrogen. The mixture was stirred at room temperature for 20 h and evaporated in vacuo to leave a pale yellow solid, which was purified by column chromatography (SiO₂, hexane/*i*PrOH 10/1) to give **2a** as white solid in 93 % yield (495 mg).

Selected data for **3**: ¹H NMR (300 MHz, CD₂Cl₂): δ = 7.77–7.83 (m, 12H), 7.30–7.39 (m, 18H), 0.82 (s, 6H), 0.81 (s, 6H), –16.5 (ddt, 1H, *J* = 7.3, 11.0, 18.3 Hz); ³¹P NMR (121.5 MHz): δ = 126.7 (dt, *J*(P,P) = 30.8, *J*(P,Rh) = 197.8 Hz), 27.5 (dd, *J*(P,P) = 30.8, *J*(P,Rh) = 96.7 Hz).

Selected data for **4**: ¹H NMR (300 MHz, CD₂Cl₂): δ = 16.52 (brs, 1H), 7.74–7.80 (m, 12H), 7.27–7.39 (m, 18H), 1.38 (s, 6H), 0.76 (s, 6H), 0.73 (s, 6H), 0.24 (s, 6H), –8.58 (double quintet-like, 1H, *J*(P,H) = 275.9 Hz); ³¹P NMR (121.5 MHz): δ = 132.6 (ddt, *J*(P,P) = 21.0, 37.4, *J*(P,Rh) = 91.6 Hz), 99.5 (ddt, *J*(P,P) = 21.0, 27.6, *J*(P,Rh) = 162.2 Hz), 36.2 (ddd, *J*(P,P) = 27.6, 37.4, *J*(P,Rh) = 98.4 Hz).

Selected data for **5**: ¹H NMR (300 MHz, CD₂Cl₂): δ = 7.28–7.68 (m, 15H), 3.58 (brs, 2H), 1.52 (s, 3H), 1.50 (s, 3H), 1.49 (s, 6H), 1.38 (s, 6H), 1.16 (s, 3H), 1.11 (s, 6H), 1.06 (s, 3H), 0.89 (s, 3H), 0.24 (s, 3H), –8.73 (ddq, 1H, *J* = 4.5, 10.1, 272.3 Hz); ³¹P NMR (CD₂Cl₂): δ = 130.7 (dddd, *J*(P,P) = 21.7, 38.2, 49.6, *J*(P,Rh) = 109.6 Hz), 124.2 (dddd, *J*(P,P) = 35.0, 49.6, 515.7, *J*(P,Rh) = 151.1 Hz), 97.3 (dddd, *J*(P,P) = 21.7, 27.0, 35.0, *J*(P,Rh) = 162.7 Hz), 36.1 (dddd, *J*(P,P) = 27.0, 38.2, 515.7, *J*(P,Rh) = 92.8 Hz).

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- [9] Although it could not be detected in this particular reaction, another PPh₃-free rhodium complex **7**, displaying ³¹P NMR signals at δ = 126–128, was also formed when a large excess of **1** was used. Pure **6** and **7** have not been isolated yet. However, as confirmed by ³¹P NMR spectroscopy, a mixture of these complexes could be generated when [RhCl(cod)]₂ was mixed with **1** (see ref. [8b]).
- [10] The P^V(O)(OR')₂ and P^{III}(OH)(OR')₂ ligands in complexes **4** and **5** are not distinguishable. They are linked together by hydrogen bonds such as Rh[P(O)(OR')₂][P(OH)(OR')₂], as suggested by X-ray diffraction (see below). In this context, complex **5** is envisioned on the basis of the ³¹P NMR spectrum to adopt a pseudo-*fac* configuration. See Supporting Information for the detailed NMR data.
- [11] Interestingly, the conversion of **4** to **3** in toluene was much slower than in CH₂Cl₂; **4** was still present in the solution even after 4 h of heating at 60 °C (3/4 ≈ 2.8/1).
- [12] Allowing the solution to stand at room temperature overnight regenerated **4** to a small extent (4/3 ≈ 8/92).
- [13] 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-150935. 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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- [17] The equilibrium between **3**, **4**, and **5** was confirmed separately. Mixing **5** (7.3 mg) with PPh₃ (2 equiv) in CD₂Cl₂ (0.5 mL) at room temperature generated a mixture of all three species (3/4/5 = 1/0.38/0.29) after 20 h.
- [18] Since the detailed structures of **6** and **7** are not known, the true amounts of these species in the mixture cannot be evaluated. The ratio given in Table 2 is a provisional value, calculated on the basis of an arbitrary assumption that only one molecule of **1** ligates Rh.
- [19] Attempted isolation of **8** failed, but the structure is evidenced by its NMR spectra (CD₂Cl₂). The ¹H NMR spectrum displays a signal for

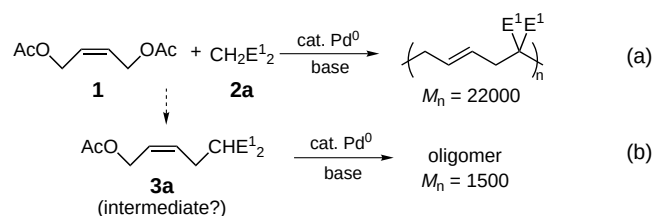
olefinic proton H^a at δ = 4.63 (dd, *J* = 16.6, *J*(H,Rh) = 4.6 Hz). The ¹H–¹H COSY technique confirms that another olefinic proton H^b is hidden at δ ~ 7.4 in the mass of phenyl proton signals. The large coupling constant indicates an *E* configuration of the double bond. The ³¹P NMR spectrum also conforms to the structure in showing a dd signal at δ = 29.0 (*J*(P,P) = 25.0, *J*(P,Rh) = 112.0 Hz, PPh₃) and a dt signal at δ = 56.3 (*J*(P,P) = 25.0, *J*(P,Rh) = 184 Hz, P(O)).

- [20] A mixture of these complexes in CD₂Cl₂ (molar ratio 3/4/5 = 1.0/1.3/1.7), generated by the reaction of [RhCl(PPh₃)₃] with an excess of **1** (6 equiv), was allowed to react with phenylacetylene (10 equiv) at room temperature. Complex **5** was completely consumed in 26 min, and **8** and **2a** were observed (molar ratio of 3/4/5/8/2a = 1.0/1.3/0/3.2/8.8).

Mechanistic Rationale of a Palladium-Catalyzed Allylic Substitution Polymerization—Carbon–Carbon Bond-Forming Polycondensation out of Stoichiometric Control by Cascade Bidirectional Allylation**

Nobuyoshi Nomura, Ko Tsurugi, and Masahiko Okada*

Palladium-catalyzed allylic alkylation has been the subject of intensive research in carbon–carbon bond-forming processes since its discovery,^[1] and it was recently extended to an allylic substitution polymerization^[2] (Scheme 1a, E¹ = CO₂Et) in which the use of bis(diphenylphosphanyl)butane (dppb) was indispensable. In a survey of recent studies on palladium-catalyzed allylation reactions,^[1b–f] π-allylpalladium(II) complex intermediates were extensively



Scheme 1. Palladium-catalyzed allylic substitution polymerization (E¹ = CO₂Et).

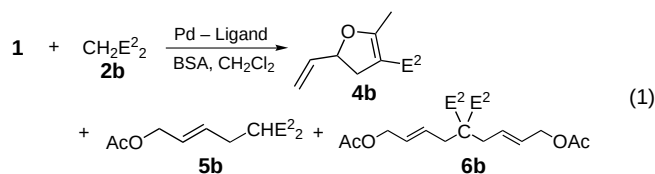
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investigated to reveal the origins of the regio-, stereo-, and enantioselectivity. However, transient olefin– L_nPd^0 complexes have not gained much attention, except for a few discussions on asymmetric recognition and induction.^[3–5] Herein we show that the reactions of olefin– L_nPd^0 complexes play a crucial role in successful polymerizations (Scheme 1 a), and that polymerization selectively proceeds by means of a cascade bidirectional allylation mechanism. Our preliminary results concerning the first example of a carbon–carbon bond-forming polycondensation out of stoichiometric control are also presented based on the mechanistic rationale.

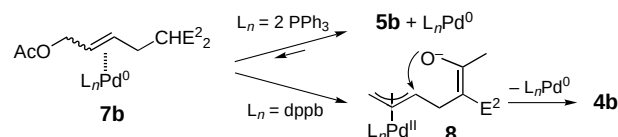
We prepared the bifunctional monomer **3a** ($E^1 = CO_2Et$, Scheme 1 b), which possessed both electrophilic and nucleophilic sites. There appeared to be two advantages in the use of **3a** instead of the two-component system of **1** and **2a**: 1) the stoichiometric control of polycondensation could be avoided, so that a polymer with a higher molecular weight should be formed; 2) under the same polymerization conditions, a half turnover number of Pd catalyst could lead to the same molecular weight of polymer (Scheme 1 a) in a shorter time. However, the polymerization of **3a** was quite sluggish and the number-average molecular weight (M_n) was estimated at only 1500 under the identical conditions^[6] (Scheme 1 b). We were surprised at this result, since **3a** was believed to be an initial intermediate.^[7]

To clarify the polymerization mechanism, we examined the model reaction between **1** and acetylacetone (**2b**, [Eq. (1)], $E^2 = COMe$). Various ligands were used in the reactions,



which were monitored by TLC and quenched soon after the quantitative consumption of **1**, or after 24 h (Table 1). Although no clear relationships between the catalytic activities and selectivity of the products were found, both were highly dependent on the ligand used. For example, dppb was found to be the most efficient ligand (Table 1, entry 4), and dppf and PPh_3 showed moderate catalytic activities (Table 1, entries 5 and 6). Other ligands were much less effective in this

reaction (Table 1, entries 1–3, 7, and 8). The main difference between using dppb and PPh_3 was the major product that was formed: both acetate groups of **1** reacted with L_nPd^0 to afford cyclic compound **4b** in the case of dppb^[7] (Table 1, entry 4), whereas in the presence of the PPh_3 system, one acetate group reacted selectively to produce **5b** and **6b** (Table 1, entry 6). The fact that **5b** hardly cyclized under the same conditions as those in entry 4, suggested that the transient olefin– L_nPd^0 complex **7b**, which was the precursor of **5b**, should be the key complex in the catalytic reaction (Scheme 2).^[8] After the



Scheme 2. Mechanism for selective cyclization ($E^2 = come$).

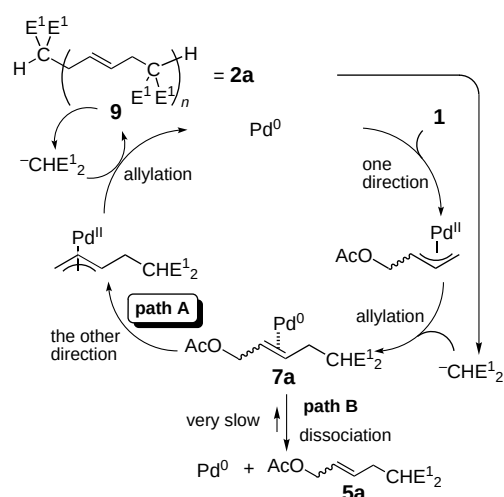
formation of **7b**, two pathways were possible. When PPh_3 was applied, **7b** selectively collapsed into **5b** and L_nPd^0 . The coordination of **5b** to L_nPd^0 was slow probably because of the steric effects of two bulky carbonyl groups introduced during the first allylation.^[9] In the dppb system, however, **7b** forms allylpalladium complex **8** at the other allylic terminal, and then intramolecular cyclization occurs (Scheme 2). Such a cascade mechanism is applicable to the polymerization reaction (Scheme 3). After the first allylation of **1**, **7a** selectively forms the allylpalladium(II) complex at the other allylic terminal when dppb is used (path A). The allylpalladium(II) complex is susceptible to intermolecular attack by the anion of **2a** to form **9**. Compound **9** is an equivalent of **2a**, and is involved in the catalytic polymerization cycle. Since **5a** showed considerably lower reactivity toward L_nPd^0 , a successful polymerization requires the high selectivity of path A and proceeds by means of the cascade bidirectional allylation mechanism. The manipulation of transient olefin– L_nPd^0 complexes, that is, controlling relative reaction rates between oxidative addition (path A) and dissociation (path B), is essential for a successful polymerization.^[5]

It is possible that this C–C bond-forming polycondensation may occur out of stoichiometric control, which is the intrinsic drawback of polycondensation.^[10] When polymerization exclusively proceeds through path A, each molecule of **1** reacts with two molecules of **2a** (or subsequently, **9**). This

Table 1. Ligand effects in Equation (1).^[a]

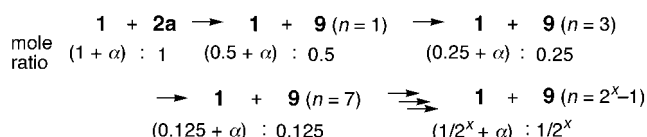
Entry	Ligand ^[b] (equiv. to Pd)	Time [h]	4b	Yield [%] ^[c] 5b	6b	Recovered [%] ^[c] 1
1	dppm (1)	24	–	–	–	93
2	dppe (1)	24	–	5	–	79
3	dppp (1)	24	traces	–	–	95
4 ^[d]	dppb (1)	1	82	–	–	0
5 ^[d]	dppf (1)	3	69	–	–	0
6 ^[d]	PPh_3 (2)	10	3	44	18	1
7	$P(o\text{-tolyl})_3$ (2)	24	–	–	–	92
8	bpy (1)	24	–	–	–	96

[a] All the reactions were carried out with **1** (0.50 mmol), **2b** (1.20 mmol), and BSA (3.0 mmol) in the presence of $[Pd_2(dba)_3]$ (1 mol %) and various ligands in CH_2Cl_2 (1 mL) at 25 °C. [b] $Ph_2P(CH_2)_nPh_2$: dppm: $n = 1$, dppe: $n = 2$, dppp: $n = 3$, dppb: $n = 4$; dppf = 1,1'-bis(diphenylphosphanyl)ferrocene, bpy = 2,2'-bipyridine. [c] Yield after column chromatography. [d] Some oligomerization was also observed.



Scheme 3. Cascade bidirectional allylation mechanism.

means that all chains undergoing polymerization are always **9**, which has malonate functions at either terminal, and that the molecular number of **1** should be the same as that of **9** (Scheme 4, $\alpha = 0$). Then, even an excess of **1** ($\alpha > 0$) does not



Scheme 4. Polycondensation without stoichiometric control. n = average degrees of repeating unit.

affect the degree of polymerization, whereas polymerization will be terminated when **2a** is in excess ($\alpha < 0$, $1/2^x + \alpha = 0$). We examined the polymerization with different ratios of **1** and **2a** (Table 2). According to the widely accepted stoichiometric principle of polycondensation,^[10] the average degrees of polymerization (DPs) in both 1.0:1.1 and 1.1:1.0 of **1/2a** are expected to be the same (DP = 21). However, we obtained quite different DPs (estimated DPs, determined vs polystyrene standards): DP = 24 (**1/2a** 1.0:1.1); DP = 66 (**1/2a** 1.1:1.0) (Table 2, entries 1 and 2). When 1.3 equivalents of **1** are used,

Table 2. Polycondensation without stoichiometric control.^[a]

Entry	Ligand	Ratio (1/2a)	Expected DP ^[b]	Obtained DP ^[c]
1	dppb	1.0:1.1	21	24
2	dppb	1.1:1.0	21	66
3	dppb	1.3:1.0	7.7	50
4	dppb	1.5:1.0	5.0	46
5	dppb	2.0:1.0	3.0	37 ^[d]
6	PPh ₃	1.5:1.0	5.0	5.0 ^[e]

[a] All the reactions were carried out under the conditions described in ref. [6], except for the reaction temperature (25 °C). Crude samples from the reaction mixture were analyzed every 6 or 12 h until the values of M_n reached the upper limits. All polymer yields based on **1** (entry 1) or **2a** (entries 2–6) were nearly quantitative ($\geq 95\%$). [b] See ref. [10]. [c] Estimated by SEC (CHCl₃, polystyrene standard, Tosoh TSK gel G2000HXL, G3000HXL, and G5000HXL columns). [d] 45% of **1** (90% of the excess amount for **2a**) was recovered by column chromatography. [e] The DP was also estimated by ¹H NMR spectroscopy (DP = 5.0).

the DP is expected to decrease drastically to 7.7, whereas the observed DP remained quite high (DP = 50, Table 2, entry 3). Although a further excess of **1** gradually reduced the DPs in this system (Table 2, entries 4 and 5),^[11] an unexpectedly higher DP (≈ 12 -fold) was still obtained in the presence of two equivalents of **1**, and excess **1** was recovered (90%). In contrast, the PPh₃ system, which prefers path B, resulted in the same DP as expected based on general polycondensation (Table 2, entry 6). These results indicate that exclusive selectivity of the reaction pathways will overcome the stoichiometric principle of polycondensation. To the best of our knowledge, this is the first example of a C–C bond-forming polycondensation out of stoichiometric control, whereas there are two systems reported in bond-forming homogeneous polymerization.^[12, 13]

In summary, the mechanistic rationale of the palladium-catalyzed allylation polymerization was investigated, and a cascade bidirectional allylation mechanism was revealed. Further studies are underway to understand the conditions for manipulating olefin–L_nPd⁰ complexes. We are also investigating systems which will make C–C carbon–heteroatom bond-forming polycondensations out of stoichiometric control more practical.

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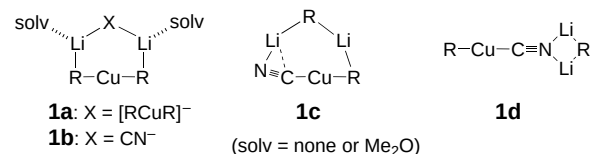
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Kinetic Reactivity of “Higher Order Cuprates” in S_N2 Alkylation Reactions**

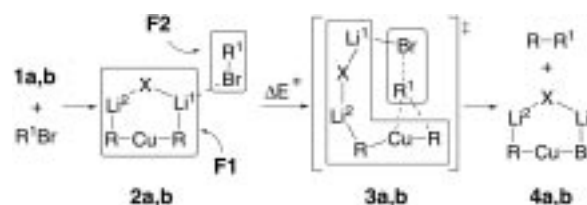
Eiichi Nakamura,* Masahiro Yamanaka, Naohiko Yoshikai, and Seiji Mori

Among a variety of organocopper reagents,^[1] “higher order” cyanocuprates have attracted much interest in the past years.^[2] Lipshutz originally offered this reagent to the synthetic society as a highly reactive substitute for the classical Gilman reagent, **1a** (denoted hereafter as series **a**



($R = Me$) throughout the text).^[3] The high reactivity was ascribed to a dianionic tricoordinated copper(I) structure,^[4] but this structure was soon challenged by Bertz.^[5] The structural debate ended recently and it was concluded that the Lipshutz reagent is not the tricoordinated species, but **1b** (denoted hereafter as series **b** throughout the text).^[6–8] The latter structure is essentially the same as that of the classical Gilman reagent **1a** except that the bridging group (X) in the Lipshutz reagent is a cyanide group instead of the $[RCuR]^-$ group, with which the Gilman reagent forms a dimeric copper structure.^[9] The Lipshutz reagent is therefore no more than a “lower order” cuprate, yet the fact still remains that it is often a more powerful nucleophile than a normal Gilman reagent. For instance, the Lipshutz reagent is the reagent of choice for S_N2 reactions, in which the Gilman and other lower order cuprates are far less reactive.^[10] Furthermore, the Lipshutz reagent shows some unusual reactivity, which suggests that a minute amount of alkyllithium is generated in equilibrium with the major $[R_2Cu]^-$ species.^[11] Thus the kinetic reactivity of the Lipshutz reagent is still an open question. We report herein density-functional studies on the S_N2 reaction of MeBr with the Lipshutz reagent **1b**, which suggest that **1b** could indeed be much more reactive than the Gilman reagent **1a**. The higher reactivity of **1b** has been ascribed both to the higher Lewis acidity of the $[LiCNLi]^+$ group, and to the energetically favorable structural change of the $[LiCNLi]^+$ moiety in the transition state (TS) of the reaction of **1b**. The studies also suggest that minor structural isomers of the Lipshutz reagent, **1c** and **1d**, might play a role in solution chemistry despite their low equilibrium concentration.^[8]

Previous studies have shown that the rate-determining step of the S_N2 reaction of the lithium organocuprate with MeBr is the C–Br bond cleavage stage (**3a, b**, Scheme 1), from which



Scheme 1. Substitution reaction between $R_2CuLi \cdot LiX$ ($R = Me$, series **a**: $X = RCuR$, series **b**: $X = CN$) and R^1Br ($R^1 = Me$).

the potential surface goes steeply downhill to the alkylation product.^[12, 13] The energy profile of the bromide displacement in series **a** and **b**, and the 3D structures of the stationary points are shown in Figures 1 and 2.^[14a] As shown in Figure 1, the activation energy from the initial coordination complex (CP, **2b**) to the displacement TS (**3b**) for the major species of the Lipshutz reagent **1b** is 3.8 kcal mol^{−1} smaller than that for the Gilman dimer **1a**.^[15, 16]

Where is the origin of this small but finite difference in the activation energies between series **a** and **b**? The answer to this question was probed by fragment energy analysis^[17] (Scheme 1 and Table 1) through the dissection of the CPs

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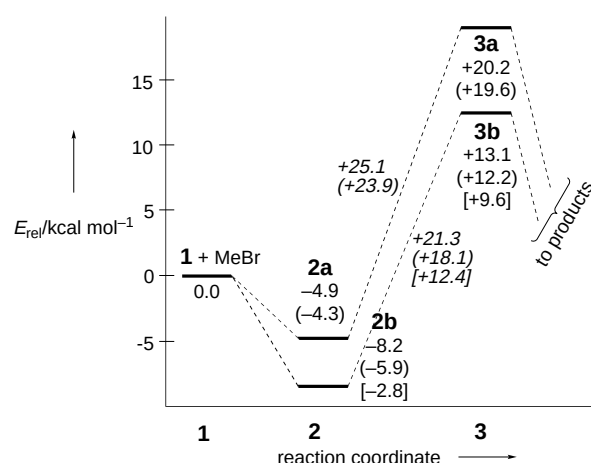


Figure 1. Energy profile of the S_N2 reaction of MeBr with the Gilman reagent (series **a**) or the Lipshutz reagent (series **b**). The potential energies of **1**+MeBr in series **a** and **b** are set to zero. The italicized numbers are the activation energies, in parentheses are the results of single point energy calculations with the self-consistent reaction field (SCRF) method based on the polarized continuum model (PCM, $\epsilon = 4.335$ for Et₂O) at the gas-phase geometries, and in brackets are the energies for the model species **1b** bearing a Me₂O molecule on each lithium atom.

and the TSs into two fragments (with a fixed geometry at the original stationary points), **F1** (lithium cuprate cluster) and **F2** (MeBr). The origin of the smaller activation energy in series **b**

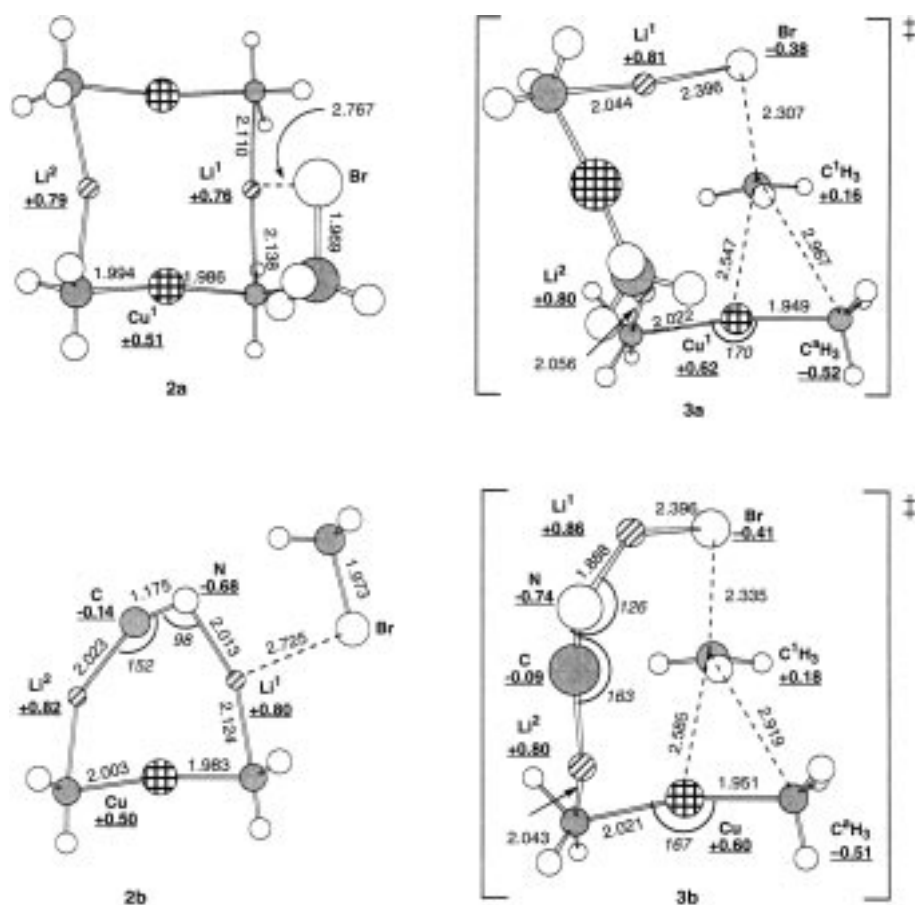


Figure 2. The 3D structures of CP and TS in series **a** and **b**, optimized at the B3LYP/631A level, with the bond lengths in Å, bond angles (italics) in degrees, and natural charges (underlined and bold). The imaginary frequencies of **3a** and **3b** are 224.0i cm⁻¹ and 220.6i cm⁻¹, respectively.

Table 1. Deformation (DEF) and interaction energies (INT) which compose the activation energy ($\Delta E^\ddagger$). See Scheme 1 for definition of **F1** and **F2**.

	Series a	Series b
INT _{CP}	-6.9	-9.2
INT _{TS}	-34.2	-37.6
DEF _{F1}	38.4	34.2
DEF _{F2}	13.9	15.5
INT _{total} ^[a]	-27.3	-28.4
DEF _{total} ^[b]	52.3	49.7
$\Delta E^\ddagger$ ^[c]	25.1	21.3

[a] INT_{total} = INT_{TS} - INT_{CP}. [b] DEF_{total} = DEF_{F1} + DEF_{F2}. [c] $\Delta E^\ddagger$ = INT_{total} + DEF_{total}.

than in series **a** has been traced back to the higher Lewis acidity of the Li^I atom and the preference of the [LiCNLi]⁺ moiety to be linear as is the case in **3b**.

Thus, in the initial coordination complexes (**2a** and **2b**), the cuprate cluster fragment (**F1**) and the MeBr fragment (**F2**) interact more strongly in series **b** (INT_{CP} = -9.2 kcal mol⁻¹) than in series **a** (-6.9 kcal mol⁻¹), which is corroborated by the shorter Li^I-Br distance (2.73 vs 2.77 Å, Figure 2). The stronger interaction of **F1** and **F2** in **2b** can be attributed to the larger positive charge of Li^I atom (+0.80) than that in **2a** (+0.76). Similarly, the interaction energy between **F1** and **F2** (INT_{TS}) is larger in **3b** (-37.6 kcal mol⁻¹) than in **3a** (-34.2 kcal mol⁻¹) owing to larger electrostatic interactions between the Li^I atom (+0.86) and the Br atom (-0.41) in **3b**. The natural charges of these atoms^[18] in **3a** are much smaller (+0.81 and -0.38, respectively). The positive charges of the lithium atom in series **b** are larger than those in series **a** both for the CP and the TS because of the attachment of the Li^I atom to the electronegative CN⁻ group instead of the [MeCuMe]⁻ group.

The propensity of the [LiCNLi]⁺ moiety for the near-linear geometry in **3b** rather than for the bent geometry in **2b** is another factor that contributes to the lower activation energy in series **b**. The deformation of **F1** upon going from **2b** to **3b** (DEF_{F1} = 34.2 kcal mol⁻¹) is much easier than that from **2a** to **3a** (DEF_{F1} = 38.4 kcal mol⁻¹). Further dissection of **F1** into [MeCuMe]⁻ and [LiXLi]⁺ fragments (data not shown) revealed that this difference is mainly a result of the energy gained from stretching the bent [LiCNLi]⁺ moiety in **2b** to the near linear geometry in **3b** (14.3 kcal mol⁻¹ gain; the [MeCuMe]⁻ fragments in series **a** and **b** are essentially identical to each other, and hence do not contribute

much to DEF_{F1}).^[19] Thus, the overall sum of the deformation energies ($\text{DEF}_{\text{total}}$) becomes 2.6 kcal mol⁻¹ smaller in series **b** (49.7 kcal mol⁻¹) than in series **a** (52.3 kcal mol⁻¹), contributing to the smaller activation energy in series **b**.

The minor isomers of the Lipshutz reagent seem to play a role in synthetic reactions (see above).^[11] Although isomer **1c** has been calculated to be much less stable than **1b** (hence not experimentally observable),^[8] a model study of $\text{S}_{\text{N}}2$ reaction (Figure 3) suggests that there is a possibility that **1c** may take

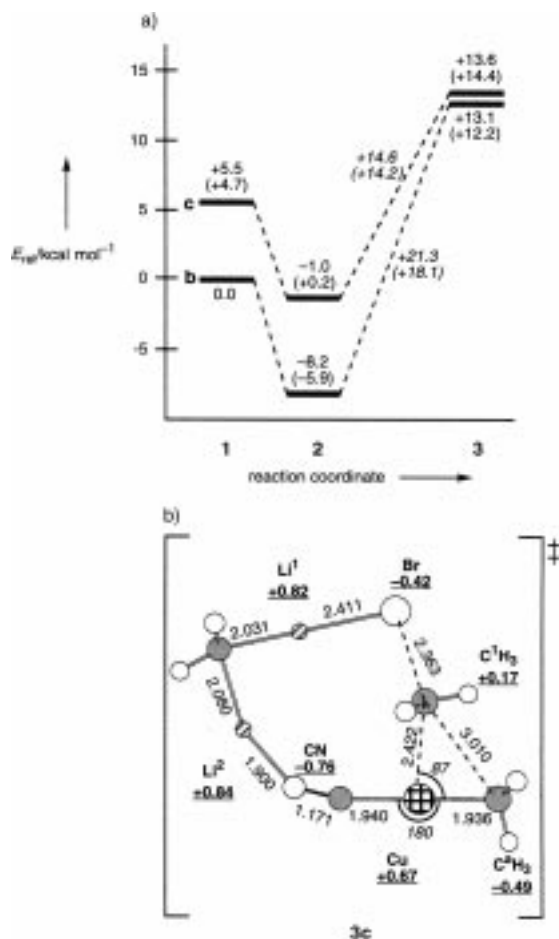
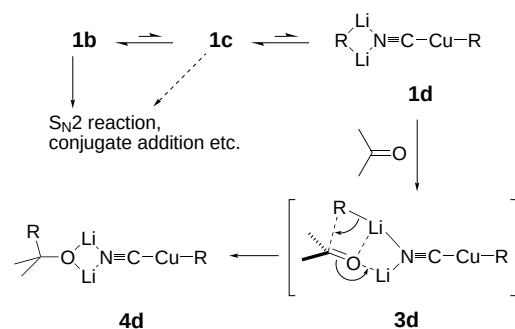


Figure 3. a) The $\text{S}_{\text{N}}2$ reaction energy profile of the minor Lipshutz reagent **1c**. The energy of **1b**+MeBr is taken as the reference. The italicized numbers are the activation energies, and results of single point energy calculations (in parentheses) were obtained by using the same method as noted in Figure 1. b) 3D structure of **3c** optimized at the B3LYP/631A level. The imaginary frequency of **3c** is 238.3i cm⁻¹.

part in the C–C bond forming reactions of the Lipshutz reagent. The activation energy of **1c** (14.6 kcal mol⁻¹) is far smaller than that of **1b** (21.3 kcal mol⁻¹),^[14b, 20] and thus **3c** is quite close in energy to **3b**.

The positive Gilman test of the Lipshutz reagent strongly suggests that RLi species are generated in solution.^[11] Whereas the species that reacts with Michler's ketone could be **1c**, it would more likely be **1d**,^[21] which would easily form from **1c** through the reorganization of the ionic bonds around the lithium atoms. Isomer **1d** is ideally disposed to undergo addition to a ketone through a six-centered TS typical for an alkyllithium reagent.^[22] Scheme 2 summarizes possible path-



Scheme 2. Alkylcopper(i)-like and alkyllithium-like reaction pathways of the Lipshutz reagent (solvent molecules on the lithium atoms are omitted).

ways for the major and the minor reactions that the Lipshutz reagents undergo in synthetic applications.

In summary, the higher reactivity of the Lipshutz reagent than the Gilman reagent in the $\text{S}_{\text{N}}2$ alkylation has been ascribed to the structural and electronic effects of the bridging cyanide moiety coordinated to the two lithium cations. The present study provides an additional example of the important role of the $[\text{LiXLi}]^+$ bridging moiety in the chemistry of lithium organocuprates. This bridging moiety has recently identified in various reactions of such cuprates.^[23] Furthermore, the studies provide a heuristic example of the kinetic importance of minor species in the reactions of organometallic clusters.^[2b, 7a, 24]

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- [15] The activation energies in series **a** and **b** calculated at the MP2/631A//B3LYP/631A level are $34.5 \text{ kcal mol}^{-1}$ for series **a** and $30.9 \text{ kcal mol}^{-1}$ for series **b**. Hence, the difference is $3.6 \text{ kcal mol}^{-1}$.
- [16] This trend also holds when the solvent polarity and explicit solvent molecules (one Me_2O on each Li atom) are considered (Figure 1). The solvation of the Cu atom only takes place after the TS of the bromide displacement in which copper(I) becomes copper(III), and hence was not considered in the present discussion (see ref. [12a]).
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Ionization of O_3 in Excess N_2 : A New Route to N_2O via Intermediate N_2O_3^+ Complexes**

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The environmental impact of N_2O , the major source of stratospheric NO_x oxides responsible for ozone depletion, and a harmful greenhouse gas,^[1–3] accounts for the active search of formation processes^[4, 5] other than microbiological soil denitrification.^[6] Inspired by the increasing recognition of the role played by ionic processes in the atmosphere^[7] and by the ability of O_3^+ to transfer oxygen atoms to simple molecules,^[8–10] we focused this study on the ionization of O_3 diluted in N_2 as a new route to atmospheric N_2O . Experiments based on Fourier-transform ion cyclotron resonance (FT-ICR) mass spectrometry were performed, utilizing an instrument equipped with an external chemical ionization (CI) ion source, fed with an O_3/O_2 mixture. The ions formed were driven into the resonance cell, maintained at 300 K, where the $^{16}\text{O}_3^+$ ions, m/z 47.9847, were isolated by removing all other ions by “soft” RF pulses, and allowed to react with N_2 , continuously admitted into the cell to reach stationary pressures ranging from 10^{-8} to 10^{-7} Torr. The results positively demonstrated the formation of N_2O^+ and O_2^+ as the primary reaction products [Eqs. (1) and (2)], through processes exothermic by 4.2 and $22.9 \text{ kcal mol}^{-1}$, respectively.^[11]



Although the nature of the experiments prevented accurate kinetic measurements,^[12] we could roughly estimate $k_1 \sim 1.4 \times 10^{-11}$ and $k_2 \sim 1.6 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$. In any case, accurate kinetic measurements were outside the scope of the experiments, whose primary goal was to exploit the unique ability of FT-ICR spectrometry to establish a parent–daughter relationship between charged species, and hence to ascertain the reaction(s) responsible for the formation of the product of interest, N_2O^+ . Next, CI experiments of N_2/O_3 mixtures, of composition adjusted to obtain the maximum reaction extent (roughly 5 mol % O_3), were performed at 373 K, 0.01–0.1 Torr. All experiments were carried out in duplicate, utilizing either $^{14}\text{N}_2$ or $^{15}\text{N}_2$ as a convenient way to simplify

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the interpretation of the mass spectra and to exclude the interference of isobaric contaminants, as generally advisable when the species probed have a low abundance. Given the consistency of the results from the two sets of experiments, we shall discuss only those pertaining to the unlabeled species.

As shown in Figure 1, the CI spectrum displays a peak at m/z 44 (46 when working with $^{15}\text{N}_2$) assigned as N_2O^+ , based on the comparison of its mass spectrometric features with

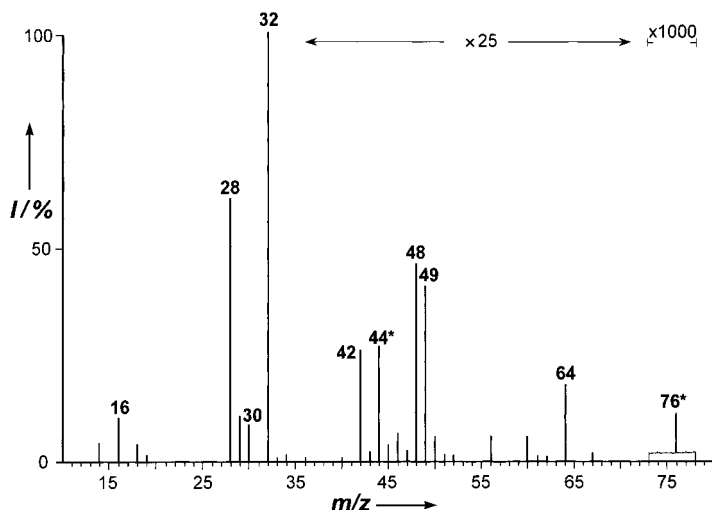


Figure 1. Typical N_2/O_3 CI mass spectrum displaying N_2^+ and O_2^+ as the major ions, together with much less abundant N^+ , O^+ , NO^+ , O_3^+ , N_2O_2^+ , O_4^+ , and N_n^+ ($n=3-4$) ions. The ions at m/z 17, 29 and 49 are formed by reactions of adventitious water (see the *Experimental Section*). The peaks of the ions of interest, N_2O^+ and N_2O_3^+ , are labeled.

those of the molecular ion of N_2O , henceforth denoted as the model ion. The collisionally activated dissociation (CAD) spectrum of the ion probed and the kinetic energy release (KER) of its metastable loss of a N atom correspond to those of the model ion.^[13] Further support is provided by neutralization–reionization (NR) experiments.^[14] Reionization of the uncharged species from the neutralization of the ion probed gives a cation of m/z 44, whose CAD spectrum corresponds to that obtained from the neutralization–reionization of the model N_2O^+ ion. The above results positively establish the formation of N_2O^+ according to Equation (1) in the N_2/O_3 plasma.

As to the *direct* formation of neutral N_2O , according to Equation (2), particularly relevant to this study, detection of O_2^+ , its charged product, in the CI experiments falls short of demonstrating the occurrence of the process, since other reactions, e.g. ionization of O_2 that invariably contaminates ozone, can also produce O_2^+ . A clue to the problem, and valuable mechanistic insight are provided by the detection of a key intermediate, the ion of m/z 76, displayed by the CI spectrum (Figure 1) and positively identified as the adduct N_2O_3^+ by diagnostic mass spectrometric experiments. The most significant piece of evidence arises from the CAD spectrum (Figure 2), whose major peaks at m/z 32 and 44 are assigned to O_2^+ and N_2O^+ , based on the comparison of their MS/MS spectra with those of the corresponding model ions. Remarkably, such fragmentation pattern denotes a

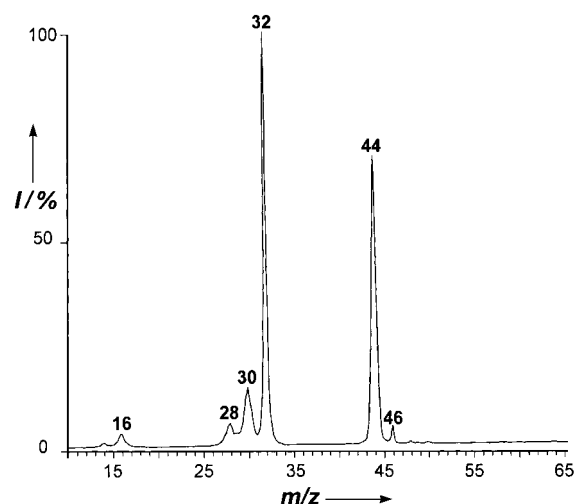


Figure 2. CAD spectrum of the adduct N_2O_3^+ (m/z 76). Ion energy: 8 keV, target gas: He.

$\text{N}-\text{N}-\text{O}\cdots\text{O}-\text{O}$ connectivity, rather than the $\text{N}-\text{N}\cdots\text{O}-\text{O}-\text{O}$ connectivity that characterizes the initial association of the monomers.

Furthermore, the O_2^+ peak present in the CAD spectrum (Figure 2) indicates the loss of either N_2O or its neutral fragments, e.g. $\text{N}_2 + \text{O}$, $\text{N} + \text{NO}$, etc. To clarify this point, the neutral species from the CAD of N_2O_3^+ were separated from all charged species and reionized. The N_r R spectrum^[14d] obtained in this way (Figure 3) displays an N_2O^+ peak at

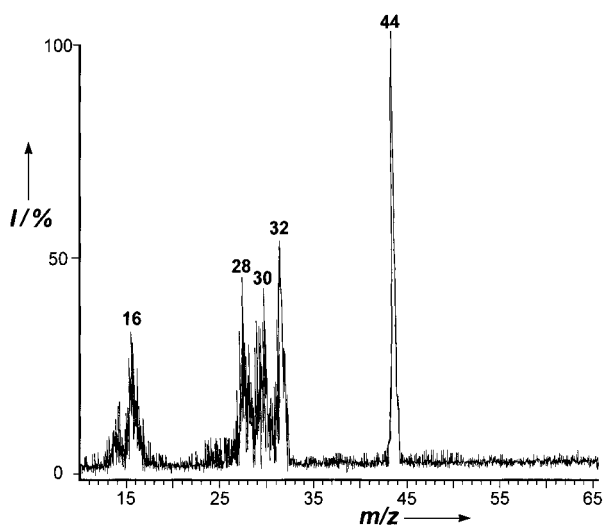
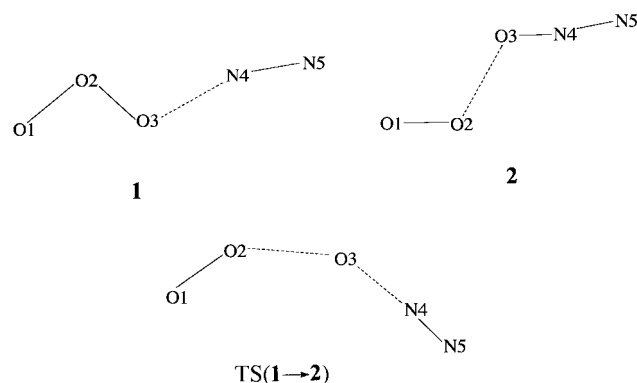


Figure 3. N_r R spectrum of the neutral species from the CAD of the adduct N_2O_3^+ .

m/z 44, showing that at least a fraction of the CAD events undergone by N_2O_3^+ yields, rather than atoms and/or diatomic neutral molecules, a bound N_2O molecule, suggestive of its presence in the complex. Finally, the assignment of the peak at m/z 76 as $[\text{N}-\text{N}-\text{O}\cdots\text{O}-\text{O}]^+$ is confirmed by the identical appearance of its CAD spectrum and that of a model obtained from O_2^+ and N_2O in $\text{O}_2/\text{N}_2\text{O}$ CI experiments.

Density functional (DF) calculation using the hybrid^[15] functional^[16–18] was utilized to locate the stationary points of

the investigated systems and to evaluate the vibrational frequencies. Transition states were located using the method of Schlegel and coworkers.^[19] The 6-311 + G(3d) basis set was used.^[20] The 0 K total energies were corrected to 298 K by standard procedures from scaled harmonic frequencies and moments of inertia relative to B3LYP/6-311 + G(3d)-optimized geometries. All calculations were performed using Gaussian 98.^[21] The optimized structures of the stationary points on the doublet potential energy surface^[22] of N_2O_3^+ are shown in Scheme 1, whereas their total energies, frequencies



Scheme 1. Optimized geometries of relevant stationary points localized on the $[\text{N}_2, \text{O}_3]^+$ potential energy surface.

and geometrical parameters are reported in Table 1. Species **1**, formed by the exothermic ($11.0 \text{ kcal mol}^{-1}$) addition of the reagents can evolve (overcoming a barrier of $10.6 \text{ kcal mol}^{-1}$ ($\text{TS}(\mathbf{1} \rightarrow \mathbf{2})$)) into **2**, more stable by $47.2 \text{ kcal mol}^{-1}$, whose dissociation into N_2O and O_2^+ is endothermic by $28.8 \text{ kcal mol}^{-1}$. The accurate theoretical description of O_3 and related species is notoriously difficult and would require

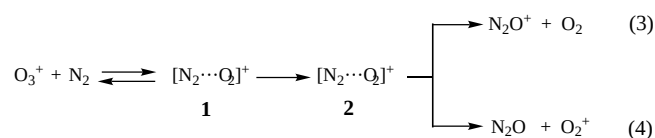
Table 1. Calculated bond lengths [$\text{\AA}$], angles [$^\circ$], total energies [Hartree], and vibrational frequencies [cm^{-1}] (intensities [km mol^{-1}]) of the structures of the stationary points on the doublet potential energy surface of N_2O_3^+ .

	1 $^2\text{A}'$	2 $^2\text{A}''$	$\text{TS}(\mathbf{1} \rightarrow \mathbf{2})$ ^2A
O2-O1	1.209	1.144	1.183
O3-O2	1.358	2.241	1.542
O3-O2-O1	113.8	108.6	123.6
N4-O3	2.245	1.204	1.977
N4-O3-O2	100.3	119.1	152.7
N4-O3-O2-O1	180.0	180.0	−70.0
N5-N4	1.094	1.119	1.094
N5-N4-O3	167.7	178.6	176.6
N5-N4-O3-O2	180.0	180.0	−175.1
E_{B3LYP}	−334.608436	−334.686027	−334.590241
ZPE ^[a]	0.012877	0.015745	0.011652
	88.5 (0.3)	47.1 (0.2)	418.2i
	108.3 (0.1)	80.1 (0.7)	50.5
	138.7 (1.2)	147.6 (0.7)	109.4
	183.0 (0.7)	315.9 (0.1)	143.8
	239.0 (23.7)	551.1 (3.5)	231.2
	557.6 (15.2)	563.1 (2.0)	294.0
	706.9 (111.3)	1228.7 (72.3)	419.8
	1209.7 (129.9)	1773.2 (1059.9)	1450.8
	2420.7 (110.1)	2204.5 (27.3)	2415.1

[a] Zero point energy.

a prohibitively complex multireference approach. The accuracy of the present results can roughly be estimated by summing up the ΔH° changes computed for the formation of **1**, its conversion into **2**, and the dissociation of the latter, which gives $\Delta H_2^\circ = -29.4 \text{ kcal mol}^{-1}$, vs. the tabulated value of $-22.9 \text{ kcal mol}^{-1}$.^[11]

Combining the experimental and computational results, one obtains a satisfactory picture: adduct **1** from the electrostatic association of the reagents can undergo back dissociation or evolve into **2**, which can dissociate by two processes [Eqs. (3) and (4)]. However, back dissociation is entropically



favorable, which accounts for the low combined efficiency (ca. 10%) of the reactions, as well as for the failure to detect N_2O_3^+ adducts in the FT-ICR experiments. At the higher pressure of CI experiments a larger fraction of **1** escapes back dissociation and evolves into **2**. This, and the more efficient collisional stabilization of N_2O_3^+ increase its steady-state concentration and make its detection in the CI spectrum possible. Furthermore, the more efficient collisional cooling of **2** is expected to affect the branching ratio of processes (3) and (4) in favor of the latter, less endothermic by $18.4 \text{ kcal mol}^{-1}$.^[11, 23] In summary, this study demonstrates a reaction sequence yielding N_2O upon ionisation of O_3 diluted in N_2 . Owing to the higher ionization potential of nitrogen compared to ozone, even initial ionization of N_2 would produce O_3^+ by fast charge exchange. In air, reaction (3) is expected to also produce neutral N_2O by fast charge exchange with O_2 .^[24]

To assess the relevance of the present results to atmospheric chemistry, one has to identify the specific environments where ionization of air enriched in ozone does occur. Such requirements are met near power lines and especially in thunderstorms. Indeed, the atmospheric relevance of lightning and corona discharges as the source of 10 to 15% of tropospheric NO is well established.^[25] It is also long known^[26] that ozone is produced by thunderstorms, and recent laboratory simulations show that actually the O_3 yield ($(4 \pm 1) \times 10^{17}$ molecules per Joule), far exceeds that of NO_2 ($(1.4 \pm 0.7) \times 10^{16}$ molecules per Joule).^[27] These results, and the intense ionization of air by lightning, coronas, and other phenomena associated with thunderstorms, suggest that the process reported in this study is a likely source of tropospheric nitrous oxide and that the present results provide a sound fundamental support to previous studies and theories, which, based on an extensive body of experimental data, postulated the formation of N_2O as a consequence of the ionization of air by natural or anthropogenic phenomena.^[28–31]

Experimental Section

The experiments were performed with a multisector mass spectrometer of the EBE-TOF configuration (ZAB SpecCoa-TOF from VG Micromass Ltd.,

Manchester, UK), modified by addition of two pairs of collision gas cells and a low-temperature CI source equipped with a thoriated filament. Typical CI source conditions were as follows: source temperature 100 °C; repeller voltage 0.0 V; ion extraction voltage 8 kV; source pressure 0.05–0.1 Torr. The CAD spectra were recorded with helium as collision gas, admitted into the cell to such a pressure as to reduce the beam intensity by 30%. The NR experiments were performed in the first pair of collision cells positioned between the magnet and the second electrostatic analyzer, reionization being achieved with O₂ as the collider. Any ions leaving the first collision cell were removed using a high-voltage (1 kV) deflector whose efficiency was checked by control experiments. The NR spectra were averaged over 20 to 50 acquisitions to achieve a satisfactory signal-to-noise ratio. The gases, research-grade products from commercial sources with a stated purity exceeding 99.95 mol%, were used as such. Ozone was prepared from dry O₂ in a commercial ozonizer, collected in a silica trap at 77 K and recovered by controlled warming. Some of the initially pure O₃ desorbed from the trap undergoes dissociation into O₂ in the transfer line and/or in the ion source. Furthermore, trace impurities such as H₂O and CO₂ are produced by unspecified reactions of O₃ with the transfer line and the source materials. ¹⁵N₂ (98 atom %) was obtained from Aldrich Chemical Co., Inc.

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Preorganization of the Bioactive Conformation of Sialyl Lewis^x Analogues Correlates with Their Affinity to E-Selectin

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Excessive infiltration of leukocytes from blood vessels into surrounding tissues can cause acute or chronic reactions as observed in reperfusion injuries, stroke, psoriasis, rheumatoid

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arthritis, or respiratory diseases.^[1] An early step in the inflammatory cascade that finally leads to leukocyte extravasation is mediated by selectin–carbohydrate interactions.^[2] With both selectin-knockout mice^[3a–c] and leukocyte adhesion deficiency type 2 patients,^[3d] it could be demonstrated that the selectin–carbohydrate interaction is a prerequisite for the inflammatory cascade to take place.

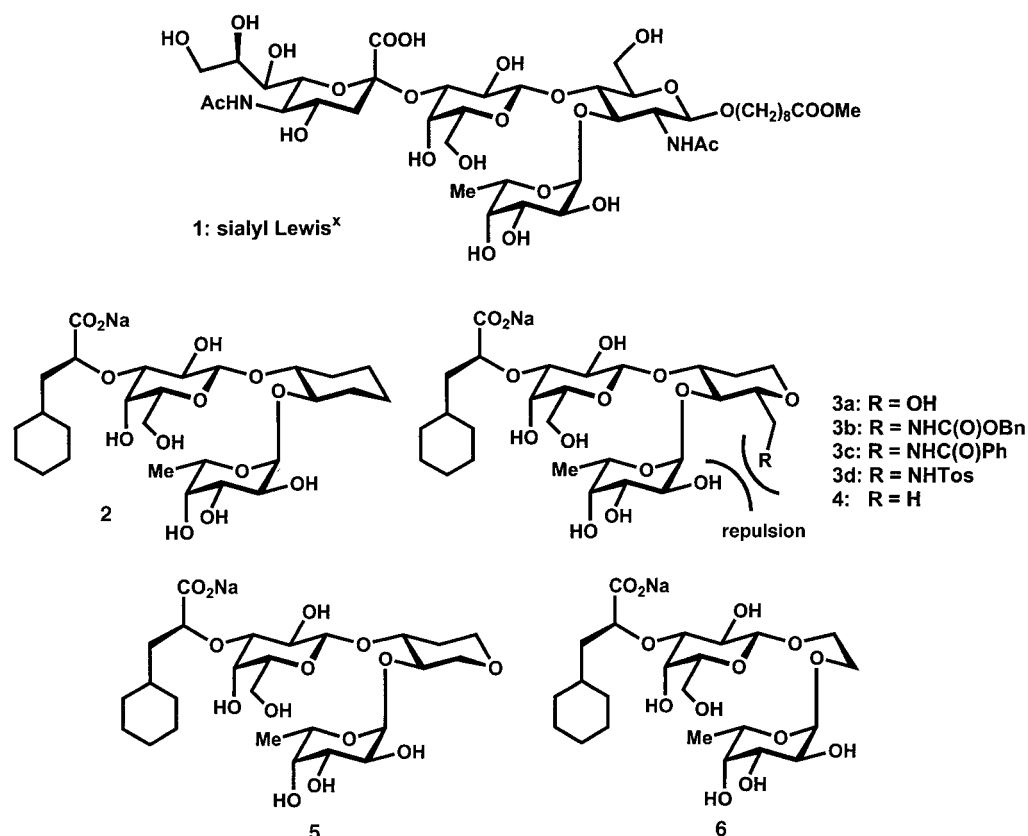
The tetrasaccharide sialyl Lewis^x (sLe^x, **1**, Scheme 1) is the carbohydrate epitope recognized by E-selectin^[4] and, therefore, became the lead structure for the design of selectin antagonists.^[5] The pharmacophores required for E-selectin recognition are the carboxylic acid function, all three hydroxyl groups of the fucose, and the 4- and the 6-hydroxyl groups of

constraints imposed by the equatorial substituent CH₂R. For this purpose we designed compound **4** (Scheme 1) which lacks the R group but still provides an equatorial substituent adjacent to the fucose that could preorganize the bioactive conformation of the core structure. Compound **5** was prepared as a control to investigate the role of the additional ring oxygen atom which could affect both the flexibility and the solvation of the molecule. Finally, compound **6** was designed to still provide all the essential pharmacophores, but with a flexible linker between fucose and galactose to substantially reduce steric constraints.

Selectin antagonist **4**^[11] was prepared from the galactose derivative **7**^[12] using the glucal-derived building block **8**^[13] and

the fucosyl donor **9**^[14] (Scheme 2). The thioglycoside **7** was transformed into the galactosyl donor **10** by tin-mediated selective alkylation with triflate **11**, followed by benzylation. Treatment of a mixture of **8** and **10** with DMTST followed by acid-catalyzed removal of the acetal gave a diol intermediate, which was then regioselectively tritylated to furnish **12**. Fucosylation with **9** and subsequent cleavage of the trityl group yielded **13**. The deoxygenation of alcohol **13** was performed by treatment with *O*-pentafluorophenyl chlorothioformate, followed by radical reduction with tri-*n*-butyltin hydride.^[15] Advanced intermediate **14** was deprotected and the final product **4** isolated as a sodium salt.

Control compound **5** was obtained from xylal **15**^[16] (Scheme 3). Regioselective



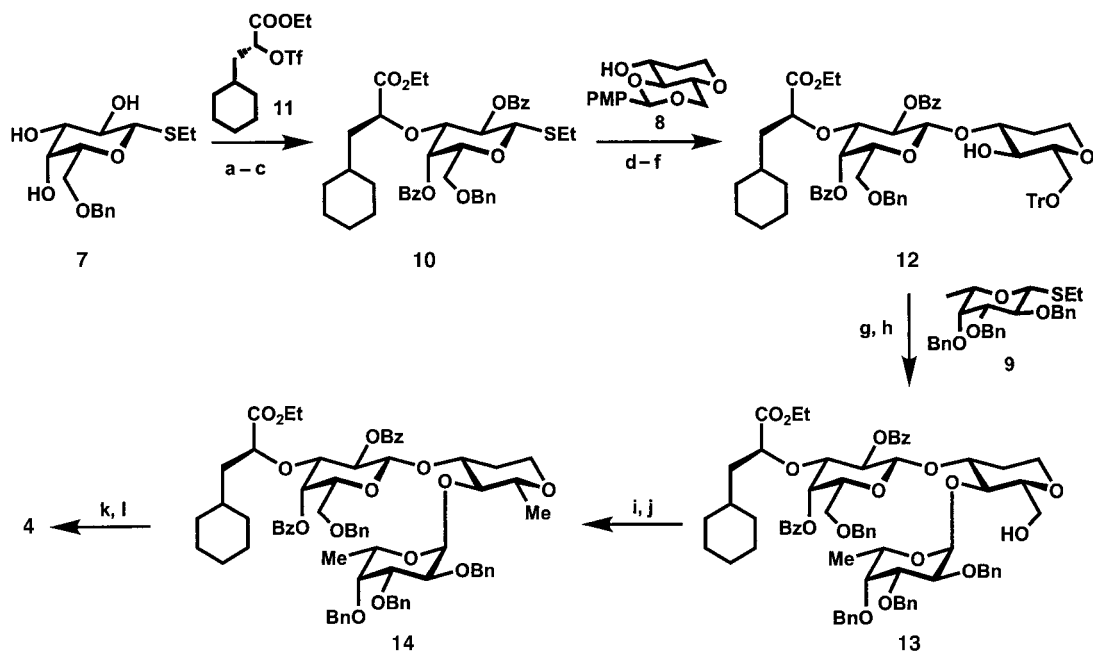
Scheme 1. Sialyl Lewis^x and analogues. Bn = benzyl, Tos = toluene-4-sulfonyl.

the galactose.^[6] By replacing *N*-acetylglucosamine (GlcNAc) with (*R,R*)-cyclohexane-1,2-diol and by introducing lactic acid derivatives instead of neuraminic acid, we discovered simplified sLe^x analogues with improved affinities (for example, **2** in Figure 1).^[7] By incorporating a glucal-derived replacement for GlcNAc we obtained the antagonist **3a**^[8] with 30-fold improved activity compared to sLe^x.^[9] Further modifications of the R group in order to explore a potential additional binding site of E-selectin did not affect the biological activity (for example, **3b–d** are similarly active to **3a**; Table 1).^[10] Thus, additional interactions of the R group with E-selectin are unlikely.

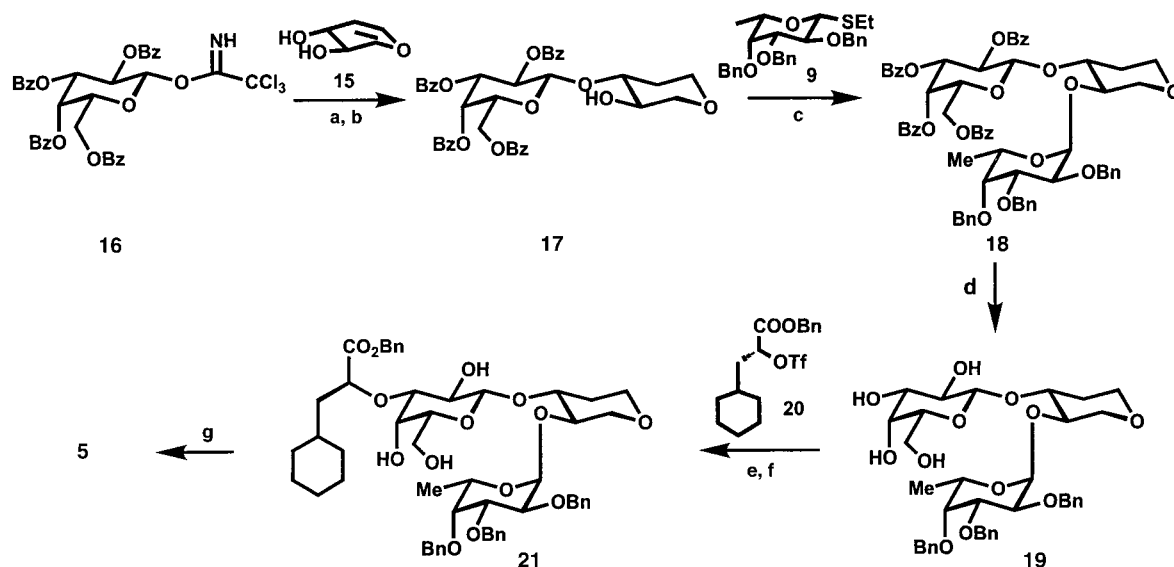
Here we show that the cause for the improved activity of all glucal-derived derivatives **3** is the improved preorganization of the bioactive conformation due to beneficial steric

β -galactosylation with trichloroacetimidate **16**,^[17] followed by hydrogenation, gave **17**. Fucosylation applying thioglycoside **9** ($\rightarrow$ **18**) and removal of the benzoate groups furnished **19**, which was selectively alkylated in the 3-position using triflate **20**. Subsequent deprotection of intermediate **21** gave **5**.^[11] Compound **6**^[11] was prepared from galactose derivative **22** and ethyleneglycol **23** as shown in Scheme 4.

Compounds **4**, **5**, and **6** were tested in a static, cell-free ligand binding assay that measures E-selectin inhibition under equilibrium conditions^[18] and the results were compared with those for antagonists **2** and **3** (Table 1). Inhibitor **4** is equally as potent as **3a–d** and showed a threefold improvement in activity relative to **2**. The control compound **5** is less active than **2**. Compound **6** with a flexible linker between galactose and fucose showed no E-selectin inhibition up to 10 mM. Antag-



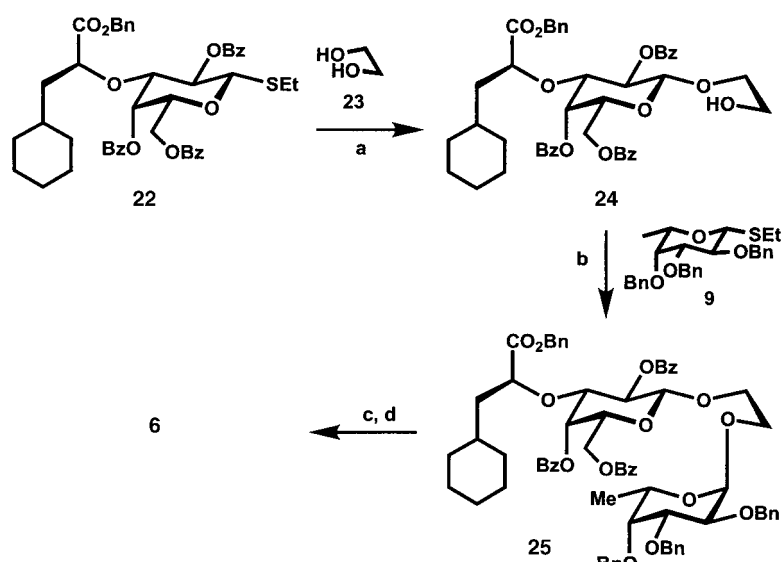
Scheme 2. a) Bu_3SnO , CH_3OH , reflux; b) ethyl (*R*)-3-cyclohexyl-2-trifluoromethanesulfonyloxypropionate (**11**), CsF , DME , 45 % over 2 steps; c) BzCl , pyr , 90 %; d) **8**, DMTST , CH_2Cl_2 ; e) CSA , CH_2Cl_2 , MeOH , 63 % over 2 steps; f) Ph_3CCl , pyr , 70 °C, 93 %; g) ethyl tri-*O*-benzyl-1-thio- β -L-fucopyranoside (**9**), Br_2 , Et_4NBr , $\text{DMF}/\text{CH}_2\text{Cl}_2$ (3/2); h) HCOOH , Et_2O , 52 % over 2 steps; i) $\text{C}_6\text{F}_5\text{OC(S)Cl}$, C_6H_6 , *N*-hydroxysuccinimide, 80 °C, 85 %; j) Bu_3SnH , AIBN , C_6H_6 , 80 °C, 48 %; k) NaOH , MeOH , dioxane, 90 %; l) H_2 , $\text{Pd(OH)}_2/\text{C}$, MeOH , AcOH , Dowex50 (Na^+ form), 83 %. AIBN = azobisisobutyronitrile, Bz = benzoyl, CSA = camphorsulfonic acid, DME = 1,2-dimethoxyethane, DMF = *N,N*-dimethylformamide, DMTST = (dimethylthio)methylsulfonium trifluoromethanesulfonate, PMP = 4-methoxyphenyl, pyr = pyridine, Tf = triflate = trifluoromethanesulfonyl, Tr = triphenylmethyl.



Scheme 3. a) Xylal (**15**), TESOTf , CH_3CN , -40 °C, 66 %; b) H_2 , PtO , MeOH , 87 %; c) ethyl tri-*O*-benzyl-1-thio- β -L-fucopyranoside (**9**), Br_2 , Et_4NBr , $\text{DMF}/\text{CH}_2\text{Cl}_2$ (3/2), 56 %; d) NaOMe , MeOH , 83 %; e) Bu_3SnO , MeOH , reflux; f) benzyl (*R*)-3-cyclohexyl-2-trifluoromethanesulfonyloxypropionate (**20**), CsF , DME , 50 %; g) H_2 , Pd/C , dioxane/ H_2O (3/1), AcOH , Dowex50 (Na^+ form), 78 %. TES = triethylsilyl.

onists **2**, **3**, and **4** were also tested in a dynamic *in vitro* assay that allows the E-selectin-dependent rolling of neutrophils on activated endothelial cells to be monitored and, hence, mimics the nonequilibrium *in vivo* conditions (Table 1).^[19] As observed under static conditions, antagonist **4** was equally as active as **3a** and **3b**, but superior to **2**. Interestingly, the improved activity of **3** and **4** relative to **2** is more pronounced in the dynamic flow assay (sixfold improvement) than in the static equilibrium assay (threefold improvement).

In order to investigate conformational effects, the solution conformations of compounds **2**, **4**, **5**, and **6** were studied by NMR spectroscopy^[20] and compared to the bioactive conformation of **2**.^[7b, 21] Three interglycosidic NOE effects ($\text{H}2^G - \text{H}5^F$, $\text{H}2^G - \text{H}6^F$, and $\text{H}6^G - \text{H}5^F$) were used to characterize the distance between the galactose and fucose moieties (Table 2). In solution, the NOE values suggest the closest proximity is in **4**, followed by **2**, **5**, and **6**. In the bound conformation of **2**, the distance between galactose and fucose is even shorter.^[22]



Scheme 4. a) Ethyleneglycol (**23**), DMTST, CH₂Cl₂, 70%; b) ethyl tri-*O*-benzyl-1-thio- β -L-fucopyranoside (**9**), DMTST, DMF/CH₂Cl₂, 80%; c) H₂, Pd/C, MeOH, AcOH, 80%; d) LiOH, MeOH/H₂O (3/1), Dowex50 (Na⁺ form), 75%.

Table 1. E-selectin inhibition in static and dynamic assays.

Compound	IC ₅₀ values [μ M]	
	Static cell-free assay	Dynamic cell assay
1 (sLe ^x)	1100 ^[a]	> 1000
2	110 ^[a]	150–200
3a	36 ^[a]	30–40
3b	33 ^[a]	20–30
3c	37 ^[b]	n.d. ^[d]
3d	42 ^[b]	74% reduction at 50 μ M
4	39 ^[a]	20–30
5	230 ^[b]	n.d. ^[d]
6	> 10000 ^[c]	n.d. ^[d]

[a] Mean value from three assay runs. [b] Mean value from two assay runs. [c] Value from one assay. [d] n.d. = not determined.

Table 2. Normalized NOE values and selected chemical shifts [ppm] for **2**, **4**, **5**, and **6** in solution and for **2** bound to E-selectin.

NOE	6 (soln)	5 (soln)	2 (soln)	4 (soln)	2 (bound)
H2 ^G –H5 ^F	0.003	0.043	0.094	0.108	0.081
H6 ^G –H5 ^F	< 0.001	0.008	0.013	0.022	0.088
H2 ^G –H6 ^F	0.006	0.062	0.070	0.157	0.172
δ (H5 ^F)	4.12	4.42	4.60	4.77	n.d.

Therefore, according to these interglycosidic NOE values the bioactive conformation of **2** is best mimicked by the solution conformation of compound **4**, followed by **2**, **5**, and **6**. Their in vitro activity increases with decreasing distance between galactose and fucose, most probably due to the decreasing entropic cost of adopting the bioactive conformation in the binding process.^[23]

Based on calculations using the experimental H2^G–H6^F NOE values (Table 2), the weighted mean distance between H2^G and H6^F is 4.1 Å for **2** and 3.55 Å for **4**. The weighted mean distance in **4** is thus very close to the distance in the

bioactive conformation of **2** (3.5 Å). If a two-site jump model with an equilibrium of the ligand in the bioactive conformation and the ligand in an extended conformation (when there is no H2^G–H6^F NOE) is considered, the bioactive conformation is populated by 40% in **2**, and by 90% in **4** according to the ratio of the corresponding NOE values.

The reduced distance between galactose and fucose in higher-affinity ligands is also reflected by the chemical shifts of protons that directly face the opposing carbohydrate. As an example, the chemical shift of H5^F changes from δ =4.12 for the inactive compound **6** to δ =4.77 for inhibitor **4** (Table 2). This pronounced downfield shift is caused by the decreasing distance between H5^F and the galactose and is in line with the binding affinities of the compounds.

In conclusion, we have demonstrated that improved preorganization of the bioactive conformation in solution contributes substantially to the affinity of E-selectin antagonists. The effects can be detected in a static equilibrium assay but are even more pronounced in a nonequilibrium flow assay. Our results suggest that NOE intensities or NMR spectroscopic chemical shifts can be used as surrogate markers to predict biological activities. Further examples are currently under investigation.

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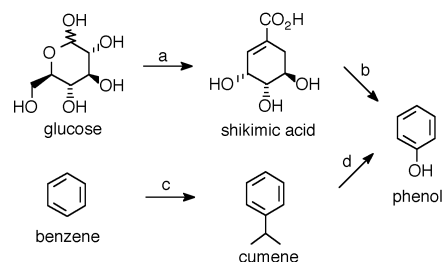
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Benzene-Free Synthesis of Phenol**

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Although phenol has been synthesized by a succession of processes, the Hock oxidation of benzene-derived cumene (Scheme 1) is currently the predominant method used in the



Scheme 1. Synthesis of phenol. Conditions: a) *E. coli* SP1.1PTS-/pSC6.090B; b) 1) H_2O , 350 °C, 2) Cu^0 , H_2O , 350 °C; c) propene, AlCl_3 ; d) 1) O_2 , 100 °C, 2) Δ , H_2SO_4 .

production of phenol, which amounts to 5×10^9 kg annually.^[1] Most of the past and currently employed phenol syntheses use benzene,^[1] a volatile organic carcinogen, as the starting

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material. Approximately 20% of the global benzene production is directed into the manufacture of phenol.^[2] As part of an effort to elaborate alternatives to benzene,^[3] the aromatization of shikimic acid in near-critical water has been examined, in which phenol is the primary reaction product. In parallel efforts, shikimic acid was synthesized in concentrations of 71 g L⁻¹ by altering the mechanism for glucose transport in *E. coli*. The chemistry of shikimic acid in near-critical water and its high-titer synthesis from glucose establish a benzene-free route to phenol.

An aqueous solution of shikimic acid was heated to 350 °C and maintained at this temperature for 30 min. Phenol, *m*-hydroxybenzoic acid, and *p*-hydroxybenzoic acid were produced in yields of 53%, 18%, and 1%, respectively. The extraction of the reaction mixture with diethyl ether and the distillation of the concentrated residue afforded white, crystalline phenol in a yield of 45%. The residue that remained from the distillation was dissolved in water and heated at 350 °C with Cu⁰ powder. After extraction and distillation, additional phenol (6%) was obtained.

The overall yield of phenol that was obtained when shikimic acid was heated in near-critical water (51%) was significantly different from that found in the acid-catalyzed reaction.^[4] When shikimic acid was heated at reflux in HCl (12 M) for 14 h, *p*-hydroxybenzoic acid and *m*-hydroxybenzoic acid were produced in yields of 40% and 13%, respectively. Similar yields were obtained when shikimic acid was heated at reflux in aqueous H₂SO₄ (8 M). The concentration of the acid catalyst could be lowered when solutions of shikimic acid in acetic acid were used: when shikimic acid was heated at 120 °C for 16 h in acetic acid that contained H₂SO₄ (1 M), *p*-hydroxybenzoic acid and *m*-hydroxybenzoic acid were obtained in yields of 57% and 9%, respectively.

Although phenol was formed in aqueous solutions of shikimic acid at temperatures as low as 250 °C, the dominant product was 3-*epi*-shikimic acid (Figure 1). At higher temper-

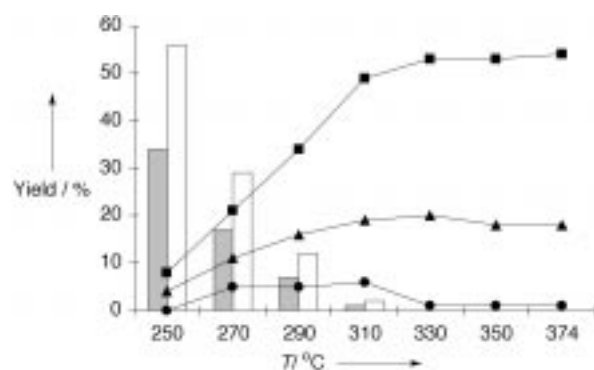
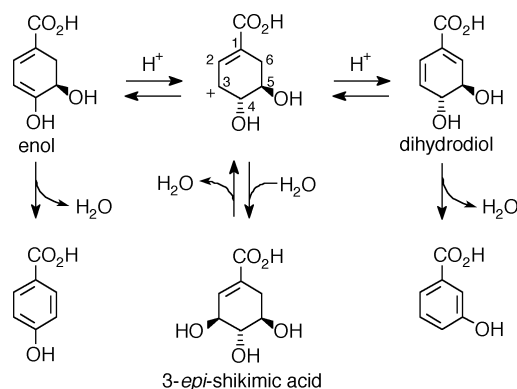


Figure 1. Phenol (■), *m*-hydroxybenzoic acid (▲), *p*-hydroxybenzoic acid (●), and 3-*epi*-shikimic acid (□), formed in aqueous solutions of shikimic acid (■) as a function of temperature. The indicated temperatures were maintained for 30 min in a Parr (Model No. 4742) high-pressure reaction vessel.

atures, the yield of 3-*epi*-shikimic acid declined and the yield of phenol increased. The yield of *p*-hydroxybenzoic acid was never higher than 6%, and only traces were detected at higher temperatures, whereas the yield of *m*-hydroxybenzoic acid

was always approximately 20%. When *m*-hydroxybenzoic acid was heated in water at 350 °C for 3 h, the yield of phenol was only 5%. In contrast, the reaction of *m*-hydroxybenzoic acid at 350 °C for 3 h in the presence of one equivalent of Cu⁰ or Cu⁰OAc resulted in phenol in yields of 96% and 95%, respectively.^[5]

The formation of 3-*epi*-shikimic acid is possibly the result of a C3 carbocation intermediate (Scheme 2). The deprotonation of the C3 carbocation would generate enol and dihy-

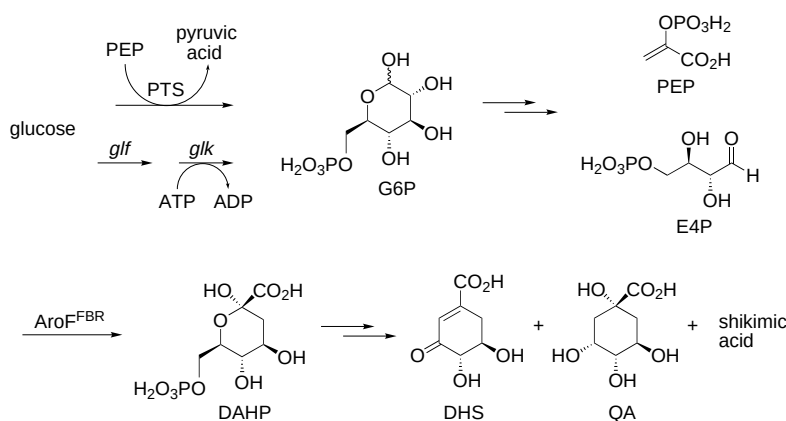


Scheme 2. Possible mechanisms for the reaction of shikimic acid in water heated from 250–374 °C.

drodiol reactive intermediates (Scheme 2) whose subsequent dehydration would produce *p*-hydroxybenzoic and *m*-hydroxybenzoic acids, respectively. Relatively little phenol is likely to be produced from the decarboxylation of *m*-hydroxybenzoic acid. The decarboxylation of *p*-hydroxybenzoic acid provides one route to phenol although decarboxylation and dehydration of a conjugated δ -keto carboxylate derived from enol tautomerization (Scheme 2) could lead to phenol without the intermediacy of *p*-hydroxybenzoic acid.

Shikimic acid has historically not been used in synthesis owing to the expense of its isolation from *Illicium* plants.^[6] With the elaboration of a microbe-catalyzed synthesis from glucose,^[7] shikimic acid is now used to synthesize the antiinfluenza drug Tamiflu.^[8] Microbes such as *E. coli* rely on the carbohydrate phosphotransferase (PTS) system, which catalyzes the transfer of the phosphoryl group from phosphoenolpyruvic acid to promote the transport of glucose and generate glucose 6-phosphate (Scheme 3).^[9] Because the byproduct, pyruvic acid, is oxidized to CO₂, the maximum theoretical yield for the synthesis of shikimic acid is 43% (mol/mol) when a microbe that relies on the PTS-mediated transport of glucose is used.^[3c, 10]

The PTS system in shikimate-synthesizing *E. coli* SP1.1 was therefore inactivated by using the mutation $\Delta(ptsH\ ptsI\ crr)::Kn^R$ to generate *E. coli* SP1.1PTS⁻.^[7, 11] The diffusion of glucose into *E. coli* SP1.1PTS⁻/pSC6.090B was mediated by the *glf*-encoded glucose facilitator whereas the reaction of glucose with adenosine triphosphate was catalyzed by *glk*-encoded glucokinase (Scheme 3).^[12] Both *glf* and *glk* genes, isolated from *Zymomonas mobilis*,^[12a] were plasmid pSC6.090B inserts (Figure 2). Improved phosphoenolpyru-



Scheme 3. Glucose transport and biosynthesis of shikimic acid and metabolically related by-products. Abbreviations: PEP = phosphoenolpyruvic acid, PTS = carbohydrate phosphotransferase system, ATP = adenosine triphosphate, *glf* = glucose facilitator protein, *glk* = glucokinase, G6P = D-glucose 6-phosphate, E4P = D-erythrose 4-phosphate, *AroF^{FBR}* = DAHP synthase, DAHP = 3-deoxy-D-arabino-heptulosonic acid 7-phosphate, DHS = 3-dehydroshikimic acid, QA = quinic acid.

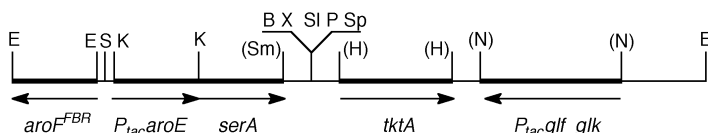


Figure 2. Restriction enzyme map of plasmid pSC6.090B.

vate availability does not increase the biosynthesis of 3-deoxy-D-arabino-heptulosonic acid 7-phosphate, a precursor of shikimic acid, unless the availability of D-erythrose 4-phosphate is increased (Scheme 3).^[13] This was accomplished with the increase in transketolase activity attendant with the expression of the *tktA* insert (Figure 2) of plasmid pSC6.090B.^[14]

E. coli SP1.1PTS⁻/pSC6.090B was cultured on a 1 L scale in minimal salts medium under controlled fermentor conditions: the culture was maintained at pH 7, 33 °C, and with a dissolved oxygen level of 10 % air saturation.^[15] SP1.1PTS⁻/pSC6.090B produced (Figure 3) shikimic acid (71 g L⁻¹, 27 % mol/mol

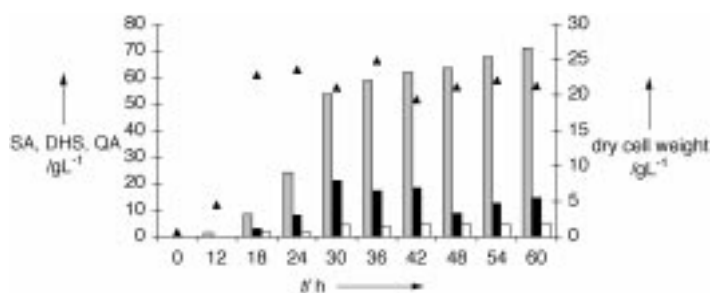


Figure 3. Growth of *E. coli* SP1.1PTS⁻/pSC6.090B (dry cell weight: ▲) and synthesis of shikimic acid (SA: ■), by-products 3-dehydroshikimic acid (DHS: ■), and quinic acid (QA: □) under fed-batch fermentor conditions.

yield) from glucose after cultivation for 60 h along with 3-dehydroshikimic acid (15 g L⁻¹) and quinic acid (5 g L⁻¹). In comparison, *E. coli* PTS⁺ strains, which lack the expression of

the *glf*-encoded glucose facilitator, produced less shikimic acid (52 g L⁻¹, 18 % mol/mol yield). The addition of ethanol to the clarified, decolorized fermentation broth followed by continuous liquid–liquid extraction with ethyl acetate provided shikimic acid (97 % recovery).

The reactivity of shikimic acid in near-critical water circumvents the potent antimicrobial activity of phenol. The employment of near-critical water also establishes a unique reaction manifold which connects hydroaromatic compounds with aromatic products, while avoiding the use of high concentrations of strong acids. This is probably a result of the 1000-fold increase in the dissociation constant of water as its critical-point temperature is approached.^[16] Shikimic acid can become more readily available, given a predicted 86 % (mol/mol) theoretical maximum yield for its synthesis in lieu of PTS-mediated glucose transport.^[3c, 10] The chirality of shikimic acid could thus become essentially disposable as a previously scarce

natural product evolves into an abundantly available commodity chemical that is used primarily for its cyclic assembly of carbon atoms.

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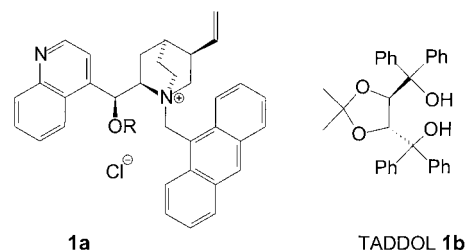
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Highly Efficient Catalytic Synthesis of α -Amino Acids under Phase-Transfer Conditions with a Novel Catalyst/Substrate Pair**

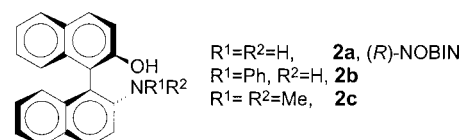
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Asymmetric phase-transfer catalysis (PTC) reactions constitute one of the most challenging fields of contemporary organic synthesis.^[1] Following the seminal work by O'Donnell et al.^[2a] and Grabowski et al.^[2b] dramatic improvements in the asymmetric efficiency of PTC reactions were achieved by introducing (9-anthracenylmethyl)cinchonidinium (**1a**, R = allyl, benzyl, H) and other cinchoninium salts as catalysts



for the enantioselective alkylation of *N*-(diphenylmethylene)glycine esters with electrophiles.^[2c–e] Purely synthetic, chiral, C_2 -symmetrical ammonium salts were recently prepared and shown to be highly efficient in the same set of reactions.^[3] Thus, preparative catalytic asymmetric syntheses of very important synthetic targets such as amino acids were developed, and enantioselectivities of up to 92–98% for the final product were achieved.^[2c–e, 3]

Unfortunately, *N*-(diphenylmethylene)glycine esters are expensive, and quaternary ammonium salts are sometimes unstable under basic conditions. Hence, the search for novel types of substrates and catalysts for the asymmetric PTC synthesis of amino acids deserves further effort. Recently, we reported on the use of 2-amino-2'-hydroxy-1,1'-binaphthyl (NOBIN, **2a**) as a novel type of PTC catalyst in the alkylation



of *N*-(phenylmethylene)alanine esters and thus the synthesis of α -methyl- α -amino acids with a modest *ee* of 68%.^[4] Our attempts to use **2a** as a catalyst for the asymmetric alkylation of *N*-(diphenylmethylene)glycine esters failed to give any asymmetric induction. We reasoned, however, that other types of achiral glycine derivatives capable of stronger interactions with NOBIN would be more suitable substrates.

Earlier, we reported on the synthesis and application of substrate **3** (see Scheme 1) in an asymmetric Michael reaction, catalyzed by (*R,R*)-TADDOL (**1b**), that led to 4-methylglutamic acid with a low *ee* (28%).^[5] Substrate **3** seemed to be a suitable model for use in other alkylation reactions with catalyst **2a**, as there are several potential centers of substrate–catalyst interaction by formation of a hydrogen bond or a metal complex. Here we report new results on the alkylation of substrate **3** (Scheme 1) with catalysis by **2a** under phase-transfer conditions, which led to a fast (as little as 5 min), efficient synthesis of α -amino acids at ambient temperature and with *ee* values of up to 93–98%.

Substrate **3** was readily prepared by the templated condensation of *N*-(2-benzoylphenyl)pyridine-2-carbamide (PBP, **4**) with glycine (Gly) and Ni(NO₃)₂ in MeOH in the presence of MeONa (Scheme 1). Complex **3** is a red, crystalline compound, easily purified by chromatography on SiO₂ and poorly soluble in most organic solvents and water. The solubility of the complex in organic solvents such as CH₂Cl₂ or (CH₂Cl)₂ was greatly increased by adding **2a**.

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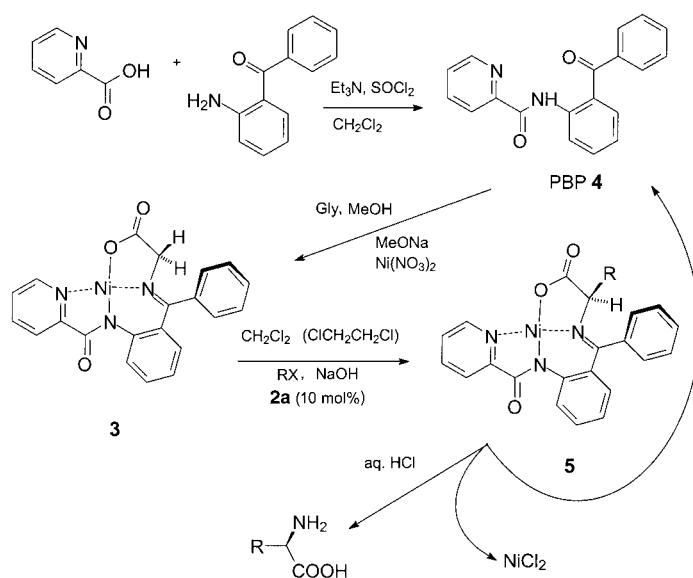
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Scheme 1. Synthesis of substrate **3**, its alkylation under PTC conditions, and recovery of the target amino acids.

While no alkylation of substrate **3** was observed in the absence of a catalyst even after 5 h, addition of **2a** resulted in a remarkable change. Table 1 summarizes the experimental results of the alkylation of **3** with benzyl bromide under PTC conditions at room temperature with different catalysts and bases in various solvents, according to Scheme 1. The salient feature of this data is the superiority of unsubstituted NOBIN, in both yield and enantioselectivity, over the traditional PTC catalyst **1a** or **1b** under similar conditions (Table 1, entries 1–6). Whereas both **1a** and **1b** gave disappointingly low yields (less than 50%), even after one hour, and *ee* values of the resulting phenylalanine (Phe) in the range of 5–16%

(entries 1–3), the reaction promoted by (*R*)-NOBIN (or (*S*)-NOBIN) in toluene gave the alkylated complex in a yield of 50% and Phe with an *ee* of 89% (entry 4). The reaction in CH_2Cl_2 gave (*R*)-Phe (or (*S*)-Phe) in 70% yield with 96–97% *ee* after 8 min (entries 5 and 6). As expected, increasing the polarity of the solvent lowered the *ee* of the alkylation product (entry 7), whereas $(\text{CH}_2\text{Cl})_2$ served as a good substitute for CH_2Cl_2 (entries 8 and 9) that allowed the reaction to be carried out at higher temperatures (up to 70°C) without a significant drop in the product *ee* (entry 9) but with significantly increased yields.

Modification of **2a** by replacing the NH_2 group with NHPh (**2b**) or NMe_2 (**2c**) invariably decreased the efficiency of the reaction by slowing the rate and bringing the *ee* down to 3–5% (Table 1, entries 10 and 11). The *O*-benzyl derivative of **2a** was catalytically inactive.

The nature of the base is important in these reactions, as the transition from solid NaOH to KOH and then to $\text{CsOH} \cdot x\text{H}_2\text{O}$ decreased the *ee* of the reaction progressively from 96 to 16 and finally to 10 (Table 1, entries 6, 12, and 13). Using 50% aqueous NaOH was also detrimental to the *ee*, which fell from 96 to 55%, and the yield, which dropped to a meager 5% after 1 h (entries 6 and 14). Significantly, NaH was almost as efficient a base as NaOH (entries 5 and 15).

Table 2 summarizes the alkylation of substrate **3** with different alkyl halides under optimal conditions (Table 1, entry 6). All of the activated alkyl halides participated in the reaction and gave the alkylated products in good yields and with high *ee* (90–98.5%) at room temperature after 4–30 min (Table 2, entries 1–7). Unactivated alkyl halides were much less reactive, and relatively low yields of the alkylated product were obtained for the alkylation of **3** with simple alkyl iodides after short reaction times (Table 2, entries 8, 9, and 11), although the *ee* values of the recovered amino acids were still good. Longer reaction times resulted in some decrease in

the *ee* of the amino acid (Table 2, entry 10). Racemization of the alkylated product during the longer time intervals might be a reason for this decline in *ee*.

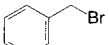
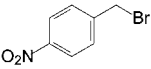
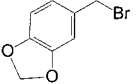
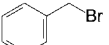
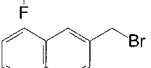
The alkylated complexes **5** could be purified by chromatography or recrystallization before recovery of the amino acid. With the crystallization procedure, the *ee* of the complex or recovered amino acid was greatly improved (Table 2, entry 1). Ligand **4** was easily recovered in quantitative yield and reused to prepare **3**. The NOBIN could also be recovered from the reaction mixture by chromatography in 50% yield, though significant amounts of *O*-alkylated NOBIN were also detected in the reaction mixture.

Table 1. Asymmetric PTC alkylation of substrate **3** with benzyl bromide promoted by different catalysts and types of bases at room temperature.^[a]

Entry	Solvent	Catalyst	Base	<i>t</i> [min]	Yield [%] ^[b]	<i>ee</i> of Phe [%] (configuration) ^[c]
1	CH_2Cl_2	1a	NaOH	60	50	16 (<i>R</i>)
2	CH_2Cl_2	1b	NaOH	10	10	12 (<i>R</i>)
3	$\text{C}_6\text{H}_5\text{CH}_3$	1b	NaOH	45	10	5 (<i>S</i>)
4	$\text{C}_6\text{H}_5\text{CH}_3$	(<i>R</i>)- 2a	NaOH	45	50	89 (<i>R</i>)
5	CH_2Cl_2	(<i>R</i>)- 2a	NaOH	8	90	97 (<i>R</i>)
6	CH_2Cl_2	(<i>S</i>)- 2a	NaOH	8	88	96 (<i>S</i>)
7	MeCN	(<i>R</i>)- 2a	NaOH	20	80	17 (<i>R</i>)
8	$(\text{CH}_2\text{Cl})_2$	(<i>R</i>)- 2a	NaOH	5	70	97 (<i>R</i>)
9 ^[d]	$(\text{CH}_2\text{Cl})_2$	(<i>R</i>)- 2a	NaOH	5	86	93 (<i>R</i>)
10	CH_2Cl_2	(<i>R</i>)- 2b	NaOH	60	10	3 (<i>R</i>)
11	CH_2Cl_2	(<i>R</i>)- 2c	NaOH	15	15	5 (<i>R</i>)
12	CH_2Cl_2	(<i>R</i>)- 2a	KOH	7	80	16 (<i>R</i>)
13	CH_2Cl_2	(<i>R</i>)- 2a	$\text{CsOH} \cdot x\text{H}_2\text{O}$	15	25	10 (<i>R</i>)
14	CH_2Cl_2	(<i>R</i>)- 2a	50% aq. NaOH	60	5	55 (<i>R</i>)
15	CH_2Cl_2	(<i>R</i>)- 2a	NaH	11	50	97 (<i>R</i>)

[a] Reaction conditions: concentration of **3** = 1.5–1.7 M, $\text{PhCH}_2\text{Br}/\text{substrate}$ = 1.15–1.2/1, (*R*)-NOBIN/substrate = 1/10, MOH/substrate = 10/1, room temperature unless indicated otherwise, under Ar, all solvents were carefully dried. [b] Yield of the alkylated complex **5** determined after its separation from recovered **3**. [c] Determined by chiral GLC analysis of Phe recovered from the complex on chiral Chirasil-Val columns. [d] The reaction was carried out at 70°C.

Table 2. Asymmetric PTC alkylation of substrate **3** with different alkyl halides promoted by (*R*)-NOBIN at room temperature.^[a]

Entry	Alkylating agent	<i>t</i> [min]	Yield [%] ^[b]	<i>ee</i> of (<i>R</i>)-amino acid [%] ^[c, d]
1		8	90	97 (>99.8% ^[e])
2		4	92 ^[f]	93
3		6	70	98.5
4		7	80	94
5		6	62	98.5
6		30	68	90
7		4	75	90
8	C ₂ H ₅ I	5	2	93
9	C ₂ H ₅ I	30	15	93
10	C ₂ H ₅ I	240	35	81
11	<i>n</i> -C ₆ H ₁₃ I	60	10	91

[a] Reactions carried out in CH₂Cl₂, concentration of **3** was 1.5–1.7 M, RX/substrate = 1.15–1.2/1, (*R*)-NOBIN/substrate = 1/10, NaOH/substrate = 10/1–20/1, room temperature, under Ar. [b] Yield of the alkylated complex **5** estimated after its separation from unreacted **3**. [c] Chiral GLC analysis of Phe recovered from the complex on chiral Chirasil-Val columns. [d] The enantiomerically enriched amino acids could be crystallized from 2-propanol/water to give the pure enantiomers. [e] The amino acid was recovered from the recrystallized complex. [f] 6% of the bis-alkylated complex was detected in the reaction mixture.

Another interesting feature of catalysis by NOBIN was the observation of a very significant positive nonlinear effect, (+)-NLE,^[6a] for the alkylation of **3** with BnBr (Figure 1). It is most likely that the mechanism of the reaction includes the

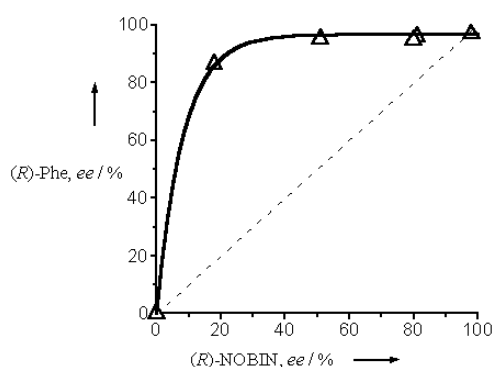


Figure 1. Positive nonlinear effect in the alkylation of **3** with BnBr, catalyzed by (*R*)-NOBIN.

formation of a chiral phenolate of NOBIN on the surface of the NaOH. The phenolate transfers into solution, deprotonates **3**, and the carbanion forms a chiral ion pair with NOBIN

by chelating the sodium cation. Support for this concept comes from the absence of any reactivity of the *O*-Bn derivative of NOBIN and the dependence of the enantioselectivity of the reaction on the cation of the base (Table 1, entries 12–14). This chiral ion pair is then alkylated by the alkyl halides with a significant enantio-bias, similar to that of TADDOL- and NOBIN-catalyzed asymmetric alkylations of Schiff bases of alanine esters.^[4] The role of the primary amino group of the ligand is crucial, since any substitution of this led to a drastic decrease in asymmetric induction (Table 1, entries 10 and 11). Likely, its role relies on interaction with Na⁺ ions.^[4] However, its direct interaction with Ni glycinate **3** should also be considered. Apparently, the mechanism in the case of **3** is more complex, as the alkylation of the *tert*-butyl ester of *N*-(diphenylmethylene)glycine with BnBr in CH₂Cl₂, with catalysis by (*R*)-NOBIN under the experimental conditions of Table 2, led to racemic Phe in 50% yield after 1 h. Similarly, alkylation of Schiff bases of alanine esters with BnBr under similar conditions always led to racemic products. The less polar solvents toluene or hexane had to be employed with these substrates to obtain reasonable *ee* values of the alkylation products.^[4] The (+)-NLE^[6] (Figure 1) indicates that, most likely, the ionized NOBIN phenolate generates heterochiral aggregates with a lower reactivity than either homochiral aggregates or the monomeric species; and/or the heterochiral aggregates have greater stability than their homochiral counterparts. As a result, the homochiral aggregates (or the remaining monomer) with higher *ee* than that of the starting ligand will be the active species. This amplification effect is related to the reservoir effect (see the discussion in ref. [6a]).

In conclusion, we have developed a new substrate/catalyst pair for the efficient and simple asymmetric synthesis of a broad range of α -amino acids. The advantage of the procedure is the ease of the synthesis of the substrate **3** and availability of both enantiomeric forms of NOBIN.^[7] Thus, both enantiomers of proteinogenic and nonproteinogenic amino acids become easily available in a remarkably short reaction time. The high reaction rate is particularly important for the synthesis of short-lived ¹¹C-labeled α -amino acids, a valuable class of compounds for PET diagnostics. Finally, the enantiomeric purity of synthetically derived NOBIN is not crucial for effective asymmetric induction (see Figure 1).

Experimental Section

Enantiomeric GLC analyses^[8] of the amino acids were performed on a Chirasil-L-Val type phase, by using *n*-propyl esters of *N*-trifluoroacetyl derivatives of amino acids. (*R*)- and (*S*)-NOBIN were prepared as previously described.^[7]

4 was prepared in 85% yield by a straightforward condensation of picolinic acid (converted to its chloroanhydride with SOCl₂ in the presence of Et₃N at 0 °C) and *o*-aminobenzophenone in CH₂Cl₂ at 25 °C. M.p. 159 °C (ref. [9]; m.p. 154–156 °C). Elemental analysis (%) calcd for C₁₉H₁₄N₂O₂: C 75.48, H 4.67, N 9.27; found: C 75.59, H 4.68, N 9.23; IR: $\tilde{\nu}$ = 1690, 1590 (amide), 1650 cm^{−1} (C=N).

3 was prepared by condensation of **4** (3.5 g, 11.6 mmol), Ni(NO₃)₂ · 6H₂O (6.75 g, 23.2 mmol), and glycine (1.74 g, 23.2 mmol) in MeOH (40 mL) in the presence of MeONa (4N, 25 mL, 97.5 mmol) under reflux for 20 min and purified by crystallization from CHCl₃. M.p. > 280 °C (decomp) [ref. [9]: m.p. > 280 °C (decomp)], yield 91% (4.39 g, 10.6 mmol). Element-

tal analysis (%) calcd for $C_{21}H_{15}N_3O_3Ni$: C 60.62, H 3.63, N 10.10; found: C 60.58, H 3.60, N 10.05; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.80 (s, 2H, CH_2), 6.8–8.9 (m, 13H, ArH); UV (CH_2Cl_2 , $lg\epsilon$ (λ_{max})): 4.60 (354 nm); IR: $\tilde{\nu}$ = 1685, 1610 (amide), 1650 cm^{-1} ($C=N$).

Asymmetric alkylation of **3** under PTC conditions (described for $RX = BnBr$): Finely ground NaOH (2.0 g, 50 mmol), substrate **3** (2.1 g, 5 mmol), and (*R*)-NOBIN (0.14 g, 0.5 mmol) in anhydrous CH_2Cl_2 (30 mL) were stirred under Ar for 3 min at 15–20 °C. Then $BnBr$ (1 g, 5.8 mmol) was added under Ar, and the mixture was stirred for an additional 8 min. The reaction mixture was quenched by the addition of 10 mL of aqueous AcOH and diluted with CH_2Cl_2 (30 mL). The organic layer was separated, and a small part of it was used to determine the *ee* (97% *R*) of the crude Phe (Table 1, entry 5). The residue was purified by flash chromatography on silica gel (to remove unconsumed **3**) with $CHCl_3$ /acetone as eluent to give **5** (2.3 g, 4.5 mmol, 90% yield, 97% *ee* according to GLC analysis of the corresponding (*R*)-amino acid). The crude complex was crystallized from C_6H_6 /acetone to give the enantiomerically pure product **5** ($R = Bn$; 1.9 g, 3.7 mmol, 74% yield); m.p. 276 °C, $[\alpha]_D^{25} = -3605^\circ$ ($c = 1$, $CHCl_3/MeOH$), *ee* > 99.8% (*R*) according to GLC on the amino acid (ref. [9]; for **5** ($R = Bn$) with *ee* 13% (*S*): $[\alpha]_D^{25} = +370^\circ$ ($c = 1$, $CHCl_3/MeOH$)). Elemental analysis (%) calculated for $C_{28}H_{21}N_3O_3Ni$: C 66.40, H 4.15, N 8.30; found: C 66.63, H 4.28, N 8.11; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.86, 3.13 (ABX system, $J_{AB} = 13.4$ Hz, 2H, CH_2), 4.36 (ABX system, $J_{AX} = 2.9$, $J_{BX} = 5.65$ Hz, 1H, CH), 6.80–7.90 (m, 18H, Ar); UV ($CHCl_3$, $lg\epsilon$ (λ_{max})): 2.80 (256), 3.79 (351), 3.68 (455 nm). IR: $\tilde{\nu}$ = 1685, 1615 (amide), 1660 cm^{-1} ($C=N$).

Recovery of amino acids, as illustrated for Phe: The crystallized complex **5** ($R = Bn$, 1.8 g, 3.5 mmol) was decomposed by refluxing a suspension in a mixture of aqueous 6N HCl (5 mL) and MeOH (6 mL) for a few minutes until the red color of the solution disappeared, as described previously.^[9] The solution was evaporated to dryness, water was added to the residue, and the insoluble material was filtered off, washed with water, and dried to afford **4**·HCl. The aqueous layer was adjusted to pH 8 with aqueous ammonia solution, and the mixture was extracted with $CHCl_3$ (3×10 mL) to remove small amounts of remaining **4**. Phe was recovered from the aqueous solution by the ion-exchange technique (DOWEX-50, H^+ form). (*R*)-Phe (0.40 g, yield 68%) was analyzed by chiral GLC (*ee* > 99.8%); m.p. 288–290 °C (decomp), $[\alpha]_D^{25} = +33.2$ ($c = 2$, H_2O), [ref. [10]: (*S*)-Phe $[\alpha]_D^{25} = -33.4$ ($c = 1.3$, H_2O)]. Elemental analysis (%) calcd for $C_9H_{11}NO_2$: C 65.44, H 6.71, N 8.48; found: C 65.36, H 6.78, N 8.44.

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Synthesis and Characterization of a Metallabenzyne**

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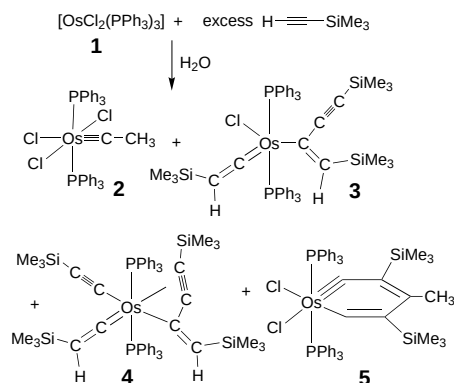
Interesting organometallic compounds can often be obtained by replacement of (hydro)carbon groups of organic compounds with isolobal transition metal fragments.^[1] For example, the CH_2 group in $CH_2=CHR$ can be replaced by 16-electron transition metal fragments $[L_nM]$ to give carbene complexes $[L_nM=CHR]$, the CH group in $HC\equiv CR$ can be replaced by 15-electron transition metal fragments $[L_nM]$ to give carbyne complexes $[L_nM\equiv CR]$, and a CH group in benzene can be replaced by 15-electron transition metal fragments to give metallabenzynes.^[2] In principle, a carbon atom in benzyne could also be replaced by 14-electron transition metal fragments to give metallabenzynes. However, such a possibility has not previously been realized. Here we describe the synthesis and characterization of the first metallabenzene.

Treatment of $[OsCl_2(PPh_3)_3]$ (**1**)^[3] with an excess of $HC\equiv CSiMe_3$ in wet benzene produced a yellow precipitate and a brown solution. The yellow precipitate was identified as

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the carbyne complex $[\text{OsCl}_3(\equiv\text{CCH}_3)(\text{PPh}_3)_2]$ (**2**). From the brown solution, complexes **3**, **4**, and the metallacyclic **5** were isolated in 22, 4.5, and 30 % yield, respectively (Scheme 1).



Scheme 1. Reaction of **1** with $\text{HC}\equiv\text{CSiMe}_3$.

All new complexes were characterized by elemental analysis and multinuclear NMR spectroscopy. The structures of **4** and **5** were also confirmed by X-ray diffraction analysis (Figures 1 and 2).^[4] Formation of complexes **2** and **3** from the

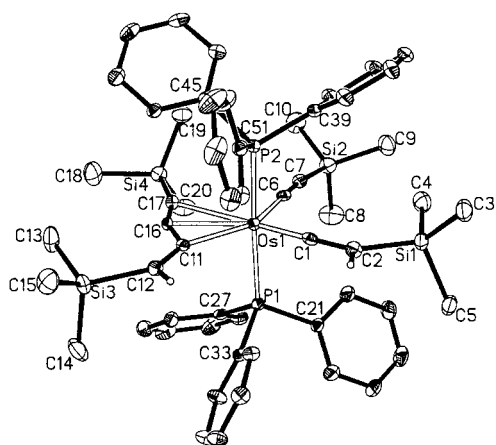


Figure 1. Molecular structure of **4**. Selected bond lengths [Å] and angles [°]: Os1-P1 2.3821(14), Os1-P2 2.3722(14), Os1-C1 1.803(6), Os1-C6 2.060(5), Os1-C11 2.126(5), Os1-C16 2.341(5), Os1-C17 2.685(5), C1-C2, 1.332(7), C6-C7 1.218(6), C11-C12 1.321(7), C11-C16 1.406(7), C16-C17 1.223(7); C2-C1-Os1 179.1(5), C1-C2-Si1 128.7(5), C7-C6-Os1 177.6(5), C6-C7-Si2 172.8(5), C12-C11-Os1 150.6(4), C11-C12-Si3 126.9(4), C16-C11-Os1 80.2(3), C16-C17-Si4 161.5(5), C11-C16-Os1, 63.5(3), C17-C16-Os1 92.3(4), C12-C11-C16 129.1(5), C17-C16-C11 155.8(5), Si4-C17-Os1 137.87(26), P2-Os1-P1 171.41(5).

reaction of **1** with an excess of $\text{HC}\equiv\text{CSiMe}_3$ can be understood, as the similar products $[\text{OsCl}_3(\equiv\text{CCH}_2\text{CMe}_3)(\text{PPh}_3)_2]$ and $[\text{OsCl}(\text{C}=\text{CHCMe}_3)\{\text{C}(\text{C}\equiv\text{CCMe}_3)=\text{CHCMe}_3\}(\text{PPh}_3)_2]$ were obtained from the reaction of **1** with an excess of $\text{HC}\equiv\text{CCMe}_3$ via the intermediate $[\text{OsCl}_2(\text{C}=\text{CHCMe}_3)(\text{PPh}_3)_2]$.^[5] Thus one might expect that $[\text{OsCl}_3(\equiv\text{CCH}_2\text{SiMe}_3)(\text{PPh}_3)_2]$ and **3** could also be produced from the reaction of **1** with $\text{HC}\equiv\text{CSiMe}_3$ via the intermediate $[\text{OsCl}_2(\text{C}=\text{CHSiMe}_3)(\text{PPh}_3)_2]$. However, desilylation apparently occurred in the formation of **2** as a result of hydrolysis of the C–SiMe₃ bond. There are many reports that reactions of

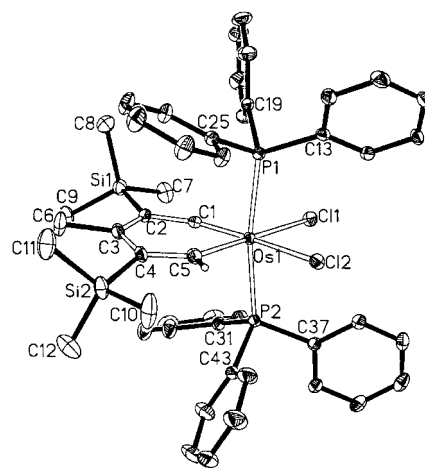
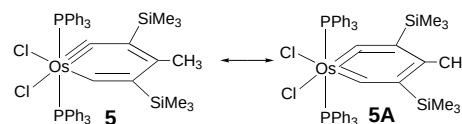


Figure 2. Molecular structure of **5**. Selected bond lengths [Å] and angles [°]: Os1-P1 2.4103(9), Os1-P2 2.4117(10), Os1-C11 2.4798(9), Os1-C12 2.4811(10), Os1-C1 1.815(4), Os1-C5 1.939(5), C1-C2 1.376(5), C2-C3 1.420(5), C3-C4 1.416(6), C4-C5 1.378(6), C3-C6 1.515(7); P1-Os1-P2 171.21(3), C1-Os1-C5 78.1(2), C4-C3-C2 124.0(4), C2-C1-Os1 148.7(3), C4-C5-Os1 138.6(5), C1-C2-C3 112.4(4), C5-C4-C3 117.7(4), C1-C2-Si1 120.0(3), C5-C4-Si2 118.8(4), C3-C2-Si1 127.6(3), C3-C4-Si2 123.4(3), C2-C3-C6 117.4(5), C4-C3-C6 118.6(5).

silylated alkynes with low-valent transition metal complexes in the presence of water can lead to hydrolysis of C–Si bonds to give C–H bonds.^[6, 7] Complex **4** is presumably formed by the reaction of **3** with $\text{HC}\equiv\text{CSiMe}_3$ and elimination of HCl.

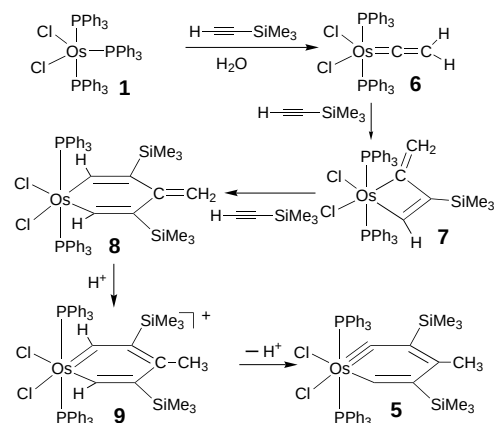
The most unusual complex formed in the reaction of **1** with an excess of $\text{HC}\equiv\text{CSiMe}_3$ is **5**. As confirmed by X-ray diffraction analysis, it contains an essentially planar six-membered metallacycle (Figure 2). The maximum deviation from the least-squares plane through Os1 and C1–C5 is 0.047 Å for C1. The C1–C2 distance (1.376(5) Å) is comparable to that of C4–C5 (1.378(6) Å), and the C2–C3 distance (1.420(5) Å) is similar to that of C3–C4 (1.416(6) Å). The Os–C1 bond length (1.815(4) Å) is slightly longer than those observed for typical $\text{Os}\equiv\text{C}$ bonds^[6, 8] and is at the lower end of those found for $\text{Os}=\text{C}=\text{CRR}'$ complexes.^[9] The Os–C5 bond length (1.939(5) Å) is slightly shorter than those observed for typical $\text{Os}-\text{C}(\text{vinyl})$ bonds^[10] and is within the range of those reported for $\text{Os}-\text{C}(\text{carbene})$ bonds.^[11] The Os–C and C–C bond lengths within the six-membered ring, together with its planar nature, indicate that the six-membered metallacycle has a delocalized structure with contributions from the resonance structures **5** and **5A**. The Os1-C1-C2 angle



(148.7(3)°) is significantly smaller than that expected for a carbyne or vinylidene complex owing to the constraint of the six-membered ring. Consistent with the solid-state structure, the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **5** displayed signals for $\text{Os}\equiv\text{C}$ and $\text{Os}-\text{CH}$ at $\delta = 306.6$ and 227.8, respectively. Since the structure of **5** is closely related to that of benzyne, complex **5** can be regarded as a metallabenzene.

Although many metallabenzenes are known,^[2] complex **5** appears to be the first well characterized example of a metallabenzynes. Benzynes^[12] are important intermediates which have been widely used in organic and organometallic synthesis and mechanistic studies. However, it is difficult to isolate free benzynes because of their low thermal stability and high reactivity. To our knowledge, no X-ray structures of free benzynes have previously been determined.

Scheme 2 shows a plausible mechanism for the formation of **5**. Reaction of $[\text{OsCl}_2(\text{PPh}_3)_3]$ (**1**) with $\text{HC}\equiv\text{CSiMe}_3$ could initially produce the vinylidene intermediate $[\text{OsCl}_2(=\text{C}=\text{CHSiMe}_3)(\text{PPh}_3)_2]$ which can undergo desilylation in



Scheme 2. A proposed mechanism for the formation of **5**.

the presence of water to give **6**. Related ruthenium vinylidene complexes $[\text{RuCl}_2(=\text{C}=\text{CHR})(\text{PPh}_3)_2]$ were prepared from the reactions of $[\text{RuCl}_2(\text{PPh}_3)_3]$ with $\text{HC}\equiv\text{CR}$.^[13] Intermediate **6** can react with additional $\text{HC}\equiv\text{CSiMe}_3$ to give **7** and **8**. Complex **8** could then rearrange to the osmabenzynes **5** by an acid-catalyzed reaction, i.e., protonation of the $=\text{CH}_2$ carbon atom of **8** to give **9** followed by deprotonation of an α -CH proton of **9**. The protonation/deprotonation process could be mediated by any proton donor (e.g., the carbyne complex **3** or H_2O) present in the reaction mixture. Consistent with the mechanism, it was shown that deuterium is incorporated into the methyl group of **5** when the reaction is carried out in the presence of D_2O .

In summary, we have synthesized the first metallabenzynes **5** from the reaction of $[\text{OsCl}_2(\text{PPh}_3)_3]$ (**1**) with $\text{HC}\equiv\text{CSiMe}_3$. We are currently preparing other metallabenzenes and investigating the chemistry of this novel class of compounds.

Experimental Section

A mixture of **1** (1.0 g, 0.95 mmol) and $\text{HC}\equiv\text{CSiMe}_3$ (1.1 mL, 7.6 mmol) in benzene (15 mL) was stirred at room temperature (RT) for 5 d to give a yellow microcrystalline solid and a brown solution. The volume of the reaction mixture was reduced to ca. 5 mL, and it was filtered. The yellow solid was washed with benzene (3 mL) and diethyl ether (2×10 mL) and dried under vacuum to give **2** (0.11 g, 14%). The filtrate was concentrated to ca. 1 mL, and hexane (30 mL) was added slowly with stirring to give a brownish green precipitate and a brownish red solution, which were separated by filtration. The solvent of the brownish red filtrate was removed under vacuum, and the residue was extracted with 10 mL of hexane and filtered. The brownish red extract was allowed to stand at

-8°C for several days to give **4** as yellow microcrystalline needles, which were collected by filtration and washed with hexane (3 mL) and dried under vacuum (0.047 g, 4.5%). Further storage of the mother liquid at -8°C after concentration to 5 mL gave **3** as brownish red blade crystals, which were collected by filtration, washed with hexane (5 mL) and dried under vacuum (0.22 g, 22%). The brownish green solid obtained above was washed with hexane (15 mL), dried, and redissolved in 2 mL of CH_2Cl_2 . A greenish blue solid formed when hexane (30 mL) was added with stirring. The solid was collected by filtration, washed with diethyl ether (2×10 mL) and hexane (2×20 mL), and dried under vacuum to give **5** (0.29 g, 30%).

2: $^3\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CD_2Cl_2): $\delta = -13.5$ (s); ^1H NMR (300.13 MHz, CD_2Cl_2): $\delta = 0.042$ (t, $^4J(\text{P,H}) = 2.5$ Hz, 3H, CH_3), 7.36–7.43 (m, 18H, PPh_3), 7.89–7.96 (m, 12H, PPh_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.40 MHz, CD_2Cl_2): $\delta = 283.7$ (t, $^2J(\text{P,C}) = 12.3$ Hz, $\text{Os}\equiv\text{C}$), 135.1–127.9 (m, PPh_3), 36.9 (s, CH_3); elemental analysis (%): calcd for $\text{C}_{38}\text{H}_{33}\text{Cl}_3\text{OsP}_2$: C 53.81, H 3.92; found: C 53.60, H 4.18.

3: $^3\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CD_2Cl_2 , 298 K): $\delta = 13.6$ (brs); ^1H NMR (300.13 MHz, CD_2Cl_2 , 298 K): $\delta = -0.38$ (s, 9H, SiMe_3), -0.33 (s, 9H, SiMe_3), 0.02 (t, $^4J(\text{P,H}) = 3.6$ Hz, 1H, $\text{Os}=\text{C}=\text{CH}$), 0.08 (s, 9H, SiMe_3), 4.68 (brs, 1H, $\text{Os}=\text{C}=\text{CH}$), 7.32–7.40 (m, 18H, PPh_3), 7.62–7.67 (m, 12H, PPh_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.40 MHz, CD_2Cl_2 , 298 K): $\delta = 272.7$ (brs, $\text{Os}=\text{C}$), 144.8 (brs, $\text{Os}=\text{C}=\text{CH}$), 143.3 (brs, $\text{Os}=\text{C}=\text{CH}$), 136.2–128.7 (m, other aromatic C and $\text{C}=\text{C}$), 91.9 (brs, $\text{Os}=\text{C}=\text{CH}$), 1.9 (s, SiMe_3), 0.0 (s, SiMe_3), -0.1 (brs, SiMe_3); elemental analysis (%): calcd for $\text{C}_{51}\text{H}_{50}\text{ClOsP}_2\text{Si}_3$: C 58.68, H 5.70; found: C 58.79, H 5.87.

4: $^3\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CD_2Cl_2 , 298 K): $\delta = 3.1$ (brs); ^1H NMR (300.13 MHz, CD_2Cl_2 , 298 K): $\delta = -0.51$ (s, 9H, SiMe_3), -0.26 (brs, 18H, $2 \times \text{SiMe}_3$), -0.02 (s, 9H, SiMe_3), 0.48 (t, $^4J(\text{P,H}) = 3.7$ Hz, 1H, $\text{Os}=\text{C}=\text{CH}$), 5.47 (brs, 1H, $\text{Os}=\text{C}=\text{CH}$), 7.28–7.32 (m, 18H, PPh_3), 7.68–7.84 (m, 12H, PPh_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.40 MHz, CD_2Cl_2 , 298 K): $\delta = 275.1$ (t, $^2J(\text{P,C}) = 11.9$ Hz, $\text{Os}=\text{C}$), 161.9 (t, $^2J(\text{P,C}) = 6.7$ Hz, $\text{Os}=\text{C}=\text{CH}$), 140.2 (s, $\text{Os}=\text{C}=\text{CH}$), 135.7–127.4 (m, other aromatic C and $\text{C}=\text{C}$), 116.7 (s, $\text{OsC}(\text{C}=\text{CSiMe}_3)=\text{CHSiMe}_3$), 93.9 (t, $^3J(\text{P,C}) = 3.7$ Hz, $\text{Os}=\text{C}=\text{CH}$), 83.5 (s, $\text{Os}=\text{C}=\text{CSiMe}_3$), 1.2 (s, $\text{Si}(\text{CH}_3)_3$), 1.0 (s, SiMe_3), -1.0 (s, SiMe_3), -1.1 (s, SiMe_3); elemental analysis (%): calcd for $\text{C}_{56}\text{H}_{68}\text{OsP}_2\text{Si}_4$: C 60.84, H 6.20; found: C 60.81, H 6.30.

5: $^3\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CD_2Cl_2): $\delta = -3.3$ (s); ^1H NMR (300.13 MHz, CD_2Cl_2): $\delta = -0.14$ (s, 9H, SiMe_3), 0.06 (s, 9H, SiMe_3), 2.27 (s, 3H, CH_3), 7.27–7.38 (m, 18H, PPh_3), 7.62–7.68 (m, 12H, PPh_3), 13.83 (s, 1H, OsCH); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.40 MHz, CD_2Cl_2): $\delta = 306.6$ (t, $^2J(\text{P,C}) = 10.1$ Hz, $\text{Os}\equiv\text{C}$), 227.8 (t, $^2J(\text{P,C}) = 6.5$ Hz, OsCH), 188.6 (s, CCH_3), 136.1 (s, CSiMe_3), 135.0 (t, $J(\text{P,C}) = 4.6$ Hz, $m\text{-PPh}_3$), 132.6 (t, $J(\text{P,C}) = 26.8$ Hz, $ipso\text{-PPh}_3$), 130.5 (s, $p\text{-PPh}_3$), 127.9 (t, $J(\text{P,C}) = 4.6$ Hz, $o\text{-PPh}_3$), 113.0 (s, CSiMe_3), 27.1 (s, CH_3), 1.7 (s, SiMe_3), 0.9 (s, SiMe_3); elemental analysis (%): calcd for $\text{C}_{48}\text{H}_{52}\text{Cl}_2\text{OsP}_2\text{Si}_2$: C 57.19, H 5.20; found: C 57.38, H 5.38.

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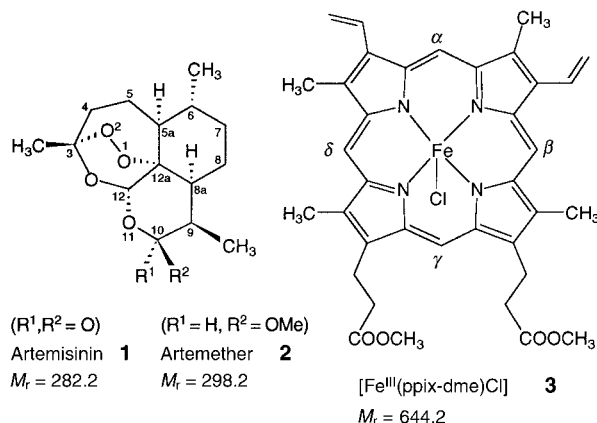
riding atoms. Crystal data for **4**: $C_{56}H_{68}OsP_2Si_4 \cdot C_6H_6$, $M_r = 1183.71$; triclinic, space group $P\bar{1}$; $a = 12.5486(16)$, $b = 13.5107(18)$, $c = 20.905(3)$ Å, $\alpha = 90.187(3)$, $\beta = 104.815(3)$, $\gamma = 116.824(2)^\circ$, $V = 3028.7(7)$ Å³; $Z = 2$, $\rho_{\text{calcd}} = 1.298$ g cm⁻³; 20 888 reflections, 13 820 independent reflections ($R_{\text{int}} = 0.0454$); $R_1 = 0.0502$, $wR_2 = 0.0736$ for 630 parameters and 8304 reflections with $I > 2\sigma(I)$. The two protons H2A and H12A attached to the vinyl carbon atoms were located in the difference Fourier maps and refined isotropically. Crystal data for **5**: $C_{48}H_{52}Cl_2OsP_2Si_2$, $M_r = 1008.12$; monoclinic, space group $P2_1/n$; $a = 12.7613(4)$, $b = 17.4260(6)$, $c = 21.4826(7)$ Å, $\beta = 104.1100(10)^\circ$, $V = 4633.1(3)$ Å³; $Z = 4$, $\rho_{\text{calcd}} = 1.445$ g cm⁻³; 30 794 reflections, 11 178 independent reflections ($R_{\text{int}} = 0.0478$); $R_1 = 0.0327$, $wR_2 = 0.0566$ for 512 parameters and 7697 reflections with $I > 2\sigma(I)$. The protons attached to C5 and C6 were located from the difference Fourier maps and refined with isotropic thermal parameters. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155319 (**4**) and CCDC-155320 (**5**). 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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Characterization of the Alkylation Product of Heme by the Antimalarial Drug Artemisinin**

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Artemisinin **1** and its hemi-synthetic derivatives such as artemether **2** are increasingly used to treat *Plasmodium falciparum* drug-resistant malaria, which causes between one and three million deaths annually.^[1] The stable endoperoxide bridge of these compounds is required for their antimalarial



activity. The activity of artemisinin is dependent on the cleavage of the endoperoxide by intraparasitic heme, which is generated by the digestion of hemoglobin within infected red blood cells.^[2–5] In fact, the reductive activation by Fe^{II} –heme results in the homolytic cleavage of the endoperoxide bond and the subsequent formation of drug-derived carbon-centered radicals, which act as alkylating agents toward either heme or vital parasite proteins. The alkylation of proteins^[6] or heme^[7] was observed after the incubation of parasites with pharmacologically relevant concentrations of artemisinin derivatives but no heme–artemisinin or protein–artemisinin adducts had been characterized up to now. Herein we report the first characterized adduct produced by the alkylation of heme by the antimalarial artemisinin.

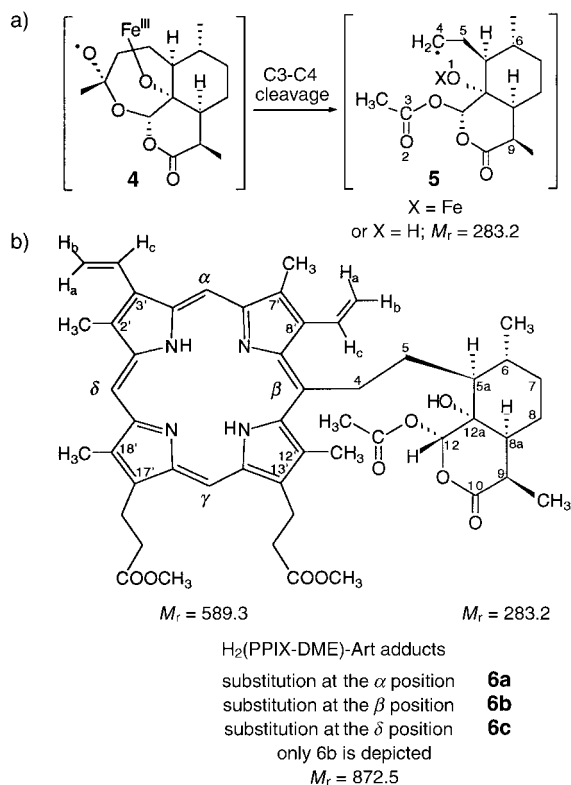
The alkylation of a synthetic metalloporphyrin heme model, manganese(II) tetraphenylporphyrin, by artemisinin,^[8] artemether, and other synthetic pharmacologically active trioxanes^[9] has been reported in recent years. Herein, the “true” target of artemisinin, heme, was used. Artemisinin was incubated under an argon atmosphere with the dimethyl ester of hemin, [$Fe^{III}(ppix-dme)Cl$] (**3**), in dichloromethane in the presence of 2,3-dimethylhydroquinone to reduce hemin to

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[Fe^{II}(ppix-dme)]. We used the dimethyl ester of heme so that both the drug and the target could be dissolved in one solvent (artemisinin is insoluble in water or in aqueous mixtures). The reductive activation of artemisinin by iron(II)–heme by means of an inner-sphere process resulted in the homolytic cleavage of the peroxide bond to give the oxygen-centered radical **4** (Scheme 1a), as previously observed with the heme model



Scheme 1. Structure of the major artemisinin–heme adducts after demetallation: three regioisomers corresponding to substitution on α -carbon **6a** (●), β -carbon **6b** (▲), δ -carbon **6c** (*). Only **6b** is depicted. Radical intermediates **4** and **5** result from the heme activation of artemisinin.

manganese(II) tetraphenylporphyrin. This radical promptly rearranged to the sterically unhindered carbon-centered radical **5** by the homolysis of the C3–C4 bond.^[8, 9] Such a reaction pathway that involves a carbon-centered radical at C4 is important for the antimalarial activity of artemisinin.^[10] The carbon-centered radical **5**, generated above the plane of the heme derivative, is able to alkylate the macrocycle and produce isomeric covalent adducts. After the reaction of heme with artemisinin for 20–30 min, the conversion of heme was 85–90%, and two new broad peaks were detected (HPLC; 1:1). These peaks correspond to at least two porphyrin derivatives, which gave rise to an intense peak in the ESI-MS at $m/z = 926.5$ [M^+] (the sum of the masses of [Fe^{III}(ppix-dme)] ($M_r = 644.2$) and artemisinin fragment **5** (Scheme 1a) after hydrolysis of the oxygen–iron bond ($M_r = 283.2$) minus one mass unit). This result clearly indicates that one hydrogen atom of the metalloporphyrin has been substituted by the artemisinin fragment, **5**, leading to metalated covalent adducts (calculated mass: 926.4) in which both the artemisinin and the heme fragments are present.

To allow a complete characterization of these modified heme residues by NMR spectroscopy, the macrocycle was demetallated *in situ* by using 17 equivalents of Fe^{II}SO₄ · 1.5 H₂O in HCl/CH₃COOH.^[11] After purification by column chromatography, the porphyrin–drug material was recovered in 80–85% yield without extensive degradation of the macrocycle. TLC analysis, MS, and NMR spectroscopic data suggested a mixture of sets of heme–drug adducts corresponding to the alkylation of the *meso* positions by the C4-centered artemisinin radical with or without modification of the lactone ring of artemisinin. The heme–drug adducts were fully characterized by MS and NMR spectroscopic analysis of the material containing the unmodified lactone ring (yield: 30–50% depending on the demetallation conditions). This demetallated material was a mixture of three isomers with the same mass of $m/z = 873.5$ [$M+H^+$]. The mass corresponds to the sum of the masses of the demetallated protoporphyrin IX-dimethyl ester ($M_r = 590.3$) and artemisinin fragment **5** after hydrolysis of the oxygen–iron bond ($M_r = 283.2$) minus one mass unit, which leads to covalent adducts **6a**, **6b**, and **6c** (Scheme 1b, calculated mass: 872.5). This result confirmed that no extensive degradation occurred during the demetallation step.

To elucidate the substitution positions by the artemisinin fragment, different NMR sequences were used, including COSY, NOESY, and 1D-NOE selective excitation. The resonance of the NH protons was detected at $\delta = -2.79$, strongly deshielded with respect to protoporphyrin IX-dimethyl ester ($\delta = -3.94$). This result was consistent with a direct substitution on the macrocycle, which leads to a lowering of the ring current effect. The main *meso* protons were detected as nine singlets at $\delta = 9.8$ –10.3, which suggests the presence of three different isomers that result from the substitution of three different *meso* positions of **6** (Figure 1a; the broad singlet at $\delta = 10.13$ is due to an impurity and does not belong to the heme-artemisinin adducts. This was confirmed by ¹H–¹³C correlation: this peak was not connected to a carbon atom with a signal at $\delta = 95$ –100, the expected region for *meso*-carbon resonances). Thus, the NMR data confirm that three regioisomers were formed. The vinylic H_c protons gave rise to signals at $\delta = 8.05$ –8.30 (2H, six doublets of doublets, Figure 1b), and H_a and H_b resulted in a complex pattern at $\delta = 5.94$ –6.39 (4H, 12 multiplets) with integration values consistent with those of other porphyrin protons, namely CH₂ units ($\delta = 4.37$, 4H; $\delta = 3.25$, 4H) and CH₃ units ($\delta = 3.5$ –3.7, 18H). This result ruled out the hypothesis of substitution of a vinylic position by the artemisinin fragment. All the significant protons of the artemisinin moiety were detected and showed the correct integration: the doublets for the methyl groups at C6 and C9 were detected at $\delta = 0.92$ and 1.22, respectively; H12 and the acetate protons were detected as singlets at $\delta = 5.60$ (compared to 5.85 in artemisinin) and $\delta = 1.59$, respectively, and H9 gave rise to a multiplet at $\delta \approx 3.21$ (compared to ca. 3.33 in artemisinin). These signals confirmed that the complete structure of artemisinin was retained and that no modification occurred on the lactone ring. Furthermore, the C4 methylene protons appeared as two broad signals at $\delta = 5.15$ and 5.45, as expected for a methylene substituent at the *meso* positions of

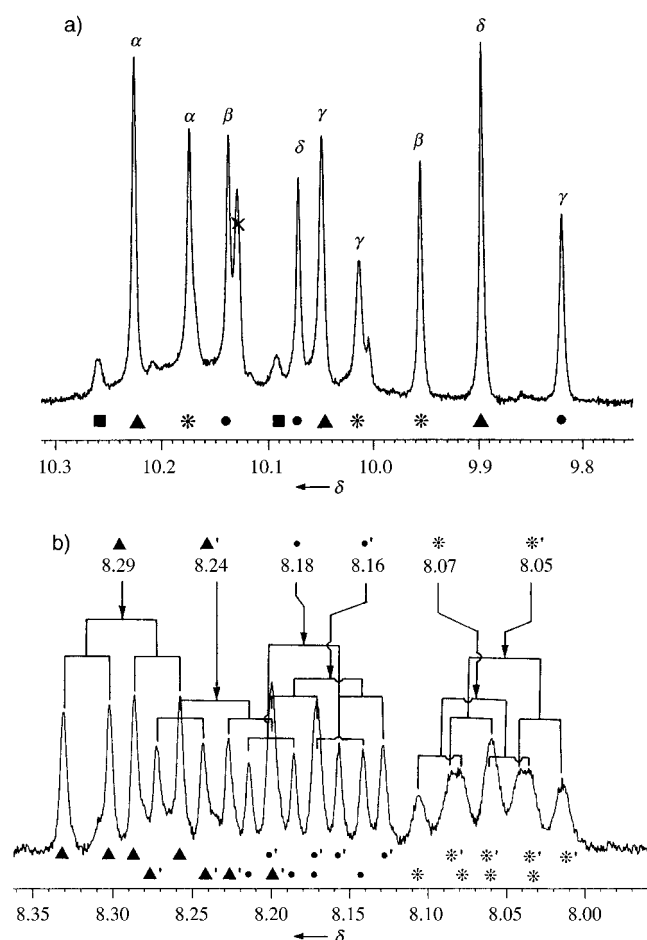


Figure 1. ^1H NMR spectrum of the artemisinin-heme adducts: a) region of *meso*-H resonances, which indicate substitution on the α -carbon **6a** (●), β -carbon **6b** (▲), δ -carbon **6c** (*). A minor covalent adduct, which corresponds to the substitution of γ -carbons, was also detected (■); b) region of H_c protons for adducts **6a** (●, α -substitution), **6b** (▲, β -substitution), and **6c** (*, δ -substitution).

protoporphyrin,^[12] and NOE interactions were observed between the C4-methylene and the vinyl H_c , thus confirming the existence of a covalent coupling between an artemisinin residue and the *meso* carbon atoms of heme.

The substituted *meso* positions were then identified by NMR spectroscopy. 1D-NOE selective irradiation of the propionate methylene protons ($\delta = 4.37$) allowed the identification of three different γ -protons. Two different δ -protons were characterized from their NOE interactions with two methyl groups each. The sequential correlations $\delta\text{-H} \rightarrow \text{H}_3\text{C-C2}' \rightarrow \text{H}_a\text{-C}=\text{C-C3}' \rightarrow \text{H}_c\text{-C-C3}' \rightarrow \alpha\text{-H}$ on one hand, and $\gamma\text{-H} \rightarrow \text{H}_2\text{C-C13}' \rightarrow \text{H}_3\text{C-C12}' \rightarrow \beta\text{-H}$ on the other hand, allowed the identification of two α - and two β -protons (Figure 1 a). We thus confirmed that the three main covalent adducts resulted from the non-regioselective substitution of artemisinin at the α - (●), β - (▲), and δ -carbons (*) (28:39:33, respectively). A minor covalent adduct which results from the substitution of γ -carbons was also detected (■; less than 7–12% of the total amount of adducts).

In control experiments, we checked that $[\text{Fe}^{\text{III}}(\text{ppix-dme})\text{Cl}]$ (**3**) did not react with artemisinin in the absence of hydroquinone derivative, and that the porphyrin macrocycle

was not modified by 2,3-dimethylhydroquinone in the absence of artemisinin. Furthermore, when *tert*-butylhydroquinone or thiobenzyl alcohol were used instead of 2,3-dimethylhydroquinone, the reaction occurred in the same way and afforded the same adducts, which confirms that the formation of adducts did not depend on the reducing agent used, provided that it was able to reduce the iron(III) center of the heme derivative to the ferrous state.

The reaction of artemether with $[\text{Fe}^{\text{II}}(\text{ppix-dme})]$ under the same conditions used for artemisinin afforded metallated adducts that showed a mass increment of 16 uma with respect to the mass spectrum of metallated covalent adducts heme-artemisinin, consistent with the difference of 16 between the molecular weight of artemisinin and that of artemether. This indicates that heme was also alkylated by artemether **4**. Unfortunately, the demetallation procedure used for artemisinin can not be used in this case, because of the lability of the B ring of artemether under strongly acidic conditions;^[9] full assignment by NMR was thus impossible.

The reductive activation of artemisinin (or artemether) by heme is able to produce covalent heme-artemisinin adducts in high yields under very mild conditions by the alkylation of the *meso* positions. The reduced heme involved in the two-step generation of the C-centered alkylating radical of artemisinin can be produced by the large excess of reducing agents present in erythrocytes (e.g. 1 mM of glutathione). The carbon-centered radicals derived from antimalarial trioxanes by activation with the reduced heme are probably able to alkylate the release heme at pharmacological concentrations of the drug,^[6] which lead to the death of the parasite through the accumulation of non-polymerizable redox-active heme adducts. In addition, the C4 radical of artemisinin or artemether might escape from reduced heme and be able to alkylate one (or several) protein(s) involved in the degradation of hemoglobin or the polymerization of heme.^[13]

Experimental Section

Iron(III) protoporphyrin-IX dimethylester chloride: $[\text{Fe}^{\text{III}}(\text{ppix-dme})\text{Cl}]$ (**3**) was prepared from $[\text{Fe}^{\text{III}}(\text{ppix})\text{Cl}]$ (hemin) according to a published procedure.^[11] MS (DCI/ NH_3^+): m/z 645 $[\text{M}+\text{H}^+]$ for $[\text{Fe}^{\text{II}}(\text{ppix-dme})]$ (the loss of the axial ligand and the reduction of the metal center are often observed during MS analyses of metalloporphyrins).^[14]

Covalent adducts **6**: $[\text{Fe}^{\text{III}}(\text{ppix-dme})\text{Cl}]$ (**3**, 40 mg, 59 μmol) and **1** (50 mg, 177 μmol , 3 equiv) were dissolved in dichloromethane (4 mL). This solution was degassed and kept under an argon atmosphere. 2,3-Dimethylhydroquinone (82 mg, 590 μmol , 10 equiv) was then added as a solid, and the solution was stirred at room temperature under argon. When the conversion of hemin was complete, an aliquot was withdrawn for MS analysis of the crude metallated adducts (MS (ESI $^+$): m/z (relative intensity): 926.5 (55) $[\text{M}^+]$, 866.5 (100) $[\text{M}^+ - \text{CH}_3\text{COOH}]$; MS (DCI/ NH_3^+): m/z : 884 $[\text{M}+\text{NH}_4^+ - \text{CH}_3\text{COOH}]$, 867 $[\text{M}+\text{H}^+ - \text{CH}_3\text{COOH}]$). Degassed acetic acid (30 mL) was then added under argon, followed by a suspension of $\text{Fe}^{\text{II}}\text{SO}_4 \cdot 1.5\text{H}_2\text{O}$ (180 mg, 1.0 mmol, 17 equiv) in 37 wt% hydrochloric acid (1.2 mL) and the mixture was stirred at room temperature. The demetallation of hemin derivatives was complete within few minutes. Dichloromethane (30 mL) was then added under air, and the organic layer was washed with aqueous sodium acetate (1M, 4 $\times$ 50 mL). The dichloromethane solution was dried over sodium sulfate, filtered, and evaporated to dryness. The adducts **6a**, **6b** and **6c** were recovered as a mixture after chromatography of the crude product over a column of silica gel 60, with hexane/dichloromethane/ethyl acetate 40:25:35, v/v/v as eluent. UV/Vis (CH_2Cl_2): λ_{nm} (relative intensity): 414 (100), 512 (10), 582_{sh} (5), 540

(6); MS (ESI⁺): *m/z* (relative intensity): 873.5 (10) [*M*+H⁺], 813.5 (100) [*M*+H⁺ – CH₃COOH]. MS (DCI/NH₃⁺): *m/z*: (relative intensity) 873 (2) [*M*+H⁺], 816 (6), 815 (20), 814 (52), 813 (100) [*M*+H⁺ – CH₃COOH], 812 (4); ¹H NMR (400.13 MHz, CDCl₃, for clarity, the signals of the porphyrin moiety are described first, and then those of the artemisinin fragment): δ = 10.23, 10.17, 10.14, 10.07, 10.05, 10.01, 9.96, 9.90, 9.82 (9 × s, 3 H, *meso*-H), 8.29, 8.24, 8.18, 8.16, 8.05, 8.07 (6 × m, 2 H, H₂), 6.39, 6.30, 6.31, 6.20, 6.16, 5.94 (4 H, H_a and H_b), 4.37 (m, 4 H, H₂C-C13' and H₂C-C17'), 3.75–3.57 (18 H, H₃C-C2', H₃C-C7', H₃C-C12', H₃C-C18', and COOCH₃), 3.25 (m, 4 H, H₂CCOOCH₃), –2.79 (2 H, NH), 5.45 and 5.15 (2 × m, 2 × H, H₂C4), 2.07, 1.77, 1.56 (H₂C5), 1.11 and 0.58 (H5a), 1.28 (m, 1 H, H6), 0.92 (d, 3 H, ³*J* = 6 Hz, H₃C-C6), 1.98 and 1.51 (H₂C7), 1.93 and 0.98 (H₂C8), 2.06 (H8a), 3.21 (m, 1 H, H9), 1.22 (d, 3 H, ³*J* = 7 Hz, H₃C-C9), 5.60 (s, 1 H, H12), 1.59 (s, 3 H, H₃CCOO-C12), 1.53 (HO-C12a).

Analytical HPLC conditions: column: C8 on Lichrosorb 10 μm (Interchrom, France); eluent A: 0.1 vol% aqueous trifluoroacetic acid, eluent B: CH₃CN; gradient program: linear from 40% to 70% of eluent B for 50 min, then linear from 70% to 100% of B for the following 15 min, 1 mL min^{–1}; products were detected at λ = 420 nm to follow the modifications of the porphyrin chromophore. To monitor the reaction, aliquots (50 μL) were evaporated to dryness, dissolved in a mixture (1 mL, 1:1, v/v) of acetonitrile and aqueous trifluoroacetic acid (0.1 vol%), and analyzed (injected volume: 100 μL). After 20–30 min of reaction time, the conversion of starting hemin (retention time = 26.6 min) was 85–90%. Two broad peaks of modified hemin derivatives were detected (retention time = 32.3, 33.1 min, respectively; ESI-MS: *m/z*: 926.5 [*M*⁺] for this mixture and for each of the two broad peaks recovered after semi-preparative HPLC.

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Assembly of Ni₇ and Ni₂₁ Molecular Clusters by Using Citric Acid**

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Exploration of the middle ground between simple molecular species and infinite arrays has led to the discovery of novel, nanoscale materials in the field of molecular magnetism. Single Molecule Magnets (SMM)^[1] offer the possibility of information storage at the molecular level, and have provided the first examples in which novel phenomena such as quantum-mechanical tunneling of magnetization can be observed.^[2] It is now understood that a large spin ground state (S) and a negative axial anisotropy (D) are a prerequisite.

However, there is a perceived need to develop synthetic approaches to larger, more complex molecules to establish further the relationship between structure and molecular properties. By utilizing simple organic ligands, such as carboxylates, it has been possible to isolate clusters containing up to 24 transition metal ions.^[3] The use of more complex ligands such as polycarboxylates^[4] or polyalcohols,^[5] has been more limited. Polydentate ligands should produce new cluster topologies by virtue of their coordinative flexibility.

We have chosen to investigate the proligand citric acid (HOC(CO₂H)(CH₂CO₂H)₂; H₄cit) which has been little employed in cluster synthesis; only two high nuclearity (N ≥ 6) transition metal citrate complexes are structurally characterized.^[6] Nevertheless, we have found that citrate displays a rich solution chemistry with Ni^{II} units and herein report our first success in isolation of two new citrate clusters containing seven and an unprecedented 21 Ni^{II} ions, respectively.

The reaction of Ni^{II} with citrate in basic aqueous solution in the presence of Na⁺ and NMe₄⁺ ions, followed by the addition of ethanol as cosolvent gives the {Ni₇} cluster **1** (see Experimental Section). The high solubility of such species in aqueous solution makes crystallization by slow evaporation difficult, as previously noted.^[6a] We have addressed this problem by adjusting solvent polarity to effect crystallization, thus removing the need for crystallization from highly concentrated, and often viscous solutions. The single crystal X-ray structure of **1** (Figure 1) shows a cluster containing two {Ni₃} trimers related by a pseudo two-fold axis passing through the central Ni (Ni4).^[7] The coordination sites at the nickel centers are occupied by the oxygen atoms from the six citrate ligands, apart from a site on both Ni3 and Ni5, which is filled

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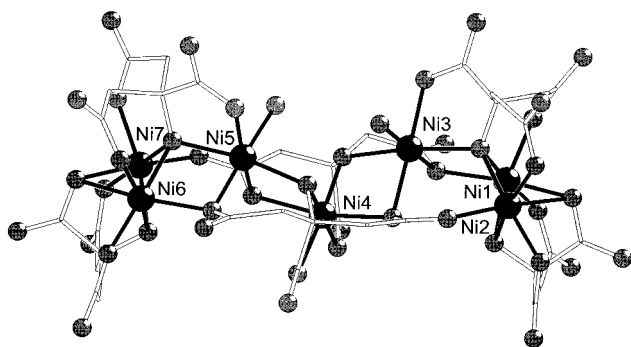
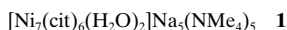


Figure 1. The molecular structure of **1**, H atoms have been omitted for clarity (Ni = black sphere; O = gray sphere; C = rods). Bond length ranges [Å; average esd 0.003 Å] Ni–O: 1.981–2.059 (citrate O[−]), 1.998–2.258 (citrate CO₂[−]); bond angle ranges [°; average esd 0.1°]: *cis* at Ni 71.0–104.3, *trans* at Ni 161.4–178.1.

by a water molecule. Geometric constraints imposed by the citrate ligands lead to a distorted octahedral nickel coordination environment. The three independent citrate ligands are tetradeprotonated, each utilizing all four binding groups, bridging two (e.g. Ni1 and Ni2), three (e.g. Ni1, Ni2, and Ni3), and five (e.g. Ni1, Ni3, Ni4, Ni5, and Ni7) metal centers. The Na⁺ and NMe₄⁺ ions in the lattice provide charge balance of the decanionic cluster.



The magnetic properties of **1** are interesting: a plot of χT versus T reveals an overall weak ferromagnetic coupling within the {Ni₇} cluster (Figure 2; the spin Hamiltonian is given

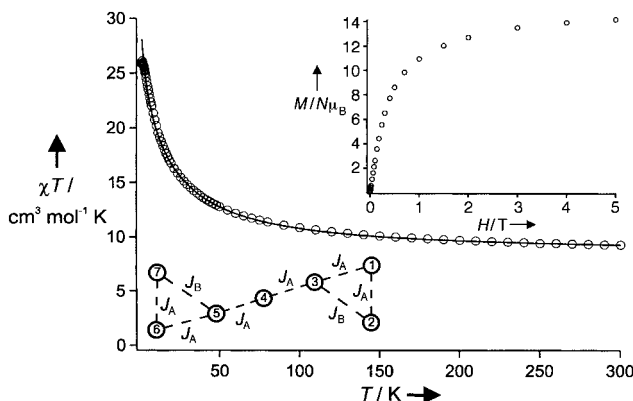


Figure 2. Temperature dependence of χT for **1**. The solid line represents a model using the two different parameters J_A and J_B as follows: $J_A = J_{12} = J_{13} = J_{34} = J_{45} = J_{56} = J_{67}$ and $J_B = J_{23} = J_{57}$. Inset shows the field dependence of the magnetization at 1.8 K.

in Equation (1)).^[8] Curie–Weiss behavior is observed above 100 K with a Weiss constant $\theta = 21.8$ K. We attempted to model the data using the simplest possible coupling scheme. Using only one J parameter is clearly inadequate, and two exchange parameters are required to model the data satisfactorily yielding values of $J_A = 10$ and $J_B = -4.5$ cm^{−1} with $g = 2.2$ (see Figure 2).^[9] The signs of J_A and J_B can be correlated with the Ni–O–Ni bridging angles; the bridging angle for the interaction J_B is 119° while the remaining angles correspond-

ing to J_A are all less than 102°, consistent with antiferro- and ferromagnetic exchange, respectively.^[10] The magnitude of the exchange parameters is consistent with that observed for other polynuclear oxo-bridged Ni^{II} complexes.^[10b] Furthermore, the model shows good agreement to low temperature without the inclusion of anisotropy, suggesting that any zero-field splitting effects are small.

$$\mathcal{H} = -2J_A(\hat{S}_1\hat{S}_2 + \hat{S}_1\hat{S}_3 + \hat{S}_3\hat{S}_4 + \hat{S}_4\hat{S}_5 + \hat{S}_5\hat{S}_6 + \hat{S}_6\hat{S}_7) - 2J_B(\hat{S}_2\hat{S}_3 + \hat{S}_5\hat{S}_7) \quad (1)$$

The spin ground state is confirmed as $S = 7$ by magnetization measurements at 1.8 K in fields up to 5 T; the magnetization is not saturated at 5 T giving a value of $M/N\mu_B = 14.2$ (calculated 15.4 for $S = 7$ and $g = 2.2$). The simple model used above shows a small exchange splitting of around 1 K between the $S = 7$ energy level and the lowest lying $S = 6$ level. Therefore, at 1.8 K the available thermal energy is significant compared with the exchange splitting and the ground state is not energetically isolated. No out of phase alternating current (ac) signal is observed between 1.8 and 10 K; although **1** has a large spin ground state it possesses nonaxial symmetry, which is not ideal for the observation of SMM properties.

We have found that it is possible to selectively crystallize a further cluster from the reaction mixture by adjusting the amount of cosolvent. Using less ethanol, **1** appears sufficiently soluble to prevent its crystallization, permitting isolation of pure samples of **2**. Single crystal X-ray analysis (Figure 3)

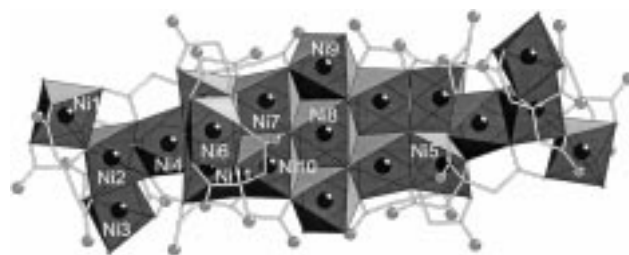


Figure 3. The structure of **2** (polyhedral representation) the H atoms have been omitted for clarity (Ni = black spheres; O = gray spheres; C = rods). Bond length ranges [Å; average esd 0.003 Å] Ni–O: 1.969–2.128 (citrate O[−]), 1.997–2.210 (citrate CO₂[−]); bond angle ranges [°; average esd 0.1°]: *cis* at Ni 76.1–106.1, *trans* at Ni 158.65–180.0.

reveals an unusual complex containing 21 Ni^{II} ions; the molecule possesses a center of symmetry at the Ni8 position.^[7] Nickel ions have been assigned as Ni^{II} centers and the 10 bridging oxygen atoms as hydroxides (calculated valence 1.09–1.13), on the basis of bond valence sum analysis.^[11] The central {Ni₇(μ₃-OH)₆} core possesses a hexagonal close-packed layer structure as found for Ni(OH)₂. This is similar to the {Fe₇(μ₃-OH)₆} core seen in {Fe₁₇} and {Fe₁₉} clusters^[4a] and portions of a {Co₂₄} cluster.^[3a] Four of the six edges of the {Ni₇(μ₃-OH)₆} core are bridged by citrate carboxylate groups; additional ligand binding sites permit cluster growth outside the core. As constraints imposed by the ligands begin to dictate the structure the Ni(OH)₂ lattice is no longer preserved leading to the unusual structure in Figure 3. Five

different ligand binding modes are seen with four of these previously unobserved in nickel citrate chemistry.



A preliminary investigation of the magnetic properties of **2** has been performed; a plot of χT versus T reveals a dominant antiferromagnetic interaction within the cluster (Figure 4).

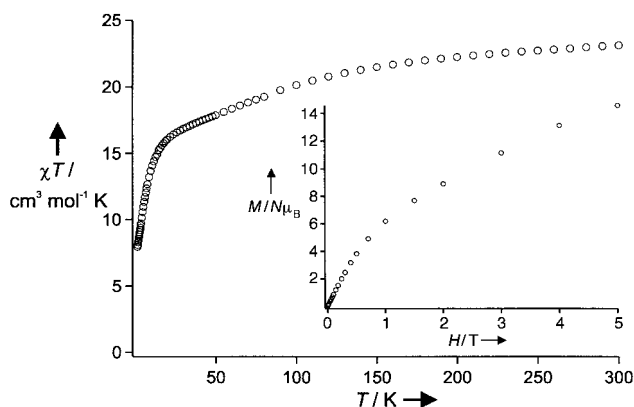


Figure 4. Temperature dependence of χT for **2**. Inset shows the field dependence of the magnetization at 1.8 K.

Curie–Weiss behavior is observed above 100 K with a Weiss constant $\theta = -24.2$ K. Below 100 K the shape of the curve implies a complicated energy-level scheme although the size of the cluster prevents modeling of the data. The exact nature of the spin ground state is difficult to obtain; the value of χT at 1.8 K suggests a spin ground state of around $S = 3$, whereas magnetization data at 1.8 K in a field of 5 T suggest that M_s levels of higher spin states are populated (Figure 4 inset).

The chemistry of citrate with Ni^{II} units in basic aqueous solution appears both fascinating and highly complicated. This study represents only a small reaction parameter space and, by careful modification of the crystallization process, has already yielded two new complexes displaying different structural and completely different magnetic properties. The ligand cit^{4-} shows a binding flexibility towards Ni^{II} centers, displaying seven different coordination modes across the two complexes, bridging up to five metal centers.

Neither of the clusters isolated exhibits SMM properties; even in **1** where a large spin ground state is present the cluster symmetry is nonaxial, reducing the possibility of observing SMM behavior. Nonetheless, it is entirely possible that further clusters are present in such solutions with their formation and crystallization governed by a number of variables. We are currently widening this study in the hope of understanding the factors that dictate the cluster assembly process.

Experimental Section

Addition of an aqueous solution (15 mL) of NaOH (3.520 g, 88.0 mmol) to an aqueous solution (25 mL) of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ (10.907 g, 41.5 mmol) gave a pale green precipitate, which was collected by filtration and washed with distilled water (3×100 mL). Dissolution of this solid in an aqueous solution (20 mL) of citric acid monohydrate (7.985 g, 38.0 mmol) gave a solution of pH 2.94. The pH was raised to 9.20 by the addition of $\text{NMe}_4\text{OH} \cdot 5\text{H}_2\text{O}$ (12.50 g, 69.0 mmol) and the aqueous solution concentrated to a volume of

35 mL. Aliquots of this solution were taken, mixed with EtOH, and kept in sealed sample tubes (the volumes of EtOH given below permit isolation of pure samples of either **1** or **2**). After one week, well-formed rod-like crystals of **1** could be isolated from solutions of composition: aqueous solution (0.4 mL) and EtOH (either 0.9, 1.0, or 1.1 mL). The crystals were dried under vacuum. Yield per 0.4 mL: 30 mg (17% based on Ni); elemental analysis calcd (%) for $\text{C}_{56}\text{H}_{148}\text{N}_5\text{Na}_5\text{Ni}_7\text{O}_{74}$ (**1** · 30 H_2O): C 25.85, H 5.73, N 2.69; found: C 25.84, H 5.54, N 2.65. After one month, rhomboid crystals of **2** could be isolated from solutions of composition: aqueous solution (0.4 mL) and EtOH (either 0.7 or 0.8 mL). The crystals were dried under vacuum. Yield per 0.4 mL: 10 mg (3% based on Ni); elemental analysis calcd (%) for $\text{C}_{108}\text{H}_{250}\text{N}_8\text{Na}_8\text{Ni}_{21}\text{O}_{138}$ (**2** · 32 H_2O · 2 EtOH): C 24.54, H 4.77, N 2.12; found: C 24.43, H 4.83, N 2.24.

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was assumed that there were 39.5 water molecules present in all, which filled the space available for solvent. For both **1** and **2** it was not possible to locate all cations because of the large amount of disordered solvent present. Charge balance requires a total of ten cations for **1** and sixteen for **2**; the relative proportions of missing Na^+ and NMe_4^+ have been assigned on the basis of microanalysis results. 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-155973 (**1**) and -155972 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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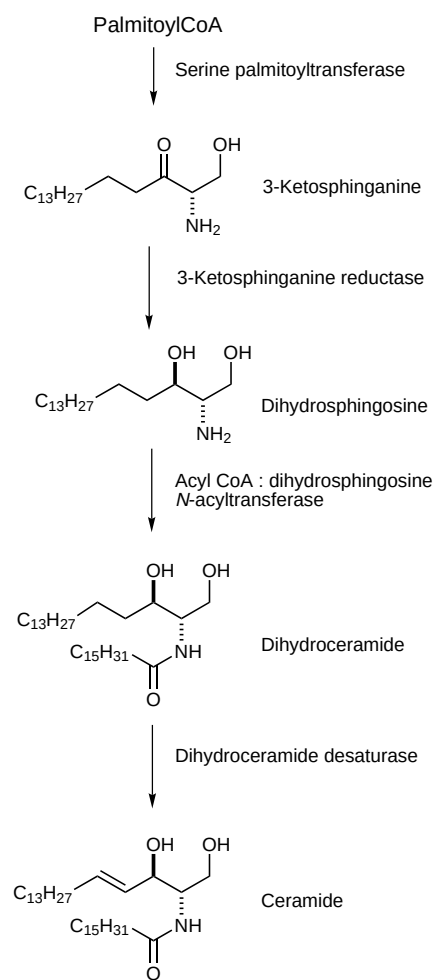
Synthesis of a Cyclopropene Analogue of Ceramide, a Potent Inhibitor of Dihydroceramide Desaturase**

Gemma Triola, Gemma Fabriàs,* and Amadeu Llebaria*

Dedicated to Professor Francisco Camps

Ceramide is a biologically relevant sphingolipid, which is intracellularly generated by either the breakdown of glycosphingolipids, the hydrolysis of sphingomyelin (sphingomyelin pathway), or the de novo biosynthesis (Scheme 1).^[1] Despite the general acceptance of ceramide as a key second messenger, some aspects of ceramide-mediated signal transduction are controversial. The selective inhibition of the different enzymes involved in the biosynthesis and metabolism of ceramide can help solve such discrepancies and to better understand the precise role of ceramide in cell biology. This fact has led to the discovery of several inhibitors of these enzymes.^[1–3]

The de novo biosynthetic pathway of ceramide (Scheme 1) is initiated with the condensation of palmitoyl CoA with serine to give 3-ketosphinganine, which is transformed into dihydroceramide upon reduction and acylation. The last step involves the introduction of the C4–C5 *trans* double bond into



Scheme 1. De novo biosynthesis of ceramide.

dihydroceramide to give ceramide. This reaction is catalyzed by dihydroceramide desaturase, for which no inhibitor has been reported previously.^[4]

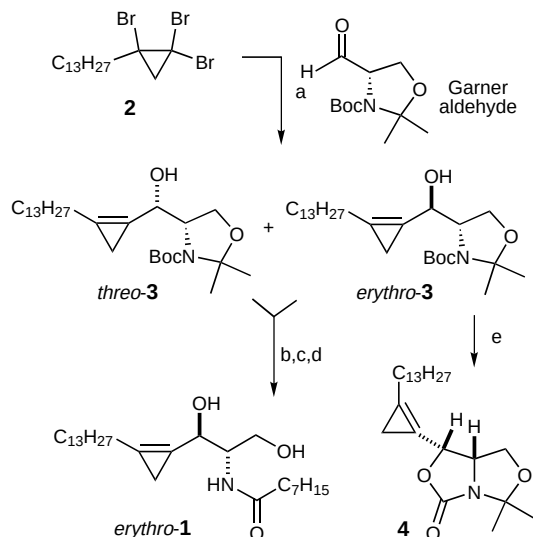
Although little information is available about dihydroceramide desaturase,^[5–10] it appears to be similar to the better known fatty acyl desaturases. After early reports on the activity of stercularic acid (9,10-methyleneoctadec-9-enoic acid) as a potent inhibitor of the Δ^9 stearoyl-CoA desaturase,^[11] the inhibitory effect of cyclopropene fatty acids on different acyl-CoA desaturases has been the subject of several publications.^[12] Although the mechanism of inhibition is still controversial,^[12] it is well established that a) stercularic acid inhibits the Δ^9 desaturation of different aliphatic acids, regardless of the chain length;^[13] b) among several synthetic cyclopropene fatty acids, only those compounds with the ring at C9 and/or C10 are effective inhibitors of the Δ^9 desaturase;^[14] and c) a structural analogue of stercularic acid with an exocyclic double bond does not inhibit the desaturation of stearic to oleic acid.^[15]

In light of these reports, the cyclopropene-containing ceramide *erythro-1* was designed as a putative inhibitor of dihydroceramide desaturation. We describe herein the synthesis of cyclopropene ceramide analogue *erythro-1*, as well as inhibition experiments that show that *erythro-1* is a potent inhibitor of dihydroceramide desaturase.

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The synthesis of *erythro*-**1** was carried out as depicted in Scheme 2. 1-Lithio-2-tridecylcyclopropene, which was generated from 1,1,2-tribromo-2-tridecylcyclopropane **2** according to a reported procedure,^[16] was treated with Garner aldehyde to afford a 3:1 diastereomeric mixture of *erythro* and *threo* alcohols **3** in 75% yield. The diastereoselectivity of the



Scheme 2. Synthesis of the ceramide analogues **1**. Reagents and conditions: a) 2.2 equiv *n*BuLi, THF, -78 to 25°C , 45 min, then Garner aldehyde, THF, -23°C , 2 h; b) flash chromatography; c) 2.2 equiv trimethylsilyl triflate, 2,6-lutidine, THF; d) octanoyl chloride, pyridine; e) NaH, THF.

reaction was improved by using hexamethyl phosphoramide (HMPA) as cosolvent.^[17] In this case, *erythro* and *threo* alcohols **3** were obtained in a 10:1 ratio. Pure *erythro*-**3** was isolated after flash chromatography. The stereochemistry of the major diastereomer formed in the addition reaction was confirmed by NOE studies on a bicyclic oxazolidinone derivative **4**.^[18] The protecting groups were removed by using trimethylsilyl triflate.^[19] Other common procedures used to cleave the Boc group resulted in the complete decomposition of alcohol **3**, probably because of the instability of the cyclopropene ring under acidic conditions. Final acylation with octanoyl chloride^[20] afforded *erythro*-**1** in 14% yield from 1-pentadecyne over 5 steps.

The inhibitory effect of *erythro*-**1** on dihydroceramide desaturase was investigated in rat liver microsomes,^[5] by using *D-erythro-N*-octanoyldihydrosphingosine as the substrate. The formation of the unsaturated product was monitored by gas chromatography coupled to mass spectrometry of the trimethylsilyl derivatives.^[21] Compound *erythro*-**1** inhibited dihydroceramide desaturase in a dose-dependent manner, with an IC_{50} of $20\text{ }\mu\text{M}$ without preincubation and a substrate concentration of $50\text{ }\mu\text{M}$ (Figure 1). Biochemical studies of *threo*-**1** showed no inhibition at a concentration of $50\text{ }\mu\text{M}$ (equimolar with substrate),^[22] thus demonstrating that the inhibitory effect of ceramide analogues **1** is stereoselective, and that the relative stereochemistry on the aminodiol head of the substrate is a prerequisite for inhibition.

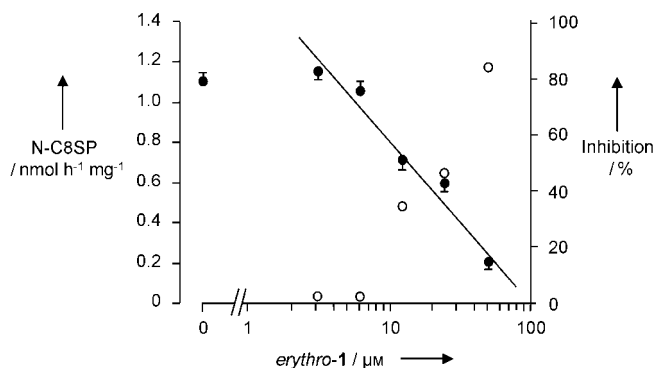


Figure 1. Dose dependence of the inhibition of dihydroceramide desaturase by ceramide analogues *erythro*-**1**. Experiments were conducted at a concentration of $50\text{ }\mu\text{M}$ (15 nmol) of substrate without preincubation. Data correspond to the average $\pm$ standard deviation of three replicates. Left ordinate axis (closed circles): amounts of desaturated product (linear fittings yield: $y = 1.59 - 0.77 \log x$ ($R^2 = 0.96$)). Right ordinate axis (open circles): percentage of inhibition.

A comprehensive investigation of the inhibition mechanism is in progress in our laboratories. Cyclopropenes react with thiols and, although it has never been demonstrated, experimental evidence suggests that the inhibition of fatty acyl CoA desaturases by cyclopropene fatty acids is irreversible and occurs by the reaction of the cyclopropene ring with a cysteine residue of the active site of the enzyme.^[12] This might also occur in the inhibition of dihydroceramide desaturase by *erythro*-**1**. Michel et al.^[5] have also demonstrated that the activity of dihydroceramide desaturase was inhibited by dithiothreitol and suggested that dihydroceramide desaturase might require one or more disulfide bonds for protein stability and/or catalytic activity. However, it has not been determined whether the active site of the enzyme contains reduced cysteine residues that are susceptible to react with the cyclopropene moiety of *erythro*-**1**.

In summary, the introduction of a cyclopropene unit to replace the double bond in the ceramide structure has led to the first potent inhibitor of dihydroceramide desaturase. This compound will be a valuable tool for the elucidation of the role of this enzyme in ceramide-mediated biological processes. Since dihydroceramide lacks the biological effects of ceramide, compound *erythro*-**1** could lead to opportunities for the therapeutic intervention in different diseases related to ceramide accumulation (caused by increased *de novo* biosynthesis^[23]) by interfering with the last step of this pathway, namely the desaturation reaction.

Experimental Section

1: 1-Pentadecyne was converted into 1,1,2-tribromo-2-tridecylcyclopropane (**2**) in two steps (addition of HBr to give 2-bromo-1-pentadecene, followed by the addition of dibromocarbene).^[16] A solution of *n*BuLi in hexane (1.55 M , 6.7 mL , 10.45 mmol) was added to a solution of **2** (2.17 g , 4.75 mmol) in THF (40 mL) at -78°C under argon. The reaction mixture was warmed to room temperature over 45 min and cooled again to -23°C . A solution of *tert*-butyl-(*S*)-(-)-4-formyl-2,2-dimethyl-3-oxazolidinonecarboxylate (0.90 g , 3.9 mmol) in THF (14 mL) was added at -23°C and stirred for 2 h at this temperature. The reaction was quenched with aqueous saturated NH_4Cl and extracted with diethyl ether. Evaporation of the solvent and flash chromatography (hexane/AcOEt 14:1) of the crude residue (which contained a 3:1 mixture of *erythro*-**3** and *threo*-**3**) allowed

the partial separation of the pure diastereomers, which were obtained in a combined yield of 75%. Removal of the protecting groups with trimethylsilyl triflate,^[19] *N*-acylation with octanoyl chloride^[20] and final chromatography afforded *erythro*-**1** in 14% overall yield from pentadecyne.

erythro-**1**: [α]_D = +3.0 (*c* = 0.8 in CHCl₃); IR (NaCl): $\bar{\nu}$ = 1550, 1644, 3010, 3287 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.87 (t, 6H, *J* = 6.2 Hz), 1.01 (s, 2H), 1.25 (s, 28H), 1.60 (m, 4H), 2.24 (t, 2H, *J* = 7.2 Hz), 2.45 (dt, 2H, *J* = 7.6, *J'* = 1.2 Hz), 3.02 (brs, 1H), 3.37 (brs, 1H), 3.71 (dd, 1H, *J* = 11.4, *J'* = 3.4 Hz), 3.87 (dd, 1H, *J* = 11.2, *J'* = 4 Hz), 4.18 (m, 1H), 4.85 (s, 1H), 6.37 (brd, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 8.36, 14.04, 14.10, 22.58, 22.66, 25.70, 25.82, 27.27, 28.99, 29.19, 29.33, 29.37, 29.44, 29.57, 29.63, 29.64, 29.64, 29.67, 31.65, 31.89, 36.77, 53.74, 63.12, 70.52, 107.52, 115.40, 174.00. HR-MS calcd for C₂₇H₅₁NO₃: 437.386895; found: 437.387000.

The dihydroceramide desaturase inhibition assay was performed by using rat liver microsomes, which were prepared as reported.^[5] The activity of dihydroceramide desaturase was determined in phosphate buffer (0.1M, pH 7.4), with *D*-*erythro*-*N*-octanoylsphingosine as substrate. The inhibitor (at the indicated concentrations) and the substrate (15 nmol) were solubilized (15 nmol of BSA in phosphate buffer/ethanol 9:1 v/v, 100 μ L), combined with the microsome suspension (1 mg of protein) and NADH (30 μ L, 1 μ M in phosphate buffer), and made up to a final volume of 300 μ L with phosphate buffer. The suspension was incubated for 30 min at 37 °C, and the reactions were terminated by the addition of CHCl₃ (0.5 mL) containing *D*-*erythro*-*N*-hexanoylsphingosine (1 nmol) as an internal standard for quantification. The lipids were extracted with CHCl₃ (2 $\times$ 250 μ L), the combined organic layers were evaporated under a stream of nitrogen, and the residue was derivatized with bistrimethylsilyltrifluoroacetamide (50 μ L, 25 °C, 60 min). After derivatization, CHCl₃ (50 μ L) was added and the samples were stored at -80 °C. Instrumental analyses were carried out by gas chromatography coupled to electron impact (70 eV) mass spectrometry using a Fisons gas chromatograph (8000 series) coupled to a Fisons MD-800 mass-selective detector. The system was equipped with a nonpolar Hewlett–Packard HP-1 capillary column (30 m $\times$ 0.20 mm i.d.), which was programmed from 100 °C to 340 °C at 7 °C min⁻¹. Analyses were carried out in the selected ion monitoring mode. Selected ions were *m/z* = 311, 313, 230, and 258. Dwell (time for which a given mass is monitored) was set at 0.02 s and the mass span at 0.5.

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Synthesis of Cored Dendrimers with Internal Cross-Links**

Laura G. Schultz, Yan Zhao, and
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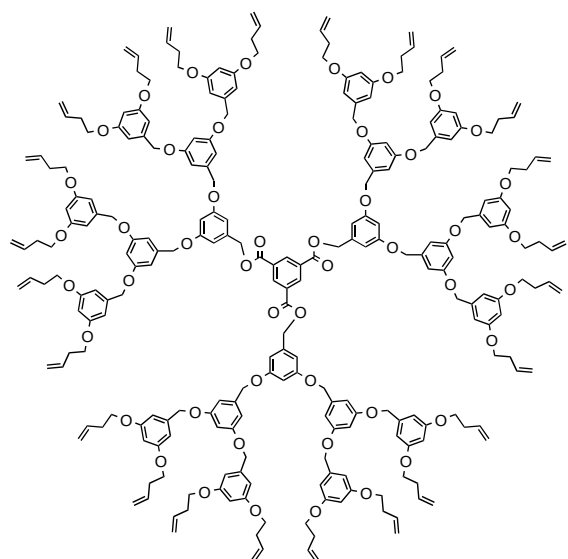
The physical properties of a dendrimer may be manipulated by post-synthetic modification of its periphery, core, or interior. Such alterations can tune the bulk properties of the dendritic system and frequently convert simple dendrimers into functional macromolecules. For example, incorporation of molecular recognition elements on the periphery of a dendrimer produces multivalent receptors capable of ligand binding or supramolecular assembly.^[1] Organometallic functional groups can also be added to the periphery, thus creating macromolecular catalysts.^[1–3] In contrast to the many reports of end-group functionalization, there are only a few examples of covalent modification of the interior of the dendrimer.^[4] We recently reported^[5] the “coring” of dendrimer **1** by ring-closing metathesis (RCM) of the peripheral homoallyl ether groups^[6] using ruthenium benzylidene catalyst **2**^[7] followed by hydrolytic removal of the core. In some respects, “cored” dendrimers resemble hollow, polymeric nanospheres or core-shell nanoparticles.^[8] Consequently, the potential of “cored” dendrimers to encapsulate or complex substances makes them outstanding candidates for delivery agents or molecular sensors.

Our reported synthesis of cored dendrimers^[5] is limited in its scalability by the requirement of high dilution (about

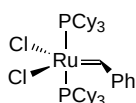
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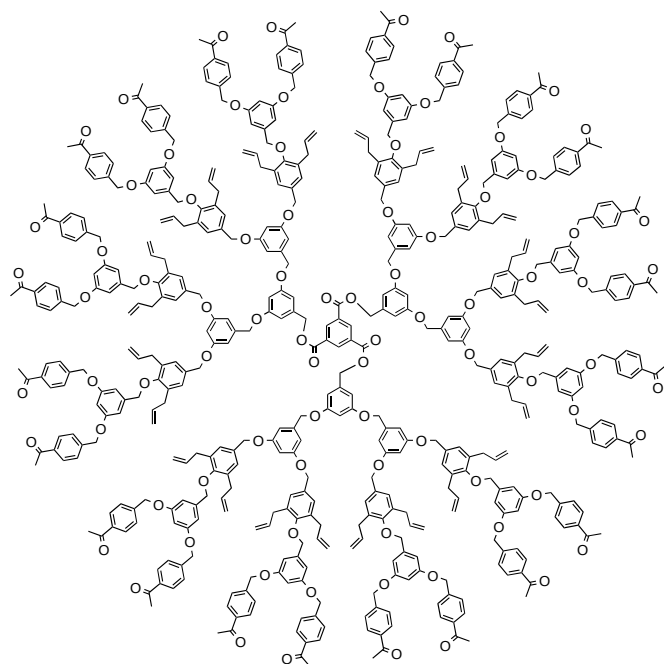


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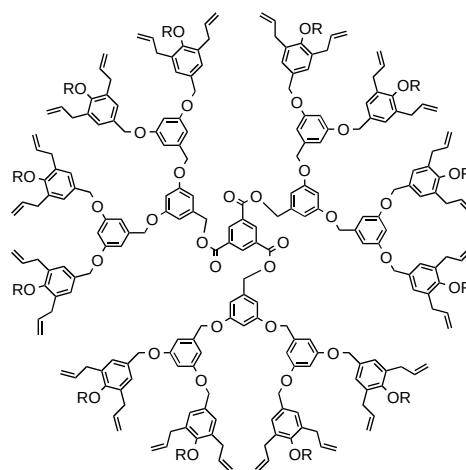


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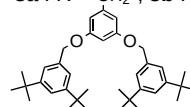
10^{-5} M) to effect intramolecular cross-linking. By internalizing the alkenes there is a possibility that intermolecular cross-linking will be disfavored, as one dendrimer would need to interpenetrate another. Armes and co-workers used a similar strategy in the synthesis of shell-cross-linked knedel (SCK) micelles.^[9] To test the idea that internalizing the cross-linking groups would favor RCM reactions at higher concentration three new dendrimers (**3a**, **3b**, and **4**) were designed and synthesized. Dendrimers **3a** and **3b** are identical except that the latter, a control compound, lacks the additional dendritic



4



3a : R = CH₂, **3b** : R = Me

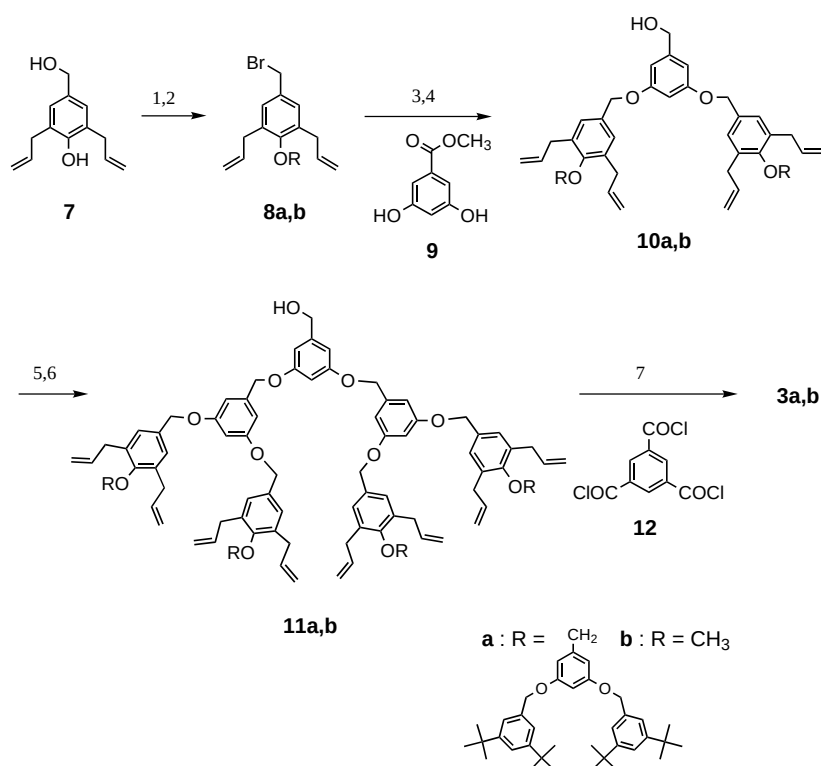


layer so the allyl groups reside on the surface. In both cases, the dendrimer contains labile ester linkages to the core.

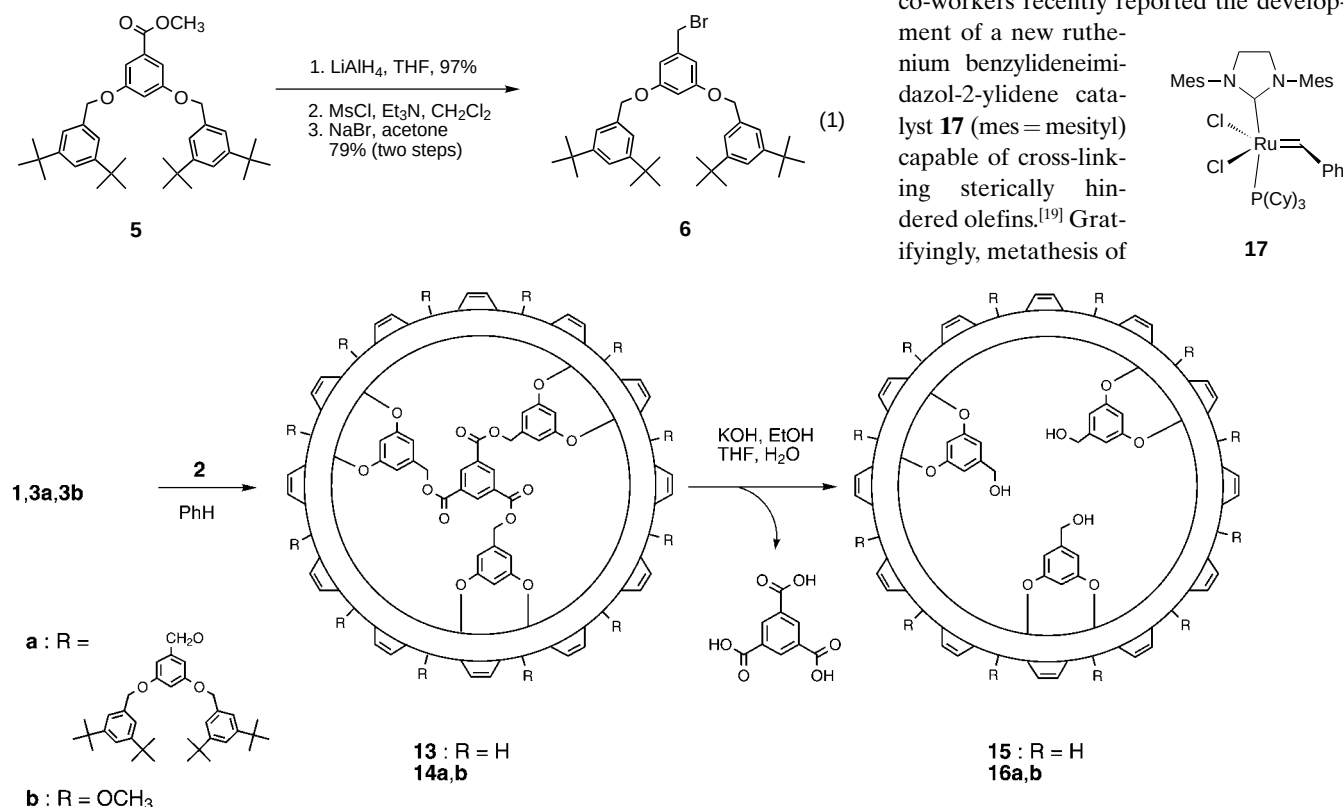
Dendrimers **3a** and **3b** were synthesized using the convergent approach^[10] employing either the Mitsunobu etherification^[11] or phenol–bromide coupling^[10] as shown by Scheme 1. The synthesis of **6**, required for the synthesis of **3a**, is shown in Equation (1) (Ms = mesyl = methanesulfonyl).^[12] Bromide **6** was then coupled with phenol **7** and converted into bromide **8a**. Phenol **7** was obtained by reduction of the corresponding aldehyde, a compound first reported by Claisen and Eisleb.^[13] The coupling of bromide **8a** with commercially available ester **9** afforded the second generation ester which was reduced to alcohol **10a**. Mitsunobu coupling of **10a** with **9** followed by reduction yielded third generation alcohol **11a**. Treatment of **12** with alcohol **11a** under Dean–Stark conditions afforded dendrimer **3a**.^[14, 15] Dendrimer **3b** was synthesized in an analogous manner (Scheme 1).

With the desired dendrimers in hand, attention was turned to the cross-linking experiments. The critical question was whether cross-linking would occur, and, if so, to what extent (both intra- and intermolecularly). Although **1** can be cross-linked completely,^[5] the alkenes are more hindered in **3b** and especially congested in **3a**. The sensitivity of some RCM catalysts to steric hindrance is well documented.^[16] All the dendrimers were cross-linked by ring-closing metathesis using Grubb's catalyst **2** in benzene (Scheme 2).^[7, 16] The catalyst was removed after the RCM reactions using a modification of a reported protocol in which the metathesis solution was treated with tris(hydroxymethyl)phosphane and then silica.^[17] Subsequent purification of all compounds by preparative size-exclusion chromatography (SEC) in toluene afforded almost quantitative recovery of the cross-linked products.

Dendrimers **1** and **3b** were cross-linked using 7 mol % of catalyst per alkene at three concentrations (1×10^{-5} , 1×10^{-4} ,



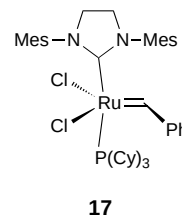
Scheme 1. Syntheses of dendrimers **3a** and **3b**. Reaction conditions: 1) a. **6**, K_2CO_3 , 2-butanone (79 %); b. CH_3I , K_2CO_3 , acetone (71 %); 2) $CBBr_4$, PPh_3 , THF (**a**: 75 %, **b**: 82 %); 3) a. **9**, K_2CO_3 , acetone, [18]crown-6 (77 %); b. **9**, K_2CO_3 , acetone (81 %); 4) $LiAlH_4$, THF (**a**: 96 %, **b**: 81 %); 5) PPh_3 , DEAD, THF, **9** (**a**: 70 %, **b**: 79 %); 6) $LiAlH_4$, THF (**a**: 94 %, **b**: 93 %); 7) **12**, DMAP, benzene (**a**: 34 %, **b**: 71 %). DEAD = diethylazodicarboxylate, DMAP = 4-dimethylaminopyridine.



Scheme 2. Synthesis of cored dendrimers.

and $1 \times 10^{-3} M$). Both ^1H NMR and mass spectrometric analysis clearly indicated that cross-linking of the allyl groups in **3b** had occurred. Thus, the ^1H NMR signals broadened significantly and the alkene methine signal shifted upfield from $\delta = 5.98$ to 5.73, which is consistent with the conversion of monosubstituted into disubstituted alkenes. Matrix-assisted laser-desorption/ionization time-of-flight spectrometry (MALDI-TOF) analysis showed the average loss of 11 molecules of ethylene, thus indicating the formation of 11 out of 12 possible cross-links.^[18] Similar results were seen in the cross-linking of dendrimer **1**.

Dendrimer **3a** was cross-linked at two concentrations (1×10^{-5} and $1 \times 10^{-3} M$) using 4 mol % of **2** per alkene. Indeed, cross-linking did occur at the concentrations examined which indicated that the catalyst could access the internal alkenes. The same ^1H NMR and MALDI analyses used for **1** and **3b** showed the cross-linking of **3a** to be less advanced. In particular, the MALDI-TOF peak assignments indicate the average formation of 8–9 out of 12 possible cross-links at $10^{-3} M$ and 10 out of 12 cross-links at $10^{-5} M$.^[18] The degree of cross-linking did not increase when higher catalyst loadings were used. Grubbs and co-workers recently reported the development of a new ruthenium benzylideneimidazol-2-ylidene catalyst **17** (mes = mesityl) capable of cross-linking sterically hindered olefins.^[19] Gratifyingly, metathesis of



3a with **17** at both 10^{-3} M and 10^{-5} M resulted in greater than 95 % cross-linking based on ^1H NMR analysis.

The extent of intermolecular cross-linking, namely, oligomer formation, was determined by both MALDI-TOF analysis and size-exclusion chromatography (SEC) using toluene as eluent. Each SEC trace consisted of two signals corresponding to formation of the monomer and oligomer (Figure 1). The relative areas of these two signals were used to

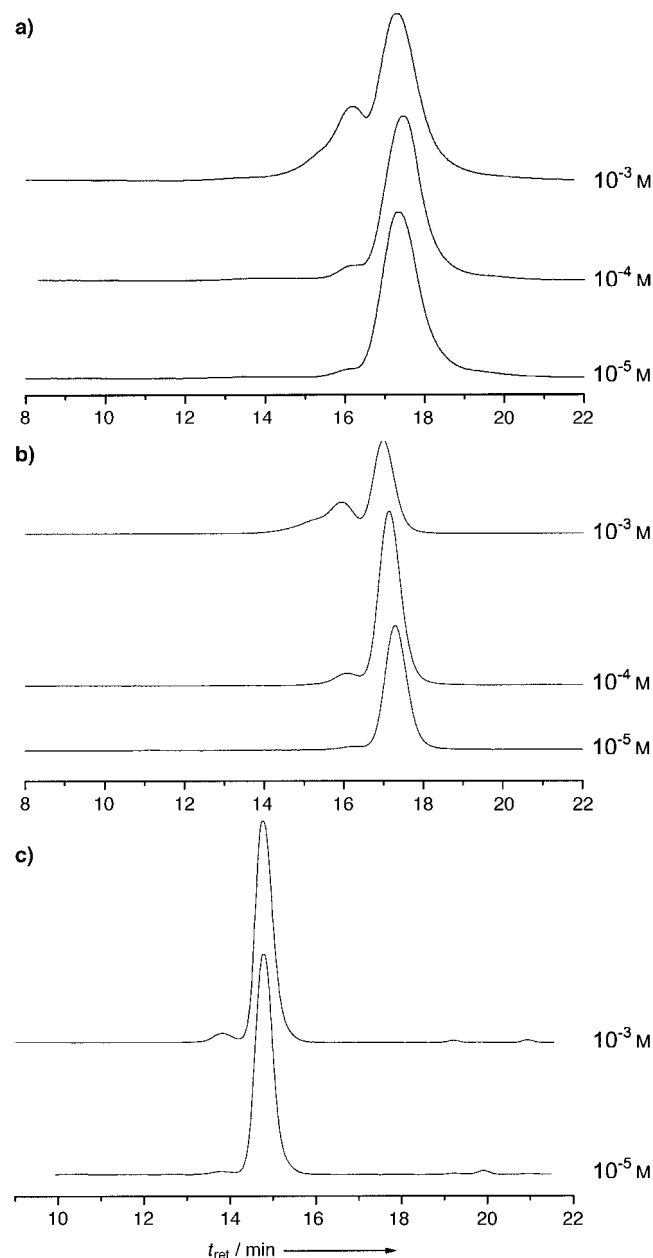


Figure 1. Comparison of cross-linked dendrimers by SEC. a) **3b**; b) **1**; c) **3a**.

calculate the percentage of oligomer formation (Table 1). The molecular weights of dendrimers, pre- and post-cross-linking, were determined using both MALDI-TOF and SEC analyses.^[18] No oligomer formation was evident in either the MALDI-TOF spectra or SEC traces of dendrimers **1**, **3a**, and **3b** cross-linked at 10^{-5} M, thus indicating that complete

Table 1. A comparative SEC analysis of intermolecular cross-linking in **1**, **3a**, and **3b** with **2**.

Conc. of RCM [M]	Relative amount of oligomer formed [%]		
	1	3a	3b
1×10^{-5}	0	0	0
1×10^{-4}	7	–	7
1×10^{-3}	38	<5	29

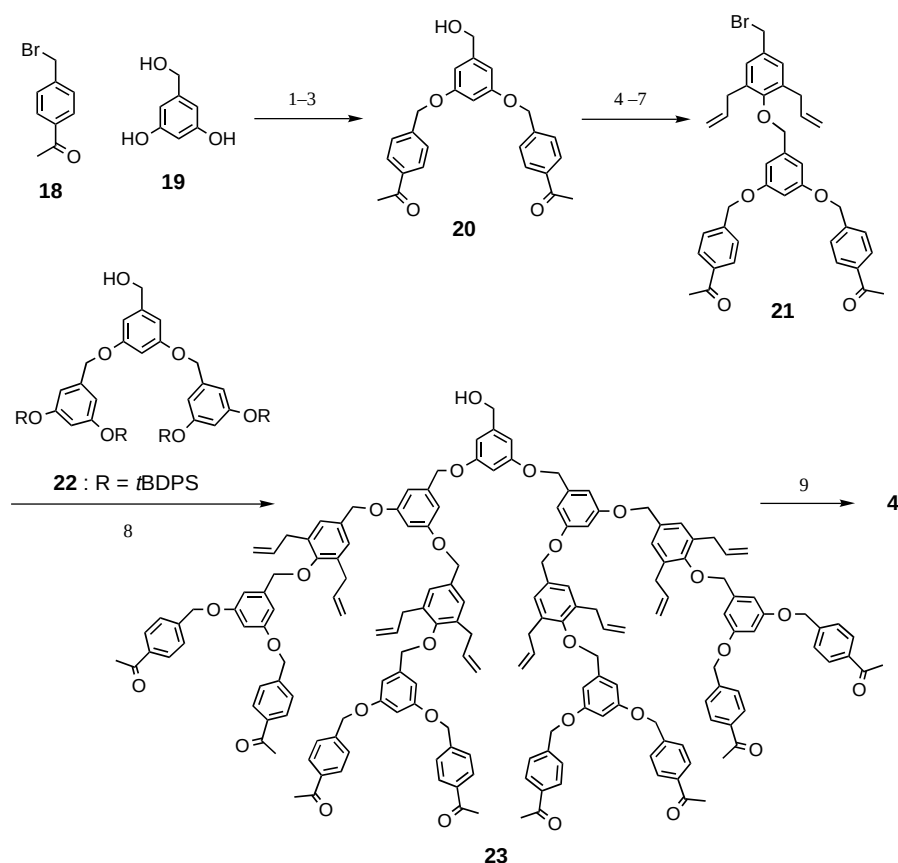
intramolecular metathesis had occurred. As the concentration of the RCM reaction was increased to 1×10^{-4} M, an additional peak evident in the SEC traces of **1** and **3b** (Figure 1a and 1b) revealed the formation of small amounts of oligomer, which MALDI-TOF analysis showed to be dimer. Substantial oligomer formation occurred with both **1** and **3b** at a RCM reaction concentration of 10^{-3} M. However, dendrimer **3a** underwent more than 95 % intramolecular cross-linking at 10^{-3} M ([alkene] = 0.024 M) with both catalysts **2** and **17**, the latter giving greater than 95 % cross-linking based on ^1H NMR analysis. This result is consistent with a model wherein the alkene groups are sterically blocked from intermolecular metathesis.

For these dendritic systems to be useful, the cross-linked dendrimer must remain intact when the core is removed. Scheme 2 also depicts the “coring” procedure. Hydrolysis of **14a** and **14b** led to complete core removal as evidenced by the loss of the aromatic signal at $\delta = 8.95$ in the ^1H NMR spectrum and a reduction of m/z 159 ($\text{C}_9\text{H}_5\text{O}_3$) in the MALDI-TOF spectrum.^[18] Whereas dendrimer **14b** produced **16b** fully intact, the MALDI-TOF and SEC data for **16a** revealed a minor amount of cross-linked mono- and didendron formed in the hydrolysis of **14a**.^[18]

The ability to fully cross-link dendrimer **3a** intramolecularly at 10^{-3} M makes this cross-linking-coring approach suitable for further development. It was considered to be particularly important to develop a system wherein the end groups could ultimately be conjugated with targeting or reporter groups or converted into groups that provide water solubility. For these reasons, a synthesis of **4** was developed (Scheme 3). Bromide **18**, prepared by bromination of 4-methylacetophenone with *N*-bromosuccinimide (NBS), was coupled with alcohol **19** to afford **20**, which was purified as its 3,5-dinitrobenzoate derivative. Conversion of **20** into the bromide, coupling with **7**, and treatment with mesyl chloride/sodium bromide afforded **21**. Coupling of **21** with *t*BDPS-protected **22**^[20] yielded **23**, which was treated with acid chloride **12** to afford dendrimer **4**. Preliminary cross-linking studies of dendrimer **4** indicated the formation of 11 of 12 cross-links at 10^{-3} M in dichloromethane using 4 mol % of catalyst **2** per alkene.

The previously reported synthesis of cored dendrimers was limited by the high-dilution conditions required for intramolecular metathesis. The current work solves this problem. Thus, larger quantities of cored dendrimers can now be produced, thus making it possible to develop a range of applications. Efforts in this direction have been successful and will be reported in due course.

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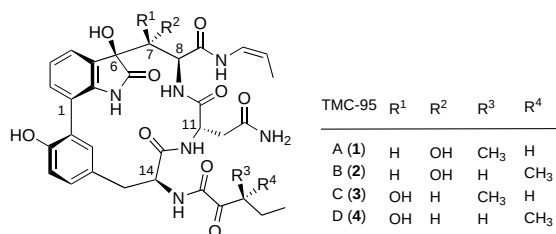
Scheme 3. Synthesis of dendrimer **4**. Reaction conditions: 1) K_2CO_3 , 2-butanone (76%); 2) 3,5-dinitrobenzoyl chloride, pyridine, DMAP (53%); 3) K_2CO_3 , MeOH (62%); 4) MsCl , Et_3N , CH_2Cl_2 ; 5) NaBr , acetone (92%); 6) K_2CO_3 , 2-butanone (85%); 7) MsCl , Et_3N , CH_2Cl_2 ; NaBr , acetone (80%); 8) **22**, KF , [18]crown-6, 2-butanone (57%); 9) **12**, DMAP, benzene (52%). Ms = mesyl = methanesulfonyl.

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Synthesis of the Functionalized Macrocyclic Core of Proteasome Inhibitors TMC-95A and B**

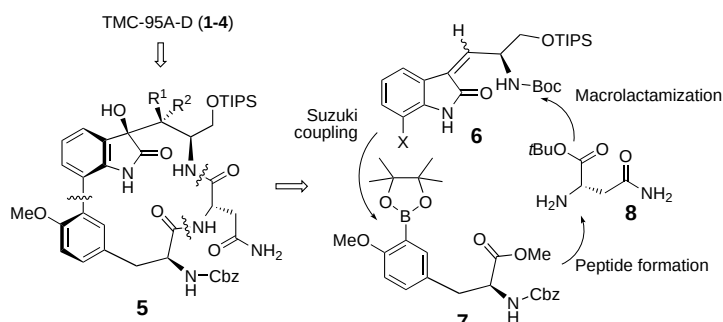
Songnian Lin and Samuel J. Danishefsky*

TMC-95A (**1**) and its diastereomers, TMC-95B, C, and D (**2–4**), are cyclic peptides recently isolated as fermentation products of *Apiospora montagnei* Sacc. TC1093 derived from



soil samples.^[1, 2] Biological studies^[1] have shown that TMC-95A inhibited the chymotrypsin-like (ChT-L), trypsin-like (T-L), and peptidoglutamyl-hydrolyzing (PGPH) activities of the 20S proteasome^[3, 4] with IC₅₀ values of 5.4, 200, and 60 nM, respectively. TMC-95B inhibited these activities to the same extent as TMC-95A, while TMC-95C and D were 20 to 150 times weaker. TMC-95A has also shown cytotoxic activities against HCT-116 (human colon carcinoma cells) and HL-60 (human promyelocytic leukemia cells) with IC₅₀ values of 4.4 and 9.8 μM, respectively. These four diastereomers are structurally characterized as novel cyclic peptides containing L-tyrosine, L-asparagine, highly oxidized L-tryptophan, (Z)-1-propenylamine, and 3-methyl-2-oxopentanoic acid moieties. Although the phenyl-indole ring attachment is found in a few natural products such as chloropeptin,^[5] complestatin,^[6] diazonamide,^[7] and the kistamicins,^[8] the presence of an oxindole ring in such macrocyclic systems is apparently rare. The structural novelty of the TMC compounds and the biological issues they raise prompted us to embark on a program directed to their total synthesis.

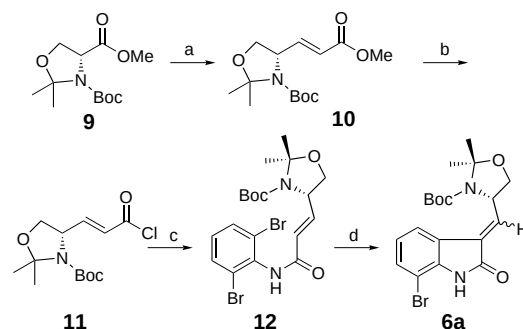
We envisioned that the 17-membered ring could be fashioned by macrolactamization. With the ring in place, attention could then be directed to inclusion of the unusual (Z)-1-propenylamide and 3-methyl-2-oxopentanoate side chains at C-8 and C-14, respectively. The installation of hydroxy groups at C-6 and C-7 could in principle be conducted prior to, or after, macrocyclization (Scheme 1). We



Scheme 1. Retrosynthetic plan. TIPS = triisopropylsilyl, Cbz = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl, X = Br or I.

further foresaw that a Suzuki reaction,^[9] which would allow the joining of **6** and **7**, might be employed to reach macrolactamization precursors en route to **5**. Below, we report the encouraging realization of several important milestones pursuant to this rough blueprint.

The synthesis of oxindole **6a** was first attempted by using a proposed palladium-mediated intramolecular Heck reaction of substituted *N*-acryl-2,6-dibromoaniline **12** (Scheme 2).



Scheme 2. Attempted synthesis of 7-bromooxindole **6a**. a) 1. DIBAL/toluene, −78 °C, 1 h; 2. methyl (triphenylphosphoranylidene)acetate, CH₂Cl₂, room temperature (RT), 88% (two steps); b) 1. LiOH, THF/MeOH/H₂O; 2. TBS-Cl, Et₃N/DMAP; 3. (COCl)₂, DMF (cat.); c) 2,6-dibromoaniline, NaH, DMF/THF, 75 °C, 1.5 h, 44%; d) [Pd(PPh₃)₄] or Pd(OAc)₂, 5–15%. DIBAL = diisobutylaluminum hydride, TBS = *tert*-butyl dimethylsilyl, DMAP = 4-dimethylaminopyridine.

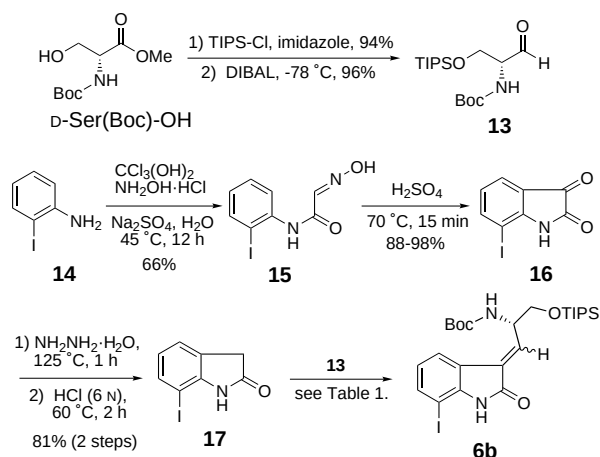
Thus, methyl ester **9** derived from D-serine^[10] was reduced with DIBAL. This was followed by treatment with methyl (triphenylphosphoranylidene)acetate to provide **10** in 88% yield over two steps. Methyl ester **10** was then converted to the corresponding acid chloride **11** under neutral conditions in a three-step procedure as shown.^[11] Acylation of 2,6-dibromoaniline with **11** was sluggish, and afforded **12** in only moderate yield. Unfortunately, attempted cyclization of dibromide **12** to 7-bromooxindole **6a** provided the desired compounds in unacceptably low yields (5–15%).

Accordingly, an alternative approach was investigated (Scheme 3). Protection of *N*-Boc-D-serine as shown, was followed by reduction of the methyl ester to provide aldehyde **13** in high yield. The required 7-iodoisatin **16** was obtained in good yield in two steps from 2-iodoaniline **14** via isonitrosoacetanilide **15**.^[12] Upon heating compound **16** with hydrazine hydrate^[13] for 1 h at 125 °C, and subsequent treatment with

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Scheme 3. Synthesis of 7-iodooxindole **6b**.

HCl (6 N) at 60 °C for 2 h, 7-iodooxindole **17** was obtained in excellent yield. Condensation of **17** and aldehyde **13** was then carried out under several conditions as summarized in Table 1. As seen, serviceable yields (74–76 %) with little or no racemization (up to 96 % *ee*) could be achieved in reaching **6b** (Table 1, entries 3 and 4).^[14] The structure of the major component of **6b** was confirmed by NOE experiments (Figure 1) to be the *E* isomer.

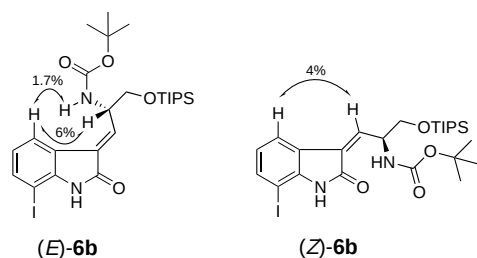
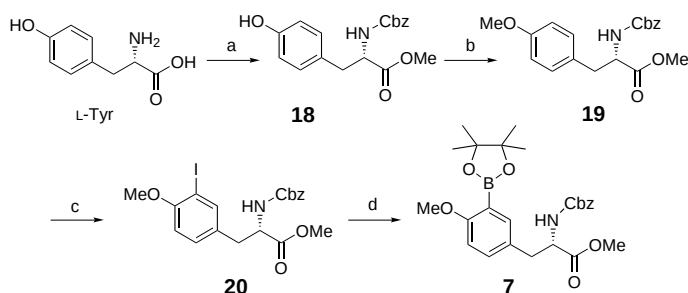


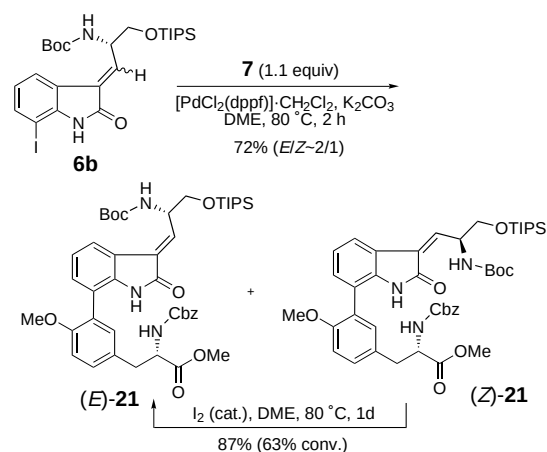
Figure 1. NOE experiments on compounds (*E*)-**6b** and (*Z*)-**6b** (CDCl₃, 400 MHz).

The aryl borate **7**, required for Suzuki cross-coupling, was synthesized starting from L-tyrosine (Scheme 4). Methyl ester formation with MeOH/SOCl₂ followed by protection of the amino group as a benzylcarbamate, afforded phenol **18** in 96 % yield over two steps. O-methylation of **18** with Me₂SO₄ in the presence of LiOH·H₂O in dry THF^[15] provided **19** in 86 % yield. Selective iodination of **19** at the 3-position *ortho* to the methoxy group was achieved in high yield with I₂/AgSO₄^[16] in methanol. Iodide **20** was then converted into aryl borate **7** in 95 % yield under Miyaura's conditions using bis(pinacolato)diboron, [PdCl₂(dppf)]·CH₂Cl₂, and KOAc in DMSO for 13 h at 80 °C.^[17]



Scheme 4. Synthesis of aryl borate **7**. a) 1. MeOH/SOCl₂; 2. Cbz-Cl, K₂CO₃, H₂O/acetone, 96 % (two steps); b) LiOH, Me₂SO₄, 86 %; c) I₂, Ag₂SO₄, MeOH, RT, 1.5 h; 93 %; d) bis(pinacolato)diboron, [PdCl₂(dppf)]·CH₂Cl₂, KOAc, DMSO, 80 °C, 13 h, 95 %. dppf = bis(diphenylphosphanyl)ferrocene.

The appropriate components, 7-iodooxindole **6b** and aryl borate **7**, were indeed joined by a Suzuki coupling.^[9, 17b] After an extensive survey of reaction conditions (catalyst loading, temperature, and reaction time, equivalents of borate and base) we identified a regimen that afforded coupling products **21** in 72 % yield with an *E/Z* ratio of 2/1. The two isomers were separable by silica gel chromatography, and the *E/Z* stereochemistry of each was determined by NOE experiments similar to those conducted on **6b**. No epimerization of the allylic amine position was observed in this reaction. However, *E/Z* isomerization apparently did occur during the Suzuki process. An *E/Z* ratio of about 2/1 was consistently obtained starting with (*E*)-**6b**, (*Z*)-**6b**, or a mixture of the two isomers. Conversion of (*Z*)-**21** to (*E*)-**21** can be affected by heating (*Z*)-**21** in DME at 80 °C for 1 day in the presence of a catalytic amount of iodine (Scheme 5).



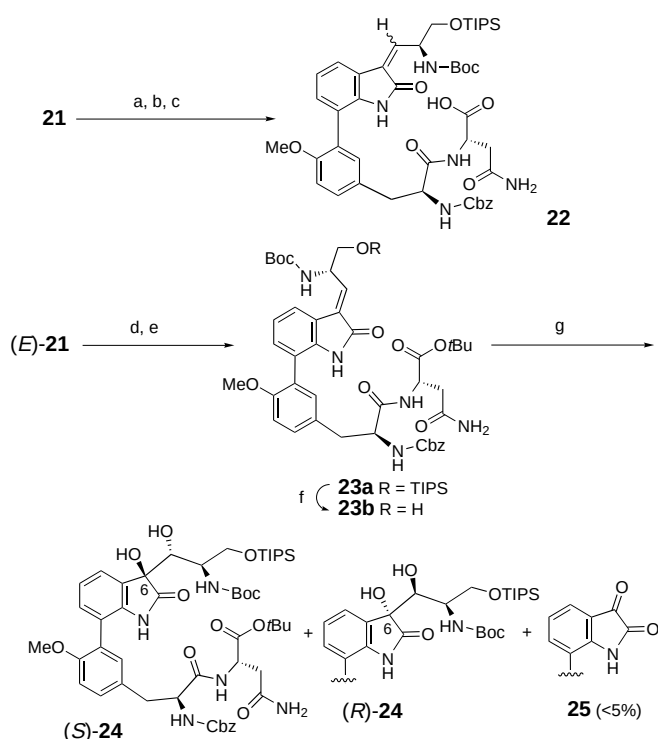
Scheme 5. Biaryl linkage formation by Suzuki coupling. DME = 1,2-dimethoxyethane.

Table 1. Condensation of iodooxindole **17** with aldehyde **13** under different conditions.

Entry	Conditions	Yield [%] ^a	<i>E/Z</i> ^b	<i>ee</i> [%] ^c
1	piperidine (cat.), MeOH or EtOH, 65 °C, 2–3 h	44–50	2.0/1	0
2	piperidine (cat.), THF, RT, 17–44 h	55	1.7/1	~10
3	1) LDA (2.1 equiv), THF, –78 °C, 1 h; 2) TEA (2.5 equiv), MsCl (1.2 equiv), CH ₂ Cl ₂ , –60 to –30 °C, 2 h	76	1.3/1	92
4	1) LDA (2.0 equiv), THF, –78 °C, 1.5 h; 2) TEA (3 equiv), MsCl (1.5 equiv), CH ₂ Cl ₂ , –70 to –50 °C, 1.5 h	74	1.2/1	96

[a] Yield of isolated product. [b] Determined by ¹H NMR spectroscopy, two isomers are separable. [c] Determined by chiral HPLC.

L-Asparagine was then appended to the seco framework. Thus, hydrolysis of the α -methyl ester of **21**, and conversion of the derived acid to its *N*-hydroxysuccinimide ester paved the way for amide formation with L-Asn hydrate (see compound **22**). Exposure of **22** to the action of HCl (4N), followed by cyclization of the resulting amino acid with pentafluorophenyl diphenylphosphonate (FDPP) and DIEA in DMF, or with EDC/HOAT in various solvents (DMF, CH₂Cl₂, MeCN), however, did not provide the cyclized product. We reasoned that the rigidity of the *exo* double bond at the 3-position of oxindole ring probably tilts the amino group away from the asparagine moiety, thereby preventing cyclization. Accordingly, we decided to carry out dihydroxylation prior to cyclization. Saponification of the methyl ester (*E*)-**21** followed by coupling with L-asparagine *tert*-butyl ester (**8**) as before provided **23a** in 70 % yield over two steps. Treatment of **23a** with HF/pyridine afforded free alcohol **23b** (Scheme 6).

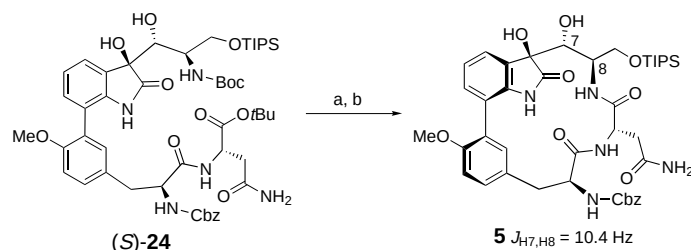


Scheme 6. Synthesis of diols **24**. a) LiOH, THF/MeOH/H₂O; b) hydroxy-succinimide, DCC, THF, 55 % (two steps); c) L-Asn · H₂O, Et₃N, THF/H₂O, RT, 4 h, 70 %; d) LiOH, THF/H₂O, 0 °C, 1.5 h; e) H-Asn-OtBu (**8**), EDC/HOAT, THF, RT, 2 h, 70 % (2 steps); f) HF/Py, 84 %; g) 1: OsO₄/NMO, (DHQD)₂PHAL, *t*BuOH/H₂O, RT, 1 h, 84 % (*S/R* ~ 1/1.8); 2: OsO₄/NMO, (DHQ)₂PHAL, *t*BuOH/H₂O, RT, 4 h; TIPS-Cl, imidazole/DMAF, 5 h, 81 % (*S/R* ~ 1/1.4). DCC = 1,3-dicyclohexylcarbodiimide, EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, HOAT = 1-hydroxy-7-azabenzotriazole, Asn = asparagine, NMO = 4-methylmorpholine *N*-oxide, (DHQD)₂PHAL = 1,4-bis(9-*O*-dihydroquinidine)phthalazine, (DHQ)₂PHAL = 1,4-bis(9-*O*-dihydroquinine)phthalazine.

Dihydroxylation of **23a** using OsO₄/NMO in the presence of (DHQD)₂PHAL^[18] at room temperature afforded the diols **24** in 84 % yield (*S/R* ~ 1/1.8),^[19] along with a small amount of isatin **25** (< 5 %). Dihydroxylation of **23b** in the presence of (DHQ)₂PHAL^[18] followed by selective reprotection of the

primary hydroxy group gave similar results (81 %, *S/R* ~ 1/1.4, Scheme 6).

Treatment of (*S*)-**24** with trifluoroacetic acid (TFA) in CH₂Cl₂ resulted in concurrent removal of the Boc protecting group and hydrolysis of the *tert*-butyl ester. The crude amino acid was then submitted to macrolactamization using EDC/HOAT under highly dilute conditions (4 mM) in CH₂Cl₂/DMF (4/1). Cyclization progressed smoothly, providing the desired product **5**^[20] in 55 % yield over two steps (Scheme 7). The



Scheme 7. Macrolactamization of (*S*)-**24**. a) TFA/CH₂Cl₂ (4/1), RT, 2 h; b) EDC, HOAT, DIEA, CH₂Cl₂/DMF (4/1, 4 mM), RT, 20 h, 55 % (two steps). DIEA = *N,N*-diisopropylethylamine.

large coupling constant (10.4 Hz) observed for H7–H8 in **5**, which is similar to those observed in TMC-95A and B (**1** and **2**),^[2] further confirmed the configurational assignments at C6 and C7. Interestingly, treatment of (*R*)-**24** under the same reaction conditions did not afford any cyclization product.

In summary, the fully functionalized macrocyclic core of proteasome inhibitors TMC-95A and B (**5**) has been assembled. There still remain significant issues to be overcome, such as selectivity enhancement en route to our total synthesis goal,^[21] which are currently being studied in considerable detail.^[22]

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- [19] The *R* configuration at C6 of (*R*)-**24** was assigned by converting (*R*)-**24** to its primary–secondary diol acetonide, whereupon the coupling constant between H7 and H8 is 0 Hz, indicating their *syn* relationship.
- [20] The atropisomer shown for **5** follows from the C6 stereochemistry (see reference [2]).
- [21] While the manuscript was being processed, it has been found that dihydroxylation of the *N,O*-acetonide derivative of **23b** under similar conditions to those shown in Scheme 6 followed by protecting group adjustment provided the desired (*S*)-**24** as the major isomer (*S/R* ~ 8/1). Details will be reported in due course. Similar results have also been observed for **6a** (see reference [14]).
- [22] **Note added in proof** (April 12, 2001): An alternative route to the biaryl moiety of the TMC-95 natural products by a Pd-catalyzed Stille cross-coupling reaction of an aryl stannane tyrosine derivative and 7-iodoisatin appeared following the acceptance of this work: B. K. Albrecht, R. M. Williams, *Tetrahedron Lett.* **2001**, *42*, 2755–2757.

Cover Picture

Bradley J. Holliday and Chad A. Mirkin

The cover picture shows a swirling mixture of transition metal fragments and simple organic ligands that assemble into supramolecular coordination compounds, depicted on the periphery of the vortex. The synthesis of such large structures requires strategies that take into account the entropic costs of not forming higher ordered oligomers and polymers. The use of transition metal ions as building blocks for supramolecular compounds has become a widely practiced strategy for making such structures. Within this quickly growing field there have emerged three general synthetic approaches for the metal-directed formation of supramolecular coordination compounds. These are described by B. J. Holliday and C. A. Mirkin on p. 2022 ff.



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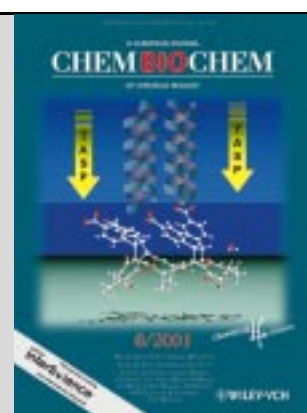
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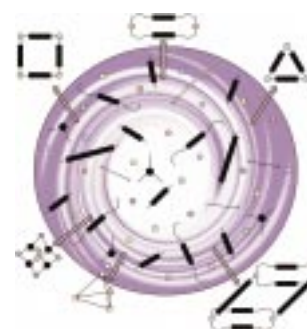


ChemBioChem 6/2001 is bound
in this issue of *Angewandte Chemie*.

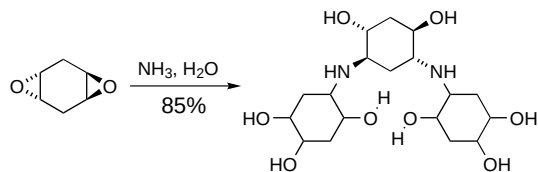


COVER PICTURE

The cover picture shows a swirling mixture of transition metal fragments and simple organic ligands that assemble into supramolecular coordination compounds, depicted on the periphery of the vortex. The synthesis of such large structures requires strategies that take into account the entropic costs of not forming higher ordered oligomers and polymers. The use of transition metal ions as building blocks for supramolecular compounds has become a widely practiced strategy for making such structures. Within this quickly growing field there have emerged three general synthetic approaches for the metal-directed formation of supramolecular coordination compounds. These are described by B. J. Holliday and C. A. Mirkin on p. 2022 ff.



Just a handful of good reactions are needed to assemble vast numbers of highly diverse organic molecules. (The graphic shows a simple example.) Yet, this easily accessible structural universe has not been mined by the medicinal chemistry community for its nuggets of desirable function. The requirements for the best reactions that can be employed, examples of such processes, and the philosophy that underlies their use are discussed in this review.



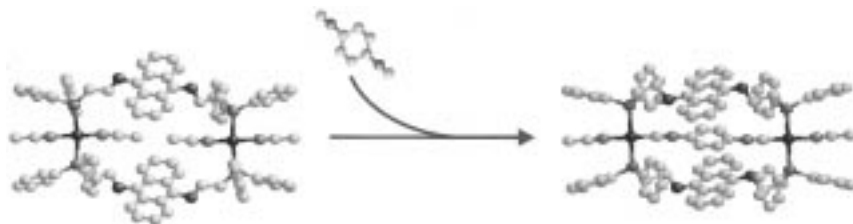
Angew. Chem. **2001**, *113*, 2056–2075

H. C. Kolb, M. G. Finn,
K. B. Sharpless* 2004–2021

Click Chemistry: Diverse Chemical
Function from a Few Good Reactions

Keywords: combinatorial chemistry •
drug research • synthesis design • water
chemistry

Supramolecular coordination complexes or coordination chemistry supramolecules? Emerging synthetic approaches for the construction of supramolecular structures by coordination chemistry (see picture) have led to a rapid expansion of the field of supramolecular chemistry. Many structures are now accessible through the general principles that define these approaches, and the applications of the structures formed from them are beginning to be explored.



Angew. Chem. **2001**, *113*, 2076–2097

B. J. Holliday, C. A. Mirkin* 2022–2043

Strategies for the Construction of
Supramolecular Compounds through
Coordination Chemistry

Keywords: coordination chemistry •
nanostructures • supramolecular
chemistry • synthetic methods •
transition metals

VIPs

The following communications are “Very Important Papers” in the opinion of two referees. They will be published shortly (those marked with a diamond will be published in the next issue). Short summaries of these articles can be found on the *Angewandte Chemie* homepage at the address <http://www.angewandte.com>

Correlating Electron Transport and Molecular Structure in Organic Thin Films

R. E. Holmlin, R. F. Ismagilov, ◆
R. Haag, V. Mujica,
M. A. Ratner, M. A. Rampi*,
G. M. Whitesides*

Targeting Molecular Recognition: Exploring the Dual Role of Functional Pseudo-Prolines in the Design of SH3 Ligands

G. Tuchscherer,* D. Grell,
Y. Tatsu, P. Durieux,
J. Fernandez-Carneado,
B. Hengst, C. Kardinal, S. Feller*

The ultimate goal of producing esters in 100 % yield from an equimolar reaction of carboxylic acid and alcohol may not be far away: The research groups of Yamamoto and Tanabe have found that effective condensation can be achieved using $\text{HfCl}_4 \cdot 2\text{THF}$ and diphenylammonium triflate catalysts, respectively. Although the first catalyst gives near quantitative yields of the esters (91–>99 %), the reaction is moisture sensitive, while the latter catalyst gives lower yields (89–96 %) but requires no dehydration reagents or equipment.

Angew. Chem. **2001**, *113*, 2099–2100

J. Otera* 2044–2045

In Search of Practical Esterification

Keywords: alcohols • carboxylic acids • esterification • homogeneous catalysis • synthetic methods

Diverse complex systems may be studied by the new methods in solid-state NMR spectroscopy described herein. These methods use magic-angle spinning (MAS) on samples in oriented bilayers (right picture) and in orientationally disordered samples (left picture). Systems as diverse as uniformly ^{13}C , ^{15}N -labeled proteins, model membrane systems, and silk, as produced by the silkworm, can be structurally characterized.



Angew. Chem. **2001**, *113*, 2100–2105

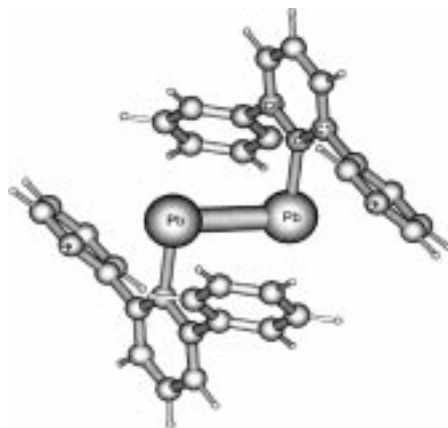
H. Schwalbe,* A. Bielecki .. 2045–2050

Recent Advances in High-Resolution Solid-State NMR Spectroscopy

Keywords: NMR spectroscopy • protein structures • structure elucidation

COMMUNICATIONS

Quantum-chemical calculations at the B3LYP level show that the bulky ligands $\text{Ar}^* = 2,6\text{-Ph}_2\text{C}_6\text{H}_3$ in $\text{Ar}^*\text{PbPbAr}^*$ yield the *trans*-bent equilibrium structure shown as the lowest lying energy minimum form. There is no Pb–Pb π bond in $\text{Ar}^*\text{PbPbAr}^*$. The parent compounds PhPbPbPh and HPbPbH have doubly bridged energy minima structures.



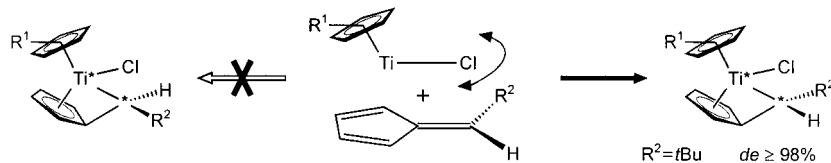
Angew. Chem. **2001**, *113*, 2108–2112

Y. Chen, M. Hartmann, M. Diedenhofen, G. Frenking* 2052–2055

Turning a Transition State into a Minimum—The Nature of the Bonding in Diplumbylene Compounds RPbPbR ($\text{R} = \text{H}, \text{Ar}$)

Keywords: bond theory • density functional calculations • diplumbylene • lead • multiple bonds

 **An alternative** to the known thermally induced syntheses of fulvene complexes of early transition metals is now provided by the direct reductive complexation of pentafulvenes to $[\text{CpTiCl}]$ fragments. These generally highly diastereoselective reactions (see scheme) enable a broad variation of substitution patterns and establish an extensive subsequent chemistry.



Angew. Chem. **2001**, *113*, 2112–2115

R. Beckhaus,* A. Lützen, D. Haase, W. Saak, J. Stroot, S. Becke, J. Heinrichs 2056–2058

A Novel Route to Fulvene Complexes of Titanium—Diastereoselective Complexation of Pentafulvenes to Cyclopentadienyltitanium Fragments

Keywords: fulvene complexes • insertion • pi interactions • titanium

Modeling with paper clips? No, a general method for the fabrication of complex three-dimensional (3D) microstructures is reported. The 3D structure is decomposed into substructures that can be patterned onto separate substrates and then these substructures are joined to form the desired microstructure. The picture shows an optical micrograph of a free-linked nickel chain mail.



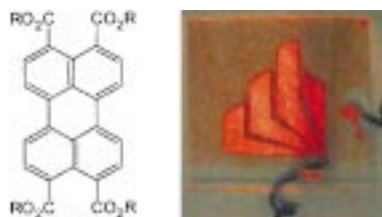
Angew. Chem. **2001**, *113*, 2115–2116

H. Wu, S. Whitesides,
G. M. Whitesides* 2059–2060

Fabrication of Micro-Chain Mail by Simultaneous, Patterned Electrodeposition on a Plane and Multiple Cylinders

Keywords: electrochemistry • lithography • microfabrication • patterning • topochemistry

Simple ester derivatives of polycyclic arenes offer access to light-emitting diodes of nearly any visible color by making use of the good charge-transport properties of the columnar liquid crystals of these derivatives. The picture shows the orange–red electroluminescence of a light-emitting diode containing the perylene 3,4,9,10-tetracarboxylic acid ethyl ester (structure shown, R = Et). Through use of multiple layers of different esters light-emitting diodes with almost white luminescence can be obtained.



Angew. Chem. **2001**, *113*, 2119–2122

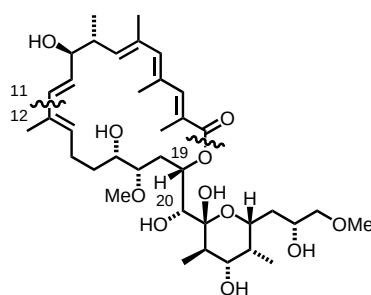
T. Hassheider, S. A. Benning,
H.-S. Kitzerow, M.-F. Achard,
H. Bock* 2060–2063

Color-Tuned Electroluminescence from Columnar Liquid Crystalline Alkyl Arenecarboxylates

Keywords: fluorescence • light-emitting diodes • liquid crystals • polycycles



A Cu^I-mediated coupling of the northern and southern units and a ring-size selective macrolactonization are the key steps in the convergent, first total synthesis of apoptolidinone, the aglycon of the potential antitumor compound apoptolidin. (The wavy lines in the picture are the retrosynthetic disconnections.)



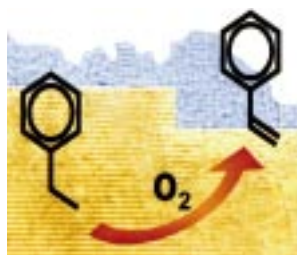
Angew. Chem. **2001**, *113*, 2125–2128

J. Schuppan, H. Wehlan, S. Keiper,
U. Koert* 2063–2066

Synthesis of Apoptolidinone

Keywords: apoptolidin • apoptosis • C–C coupling • natural products • total synthesis

Special carbon! Carbon nanofilaments differ from graphite and soot catalysts in their high stability during the oxidative dehydrogenation of ethylbenzene to styrene (see picture). The high yields of styrene achieved suggest that a first industrial application of carbon nanofilaments in catalysis is possible.



Angew. Chem. **2001**, *113*, 2122–2125

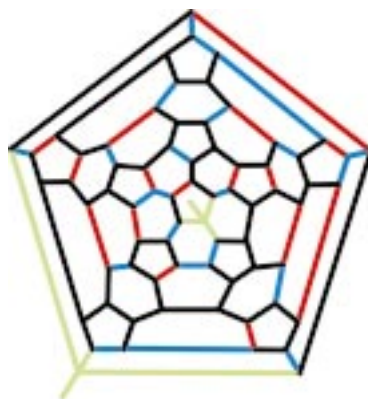
G. Mestl, N. I. Maksimova, N. Keller,
V. V. Roddatis, R. Schlögl* . 2066–2068

Carbon Nanofilaments in Heterogeneous Catalysis: An Industrial Application for New Carbon Materials?

Keywords: carbon • dehydrogenation • heterogeneous catalysis • nanofilaments

Under mild conditions, a linear polymeric (C_{70}^{2-})_n fulleride was synthesized as single crystals which allow, for the first time, a complete structural analysis of a polymeric fulleride. Starting from the strongest “disturbance” of the cage geometry at the linkage sites, the pronounced alternation of the bond lengths decreases towards the middle of the C_{70} units (see Schlegel diagram of the C_{70}^{2-} building block; color coding of the bond lengths [Å]: blue < 1.39, black 1.39–1.47, red 1.47–1.52 Å, green > 1.52).

Angew. Chem. **2001**, *113*, 2117–2119



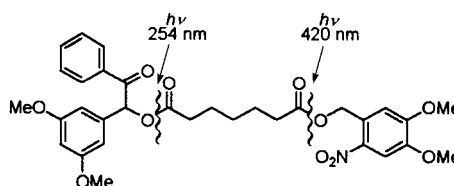
H. Brumm, E. Peters,
M. Jansen* 2069–2071

Linear Polymeric C_{70}^{2-} Ions

Keywords: anions • barium • fullerenes • polymers • solid-state chemistry

The selective activation of photolabile protecting groups was made possible by the use of monochromatic light of suitable wavelength. This new approach allowed the orthogonal deprotection of a substrate containing several photosensitive groups (see picture).

Angew. Chem. **2001**, *113*, 2140–2142



C. G. Bochet* 2071–2073

Orthogonal Photolysis of Protecting Groups

Keywords: chemoselectivity • chromophores • cleavage reactions • photochemistry • protecting groups



New light on the origin of the high enantioselectivities achieved in the Jacobsen–Katsuki epoxidation is shed by the results of density functional calculations. Axial ligation to the metal center not only enhances the epoxidation rate, but in addition leads to highly nonplanar, bent conformations of the active catalyst (see picture).

Angew. Chem. **2001**, *113*, 2131–2134



J. El-Bahraoui, O. Wiest,* D. Feichtinger,
D. A. Plattner* 2073–2076

Rate Enhancement and Enantioselectivity of the Jacobsen–Katsuki Epoxidation: The Significance of the Sixth Coordination Site

Keywords: density functional calculations • epoxidation • ligand effects • manganese • oxidation



Synthetic ion channels containing δ -amino acids can become cation selective! δ -Amino acids with a cyclohexylether unit (see structure) were combined with structural motives from gramicidin A and led to channels with a NH_4^+/K^+ permeability ratio of > 10/1. (The current trace for an NH_4^+ channel is shown.)



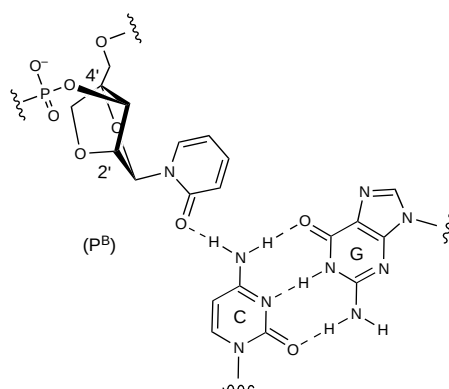
Angew. Chem. **2001**, *113*, 2137–2140

H.-D. Arndt, A. Knoll,
U. Koert* 2076–2078

Cyclohexylether δ -Amino Acids: New Leads for Selectivity Filters in Ion Channels

Keywords: amino acids • bioorganic chemistry • gramicidin A • ion channels • peptides

Significantly enhanced binding affinity to C·G base pairs without loss of sequence selectivity is achieved by using a nucleotide containing a 2-pyridone and a 2'-O,4'-C-methylene-bridged nucleic acid analogue (P^B , see picture). The degree of stabilization of the triplex formed enables C·G interruptions in a homopurine·homopyrimidine double-stranded DNA to be detected.



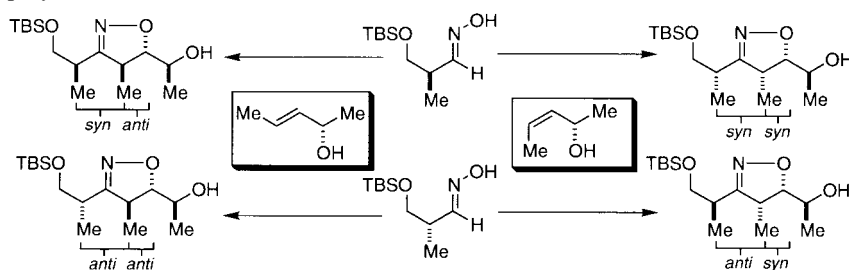
Angew. Chem. **2001**, *113*, 2149–2151

S. Obika, Y. Hari, M. Sekiguchi,
T. Imanishi* 2079–2081

A 2',4'-Bridged Nucleic Acid Containing 2-Pyridone as a Nucleobase: Efficient Recognition of a C·G Interruption by Triplex Formation with a Pyrimidine Motif

Keywords: DNA recognition • nucleic acids • nucleobases • oligonucleotides

A single, convenient reaction protocol and the same set of readily available starting materials suffice for the modular synthesis of all possible polypropionate diastereomers (see scheme). This general method for the diastereoselective synthesis of *syn*, *anti*, and methyl ketone aldol adducts utilizes a powerful Mg^{II} -mediated, hydroxy-directed nitrile oxide cycloaddition. The free hydroxy group provides an ideal synthetic handle enabling the rapid assembly of complex polyketide structures. TBS = *t*BuMe₂Si.



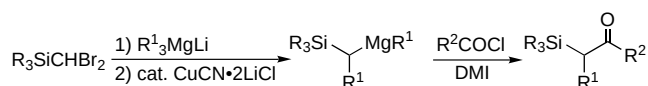
Angew. Chem. **2001**, *113*, 2128–2131

J. W. Bode, N. Fraefel, D. Muri,
E. M. Carreira* 2082–2085

A General Solution to the Modular Synthesis of Polyketide Building Blocks by Kanemasa Hydroxy-Directed Nitrile Oxide Cycloadditions

Keywords: aldol reaction • cycloaddition • erythronolides • polyketides

Magnesium–bromine exchange to provide the 1-bromo-1-silylmethylmagnesium species is mediated by treatment of dibromomethylsilane with an trialkylmagnesium reagent. The addition of a copper catalyst induces facile migration of an alkyl group to afford an α -silylalkylmagnesium compound, which furnishes α -silyl ketones in good yield upon treatment with acyl chloride (see scheme).



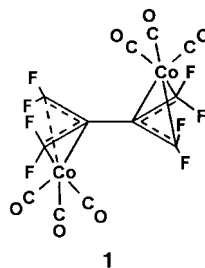
Angew. Chem. **2001**, *113*, 2146–2148

J. Kondo, A. Inoue, H. Shinokubo,
K. Oshima* 2085–2087

Alkylative Preparation of α -Silylalkylmagnesium from $R_3SiCHBr_2$ Using a Magnesate Reagent

Keywords: acylation • ate complexes • magnesium • metalation • silanes

Cobalt and manganese complexes provide access to novel fluoroallyl ligands: Fluorinated bis(enyl) ligands can be easily synthesized by metal-induced dimerization of 1,1-difluoroallene and tetrafluoroallene. By using octacarbonyldicobalt the coupling reaction occurs at the central carbon atom of the allene leading to the formation of fluorinated μ -(η^3 : η^3 -2,3-dimethylenebuta-1,4-diyl) ligands such as those in complex **1**. Additional products arise from fluoride abstraction and CO insertion reactions. Decacarbonyldimanganese reacts with 1,1-difluoroallene under C–C coupling of the methylene group to give decacarbonyl- μ -(η^1 : η^1 -1,1,6,6-tetrafluoro-1,5-hexadiene-2,5-diyl)dimanganese.



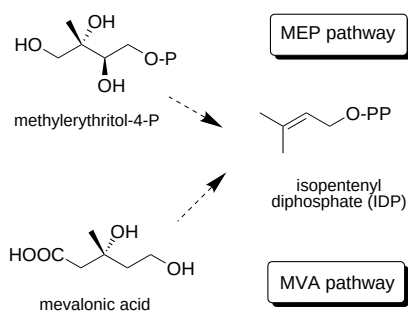
Angew. Chem. **2001**, *113*, 2142–2146

D. Lentz,* S. Willemsen 2087–2091

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

Keywords: allenes • allyl complexes • carbonyl complexes • C–C coupling • dimerization

Plants utilize two different pathways for the biosynthesis of isopentenyl diphosphate, the universal building block of all terpenes (see scheme). Application of compound-specific isotope-ratio mass spectrometry (GC-C-IRMS) to volatile terpenoids allows distinction between the pathways on the basis of natural $^{12}\text{C}/^{13}\text{C}$ ratios.



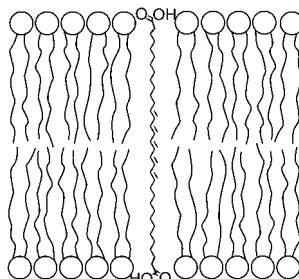
A. Jux, G. Gleixner,
W. Boland* 2091–2094

Classification of Terpenoids according to the Methylerythritolphosphate or the Mevalonate Pathway with Natural $^{12}\text{C}/^{13}\text{C}$ Isotope Ratios: Dynamic Allocation of Resources in Induced Plants

Keywords: biosynthesis • isotope effects • mass spectrometry • terpenes

Angew. Chem. **2001**, *113*, 2134–2137

Inspired by Archaeobacterial lipids, transmembrane probes anchor a sensing fluorescent polyene with Ångström resolution deep within a lipid layer (see figure). These new bolaamphiphiles are obtained in good yields from a double cross-coupling between esters with a terminal acetylene group and conjugated 1, ω -dihalopolyenes, followed by partial reduction of the triple bond.



E. Quesada, A. U. Acuña,*
F. Amat-Guerri* 2095–2097

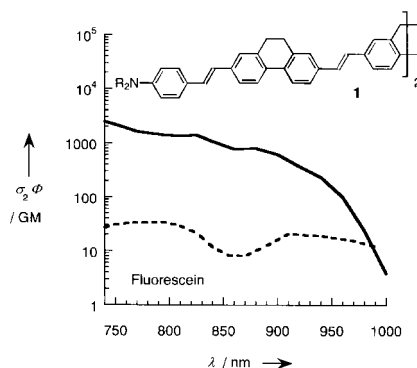
New Transmembrane Polyene Bolaamphiphiles as Fluorescent Probes in Lipid Bilayers

Keywords: amphiphiles • fluorescence • lipids • membranes • polyenes

Angew. Chem. **2001**, *113*, 2153–2155



Outperforming fluorescein by far, elongated fluorophores (e.g. **1**) give rise to large two-photon absorption cross-sections σ_2 in the visible-red or NIR region and high quantum fluorescence yields Φ (see figure; $\text{GM} = 10^{-50} \text{ cm}^4 \text{ s photon}^{-1}$). This opens interesting prospects in the field of two-photon microscopy imaging of cell membranes.



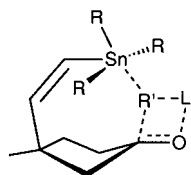
L. Ventelon, S. Charier, L. Moreaux,
J. Mertz,
M. Blanchard-Desce* 2098–2101

Nanoscale Push–Push Dihydrophenanthrene Derivatives as Novel Fluorophores for Two-Photon-Excited Fluorescence

Keywords: chromophores • fluorescence • membranes • two-photon absorption • Wittig reactions

Angew. Chem. **2001**, *113*, 2156–2159

syn to tin is the preferred mode of addition of organolithium reagents to the carbonyl group of cyclic ketones with a β -stannylvinyl group. This remarkable remote control is a consequence of the anchoring of the organolithium reagent by the tin and carbonyl groups (see picture).



A. Barbero, F. J. Pulido,* J. A. Rincón,
P. Cuadrado, D. Galisteo,
H. Martínez-García 2101–2103

Remote Stereocontrol in Carbonyl Additions Promoted by Vinylstannanes

Keywords: alkenes • cuprates • diastereoselectivity • ketones • tin

Angew. Chem. **2001**, *113*, 2159–2161

Nitroaromatic explosives can be detected in a simple and rapid method by the quenching of the photoluminescence of fluorescent polysiloles. Quenching is achieved by electron transfer from the conduction band of the polysiloles to electron-poor molecules such as picric acid, nitrobenzene, 2,4-dinitrotoluene (DNT), and 2,4,6-trinitrotoluene (TNT). Dilute polymer solutions can also be employed as a forensic spray-on reagent to visualize TNT or picric acid residues under a UV lamp (see picture of the print of a nitrile-gloved hand that had been in contact with TNT).



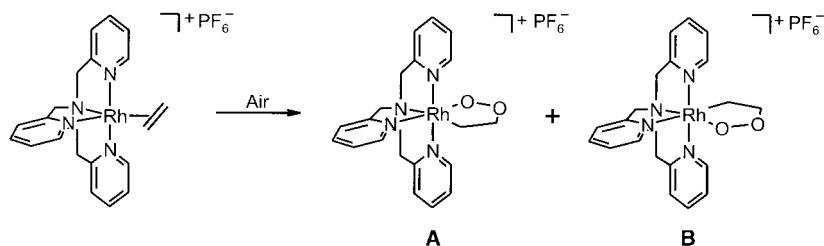
H. Sohn, R. M. Calhoun, M. J. Sailor,*
W. C. Trogler* 2104–2105

Detection of TNT and Picric Acid on Surfaces and in Seawater by Using Photoluminescent Polysiloles

Keywords: luminescence • nitroarenes • polymers • sensors • silicon

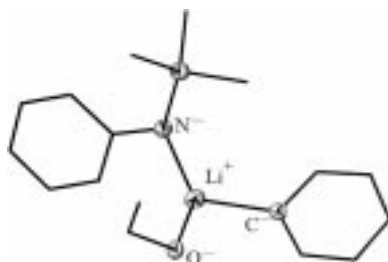
Angew. Chem. **2001**, *113*, 2162–2163

Proposed as intermediates in the catalytic oxidation of olefins to ketones, 3-rhoda-1,2-dioxolanes (κ^2C^1, O^2 -2-peroxyethyl rhodium complexes) have now been prepared by oxygenation of *solid* $[(N_4\text{-ligand})Rh^I(\text{ethene})]PF_6$ (see scheme) with air. This process leads to stable isomeric 3-rhoda-1,2-dioxolanes **A** and **B**. Upon substitution of PF_6^- by BPh_4^- only isomer **B** is obtained. The X-ray structure of isomer **B** is presented.



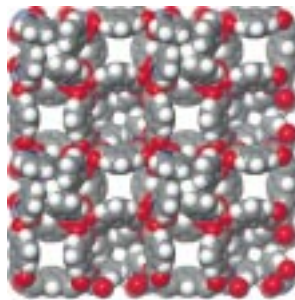
Angew. Chem. **2001**, *113*, 2164–2166

The three most important “super-base” anionic building blocks are contained in the striking decalithium aggregate in the structure of which a single lithium atom is surrounded solely by an amide, an alkoxide, and a carbanion (see picture).



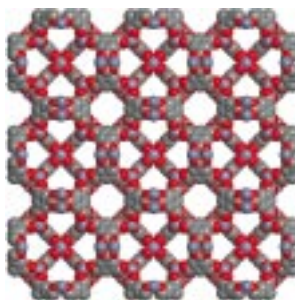
Angew. Chem. **2001**, *113*, 2166–2169

A series of bowls separated by hour-glass-shaped channels characterizes the structure of the undulating two-dimensional coordination polymer (see picture) that is prepared from a nanoscale secondary building unit (nSBU), which is formed by four square metal(II)carboxylate SBUs that have 1,3-benzenedicarboxylate units as 120° spacers.



Angew. Chem. **2001**, *113*, 2169–2171

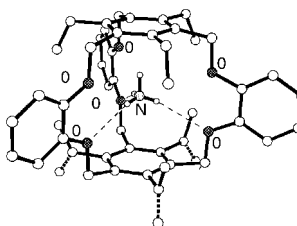
Small rhombihexahedra and small cubicuboctahedra (see picture), namely faceted polyhedra, form the basis of two novel low-density framework solids that are afforded by the self-assembly of molecular squares only or molecular squares and triangles, respectively.



Angew. Chem. **2001**, *113*, 2171–2174



A cage-type receptor binds an NH_4^+ ion by cation– π interactions and hydrogen bonding (see picture) with high sensitivity and selectivity, comparable or even superior to those of the natural antibiotic nonactin over a wide pH range. The high performance, low cost, and easy synthesis may offer practical applications for this receptor as an ammonium ion sensor.



Angew. Chem. **2001**, *113*, 2174–2177

M. Krom, R. G. E. Coumans,
J. M. M. Smits, A. W. Gal* 2106–2108

3-Rhoda-1,2-dioxolanes through
Dioxygenation of a Rhodium–Ethene
Complex by Air

Keywords: alkene complexes •
metallacycles • N ligands • oxygenation •
rhodium

P. C. Andrews, G. B. Deacon,*
C. M. Forsyth, N. M. Scott ... 2108–2111

A Striking, Multifaceted, Decalithium
Aggregate with Carbanion, Organoamide,
and Alkoxide Functionalities

Keywords: aggregation • alkoxides •
amides • carbanions • lithium

S. A. Bourne, J. Lu, A. Mondal,
B. Moulton,
M. J. Zaworotko* 2111–2113

Self-Assembly of Nanometer-Scale
Secondary Building Units into an
Undulating Two-Dimensional Network
with Two Types of Hydrophobic Cavity

Keywords: copper • crystal engineering •
self-assembly • supramolecular
chemistry • zinc

J. Lu, A. Mondal, B. Moulton,
M. J. Zaworotko* 2113–2116

Polygons and Faceted Polyhedra and
Nanoporous Networks

Keywords: crystal engineering •
networks • self-assembly •
supramolecular chemistry • zinc

S. Y. Jon, J. Kim, M. Kim, S.-H. Park,
W. S. Jeon, J. Heo, K. Kim* . 2116–2119

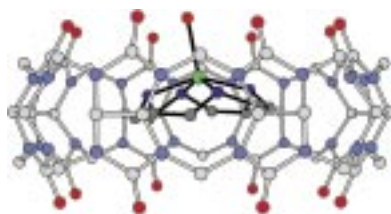
A Rationally Designed NH_4^+ Receptor
Based on Cation– π Interaction and
Hydrogen Bonding

Keywords: ammonium ion • hydrogen
bonds • molecular recognition •
 π interactions • supramolecular
chemistry



Reminiscent of Russian Matryoshka

dolls, tetraazamacrocycles (1,4,7,10-tetraazacyclododecane (cyclen) and 1,4,8,11-tetraazacyclotetradecane (cyclam)) and their transition metal complexes are encapsulated in the cavity of cucurbit[8]uril (CB[8]). The X-ray crystal structure of the [Cu(cyclen)] in CB[8] complex (see picture; copper: green, oxygen: red, nitrogen: blue, carbon: gray) reveals a five-coordinate Cu^{II} center in a square-pyramidal environment with a water molecule bound to the axial position.



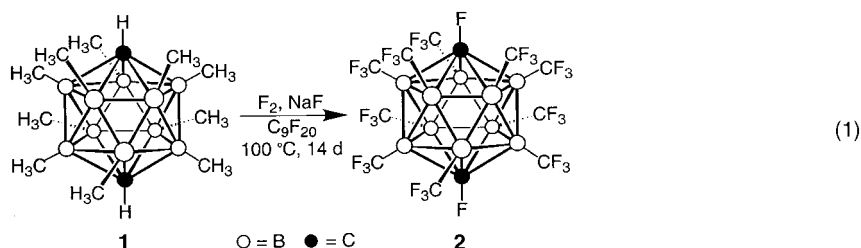
Angew. Chem. **2001**, *113*, 2177–2179

S.-Y. Kim, I.-S. Jung, E. Lee, J. Kim,
S. Sakamoto, K. Yamaguchi,
K. Kim* 2119–2121

Macrocycles within Macrocycles: Cyclen, Cyclam, and Their Transition Metal Complexes Encapsulated in Cucurbit[8]uril

Keywords: host–guest systems • macrocycles • solid-state structures • supramolecular chemistry • transition metals

Exhaustive fluorination of deca-*B*-methyl-*para*-carborane (**1**) furnishes perfluoro-deca-*B*-methyl-*para*-carborane (**2**) almost quantitatively [Eq. (1)]. Compound **2** represents the first neutral perfluorinated sphere mimicking a “Teflon ball”. The properties of **2** as well as its X-ray structure are discussed.



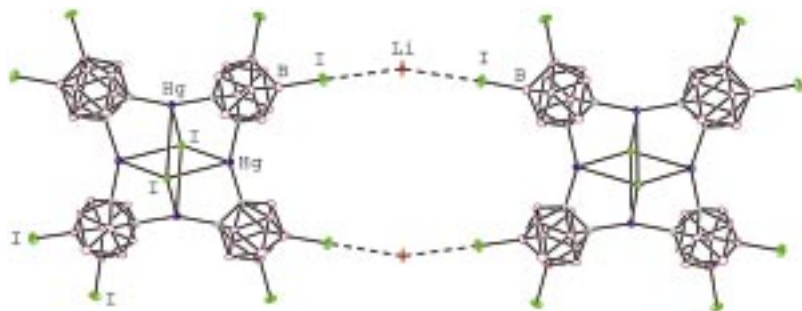
Angew. Chem. **2001**, *113*, 2179–2181

A. Herzog, R. P. Callahan,
C. L. B. Macdonald, V. M. Lynch,
M. F. Hawthorne,*
R. J. Lagow* 2121–2123

A Perfluorinated Nanosphere: Synthesis and Structure of Perfluoro-deca-*B*-methyl-*para*-carborane

Keywords: carboranes • electron-deficient compounds • fluorine • Raman spectroscopy

Modular units of Li₂[*B*-octaiodo-12-mercuracarborand-4·I₂] (Li₂[(HgC₂B₁₀H₈I₂)₄·I₂]) self-assemble forming infinite one-dimensional chains and microporous channels in the solid state (see picture). Self-assembly is directed by a unique B–I···Li···I–B intermolecular interaction involving electron-rich B–I vertices and electron-deficient lithium cations.



Angew. Chem. **2001**, *113*, 2182–2184

H. Lee, C. B. Knobler,
M. F. Hawthorne* 2124–2126

Modular Self-Assembly of a Microporous Solid Based upon Mercuracarborand-4 and a New Bonding Motif

Keywords: carboranes • Lewis acids • macrocycles • microporosity • supramolecular chemistry

UV irradiation was found to accelerate the rate of gas incorporation into wide-bandgap ionic crystals and thus the rate of stoichiometry change. Up to now, this could only be achieved by changing the temperature, the dopant concentration, or adding catalytic coatings. The stoichiometry strongly affects the electrical conductivity of the crystal. The investigation of this effect provides valuable information on the mechanism of the surface reaction as well as offering new possible applications.

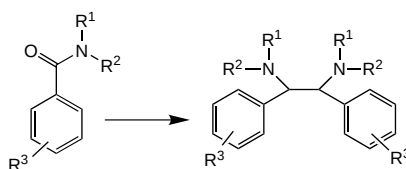
Angew. Chem. **2001**, *113*, 2184–2187

R. Merkle, R. A. De Souza,
J. Maier* 2126–2129

Optically Tuning the Rate of Stoichiometry Changes: Surface-Controlled Oxygen Incorporation into Oxides under UV Irradiation

Keywords: kinetics • oxygen incorporation • semiconductors • surface chemistry • UV irradiation

A sequence of reduction, deoxygenation, and coupling steps results in a remarkable reaction, which represents an important new method for the synthesis of 1,2-diamines. The vicinal diamines are formed by the facile coupling of aromatic amides in the presence of titanocene catalysts and PhMeSiH_2 (see scheme).



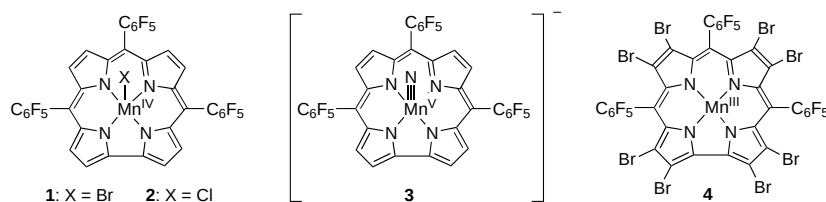
Angew. Chem. **2001**, *113*, 2187–2189

K. Selvakumar, J. F. Harrod* 2129–2131

Titanocene-Catalyzed Coupling of Amides in the Presence of Organosilanes To Form Vicinal Diamines

Keywords: amides • diamines • homogeneous catalysis • silanes • titanium

On pyrrole! The pyrrole-based corrole ligands can offer an alternative to porphyrin systems. The manganese corroles **1–4** are readily synthesized, undergo metal- not ligand-based redox chemistry, and **4** in particular shows impressive catalytic activity in the oxygenation of styrene with iodosylbenzene.



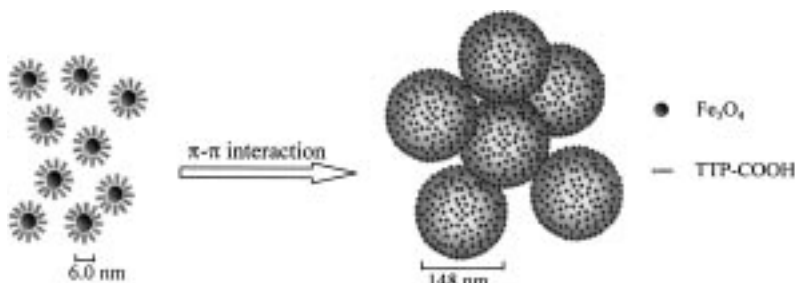
Angew. Chem. **2001**, *113*, 2190–2192

G. Golubkov, J. Bendix, H. B. Gray,*
A. Mahammed, I. Goldberg,*
A. J. DiBilio, Z. Gross* 2132–2134

High-Valent Manganese Corroles and the First Perhalogenated Metallocorrole Catalyst

Keywords: corroles • epoxidation • homogeneous catalysis • manganese • porphyrinoids

Nanoparticles of Fe_3O_4 coated with 2-carboxyterthiophene (TTP-COOH) self-assemble through π – π interactions to form uniform transparent microspheres (see schematic representation). The interaction between individual particles is relatively weak and the spherical aggregates can be destroyed by sonication to leave the monodispersed nanoparticles.



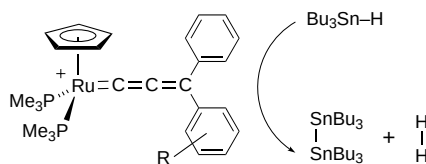
Angew. Chem. **2001**, *113*, 2193–2196

J. Jin, T. Iyoda, C. Cao, Y. Song,
L. Jiang,* T. J. Li,*
D. B. Zhu 2135–2138

Self-Assembly of Uniform Spherical Aggregates of Magnetic Nanoparticles through π – π Interactions

Keywords: aggregation • magnetic properties • nanoparticles • pi interactions • self-assembly

Conjuring with conjugation: catalysis by ruthenium–allenylidene complexes has been observed for the conversion of tin hydrides into distannanes and dihydrogen (see scheme). Alkyne or alkene groups (R) in conjugation with an aromatic ring are required for catalytic activity, providing an unusual example of control of metal-centered reactivity by a remote substituent.



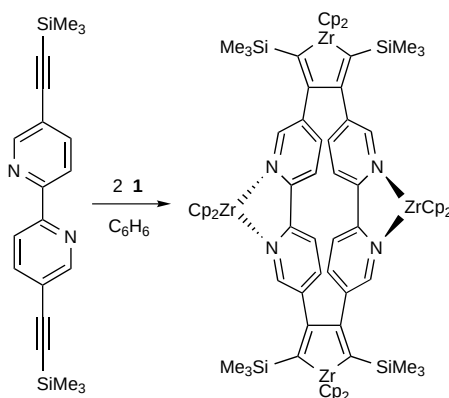
Angew. Chem. **2001**, *113*, 2196–2199

S. M. Maddock, M. G. Finn* 2138–2141

Dehydrogenative Dimerization of Tin Hydrides Catalyzed by Ruthenium–Allenylidene Complexes

Keywords: allenylidene complexes • dehydrogenation • homogeneous catalysis • ruthenium • tin

A zirconocene double act: The course of zirconocene-mediated macrocyclization is controlled by templating effects. In macrocyclizations of bipyridine-containing diynes, the zirconocene reagent $[\text{Cp}_2\text{Zr}(\text{py})(\text{Me}_3\text{SiC}\equiv\text{SiMe}_3)]$ (**1**; py = pyridine) acts as both coupling and templating agent. Thus, by controlling the stoichiometry, dimeric (see scheme) or trimeric macrocycles are obtained.



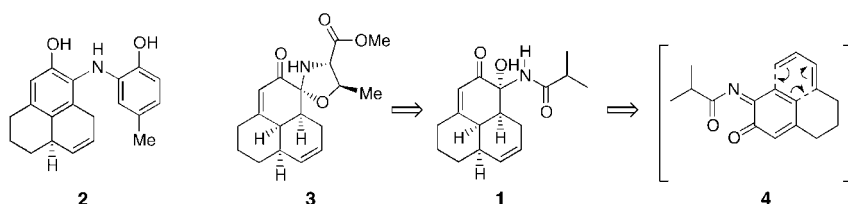
Angew. Chem. **2001**, *113*, 2200–2203

J. R. Nitschke, T. D. Tilley* . 2142–2145

Novel Templating Effect in the Macrocyclization of Functionalized Diynes by Zirconocene Coupling

Keywords: cyclodimerization • cyclotrimerization • macrocycles • template synthesis • zirconium

A multitude of natural product like molecules such as **2** and **3** can be readily obtained from hydroxyketoamide **1**. The versatile **1** is derived, via the intermediate *o*-azaquinone **4**, from the Dess–Martin periodinane oxidation of the corresponding anilide.



Angew. Chem. **2001**, *113*, 2203–2207

K. C. Nicolaou,* Y.-L. Zhong, P. S. Baran, K. Sugita 2145–2149

Rapid Access to Complex Molecular Architectures via *o*-Azaquinones

Keywords: azaquinones • cycloaddition • domino reactions • oxidation • synthetic methods

Getting spliced? Pre-mRNA splicing is catalyzed by the spliceosome, a complex assembly of proteins and RNA, which forms in an ordered fashion on the substrate. If one of the residues of the substrate is caged with a photolabile *o*-nitrobenzyl group, the splicing reaction can be transiently blocked, until subsequent initiation by photolysis of the complexes (see scheme). This RNA-caging approach effectively separates the spliceosome assembly from the catalytic reaction and allows the two processes to be studied independently.



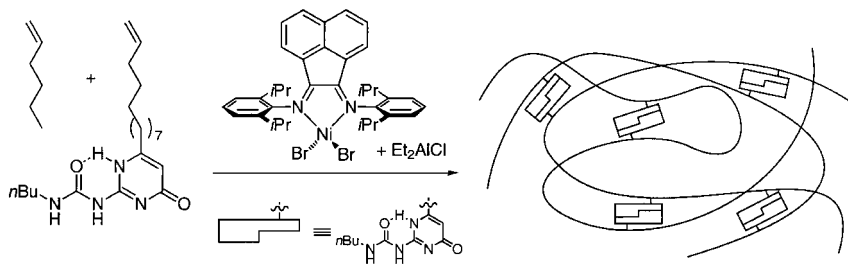
S. G. Chaulk, A. M. MacMillan* 2149–2152

Separation of Spliceosome Assembly from Catalysis with Caged pre-mRNA Substrates

Keywords: mRNA • photolysis • protein–RNA interactions • splicing

Angew. Chem. **2001**, *113*, 2207–2210

Mimicking nature: The central mechanisms of living organisms depend on the formation of specific hydrogen bonds. Advances in the areas of catalysis and supramolecular chemistry have been applied here for the synthesis of a novel class of elastomeric polyolefins (see scheme) with properties dependent upon strong intermolecular hydrogen bonding.



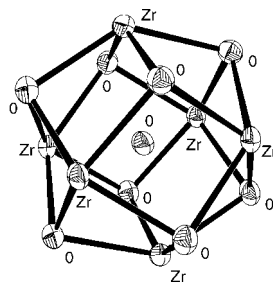
Angew. Chem. **2001**, *113*, 2211–2214

L. R. Rieth, R. F. Eaton, G. W. Coates* 2153–2156

Polymerization of Ureidopyrimidinone-Functionalized Olefins by Using Late-Transition Metal Ziegler–Natta Catalysts: Synthesis of Thermoplastic Elastomeric Polyolefins

Keywords: homogeneous catalysis • hydrogen bonds • polymerization • self-assembly • supramolecular chemistry

KH and the two-phase system liquid ammonia/toluene provide the basis for a new method for the synthesis of organozirconium oxides such as $[(\text{EtMe}_4\text{C}_5\text{Zr})_6(\mu_6\text{-O})(\mu_3\text{-O})_8] \cdot \text{C}_7\text{H}_8$ (the central inorganic core of the cluster is shown). Altering the solvent to mesitylene has no influence on the core structure of the resulting organozirconium oxide.



G. Bai, H. W. Roesky,* P. Lobinger, M. Noltemeyer, H.-G. Schmidt 2156–2159

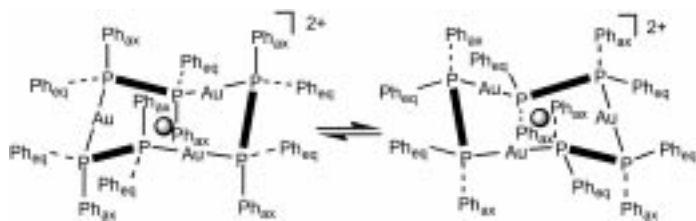
Base-Assisted Formation of Organozirconium Oxides with the $[\text{Zr}_6(\mu_6\text{-O})(\mu_3\text{-O})_8]$ Core Structure

Keywords: ammonia • cluster compounds • hydrolysis • oxides • zirconium

Angew. Chem. **2001**, *113*, 2214–2217



A chair of gold: Analogous to cyclohexane, the trinuclear gold ring $[\text{Au}_3(\text{PANP})_3] \cdot [\text{ClO}_4]_3$ (PANP = 9,10-bis(diphenylphosphino)anthracene) shows a chair conformation and diastereotopic axial and equatorial phenyl rings. Variable temperature and 2D EXSY NMR studies reveal that the gold ring undergoes cyclohexane-like ring inversion (enantiomerization) in solution. In addition, the gold ring exhibits intense excimeric emission at room temperature. = anthracene ring system in PANP, = ClO_4^- .



Angew. Chem. **2001**, *113*, 2217–2220

J. H. K. Yip,* J. Prabhavathy 2159–2162

A Luminescent Gold Ring That Flips Like Cyclohexane

Keywords: conformations • fluxionality • gold • luminescence • NMR spectroscopy



A supramolecular recognition interface is formed through the self-assembly of cyclic D,L-peptides. Phenyl–phenyl interactions direct the solid-state organization of dimeric peptide *cyclo*[(L-Phe-D-MeN-Ala-L-hPhe-D-MeN-Ala)₂] (**1**) by forming clusters of edge-to-face contacts between dimers (shown left), which suggests that these peptide scaffolds may be useful subunits for crystal engineering.



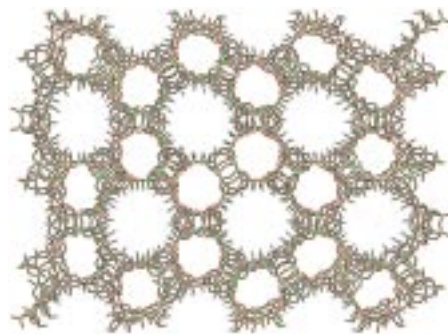
Angew. Chem. **2001**, *113*, 2221–2224

D. T. Bong, M. R. Ghadiri* 2163–2166

Self-Assembling Cyclic Peptide Cylinders as Nuclei for Crystal Engineering

Keywords: crystal engineering • nanostructures • peptides • pi interactions • self-assembly

Pores for thought: A new extra large germanate zeolite-type structure has been synthesized by using high-charge multiamine as a template in a pseudo-aqueous system (DMF/H₂O). The novel zeolite-type germanate with low framework density (11.1) has a 24- and 12-membered ring honeycomb array (see picture) with three-dimensional intersecting channels.



Angew. Chem. **2001**, *113*, 2224–2226

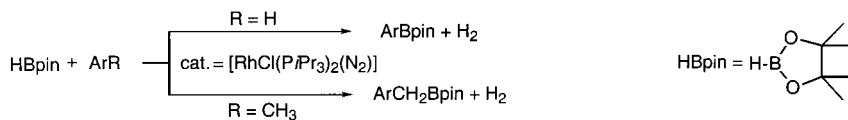
Y. Zhou, H. Zhu, Z. Chen, M. Chen, Y. Xu, H. Zhang, D. Zhao* 2166–2168

A Large 24-Membered-Ring Germanate Zeolite-Type Open-Framework Structure with Three-Dimensional Intersecting Channels

Keywords: germanium • microporosity • template synthesis • zeolite analogues

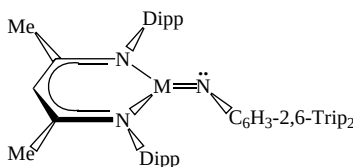


Direct borylation of C–H bonds in aromatic compounds can be achieved by using the efficient homogeneous catalyst precursor $[\text{RhCl}(\text{P}i\text{Pr}_3)_2(\text{N}_2)]$ and pinacolborane (HBpin; see scheme). High selectivity for the benzyl positions, observed for toluene, *p*-xylene, and mesitylene, was attributed to the formation of η^3 -benzyl intermediates.



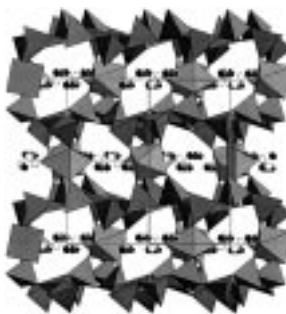
Angew. Chem. **2001**, *113*, 2226–2229

A short Ga–N bond with double-bond character is displayed by the first monomeric imide of gallium, which was obtained by the reaction of $[\{\text{HC}(\text{MeCDippN})_2\}\text{M}]$ (Dipp = 2,6-*i*Pr₂C₆H₃, M = Ga; see picture) with N₃-2,6-Trip₂C₆H₃ (Trip = 2,4,6-*i*Pr₃C₆H₂). The analogous aluminum (M = Al) compound is also readily available.



Angew. Chem. **2001**, *113*, 2230–2232

Silicate layers cross-linked by interlayer VO₅ square pyramids form the basis of the three-dimensional frameworks of the structures of the title compounds (the structure of K₂(VO)(Si₄O₁₀)·H₂O is depicted). Alkali metal cations (●) and water molecules (○) occupy nonframework sites in these structures, which were synthesized hydrothermally.



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Formation of Aryl- and Benzylboronate Esters by Rhodium-Catalyzed C–H Bond Functionalization with Pinacolborane

Keywords: boron • C–H activation • homogeneous catalysis • phosphanes • rhodium

N. J. Hardman, C. Cui, H. W. Roesky,
W. H. Fink, P. P. Power* 2172–2174

Stable, Monomeric Imides of Aluminum and Gallium: Synthesis and Characterization of $[\{\text{HC}(\text{MeCDippN})_2\}\text{MN}-2,6\text{-Trip}_2\text{C}_6\text{H}_3]$ (M = Al or Ga; Dipp = 2,6-*i*Pr₂C₆H₃; Trip = 2,4,6-*i*Pr₃C₆H₂)

Keywords: aluminum • β -ketimines • gallium • imides • multiple bonds • terphenyls

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The Novel Open-Framework Vanadium Silicates K₂(VO)(Si₄O₁₀)·H₂O (VSH-1) and Cs₂(VO)(Si₆O₁₄)·3H₂O (VSH-2)

Keywords: hydrothermal synthesis • silicates • solid-state structures • vanadium

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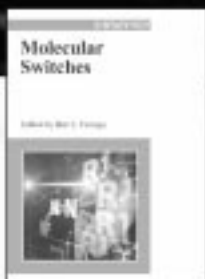
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Switch to new horizons



B. L. FERINGA, (Ed.) University of Groningen, The Netherlands

Molecular Switches

2001. XVI, 464 pages. Hardcover.
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Every day we use switches to turn electric appliances on and off and no computer could function without them. Molecular switches work in the same way, changing from state one to another depending on environmental influences. However, as opposed to normal switches, molecular switches are extremely tiny and their application in nanotechnology, biomedicine and computer chip design opens up whole new horizons.

In this manual, the editors and authors describe molecular switches made of catenanes and rotaxanes, dihydroazulenes, fulgides, liquid crystals and polypeptides. The spectrum of topics discussed ranges from chiroptical switches via multifunctional systems to molecular logical switches.

A wealth of information for chemists and materials scientists in industry and academia interested in one of the most innovative branches of their discipline.

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- Introduction on molecular switches
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- Biomolecular switches.

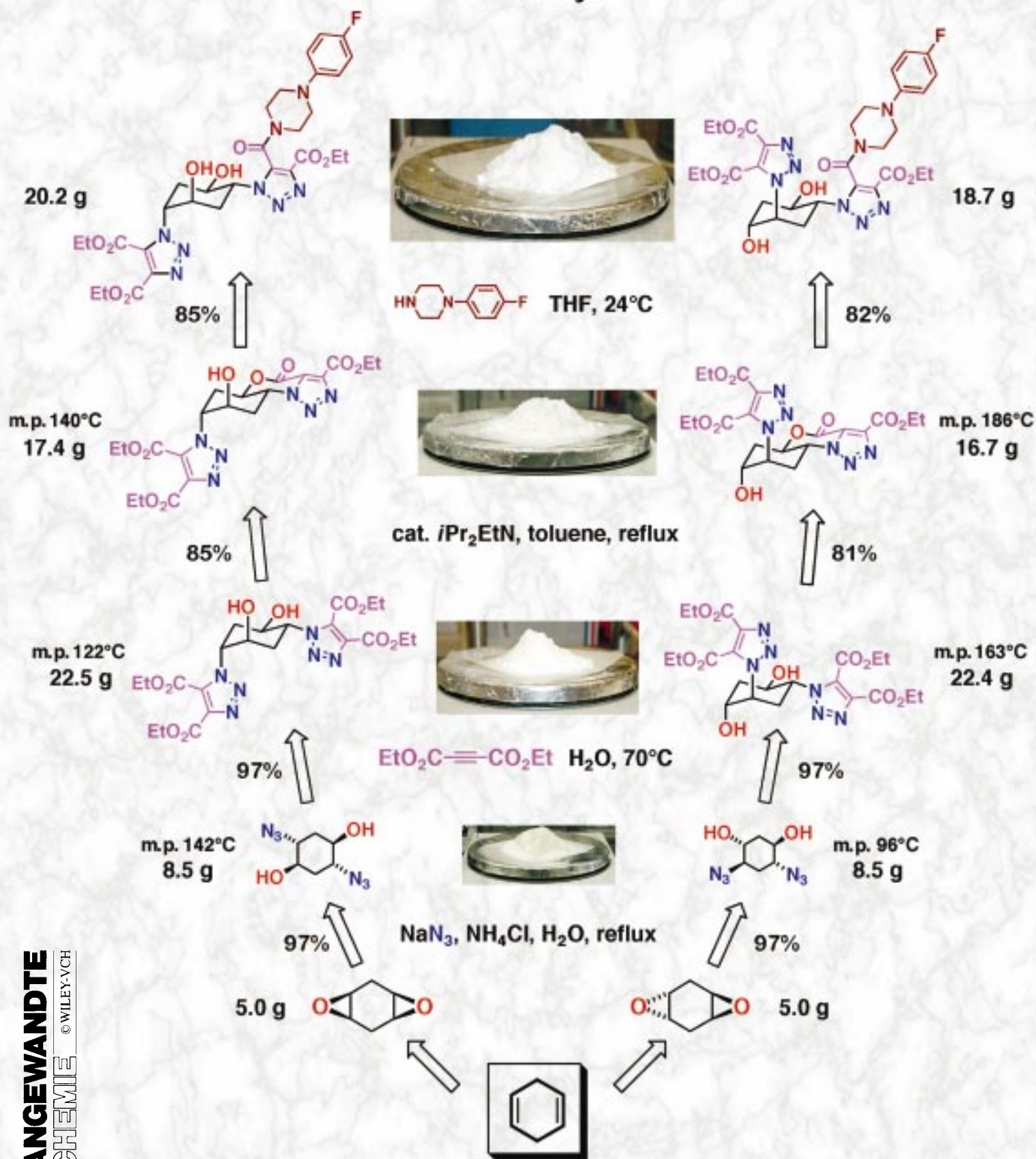
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"CLICK" CHEMISTRY

Olefins, spring-loaded electrophiles, and heteroatom connections are key elements in a fast, modular, process-driven approach to molecular discovery.



Click Chemistry: Diverse Chemical Function from a Few Good Reactions

Hartmuth C. Kolb, M. G. Finn, and K. Barry Sharpless*

Dedicated to Professor Daniel S. Kemp

Examination of nature's favorite molecules reveals a striking preference for making carbon–heteroatom bonds over carbon–carbon bonds—surely no surprise given that carbon dioxide is nature's starting material and that most reactions are performed in water. Nucleic acids, proteins, and polysaccharides are condensation polymers of small subunits stitched together by carbon–heteroatom bonds. Even the 35 or so building blocks from which

these crucial molecules are made each contain, at most, six contiguous C–C bonds, except for the three aromatic amino acids. Taking our cue from nature's approach, we address here the development of a set of powerful, highly reliable, and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through heteroatom links (C–X–C), an approach we call “click chemistry”. Click chemistry is at once

defined, enabled, and constrained by a handful of nearly perfect “spring-loaded” reactions. The stringent criteria for a process to earn click chemistry status are described along with examples of the molecular frameworks that are easily made using this spartan, but powerful, synthetic strategy.

Keywords: combinatorial chemistry • drug research • synthesis design • water chemistry

1. Introduction: Beyond the Paradigm of Carbonyl Chemistry

Life on Earth requires the construction of carbon–carbon bonds in an aqueous environment. Carbonyl (aldol) chemistry is nature's primary engine of C–C bond formation. Not only do the requisite carbon electrophiles (carbonyls) and nucleophiles coexist in water, but water provides the perfect environment for proton shuttling among reactants, which is required for reversible carbonyl chemistry.

With CO₂ as the carbon source and a few good carbonyl chemistry based reaction themes, nature achieves astonishing structural and functional diversity. Carbonyl chemistry is used to make a modest collection of approximately 35 simple building blocks, which are then assembled into biopolymers. The enzymatic polymers serve, in concert with increments of energy provided by adenosine triphosphate, as selective

catalysts which prevent nature's carbonyl chemistry based syntheses from collapsing into chaos. Since many biosynthetic pathways require a unique enzyme for each step, the enzyme-control strategy required a heavy investment of time and resources for catalyst development. With a few billion years and a planet at her disposal, nature has had both time and resources to spare, but we, as chemists on a human timescale, do not.

Nevertheless, carbonyl-based reactions have always been profoundly appealing to students and practitioners of organic chemistry. It is our contention that organic synthesis conducted, as it has been, in imitation of nature's carbonyl chemistry is ill-suited for the rapid discovery of new molecules with desired properties.

Many transformations that form “new” carbon–carbon bonds are endowed with only a modest thermodynamic driving force. In particular, equilibrium “aldol” reactions are often energetically favorable by less than 3 kcal mol^{−1}.^[1] For these processes to reach completion in the laboratory, an additional “push” must be provided, often by application of Le Chatelier's principle (for example, azeotropic removal of water), by coupling the desired process to an exothermic co-reaction (for example, a strong “base” + a strong “acid”), or by virtue of favorable entropic considerations (such as intramolecular ring closure) without enthalpic penalties (such as formation of strained rings). Thus, due in effect to the loss of one “equivalent” of ester, resonance stabilization, the first

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step of the intermolecular Claisen condensation (for example, two molecules of ethyl acetate $\rightarrow$ ethyl acetoacetate + ethanol), is endothermic by approximately 11 kcal mol⁻¹, but the next step—deprotonation of the β -ketoester to its enolate—is highly exothermic and drives the process to completion when a stoichiometric amount of the alkoxide base is provided. Approximately 30 years ago the development of *kinetically controlled* enolate chemistry, enabled by even stronger bases like lithium diisopropylamide, provided the ultimate form of this type of reaction control. Natural products of bewildering complexity are synthesized almost routinely in this manner by the elite practitioners of the art, so it is obviously a powerful strategy, and the best work in this area is fascinating to study as a rich source of new insights into factors which affect chemical reactivity. However, as discussed below, we believe that this approach ultimately pulls organic synthesis in troubling directions, the most insidious problem being the complexity engendered by the need for global protection and deprotection of protic functional groups.

“The most fundamental and lasting objective of synthesis is not production of new compounds, but production of properties.”

George S. Hammond, Norris Award Lecture, 1968

If useful properties are our goal—for example, better pharmaceuticals—then the use of complicated synthetic strategies is justified only if they provide the best way to achieve those properties. The bioactive natural products that have most intrigued synthetic organic chemists have frameworks which are difficult to construct largely because there are too many contiguous carbon–carbon bonds. However, these are not the only kinds of molecules that can have useful biological effects. The long and admirable history of natural products synthesis, culminating as it has in the protection-laden schemes of kinetic carbonyl chemistry, perhaps blinds us to the possibility of developing synthetic strategies that enable much more rapid discovery and production of molecules with a desired profile of properties.

K. Barry Sharpless and his co-workers have discovered and developed many widely used catalytic oxidation processes, including the first general methods for stereoselective oxidation—the Sharpless reactions for asymmetric epoxidation, dihydroxylation, and aminohydroxylation of olefins. His mentors at Dartmouth College (BA in 1963), Stanford University (PhD in 1968 and postdoctoral research), and Harvard University (further post-



K. B. Sharpless



M. G. Finn



H. C. Kolb

doctoral research) were Prof. T. A. Spencer, Prof. E. E. van Tamelen, Prof. J. P. Collman, and Prof. K. Bloch, respectively. Before 1990, when he became W. M. Keck Professor of Chemistry at The Scripps Research Institute, Prof. Sharpless was a member of faculty at the Massachusetts Institute of Technology (1970–77, 1980–90) and Stanford University (1977–80). Prof. Sharpless's honors include the Chemical Sciences Award of the National Academy of Sciences (of which he is a member), the Roger Adams and Arthur C. Cope Awards from the American Chemical Society, the Tetrahedron Award, the King Faisal Prize, the Prelog Medal, the Wolf Prize, and honorary doctorates from five American and European universities. The Sharpless research group continues to search for new homogeneous oxidation catalysts and for transition metal catalyzed asymmetric processes.

M. G. Finn received his PhD degree from the Massachusetts Institute of Technology, working with Prof. K. B. Sharpless. This was followed by an NIH postdoctoral fellowship with Prof. J. P. Collman at Stanford University. He joined the faculty of the University of Virginia in 1988, and moved to his present position on the faculty of the Department of Chemistry and The Skaggs Institute for Chemical Biology at The Scripps Research Institute in 1998. His group has studied the reactivity of Fischer carbene complexes, metal-substituted phosphorus ylides, and a variety of transition metal catalyzed processes. His current interests include methods for combinatorial catalyst discovery and the use of viruses as molecular building blocks.

Hartmuth Kolb received his PhD in synthetic organic chemistry under the supervision of Prof. S. V. Ley at Imperial College in London. After two years of postdoctoral study with Prof. K. B. Sharpless at The Scripps Research Institute, he joined the Central Research Laboratories of Ciba–Geigy in Basel. Four years later, he moved to Princeton, New Jersey, to join the Coelacanth Corporation, a high-performance chemistry company founded by K. B. Sharpless and A. Bader. Currently, he is Vice President of Chemistry at the Coelacanth Corporation. His research interests include natural product and carbohydrate synthesis, investigation of reaction mechanisms, molecular modeling, medicinal chemistry, process chemistry, and combinatorial chemistry.

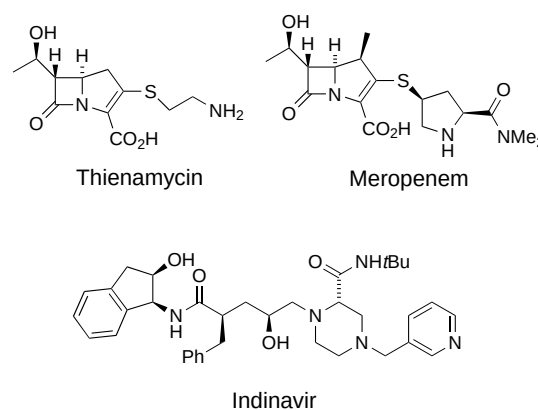
2. A “Process Chemistry” Point of View

The molecules produced by living systems have always fascinated and inspired synthetic organic chemists. As our skills and tools have advanced, the compounds chosen for synthesis have become ever more challenging. So it is no surprise that today's favorite targets are found among the most diabolically complex natural substances ever discovered—the various *secondary metabolites* produced by plants and microorganisms for self-defense. No expense or effort is spared to synthesize even minute quantities of these extraordinary molecules.^[2, 3]

The pharmaceutical industry, a direct scion of natural products chemistry,^[4] has not been put off by difficult syntheses and many compounds being explored today as drug candidates represent substantial synthetic challenges.^[5] While it sharpens the skill and fraternal esteem of the research team, implicit in the decision to pursue a complex drug target is the acceptance of enormous constraints on the scope of the structure space to be explored. When natural products are the models, it usually takes so long to synthesize analogues in a given series that even the most ambitious exploratory efforts, viewed objectively, are often superficial. The process of probing structure–activity relationships (SAR) in these situations has a perverse tendency to discover the “best” candidates in difficult synthetic territory, near the outer limits of “accessibility.” Difficult syntheses also tend to arise when trying to reach patentable structural territory after original discoveries have been made by a competitor.

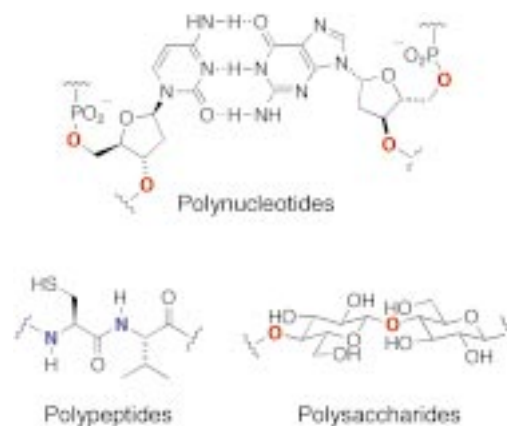
The time required for SAR probing and then synthesis of enough of the better compounds for pharmacokinetic and toxicity profiling is staggering, and goes a long way toward explaining why this phase of pharmaceutical research takes so long. And yet, buoyed by the eventual success in obtaining complex target structures, discovery chemists and top executives alike display little concern for issues of synthetic accessibility. Ignored is the fact that any lead or development series that has supply problems risks inadequate SAR conclusions and development decisions. The story of the carbapenem antibiotic thienamycin^[6–8] is illustrative: it required *six years* of superb effort by several research groups in both industry and academia to develop the final therapeutic agent (meropenem,^[9] a derivative of thienamycin) after the initial synthesis of thienamycin was published.^[10a] The AIDS protease inhibitor Crixivan (indinavir) provides a more recent example—a very difficult synthesis at nearly commodity-chemical scale.^[10b]

Only at the end are issues of process development considered, and synthesis on production scale is often expensive. Nevertheless, the prospect of a blockbuster drug is such a powerful motivator for a synthesis team that the job nearly always gets done. The crucial point is that the cost which complex synthesis adds to the final drug, while substantial, is insignificant compared to all the “hidden” costs imposed on the speed and quality of the discovery/development phase by this same complex style of synthesis. In other words, *the way organic synthesis is done has pervasive effects on the entire process of drug discovery, development, and*



manufacture. If a more modular, faster style of synthesis were to prove effective, lower manufacturing costs should be the least of its benefits. Lead structures should not be synthetically “precious”, and one should be able to jump easily from one series to another. As it is now, most discovery endeavors suffer from being too invested in *structure*, when *function* is what is sought.

Consider how nature synthesizes her most important molecules, the *primary metabolites*. While the aforementioned secondary metabolites have extensive networks of contiguous carbon–carbon bonds, and have claimed the lion's share of synthetic organic chemists' attention, it is reversible condensation processes involving carbon–heteroatom connections that are used to assemble polynucleotides, polypeptides, and polysaccharides—the three families of macromolecules that are central to life processes. By embracing the strategy of making large oligomers from small building blocks,



nature is also a consummate combinatorial chemist^[11] and achieves astonishing diversity from less than 40 monomers. These building blocks contain at most six contiguous C–C bonds, with the exception of the three aromatic amino acids. Thus, nature is a promiscuous creator of carbon–heteroatom connections, choosing this method to encode and express information.

Nature's ability to create and control biomolecular diversity is largely dependent on the exquisitely selective catalysts she deploys. Our devices for managing reactivity and selectivity are much less sophisticated, particularly with respect to C–C

bond formation. Therefore, the chemist who plans a synthesis that requires the construction of C–C bonds that are not present or latent (for example, $\text{CH}-\text{CX}+\text{base} \rightarrow \text{C}=\text{C}$) in the available starting materials is asking for trouble, particularly if such a synthesis must be reliable for a number of substrates (as for combinatorial searches or SAR studies) or applicable to practical, large-scale production. Problems are less likely if one only needs to unite, functionalize, and/or reorganize starting materials and intermediates in ways which do not require de novo C–C bond construction. If such “new” C–C bonds are required, it is best to make them *intramolecularly*,^[12] but it is better still to leave the really tough C–C bond synthesis to nature.^[13]

There is, however, still plenty of room for discovery: Guida and co-workers have estimated the pool of “reasonable” drug candidates (≤ 30 non-hydrogen atoms; ≤ 500 daltons; consisting of only H, C, N, O, P, S, F, Cl, and Br; likely to be stable at ambient temperature in the presence of water and oxygen) at between 10^{62} and 10^{63} discrete molecules.^[14] With this kind of structure space available,^[15] we contend that it makes little sense to search in hard-to-reach places for a desired function. Instead, we present here synthetic methods for drug discovery that adhere to one rule: *all searches must be restricted to molecules that are easy to make*. We hope to convince the reader that a wide diversity of interesting molecules *can* be easily made, and that the chances for achieving desirable biological activity are at least as good with such compounds as with the traditional target structures now favored by medicinal chemists.

2.1. “Click Chemistry”

Following nature’s lead, we endeavor to generate substances by joining small units together with heteroatom links (C–X–C). The goal is to develop an expanding set of powerful, selective, and modular “blocks” that work reliably in both small- and large-scale applications. We have termed the foundation of this approach “click chemistry,” and have defined a set of stringent criteria that a process must meet to be useful in this context. The reaction must be *modular*, *wide in scope*, give *very high yields*, generate only *inoffensive byproducts* that can be removed by nonchromatographic methods, and be *stereospecific* (but not necessarily enantioselective). The required process characteristics include *simple reaction conditions* (ideally, the process should be insensitive to oxygen and water), *readily available starting materials and reagents*, the use of *no solvent or a solvent that is benign* (such as water) *or easily removed*, and *simple product isolation*. Purification—if required—must be by nonchromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions.

It is important to recognize that click reactions achieve their required characteristics by having a high thermodynamic driving force, usually greater than 20 kcal mol^{-1} . Such processes proceed rapidly to completion and also tend to be highly selective for a single product: we think of these reactions as being “spring-loaded” for a single trajectory. Carbon–heteroatom bond forming reactions comprise the

most common examples, including the following classes of chemical transformations:

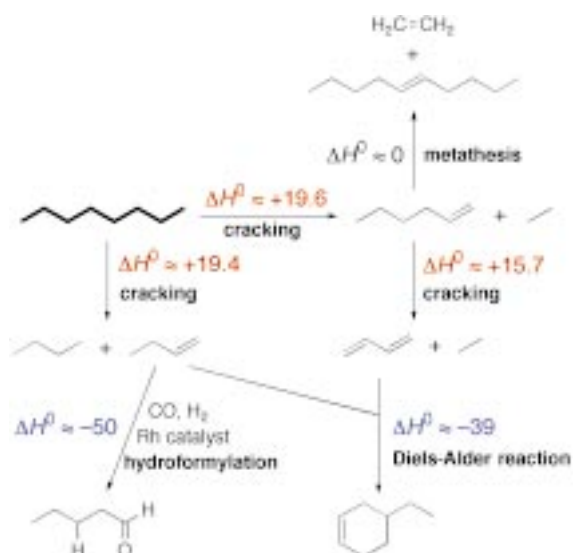
- cycloadditions of unsaturated species, especially 1,3-dipolar cycloaddition reactions, but also the Diels–Alder family of transformations;
- nucleophilic substitution chemistry, particularly ring-opening reactions of strained heterocyclic electrophiles such as epoxides, aziridines, aziridinium ions, and episulfonium ions;
- carbonyl chemistry of the “non-aldol” type, such as formation of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones, and amides; and
- additions to carbon–carbon multiple bonds, especially oxidative cases such as epoxidation, dihydroxylation, aziridination, and sulfonyl halide addition, but also Michael additions of Nu–H reactants.

2.2. Olefin-Based Organic Synthesis

Consider, as a counterpoint to the pharmaceutical industry, the world of petrochemicals and the materials it has spawned (textiles, resins, plastics, etc.). The petrochemist’s starting materials are “gifts” prepared by the carbonyl-based syntheses of ancient organisms; in fossil oils are stored the energy of CO_2 -based photosynthesis, and, more importantly, countless carbon–carbon bonds. However, natural petroleum, being almost completely saturated, is useless for most organic synthesis needs. The petroleum industry is therefore based upon the manipulation of C–C bond “currency”, which entails exchanging C–C σ bonds for new C–C π bonds by “cracking”, and creating new C–C π bonds at the expense of C–H bonds by “reforming”. The products of these processes are a small number of reactive monomers, which are then assembled, with a battery of selective catalysts, into myriad useful materials. Thus, the manufacture of petrochemical products, based as it is on a modular, and supremely efficient, synthetic strategy, makes the energy expended on “upgrading” saturated hydrocarbons to olefins seem insignificant.

In a general sense, life chemistry and petrochemistry have evolved identical strategies for the synthesis of substances with diverse functions/properties: modular assembly of specially synthesized monomers under the control of selective catalysts. That one depends on *reversible* carbonyl chemistry and the other on *irreversible* olefin chemistry should not obscure the striking similarity at the heart of the two approaches. We are denied the ability to realistically imitate nature’s modular carbonyl-based synthesis style (see above), so the modular olefin-based style given to us by the petroleum chemist is the model we choose to follow.^[16]

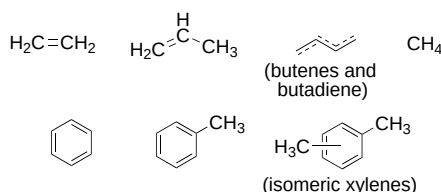
The concept of the C–C bond as a unit of “currency” is central to an appreciation of the value of click chemistry in organic synthesis. Scheme 1 depicts examples of how the currency can be exchanged. The bookkeeping device to keep track of the “total C–C bond count” is often, but not necessarily, connected to demonstrable interconversions. Starting with *n*-octane, the total C–C bond count remains constant at seven regardless of the number of transformations of a saturated C–C bond into a C=C π bond, for example, $\text{C}^1-\text{C}^2-\text{C}^3-\text{H} \rightarrow \text{C}^1-\text{H} + \text{C}^2=\text{C}^3$. Such a transformation is of



Scheme 1. The C–C bond as a unit of “currency” (ΔH° in kcal mol^{−1}; the value given for hydroformylation compares olefin and aldehyde only). No new C–C bonds are formed in these processes.

course endothermic, but becomes favorable at high temperatures, thanks to a substantial positive entropy term. The petrochemical industry practices “steam cracking” (a gas-phase process at approximately 850 °C) on enormous scales, to make available a family of inexpensive olefins. The newly created C=C π bonds are highly reactive, having about 22–25 kcal mol^{−1} greater free energy content^[17] than a C–C σ bond; in effect, the energy expended in “cracking” is partly captured/stored in the C=C linkage. This becomes apparent in processes such as the Diels–Alder reaction and hydroformylation, which gain σ links by reorganizing π C=C links, again without altering the total C–C bond count. Olefin metathesis provides an extraordinarily facile way to redistribute C=C links for further manipulation. (Acetylene links (counting as 3 C–C bonds), with two unstable π bonds, are even better than olefins for driving a host of useful $\pi \rightarrow \sigma$ carbon–carbon bond reorganizations.) Many such processes are highly reliable precisely because no “new” C–C bonds are created; all are nascent in the reactant’s π bonds.

Olefins are the most attractive starting materials available to the synthetic chemist, readily accessible in large quantities and in many varieties, especially if one includes the naturally abundant terpenes. The simplest are the handful of C₁–C₈ blocks shown in Scheme 2. Produced by the petrochemical

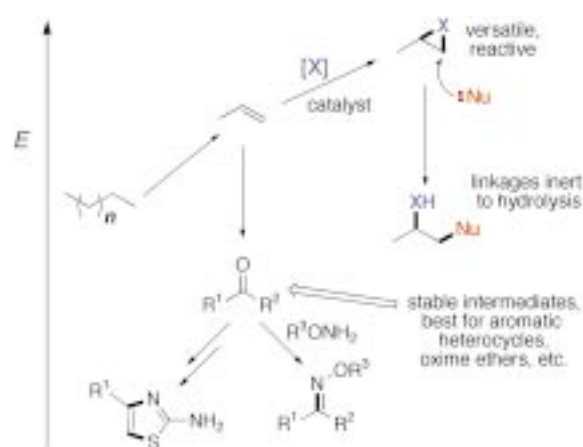


Scheme 2. Small carbon building blocks from petroleum.

industry on a massive scale, they are the ultimate starting materials for 90 % by weight of all useful man-made organic compounds.^[18] The Wilke cyclooligomerizations of butadiene

to cyclooctadiene and cyclododecatriene are perfect examples of processes that further expand the core olefin structures available to us at modest cost.^[19] The π bonds of butadiene are reorganized effortlessly by the catalyst, to regio- and stereo-selectively create sophisticated new carbon skeletons while leaving behind one olefinic linkage per butadiene monomer for the “decoration” steps to follow. Thus, between natural olefin sources (terpenes, fatty acids,^[20] etc.) and “reworked” natural hydrocarbons (olefins derived from petroleum) we have been richly endowed by living systems with a diverse olefinic starting material platform. It would be fitting if we could devise short sequences for assembling these “gift” olefins into new substances with beneficial biological functions.

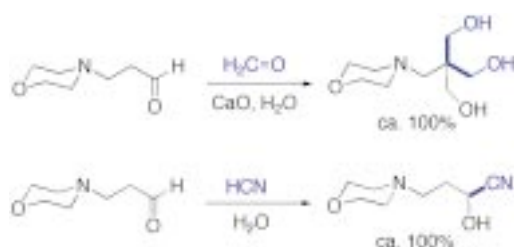
The importance of olefins is dramatically enhanced by their role as progenitors of still higher energy intermediates, such as epoxides, aziridines, episulfonium ions, and aziridinium ions—all nearly perfect for click chemistry transformations (Scheme 3). This sequence of oxidative creation/nucleophilic



Scheme 3. Examples of the genesis and relative energetics of click chemistry components. New bonds made with click reactions are in bold. Nu = nucleophile.

quenching of reactive electrophiles is what most enables the crucial block ligation steps at the heart of click chemistry. Thus, the chemistry of olefins provides for the creation of diverse scaffolds and the attachment and display of myriad functionality through oxidative addition of heteroatoms to specifically placed olefinic sites.^[21] The robust nature of these reactions is predicated on the irreversible progression from systems of high energy to systems of lower energy in a *stepwise* fashion. Each step has a high driving force, the *sine qua non* condition of click chemistry, which enables reliable *intermolecular* connections to be established.

Carbonyl compounds, by contrast, are quite stable thermodynamically relative to olefins and even relative to their hydrocarbon progenitors. Hence, their repertoire of click chemistry transformations is limited. Among the few general and highly reliable reactions starting from aldehydes and ketones are their *imine-forming condensations* to give oximes and hydrazones, and particularly to generate aromatic heterocycles (see below). Also noteworthy, are the few *intermolecular* carbonyl-based new C–C bond forming reactions which approach perfection (Scheme 4): 1) hydroxymethylation and



Scheme 4. Strongly driven *intermolecular* C–C bond forming reactions.

aminomethylation reactions using formaldehyde, the least stable carbonyl representative, and 2) HCN additions to carbonyl compounds, driven by the great stability of the resulting cyanohydrin unit (primarily due to the nitrile group's attachment through an sp-hybridized bond, made even stronger by a substantial dipolar contribution). Another excellent carbonyl-based process for intermolecular C–C bond formation is the Michael reaction, an exception which proves the rule, since no new C–C bond is created. Its $>20 \text{ kcal mol}^{-1}$ driving force is provided by the C=C bond which is consumed in the H–Nu addition step.

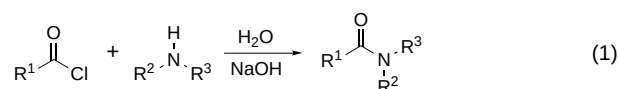
Since click chemistry is intended to provide a foundation for the rapid assembly of new and *pure* molecular entities, stereochemistry is important. The ideal click reactions are based on *stereospecific* processes, but absolute stereochemistry need not be so stringently controlled. In any case, when only one stereogenic element is involved, generation of the racemate for initial biological screening will be preferred. Even when two stereogenic elements are united or created in a ligation step, it should be advantageous to test the racemic mixtures of two or three diastereomers in the first pass at a biological target.^[22] With the accelerating development of improved analytical and separation techniques for deconvolution of complicated mixtures,^[23] even greater relaxation of stereochemical restrictions on assembly reactions will be feasible in the near future.

Nature achieves highly specific syntheses of complex substances by the uniquely selective action of enzyme catalysts. However, the success of a desired click chemistry sequence requires that virtually all of the control elements and the enabling “energy packets” be present in the reactive components. At first, this plan may sound fanciful—how could any but the most trivial set of reactive components be “self-contained” regarding the instructions and potential energy needed to direct a reaction cascade to a unique synthetic endpoint? Happily, we are finding that this goal is not so difficult, provided one plans carefully and, above all, uses only the handful of “perfect” reactions for the crucial intermolecular block ligation steps.

2.3. Click Chemistry in Water

Over the past two years, we have found that many of the reactions that meet click chemistry standards often proceed better in water than in an organic solvent. This is a natural outcome of one or more of the following five factors.

- 1) Click reactions often proceed readily in hot water, to give a single product, *even when one or more of the reactants, as well as the product, appear to be insoluble in this medium*. The fact that reactions between organic species in aqueous solution can have higher apparent rate constants than the same processes in organic media has been observed and exploited by a number of laboratories.^[24] Among the many explanations offered for such phenomena, we call particular attention to the notion that the free energies of organic molecules are substantially greater when poorly solvated in water, and often impart increased reactivity, which compensates for the low concentration of the participants.^[25]
- 2) Nucleophile additions to epoxide^[26] (“homocarbonyl”) and aziridine (“homoimine”) electrophiles (as well as aziridinium and episulfonium ions) are favored by solvents best able to respond continuously to the demanding range of hydrogen-bonding situations that arise during these processes. In this respect, water is unique, and for the same reasons, it is the perfect milieu for reversible carbonyl chemistry.
- 3) Two important subsets of olefin and acetylene click reactions are oxidations by electrophilic reagents and cycloaddition reactions. These processes are either concerted or involve polarizable nucleophiles/electrophiles, so that water is not an interfering medium.^[27] More generally, it should be appreciated that the use of water offers the greatest leverage for differentiating the reactivities of competing “hard” (nonpolarizable) and “soft” (polarizable) species.
- 4) A highly favorable reaction of two solutes (say at 0.1M concentration) is usually much faster than a low driving force side-reaction of one of the solutes with solvent water (55M).^[28] The Schotten–Baumann method for making amides from acyl or sulfonyl halides in water is a well-known example [Eq. (1)].^[29]



- 5) Water is a superb heat sink, due to its high heat capacity, and has a convenient boiling temperature; both are useful for large-scale processes.

Water is usually regarded as an ideal solvent in terms of its environmental impact and low cost. A benefit which is little appreciated but has enormous consequences is that most hydroxy O–H and amide N–H groups will not interfere with click reactions performed in water. As a consequence, the installation and removal of protecting groups is avoided—probably the best single reason for adopting this style of synthesis. Indeed, we view many of the best reactions for installing “protecting groups” as good click reactions in their own right (see Section 3.3).

These considerations highlight the fact that, although click reaction components are necessarily highly reactive, their chemoselectivity profiles are quite narrowly defined, that is, “orthogonal” to an unusually broad range of reagents,

solvents, and other functional groups. This attribute allows for reliable and clean sequential transformations of broad scope.^[30] For example, opening epoxide or aziridine rings by “HN₃” installs a highly reactive “sticky spot” for [3+2] cycloaddition with alkynes, but one that is “invisible” to most other functional groups.

The types of reactions, and especially reaction conditions, that fall into the click chemistry category were more common in the organic literature of 50 to 100 years ago.^[31] Few solvents were used then, and heat was the preferred way to speed up reactions. The dearth of available purification techniques meant that processes were chosen for their reliability in giving a single isolable product. Without seeking to collect an exhaustive list of click or click-like reactions,^[31] an attempt is made here to illustrate the scope of this approach with a number of representative examples taken both from the literature and from our own work. We focus on nucleophilic openings of the reactive small-ring species readily made by oxidative addition of heteroatoms to olefins, and on concerted cycloadditions and carbonyl/imine condensation reactions to aromatic heterocycles.

2.4. Comments on “Solid-Phase” Synthesis

We are proposing here the use of click reactions in combinatorial style to generate molecules of highly diverse structure and function. Much of the enormous effort in library synthesis currently pursued in academic and industrial laboratories makes use of polymeric supports for the stepwise construction of products.^[32] In our view, solid-phase organic synthesis is popular precisely because it allows reactions that fall short of “click” status to be employed as click reactions—that is, in situations where extremely high yields and simple purification procedures are required. These attributes are achieved by using a large excess of the reactants in the mobile phase. While this approach has been very effective for the synthesis of large libraries, the final products tend to be too lipophilic to probe the full range of biological interactions. The hydrophobic character of these collections may, in part, be due to the absence of “bystander” protic functional groups, which tend to be omitted, intentionally or otherwise, to avoid extra protection/deprotection steps.

Most importantly, the solid-phase approach is ill-suited to “process-driven” discovery: it is very expensive and highly wasteful of reagents and solvents; it is difficult to make large amounts of products, and when such large-scale syntheses are attempted, the yield per unit volume is poor; intermediates bound to polymeric supports are difficult to analyze directly by standard spectroscopic methods; and another layer of chemical technology—the installation and cleavage of a “linker”—is required. In other words, since solid-phase

combinatorial approaches to the discovery of biologically active compounds ignore most of the issues that constrain practical organic syntheses, the most likely outcome is a trend toward drugs that are even harder to manufacture.

2.5. Creation of Modules by Oxidative Addition of Heteroatoms to Olefins

The potential of olefins for generating diversity is unlocked by their oxidative functionalization. Much of our effort for the past three decades has centered on this goal, and a useful set of reliable transformations has emerged from a number of laboratories including our own. The broad scope and high yields of many olefin oxidation processes, and the fact that olefins are the primary organic starting materials, render these reactions the most fundamental enablers of click chemistry. The oxidation step generates highly reactive, yet stable intermediates such as epoxides and aziridines. Both the oxidations to the intermediates *and* their subsequent fusion with nucleophiles are stereospecific, and thus very predictable; Table 1^[33–39] shows the processes we use most often. Most of the oxidation steps depend on transition metal catalysis for which efficient enantioselective versions are well established.

A nearly ideal case is our recent discovery of a class of olefins that exhibits unique reactivity in osmium-catalyzed aminohydroxylation and dihydroxylation reactions performed in water or water/organic mixtures. Unlike most olefins, these special substrate classes undergo rapid and nearly quantitative aminohydroxylation, with very low catalyst loading, in the *absence* of cinchona alkaloid ligands, and with only one equivalent of the haloamine salt. Moreover, the reactions can be conducted at molar concentrations in substrate, whereas the standard asymmetric aminohydroxylation process is best performed at ≤ 0.1 molar concentration. Among the substrates that exhibit this type of enhanced reactivity are α,β -unsaturated acids and amides; Scheme 5 gives five examples.^[40]

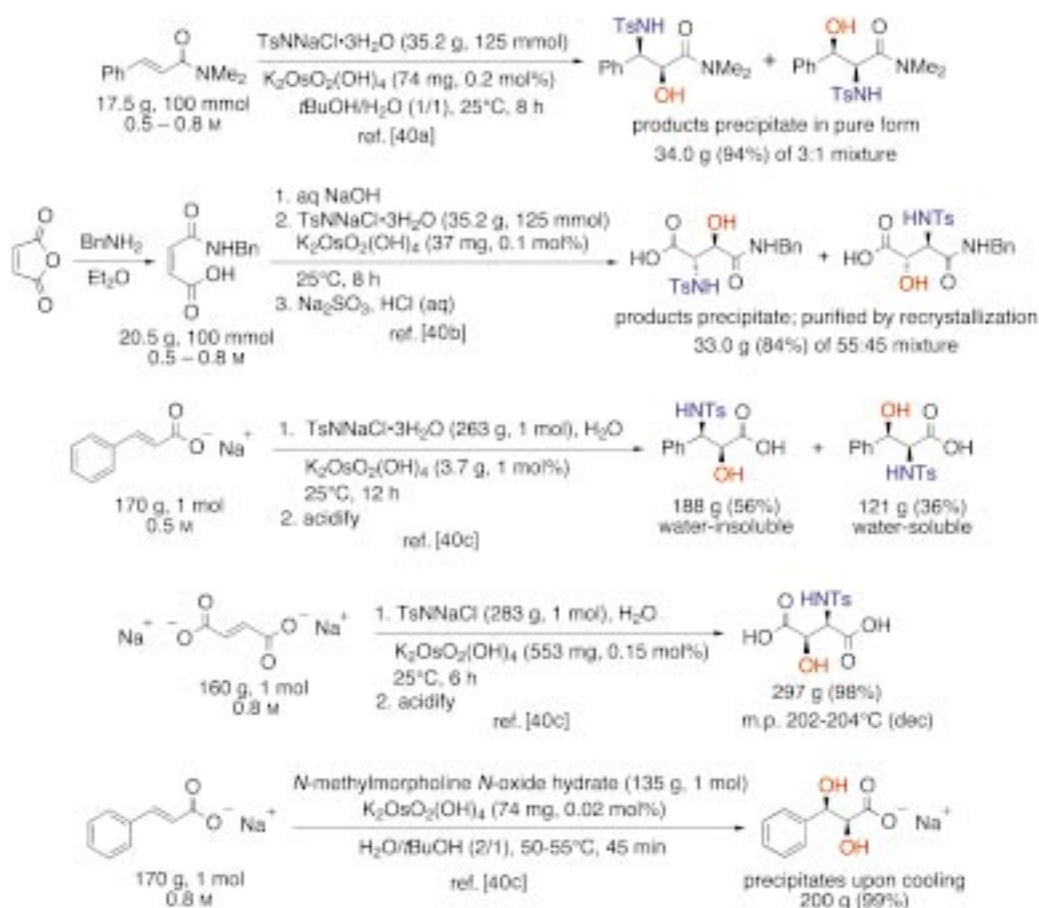
3. Click Chemistry Reaction Types

Below appears a description of the three most useful click reactions presently in use in our laboratory. The best are *pure*

Table 1. Processes used to create oxidized electrophiles or their precursors from olefins.^[33–39]

					
racemic		TsNNaCl, ^[a] PhNMe ₃ ⁺ Br ₃ [−]	cat. MeReO ₃ , H ₂ O ₂ , pyridine	cat. OsO ₄ , cooxidant	RN(Cl)Na, cat. OsO ₄
asymmetric			<i>allylic alcohols</i> : Ti(O ^{<i>i</i>} Pr) ₄ , Me ₃ COOH, dialkyl tartrate; <i>unfunctionalized olefins</i> : [(salen)Mn ^{III}], ^[b] oxidant	cat. OsO ₄ , cooxidant, cinchona alkaloid	RN(Cl)Na, cat. OsO ₄ , cinchona alkaloid

[a] Ts = tosyl = toluene-4-sulfonyl. [b] H₂salen = *N,N'*-bis(salicylidene)ethylenediamine.



Scheme 5. Examples of unusually efficient osmium-catalyzed aminohydroxylation and dihydroxylation of olefins. Bn = benzyl.

fusion processes, which means that the combined formulae of the reactants equals the formula of the product.^[41] They can be divided into two classes: those in which protons must be shuffled about (epoxide ring opening, for example) and those in which no σ -bond connections are severed (cycloaddition reactions, the most useful and reliable being the Huisgen dipolar cycloadditions). The former tend to benefit dramatically from an aqueous environment, while the latter reveal little solvent dependence and are better overall in their adherence to click chemistry ideals. Indeed, the azide + acetylene $\rightarrow$ triazole version of Huisgen's [2 + 3] cycloaddition family of processes is about as good as a reaction can get. Nevertheless, it is the “less ideal” epoxide and aziridine opening processes which are the workhorses for installing, often in the penultimate step of a block synthesis, the azide or alkyne moieties.

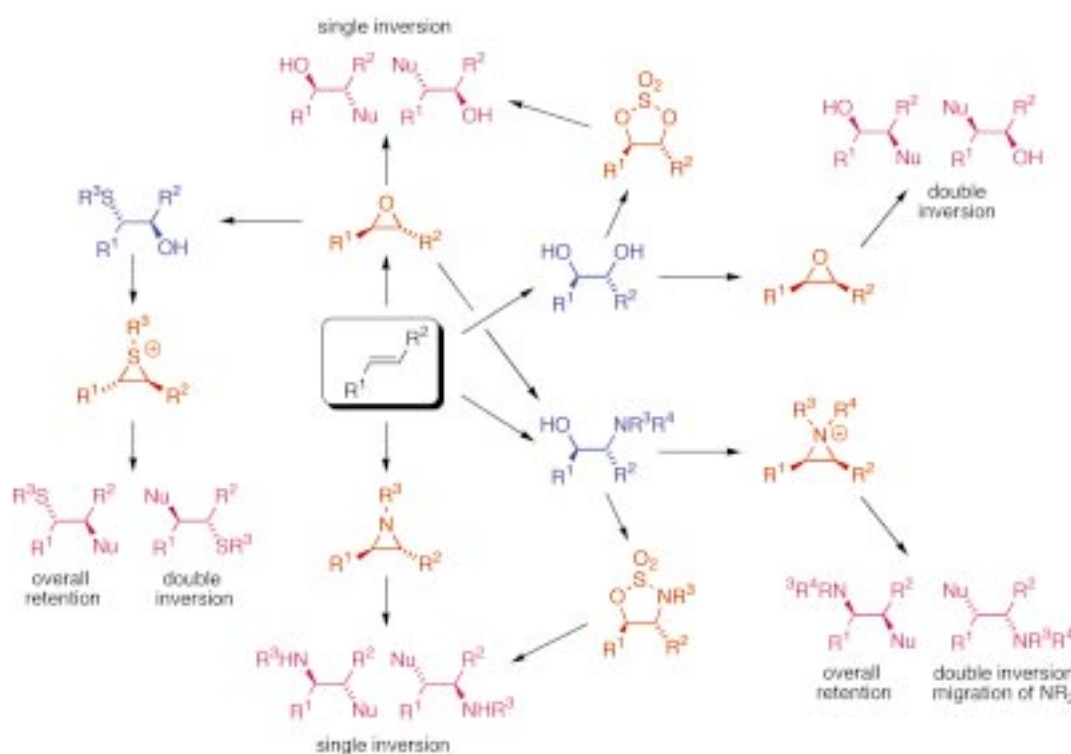
3.1. Nucleophilic Opening of Spring-Loaded Rings

The four types of primary olefin oxidation products shown in Table 1 are themselves high-energy species or may be readily converted into such intermediates. The S_N2 ring-opening reactions of these molecules—epoxides, aziridines, cyclic sulfates, cyclic sulfamidates, aziridinium ions, and episulfonium ions—are reliable, stereospecific, often highly regioselective, and nearly quantitative—all in all, surpassingly

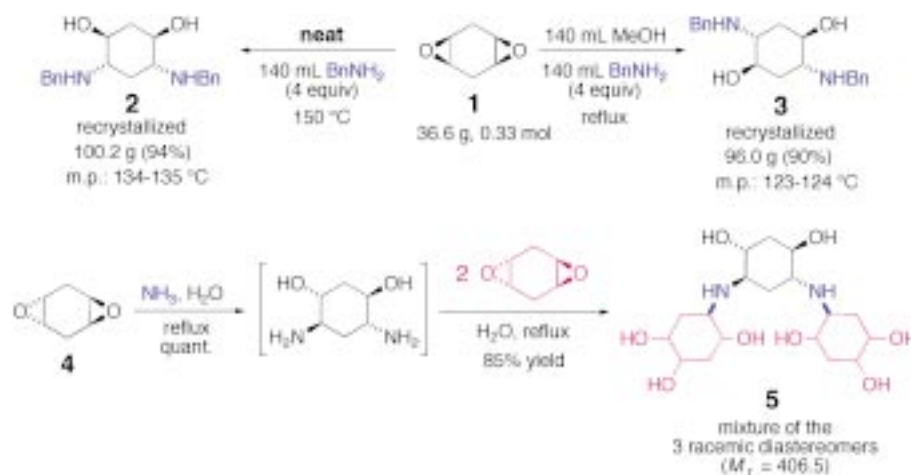
useful (Scheme 6). We focus here on the chemistry of three-membered ring heterocyclic electrophiles.

The paramount advantage of nucleophilic openings of three-membered rings is that competing elimination processes are stereoelectronically disfavored,^[42] which results in high yields and easy product isolation. All of the ring opening reactions shown in Scheme 6 are fusion events, and most can be performed in the absence of solvents^[43] or in water, alcohol, or water/alcohol mixtures. In a number of cases, the regioselectivity can be controlled by the choice of solvent, a perfect example being the reaction of *cis*-cyclohexadiene diepoxide **1**^[44] with amines^[45] (Scheme 7). In the absence of solvents, the bis-epoxide reacts with amines to give the amino alcohol **2**, in which the entering nucleophiles are 1,3-related. When protic solvents are added, the same reactants give regioisomer **3**, with the entering nucleophiles in the 1,4-relationship.^[46, 47] In both cases, the diamino diol products are isolated in pure form by direct crystallization from the crude reaction solution, which enables reactions at any scale. Regioselectivity is similarly well-controlled for the ring opening of the *trans* diepoxide **4**; the example in Scheme 7 shows the one-pot stitching of three diepoxide units with two equivalents of ammonia to give **5** (85 % yield) as a mixture of its three possible racemic diastereomers.

Aziridines, the aza analogues of epoxides, are readily prepared by direct aziridination of olefins,^[48] by manipulation



Scheme 6. Generation and opening of spring-loaded cyclic electrophiles (shown in red) from olefins or their oxidation products (blue).

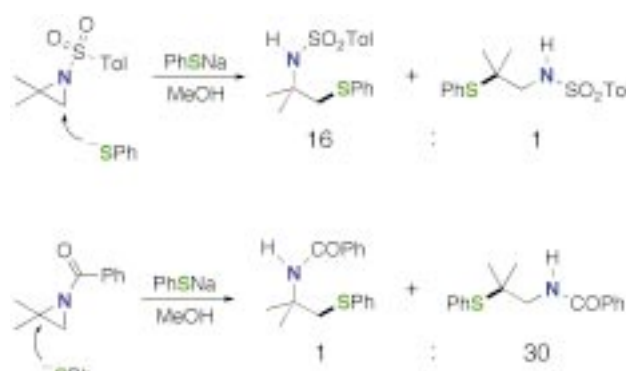


Scheme 7. Amine reactivity with cyclohexadiene diepoxides.

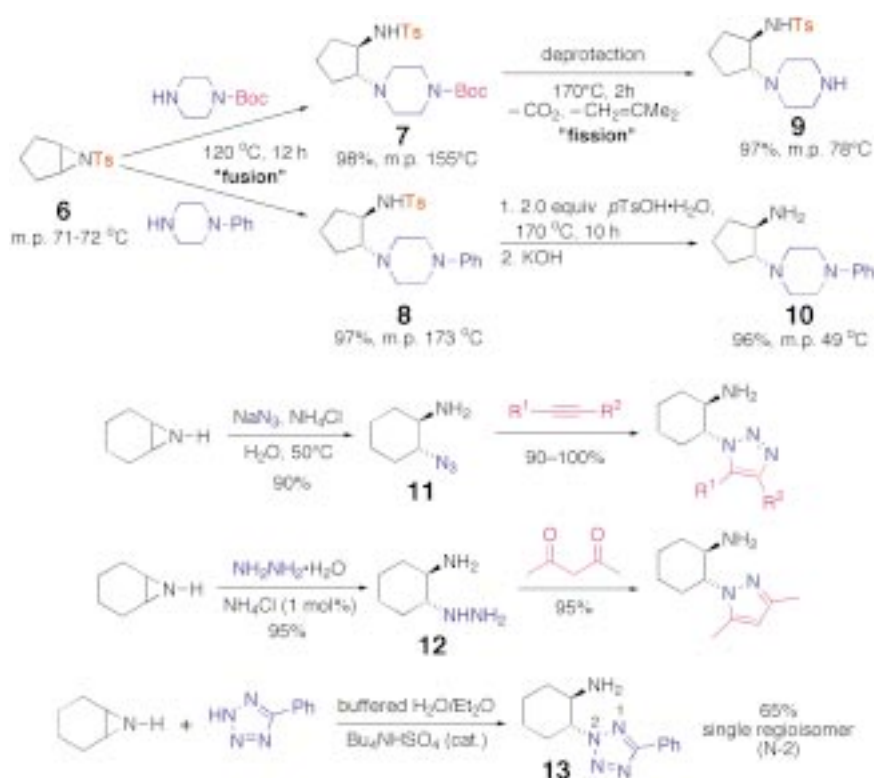
of epoxides^[49] or amino alcohols,^[50] and by haloazidation of olefins followed by reductive cyclization.^[51] Through variation of the substituent on the ring nitrogen, aziridines enable much greater product diversity than epoxides. Their ring-opening reactivities can be modulated over an enormous range,^[52] and, most importantly, the nitrogen substituent and the nature of the solvent can be used to control the regioselectivity of ring opening in unsymmetrical cases.^[53] The example in Scheme 8 from Stamm and co-workers reveals just how dramatic the effect of the nitrogen substituent can be.^[54] Effects deriving from the tendency of sulfonamides to be pyramidal at nitrogen and amides to be planar cause *N*-sulfonyl aziridines usually to furnish the regioisomer derived from attack of the nucleophile at the sterically least hindered center, while *N*-acyl aziridines favor the opposite regioisomer.^[53] Thus,

aziridines have even more potential than epoxides from the standpoint of click chemistry applications.^[55]

While *N*-H and *N*-alkyl aziridines are perfectly stable under basic conditions, we and others have found that they can be readily opened, particularly by heteroatom nucleophiles, under buffered conditions in various solvents including water.^[56, 57] The examples in Scheme 9 illustrate the practicality of aziridine-based click chemistry.^[58a] A solvent is often not required,^[58b] so that the ring-opened compounds **7** and **8** are obtained in pure form by neat fusion of **6** with the appropriate secondary amine at ap-



Scheme 8. Influence of the nitrogen substituent (sulfonyl, acyl) on the regioselectivity of aziridine opening.^[54] Tol = tolyl.



Scheme 9. Use of activated and nonactivated aziridines as building blocks. Boc = *tert*-butoxycarbonyl.

proximately 120 °C. Neat thermal fission then removes the *N*-Boc group in **7** to provide the secondary amine **9**, while the primary amine in **10** is unmasked in excellent yield by heating compound **8** at 170 °C with two equivalents of $p\text{-TsOH} \cdot \text{H}_2\text{O}$, again in the absence of solvent. The high temperatures of these solvent-free processes are presented to highlight the reliability of the bond-forming events under any conditions. Each of these reactions can also be done in standard solvents at ≤ 70 °C.

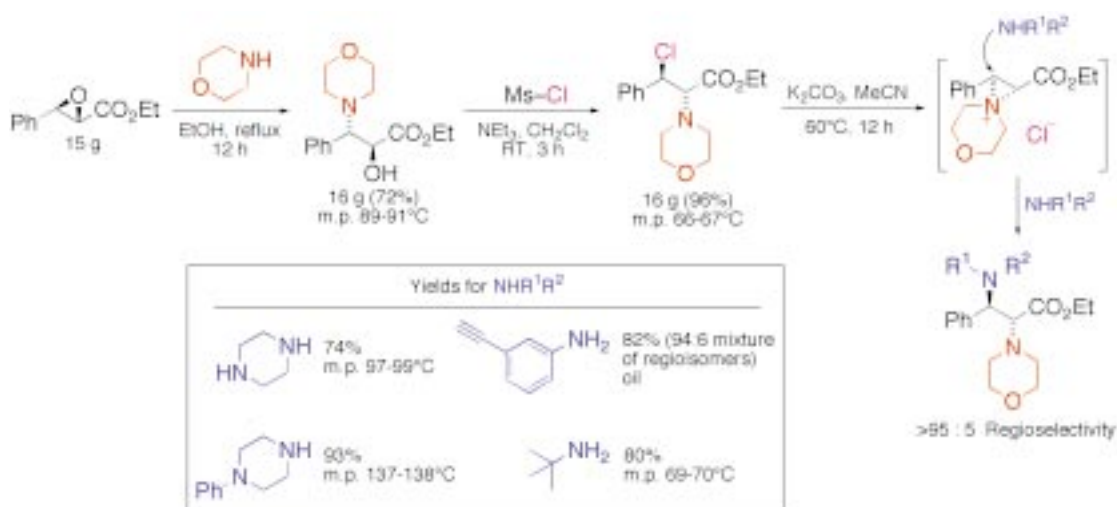
The opening of even unactivated aziridines proceeds readily in water with buffered azide (to give **11** at 50 °C) and with

hydrazine (to give **12** at 25 °C). The resulting intermediates are highly useful; their cycloadditions and condensations with alkynes and β -diketones, respectively, are reliable click reactions in their own right (see Section 3.2). Water is often the solvent of choice, as illustrated by the opening of a simple aziridine with 5-phenyltetrazole to give heterocycle **13**. Such a modular approach allows for the formation of a large variety of useful organic intermediates.

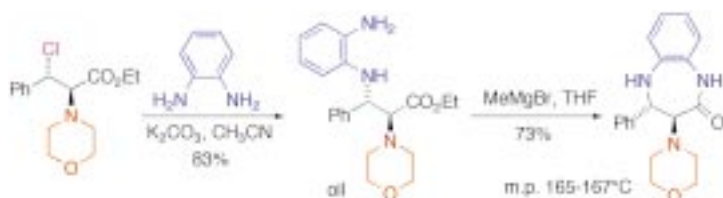
Highly activated aziridinium systems are easily generated in situ in the course of neighboring group assisted nucleophilic substitution starting from amino alcohols,^[59] or β -halo amines^[60] and related compounds^[61] (Scheme 6). The reactions of the analogous episulfonium systems^[62] are even more facile.^[63] All these substitutions are stereospecific and proceed with double inversion, and hence net retention of configuration in cases where the nucleophilic attack on the aziridinium or episulfonium ion occurs at the center bearing the leaving group, or with inversion of both centers in cases where the amino or thioether group undergoes a 1,2-shift. The broad scope of these reactions

and the easy access to the starting materials from the corresponding epoxides makes them perfectly suited for the rapid generation of building blocks and combinatorial libraries (Scheme 10).^[64] An example of the swift access provided by aziridinium chemistry to “druglike” molecules is shown by the preparation of a 1,5-benzodiazepine derivative (Scheme 11).

Aziridinium and episulfonium chemistry is particularly well-suited to the aqueous phase because the spring-loaded three-membered ring intermediates bear a positive charge, balanced by the anionic counterion which served as the

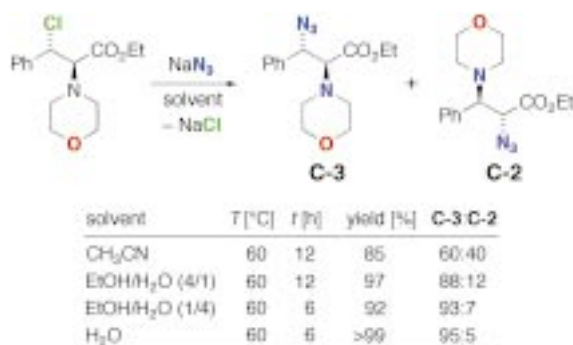


Scheme 10. Aziridinium intermediates in combinatorial assembly. Ms = mesyl = methane sulfonyl.



Scheme 11. Efficient assembly of a benzodiazepine via an aziridinium intermediate.

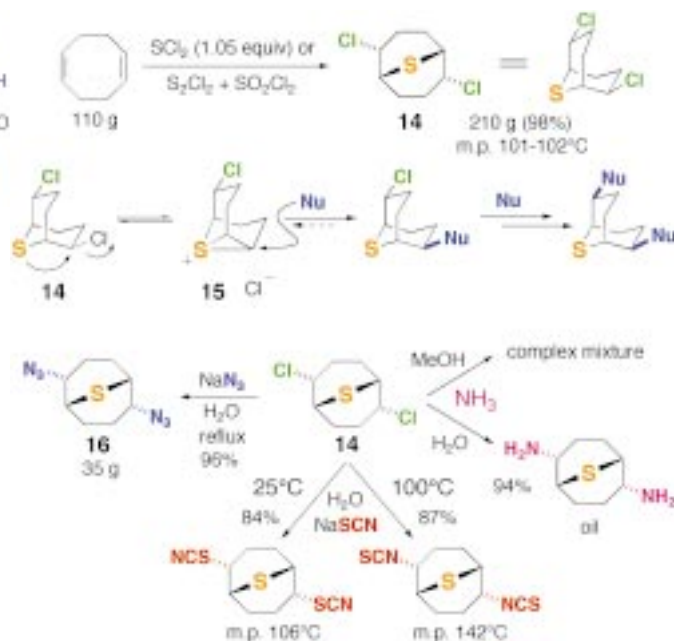
leaving group. We have noted that, when this leaving group is chloride or, particularly, sulfonate, the beneficial effects of water are most apparent, whereas little or no improvement is noted on changing the solvent from acetonitrile to water when the leaving group is iodide or bromide.^[65] The greater stabilization offered by strong protic solvation of the harder anions in water is probably the dominant factor. Furthermore, these “homocarbonyl” electrophiles, like the acyl halides that participate in Schotten–Baumann reactions, are much more reactive toward a range of heteroatom nucleophiles in water than toward the solvent. An example of the beneficial effects of performing these types of reactions in water is given in Scheme 12, in which both yield and selectivity are shown to be



Scheme 12. Solvent dependence of aziridinium ring opening by azide.

improved as the water content of the reaction medium is increased. For the last two sets of conditions shown, which lead to the highest selectivities, neither the starting material nor the products are soluble in the reaction solvent.

In this context, it should also be noted that the mustard-type sulfur compounds are directly accessible from olefins in very high yields by addition of sulfonyl halides (RSX)^[66] or the inorganic parent SCl₂^[67] (Scheme 13, top). The addition often proceeds under thermodynamic control, allowing reliable prediction of the products. The exceptional reactivity of the resulting compounds such as **14** enables many additional click chemistry transformations through neighboring-group participation, which provides episulfonium intermediates such as **15**.^[68] These pathways, and especially the required ejection of anionic leaving groups (for example, the chloride in **14**), are uniquely assisted by an aqueous environment. In the cases shown at the bottom of Scheme 13,^[69] the reactions proceed cleanly and rapidly from solid-to-solid in aqueous suspension; presumably, the episulfonium ion intermediates are the only water-soluble species on the path from starting materials to



Scheme 13. Generation and reactions of activated sulfonium (thiuranium) electrophile **14**.

products. The dramatically different outcomes for reaction of **14** with saturated solutions of NH₃ in CH₃OH or H₂O underscore the crucial role played by solvation in these substitutions and the unique properties of water as a solvent, especially when solvent separation of ion pairs and/or efficient proton shuttling through solvent hydrogen-bonding networks are important.

3.2. Cycloaddition Reactions

Click chemistry ideals are beautifully represented among cycloaddition reactions involving heteroatoms, such as hetero-Diels–Alder^[70, 71] and, especially, 1,3-dipolar^[72–74] cycloadditions. These modular fusion reactions unite two unsaturated reactants and provide fast access to an enormous variety of interesting five- and six-membered heterocycles.^[75]

As already mentioned, in this powerful class of concerted click reactions we have come to regard the Huisgen dipolar cycloaddition of azides and alkynes^[76] as the “cream of the crop”. However, probably because of concerns about the safety of the azide moiety,^[77] medicinal chemists have not given these transformations the special attention they deserve.^[78] The actual cycloaddition step may be as reliable for other types of [2+3] reactions, but the azide group is by far the most convenient of the 1,3-dipolar components to introduce and to “carry” until needed. Indeed, it may be the only one which is stable toward dimerization and/or hydrolysis. While azides are widely valued for their ease of introduction and reduction to primary amino groups, the remarkable stability (orthogonality) of *aliphatic* azides to a wide variety of other standard organic synthesis conditions seems largely unappreciated. With a few interesting exceptions, they remain “invisible” unless a good dipolarophile is present.

Two typical examples of azide cycloadditions are shown in Scheme 14.^[79] Bis(azide) **16** readily adds two molecules of alkyne to give bis(triazole) **17**. A wide variety of alkynes



Scheme 14. Examples of azide cycloaddition reactions.

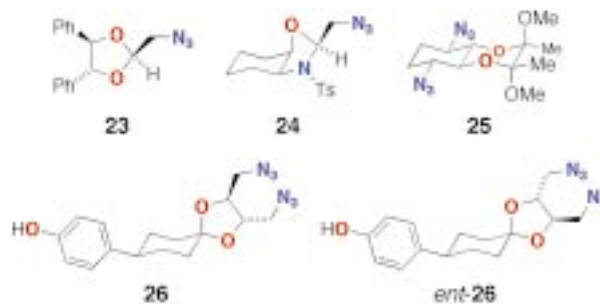
engage in such reactions, with electron-deficient cases usually being the most reactive. Azide **18** reacts with the cyanoacetylene equivalent, 2-chloroacrylonitrile, to give only one regioisomer of triazole **19**, which retains its isolated olefins for further decoration.

Other (that is, non-azide) 1,3-dipolar cycloaddition processes provide interesting five-membered heterocycles, such as the examples shown in Scheme 15, in good yields.^[80] The

3.3. “Protecting Group” Reactions

While hydroxy groups are nearly “invisible” in aqueous solution, in the absence of water a pair of *neighboring* hydroxy groups often exhibit unique reactivity. Thus, acid-catalyzed reactions with aldehydes and ketones provide cyclic 1,3-dioxolane rings in high yields. Instead of their ubiquitous role as diol protecting groups, should not acetals, ketals, and some of their aza-analogues be better viewed as an attractive class of heterocycles for medicinal chemistry applications? They are generally stable at physiological pH,^[81a] have already appeared as components in orally available drugs,^[81b] contribute several hydrogen bond acceptor sites and interesting dipole effects, provide constrained scaffolds with well-defined projections and spatial orientations of their substituents, are assembled from modular and abundant components, and represent one of the rare click chemistry modules based on *reversible* carbonyl chemistry.

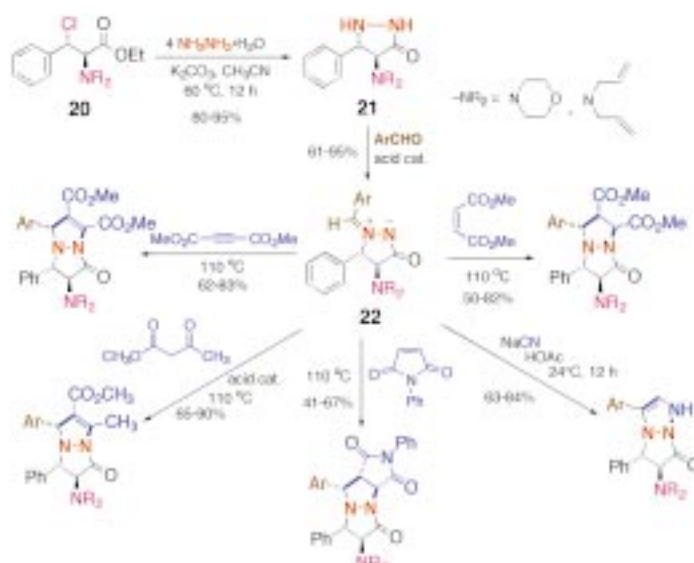
The five acetal-like derivatives (**23–26** and *ent*-**26**) were easily prepared on multigram scales from the appropriate diols or hydroxysulfonamides.^[82] As a consequence of their



heteroatom substituent inductive effects, they are resistant to standard acidic hydrolysis conditions, all the more so if the azide group is reduced to the amine. The saturated dioxolane cores can be regarded as permanent elements of the block's structure under most physiological and chemical conditions, and if further transformations are desired the pendant azide substituents offer many diverse and reliable options.

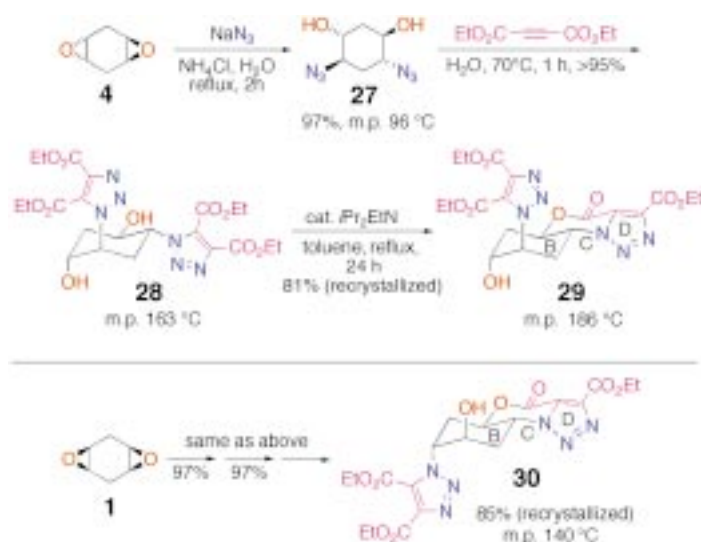
4. Examples of Click Chemistry Sequences—Diversity with Ease

Complex structures can be rapidly assembled using short sequences of simple click chemistry transformations. An example is the formation of the tricyclic molecule **29** in just three steps, conducted sequentially in one pot and starting from bis-epoxide **4**^[34, 44] (Scheme 16).^[83] The nucleophilic opening of **4** with buffered azide is highly regioselective, resulting in the formation of the crystalline azido alcohol **27** in excellent yield. The bis-triazole **28**, formed by 1,3-dipolar addition of the bis-azide with diethylacetylene dicarboxylate, can be collected from the reaction mixture by filtration. The *C*₂-symmetry of the system is then broken during base-catalyzed lactonization to furnish lactone **29**, the three rings of which resemble the B, C, and D rings found in



Scheme 15. Cycloaddition reactions based on the hydrazine-derived [2+3] dipole **22**.^[80a]

sequence starts with addition of hydrazine to the aziridinium intermediate generated from **20**. The resulting cyclic hydrazide **21** then undergoes condensation with aromatic aldehydes to give azomethine ylides **22**, which react with a variety of unsaturated components to give [3+2] cycloadducts. The rich array of functionality displayed by these products provides opportunities for the creation of unique combinatorial libraries.

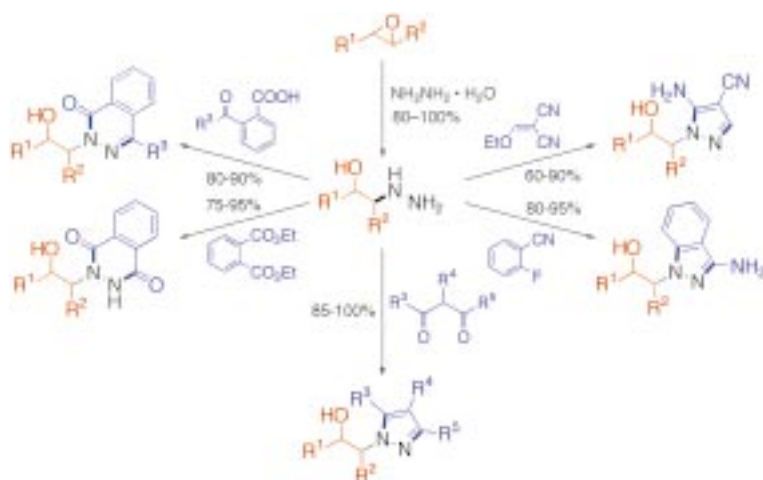


Scheme 16. Steroid-like skeletons assembled from cyclohexadiene diepoxides.

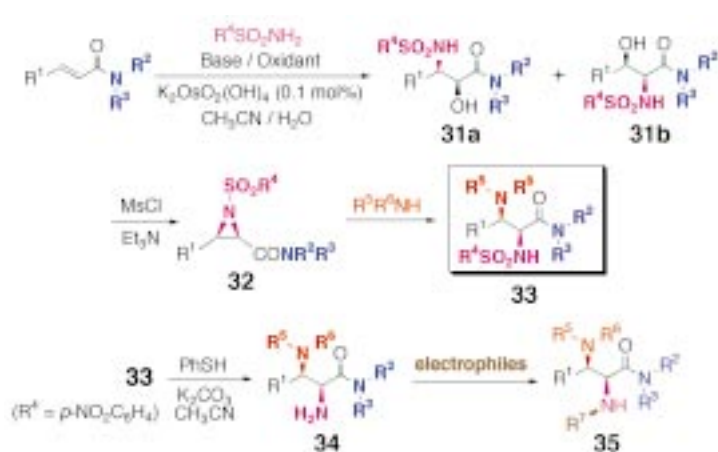
steroids. The analogous *cis*-diepoxide **1**, through the same three-step sequence, gives the related lactone **30**, which is identical to **29** except that the two “B”-ring substituents have switched positions. All steps for both sequences proceed in excellent yield. (See the frontispiece for large-scale sequences in this series.)

The capabilities of such reaction sequences for library synthesis are illustrated in Scheme 17. Epoxide ring opening with hydrazine and subsequent condensation with a variety of β -dicarbonyls or other bis-electrophiles provide entry to an enormous range of heterocyclic structures. Library synthesis using these protocols is highly efficient, and achieves excellent diversity from the large, available pool of epoxides.^[84]

The facile osmium-catalyzed aminohydroxylation of α,β -unsaturated amides is also an attractive starting point for the synthesis of diverse molecules based on the previously rare α,β -diamino acid motif (Scheme 18). In this sequence, the hydroxysulfonamide regioisomers **31a** and **31b** produced in the aminohydroxylation step conveniently provide the same *cis*-*N*-sulfonylaziridine intermediates **32** upon cyclization.^[85]



Scheme 17. Click chemistry sequences from epoxides and hydrazine.^[84]



Scheme 18. A click chemistry library sequence from olefinic acids.^[88]

Regioselective aziridine ring opening by a diverse set of primary and secondary amines then yields the *threo*-3-amino-2-sulfonamides **33**. The aminohydroxylation was also performed with the chloramine salt of *p*-nosyl sulfonamide (see above), and the β -aminosulfonamide products **33** ($R^4 = p\text{-NO}_2\text{C}_6\text{H}_4$ (*p*-nosyl)) were freed of their sulfonamide group through the Fukuyama deprotection method,^[86] to give **34**. The resulting primary 2-amino group of compounds **34** have been capped with more than sixty electrophiles to date, including acid chlorides, sulfonyl chlorides, anhydrides, isocyanates, and isothiocyanates, to give structures of the general form **35**.^[87] The biological activities discovered in various screens of this library will be reported elsewhere.

5. Summary and Outlook

We have described here the basic elements of a new style of organic synthesis, or, perhaps more accurately, the reinvigoration of an old style of organic synthesis. Its purpose is to accelerate the discovery of substances with useful properties, new medicines being the example emphasized. The approach derives from a keen awareness of nature's preferred methods of synthesis, but does not seek to emulate them too closely.

Nature is a matchless creator of C–C linkages and we propose leaving the tough job of C–C bond synthesis as much as possible to her. Instead, it is sensible for us to specialize in quick and easy chemistry that nature uses only sparingly, by focusing on the high driving force reactions that emanate from the olefins that she has provided either directly (for example, terpenes) or that are produced by the petroleum industry.

It is no accident, given the high energy content of the olefinic π bond, that the most reliable and most useful organic reactions all involve olefins, their unsaturated cousins, or their uniquely accessible heteroatom oxidative addition products. The latter compounds either are, or can easily be transformed into, the reactive building blocks that are ideal for the fast, irreversible assembly (for example, through

click chemistry) of diverse molecules with druglike structural features. Three-dimensional space is efficiently accessed by the stereospecific nucleophilic openings of such spring-loaded rings, and when these spring-loaded units are embedded in cyclohexane frameworks, the level of regio- and stereochemical control available for core creation/decoration sequences reaches a zenith. Nature certainly uses heteroatom connections, but not in this fashion. Therefore, the structures assembled by opening aziridines and epoxides are usually novel, and almost invariably so when the assembly sequence involves two or more such ligations.

Nature's giant molecules are constructed from a small set of building blocks using a few types of reactions for stitching them together. If we are to build small molecules which interact specifically with these large and diverse structures, we will need more components than nature has developed. While new building blocks will always be welcome, we expect that a good set of 500 or so will prove effective for many targets.

Our thinking about C–C bonds as gifts of nature has been a constant source of inspiration during the framing and the ongoing refinement of this minimalist synthetic strategy. In any event, endeavoring to transform these matchless building blocks into substances with diverse and useful functions seems an appropriate way to honor the bestowal of such an embarrassment of riches.

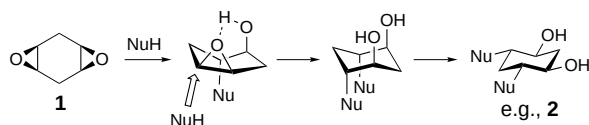
This review is dedicated to Professor Daniel S. Kemp, master teacher of carbonyl chemistry to a generation of MIT students and at least one assistant professor. We are very grateful to the following co-workers for their willingness to sail the click chemistry waters, and especially to those who have waited as long as several years to see their efforts reach the printed page: Michael Bartsch, Kristina Burow, John Cappiello, Han-Ting Chang, Bin Chao, Zhengming Chen, Jay P. Chiang, Tsung-Huang Chuang, Antonella Converso, Zachary Demko, Klaus R. Dress, Valery V. Fokin, Alexander V. Gontcharov, Vincent Jeanneret, Jae-uk Jeong, Dongyeol Lim, Hong Liu, Susan Maddock, Andreas Marzinzik, Dominique Michel, David S. Nirschl, Janet Elizabeth Pease, Wallace C. Pringle, K. Laxma Reddy, Paul Richardson, A. Erik Rubin, Zai-Cai Shi, Erland Stevens, Beata Tao, Allen A. Thomas, Andrew R. Vaino, Koenraad P. M. VanHessche, Martin A. Winter, Andrei K. Yudin, and Zhi-Min Wang. We also thank Dr. Thomas Archibald (Aerojet Fine Chemicals, Inc.) for educating us on the safe handling of azides and other reactive compounds, Prof. Joseph Gajewski (Indiana University) for insightful mechanistic discussions, and Prof. Subhash Sinha (The Scripps Research Institute) for performing the reactions highlighted in the frontispiece.

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- [11] While nature was the first combinatorial chemist, Ivar Ugi may be regarded as the second. His idea of using one-step solution-phase processes, such as his four-component coupling reaction, in such applications was a stroke of genius, and about 30 years ahead of its time: “Since four different starting materials take part in the four-component condensation, the reaction is extremely versatile. If, for example, 40 each of the different components are reacted with one another, the result is $40^4 = 2560000$ reaction products, which is quite a high figure considering that it is of the same order of magnitude as the total number of chemical compounds described to date.” (G. Gokel, G. Lüdke, I. Ugi, in *Isonitrile Chemistry* (Ed.: I. Ugi), Academic Press, New York, **1971**, pp. 145–199; see also: I. Ugi, R. Meyr, U. Fetzter, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 386). When the pharmaceutical industry “discovered” combinatorial chemistry about 20 years later, the solid-phase approach, pioneered by Merrifield for multistep synthesis of large biopolymers, was adapted for multistep syntheses of druglike molecules. Only recently, following ArQule's lead, has the drug-discovery community realized the power of Ugi's vision for quickly generating molecular diversity through robust, yet simple, reaction cascades that assemble multiple components in solution.
- [12] The venerable Robinson annelation sequence is an example. The components are first connected intermolecularly by the Michael reaction (no new C–C bonds made, only the favorable exchange of a π for a σ bond; $\Delta H < -20$ kcal mol⁻¹) and only then is the hard part (the aldol step) accomplished intramolecularly. The Dieckman condensation has enormous scope because it is intramolecular, whereas the intermolecular parent reaction (Claisen condensation) is only reliable for the simplest case ($R = H$ in RCH_2COOR').

- [13] We do not consider here the many polymerization (Ziegler–Natta) reactions of olefins and acetylenes and related processes, which account for the vast majority of man-made materials based on contiguous carbon–carbon bond networks. Being strongly exothermic and superbly efficient, these polymerizations are clearly based on click reactions, but ones which are hard to control for the construction of small molecules in the stepwise “modular” fashion of the reactions discussed above.
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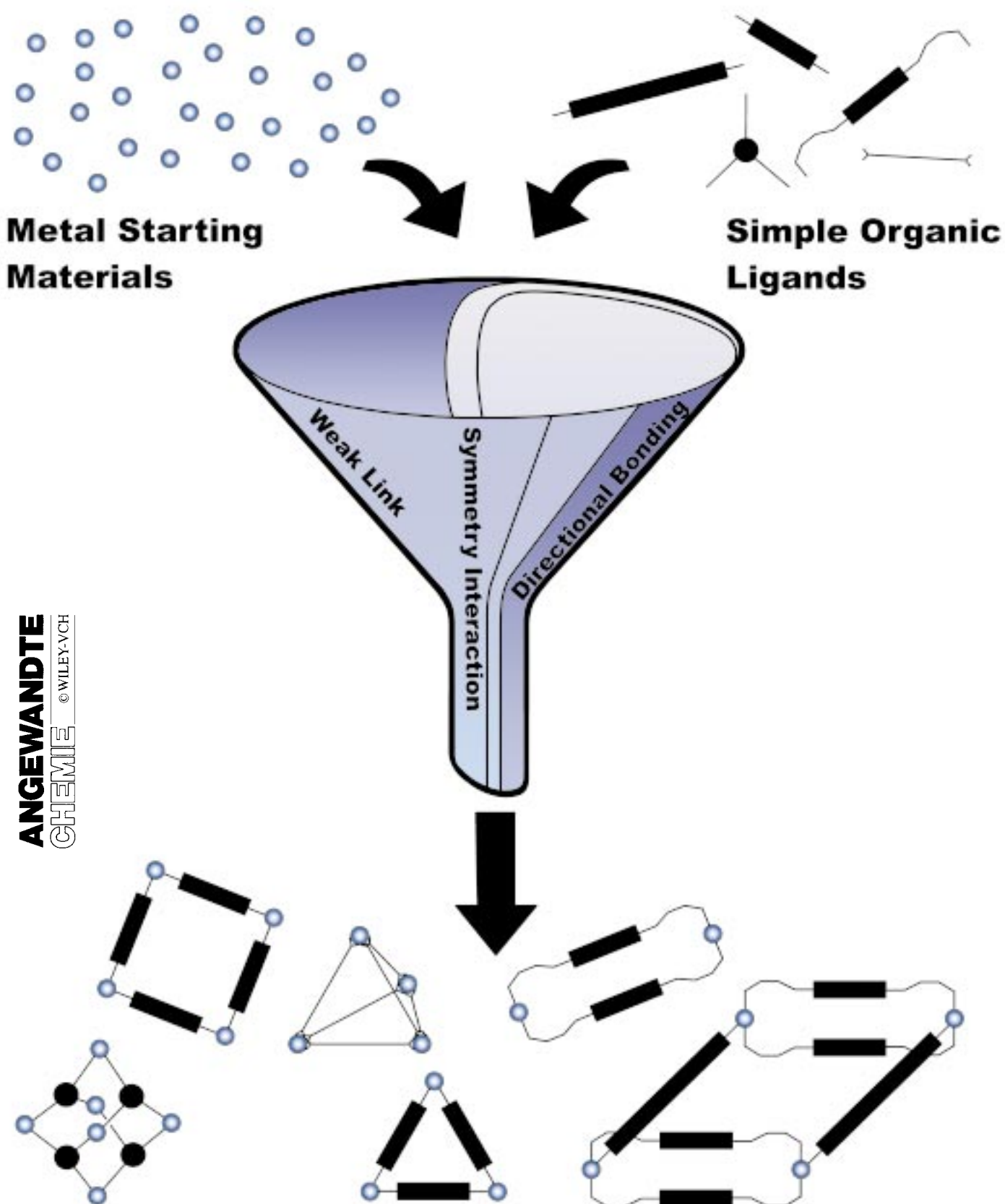


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Supramolecular Coordination Chemistry



Strategies for the Construction of Supramolecular Compounds through Coordination Chemistry

Bradley J. Holliday and Chad A. Mirkin*

Synthetic organic chemists enjoy the luxury of having a large collection of reliable reactions at their disposal for preparing small molecules, mesoscopic structures, and polymers. Coordination chemists, on the other hand, are faced with the fact that transition metal chemistry, when normalized for the number of transition metals, has relatively few high-yielding reactions, when compared to the chemistry of carbon, for preparing even small molecule structures. This lack of control is manifested, in large part, in the weak metal–ligand interactions found in coordination complexes as compared with the strong covalent bonds in

organic compounds. Weak bonding often translates into many reaction pathways that are not substantially different from an energetic point of view, and therefore, results in poor selectivity. As a result, many coordination chemists in recent years have come to the realization that it may be easier and more productive to develop straightforward and reliable routes to mesoscopic supramolecular structures by capitalizing on the modest collection of high-yielding reactions in coordination chemistry, the directional bonding afforded by metal centers, and strategies aimed at taking advantage of the weak metal bonds found in

coordination complexes. Three emerging synthetic strategies, the symmetry-interaction, directional-bonding, and weak-link synthetic approaches, all use metal centers as structural building blocks to rationally assemble molecular components into supramolecular metallocyclophanes. These three approaches are discussed herein, and the fundamental principles underlying each as well as their capabilities are compared and contrasted.

Keywords: coordination chemistry • nanostructures • supramolecular chemistry • synthetic methods • transition metals

1. Introduction

In the last twenty-five years supramolecular chemistry has developed at a tremendous rate. This expansion has been driven by the growing knowledge regarding synthetic and characterization methods for complex structures.^[1–3] Chemistry “beyond the molecule”^[1] is as old as life itself and epitomized in nature by the hydrogen-bonded structure of DNA, the elegant ability of enzyme receptor sites to act on one molecule with absolute selectivity, and the control exhibited by metalloproteins, such as hemoglobin, over a metal coordination environment. Only in the past two decades have we begun to develop ways of mimicking the properties and functions of these systems on the most rudimentary levels. Interest in these complex systems lie in the scientific fields of chemistry (recognition and selective transformations), biology (translocation of drugs across

membranes), and materials science (construction of macroscopic architectures and devices on the molecular level).^[2, 4] In fact, the study of supramolecular systems blurs most of the traditional divisional boundaries of science and thus represents a truly interdisciplinary field.

As chemists, we take on the task of building supramolecular systems by designing rational synthetic schemes that begin with our knowledge of reactivity on the atomic scale (functional groups) and then build up. The development of linear step-wise syntheses, which entail the controlled manipulation of reactive sites on individual molecules, has increased, by many-fold, the number of organic molecules that can now be produced synthetically. The initial work on the synthesis and properties of organic macrocycles as selective hosts^[5] paved the way for the synthesis of larger, more complicated arrays, many of which now contain one or more metal atoms. However, as the scale and complexity of target molecules increases, the step-wise synthesis of large discrete supermolecules from molecular building blocks becomes increasingly difficult, often low-yielding, and specific to only a few approaches.^[6]

The use of transition metal centers and coordination chemistry for directing the formation of complex structures

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has evolved into one of the most widely used strategies for organizing molecular building blocks into supramolecular arrays. The synthesis of large symmetric structures requires careful consideration of the entropic and enthalpic costs involved. While nature has refined the construction of macromolecules (for example, DNA, RNA, or proteins) utilizing a plethora of relatively weak interactions within each assembly: hydrogen bonding, van der Waals forces, Coulombic interactions, and dipole–dipole interactions, our mastery of these subtle interactions as synthetic tools is in an early stage of development. In supramolecular arrays the use of weak interactions becomes important for two reasons:

- 1) the weak forces holding the molecules together incorporate a large degree of flexibility into biomolecules which allows conformational changes that are often necessary for function, and
- 2) the large number of weaker interactions allow for greater specificity through annealing processes which ultimately form the most thermodynamically favorable structure.^[7]

The latter observation can be an extremely important consideration when designing supramolecular assemblies and represents a significant advantage that metal-mediated assembly holds over conventional covalent organic synthesis.

The covalent coordination bonds formed to transition metal centers are of intermediate strength relative to the weak interactions discussed above and the strong covalent carbon–carbon bonds of most organic compounds. Significantly, the heteroatom–metal bonds are thermally labile. This property allows one to intentionally select either a thermodynamic or kinetic product through the judicious choice of ligands, transition metals, and reaction conditions. Therefore, defect structures can often be corrected or annealed to the desired product by adjusting reaction times and conditions. In addition to thermal annealing, the metal-directed assembly of supramolecular structures can be aided by chelation effects

which can significantly decrease the entropy of formation relative to organic systems which typically couple through one point of contact in the form of a carbon–carbon bond. These characteristics make the formation of large, symmetric supramolecular arrays through transition metal mediated assembly an attractive strategy that has been exploited by many research groups. While the metal–ligand interactions are at the cornerstone of these synthetic strategies, distinct subsets can easily be delineated.

Several general and high-yielding synthetic approaches have emerged from this large body of work. The purpose of this Review is to define and discuss these strategies in the context of the current progress being made in this field. Comprehensive reviews cataloging the molecules synthesized by some of the approaches discussed below have been reported elsewhere.^[8–14] Herein, we intend to highlight some of the basic structures which these strategies have produced, review the more extraordinary structures reported in the recent literature, and discuss a relatively new general synthetic approach which has been overlooked in other review articles.

2. Supramolecular Structures Formed through Coordination Chemistry

2.1. The Directional-Bonding Approach

2.1.1. Preface

The directional-bonding approach, as used here, or the “molecular library” approach, as coined by Stang and co-workers,^[12] involves the assembly of large metal-containing structures wherein the metal centers act as highly directional corner or side units in the resulting geometric shapes or

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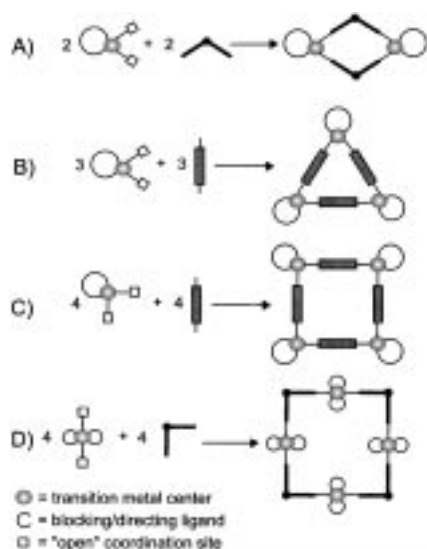
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polyhedra. Typically, the metals are introduced into these structures with directing or blocking ligands that only make coordination sites available to incoming ligands with the appropriate angle to form the desired shape (Scheme 1). In



Scheme 1. The construction of large structures by the directional-bonding approach. The metal centers have a high directional effect on the resulting geometric shapes. The metals are introduced with directing or blocking ligands.

this strategy, the target molecule's shape is predetermined by careful selection of the metal starting material, coordinatively inert directing ligands, and rigid bridging ligands. For example, a dinuclear macrocycle can be assembled by using a metal complex with a 60° angle between the coordinately labile sites and a rigid ligand with a 120° kink (Scheme 1 A). This same metal complex can be used to construct a molecular triangle by using a linear ligand system (Scheme 1 B). Finally, there are two complementary ways to construct a molecular square: 1) by using a metal starting material with a 90° angle between the coordination sites and a rigid linear ligand (Scheme 1 C) or 2) by utilizing a metal complex with a 180° geometry and a ligand system with a 90° turn (Scheme 1 D). More complicated polyhedra that can be accessed through this strategy will be discussed in Section 2.1.7.

The corner angles are essential to the closure of the appropriate geometric shape and hence, as defined by Stang and co-workers, the ligands must be "rigid, highly directional multibranchedly monodentate ligands, which bind to partially coordinatively unsaturated transition-metal complexes via dative bond interactions".^[12] Since either the ligand or metal used in this approach has a directing influence, we feel the term "directional-bonding approach" is more descriptive than molecular-library approach, and will be used throughout to describe this approach.

2.1.2. Advantages and Limitations of this Approach

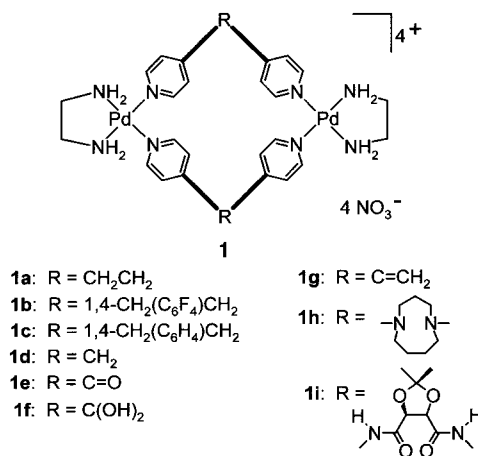
The directional-bonding approach to the synthesis of supramolecular coordination complexes is a general, high-yielding synthetic strategy that grants researchers access to complexes with a wide range of sizes and shapes which can be

controlled through rational choices of metals and ligands. The generality of this approach for the incorporation of ligands with many different desirable physical properties for applications has also been demonstrated by various research groups.

However, there are some inherent limitations to this approach. First, the ligand systems used are rigid linking groups which preclude the formation of flexible supramolecular arrays; this rigidity limits the formation of molecular switches or other applications which require conformational changes in the complex other than rotation. Second, the metal centers in the final structures are coordinatively inert, which severely limits applications such as size- and shape-selective metal-based catalysis and use of the metal centers to form more complex structures through further coordination chemistry. Indeed, any catalysis or formation of extended arrays from preformed, discrete supermolecules is ligand based and is encumbered by the limits of organic manipulation on this scale (see Section 1). Finally, the physical properties of both the ligand and metal building blocks are often greatly perturbed as a result of the direct coordination and often conjugation between the transition metal centers and the rigid heteroatom-containing ligands employed in this synthetic strategy. For example, strongly luminescent ligands have been incorporated into several molecular squares only to have the ligand-based luminescence quenched completely by the metal centers.^[15, 16]

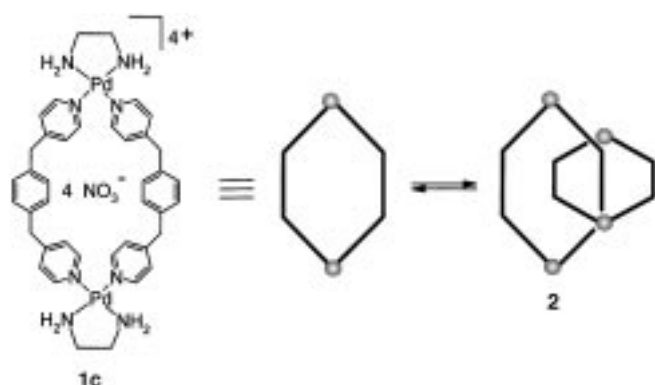
2.1.3. Dinuclear Macrocycles

Dinuclear metallomacrocycles containing transition metal atoms in the backbone have been made by the directional-bonding approach. Initial work in this area by Fujita et al. includes the synthesis of a series of ligand systems and the investigation of the dynamic behavior of the macrocycles **1** in solution.^[17–21] The ligand systems used are all based on a bis(pyridine) dative donor group and its coordination chem-



istry with a palladium(II)–ethylenediamine complex. Also, Hosseini and co-workers have prepared analogous metallomacrocycles by incorporating diazacycloalkanes into the organic backbone (**1h**),^[22] and Hong and co-workers have reported the synthesis and dynamic guest-induced solution structure of macrocycles possessing a hydrophobic cavity incorporating a chiral group in the backbone (**1i**).^[23] The fluorinated version of this system (**1b**) has been shown to

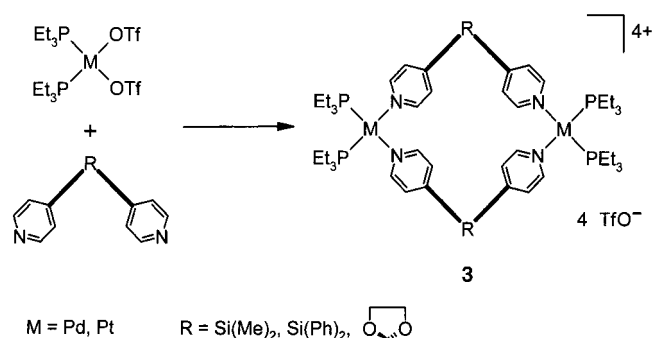
recognize electron-rich aromatic guests in aqueous solutions.^[17] Furthermore, dilution studies of complex **1c** in D₂O by ¹H NMR spectroscopy have established the presence of inorganic catenane **2** (two interlocked molecular rings) in equilibrium with the monomeric ring structure (Scheme 2).^[18]



Scheme 2. The monomeric ring structure **1c** is in equilibrium with catenane **2** in D₂O.

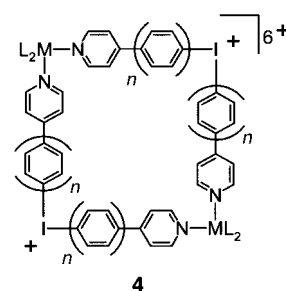
By changing to platinum, which forms stronger bonds with the pyridine donors, Fujita et al. have been able to force the equilibrium to a stable inorganic catenane.^[19] Finally, Fujita et al. have reported the synthesis of two unique inorganic [2]catenanes formed from molecular rectangles that are remarkably stable in solution, with no evidence of monomer rings even at low concentrations (mM).^[21]

In a similar manner, Stang and co-workers have assembled dinuclear macrocycles through dative coordination bonds. They have reported the synthesis of several rhomboids by the reaction of bis(triethylphosphane)platinum(II) and -palladium(II) bistriflates with the corresponding bis(pyridine) ligands (Scheme 3).^[24] A single-crystal X-ray diffraction study



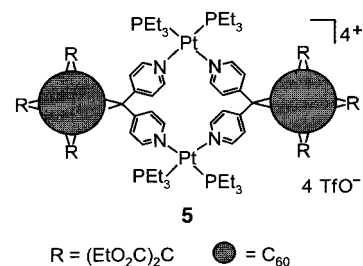
Scheme 3. Synthesis of the various rhomboids through the reaction of bis(triethylphosphane)platinum(II) and -palladium(II) bistriflate with the corresponding bis(pyridine) ligand.^[24]

of the dimethylsilaneplatinum version of rhomboid **3** confirmed its cyclic structure and revealed an internal cavity of 10.9×8.0 Å.^[24] Stang and co-workers have also reported the synthesis of homodimetallic macrocyclic structures which incorporate iodonium salts as the turn in the organic ligand (**4**; see Table 1 for abbreviations, dppf = 1,1'-bis(diphenylphosphine)ferrocene).^[25–29] The rigid and highly directional cationic organohalogen salts are ideal for the synthesis of supra-



- 4a:** M = Pt or Pd, L₂ = dppp, n = 0
4b: M = Pt or Pd, L₂ = PET₃, n = 0
4c: M = Pt or Pd, L₂ = dppp, n = 1
4d: M = Pt or Pd, L₂ = PET₃, n = 1
4e: M = Pt or Pd, L₂ = binap, n = 1
4f: M = Pt or Pd, L₂ = binap, n = 0
4g: M = Pt or Pd, L₂ = dppf, n = 1
4h: M = Pt, L₂ = diphosphinocalix[4]arene

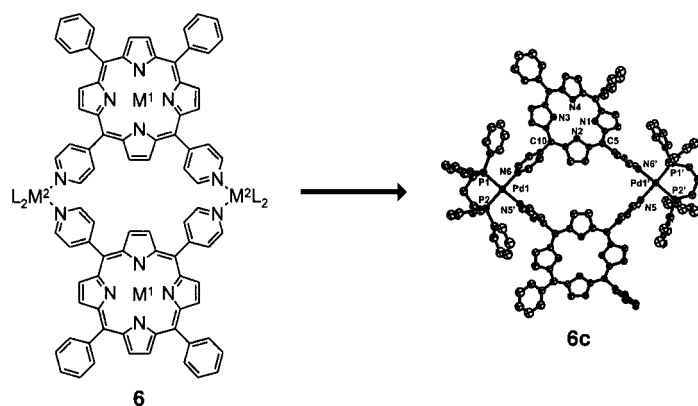
molecular arrays by the directional-bonding approach.^[30] These iodonium salts have been used as the corners in a number of complexes which can be prepared in good yields (50–100%) and have been characterized by standard techniques (IR and multinuclear NMR spectroscopies, combustion analysis, and single-crystal X-ray molecular structure determination). Additionally, the incorporation of fullerenes into supramolecular assemblies has been a long-standing goal of many chemists because the unique physical properties of these compounds offer the potential of creating novel materials with rich electronic chemistry.^[31] The directional-bonding approach has been used to synthesize a diplatinum complex **5** which contains two bis(pyridine)-functionalized C₆₀ molecules.^[32]



This synthetic scheme reported by Diederich and co-workers is significant because it demonstrates the covalent attachment of ligating groups onto the surface of C₆₀ which allows the incorporation of these molecules into many supramolecular assemblies by the directional-bonding approach.

Building supramolecular structures which incorporate porphyrin subunits is of great interest to many research groups. The rich photochemistry and redox properties (for example, photoinduced electron transfer, luminescence, and light-harvesting) of porphyrins have driven this interest. In addition, when functionalized with the appropriate heteroatom-containing groups, porphyrins have a rich coordination chemistry that allows the inclusion of many different metal centers within the ring and at the periphery. The ability to align the porphyrin chromophores in well-defined geometries, so as to tailor the distances and cofacial interactions between them, paves the way for important studies of the ground-state

and excited-state interactions of these molecules. A 5,10-dipyridylporphyrin has two ligating groups oriented at 90° to each other, which makes it ideal for use as a molecular corner in either dimetallic macrocycles or molecular squares (see Section 2.1.5), and allows them to be used as building blocks in the directional-bonding approach.^[16, 24, 33] Figure 1 depicts a



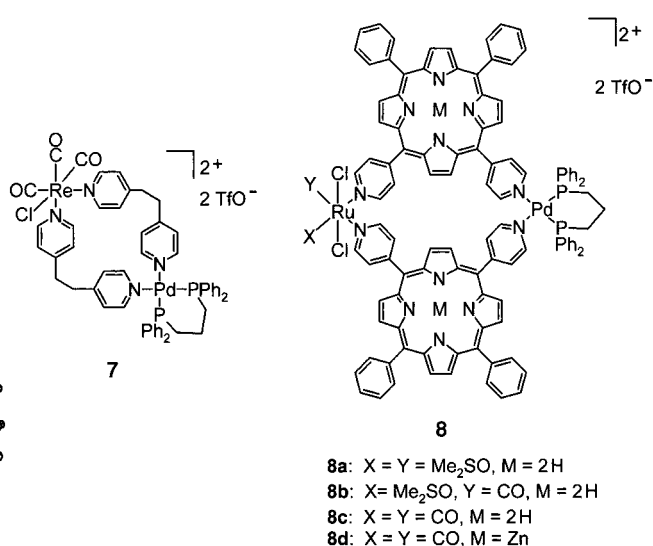
- 6a:** $M^1 = 2H$, $M^2 = Pd$, $L_2 = 2Cl$
6b: $M^1 = Zn$, $M^2 = Pd$, $L_2 = 2Cl$
6c: $M^1 = 2H$, $M^2 = Pd$, $L_2 = dppp$
6d: $M^1 = Zn$, $M^2 = Pd$, $L_2 = dppp$
6e: $M^1 = 2H$, $M^2 = Pd$, $L_2 = binap$

Figure 1. Generalized diagram of dinuclear macrocycle **6** and the X-ray crystal structure of **6c**. Reprinted with permission from ref. [24].

summary of these structures and the solid-state X-ray crystal structure of one such molecule reported by Stang and co-workers.^[24] These molecules can be synthesized in good yields and are well characterized in solution. The solid-state molecular structure of **6c** reveals that these structures possess a large internal cavity measuring $14.1 \times 4.8 \text{ \AA}$.

The dinuclear systems discussed above are all homodimetallic systems, but there are two examples of mixed-metal systems reported by Hupp and co-workers and Iengo/Alessio and co-workers.^[34, 35] Hupp and co-workers, in an effort to synthesize a molecular square using a flexible ligand system (bis(pyridyl)ethane), isolated compound **7**. Significantly, they found that the luminescence in this system was completely quenched.^[34] The stepwise synthesis of compound **8** was reported by Iengo, Alessio, and co-workers.^[35] First, the bisporphyrin/ruthenium complexes were isolated in moderate yields (40–70%) followed by reaction with bisphosphane-palladium(II) bistriflates to form the dinuclear complex **8** in good yield (80%). The metalation with zinc resulted in the formation of **8d**. This stepwise synthesis provides a rational route to mixed-metal dinuclear supramolecular complexes.

Finally, there have been relatively few examples of dinuclear metallomacrocycles formed with metal centers other than Pd^{II} or Pt^{II} . Two complexes that incorporate osmium and molybdenum into the framework of the macrocycle by the directional-bonding approach. Jeong et al. have reported the spontaneous assembly of a series of homodimetallic Os^{VI} complexes from osmium tetroxide, 2,3-dimethyl-2-butene, and bis(pyridyl) ligands.^[36, 37] In this synthesis, OsO_4 is treated with a 1:1 mixture of the olefin and bis(pyridyl)



ligand. The resulting octahedral metal center contains two available coordination sites at 90° to one another to which the pyridyl groups bind. The dinuclear products are formed and isolated in near-quantitative yields. Figure 2 shows the

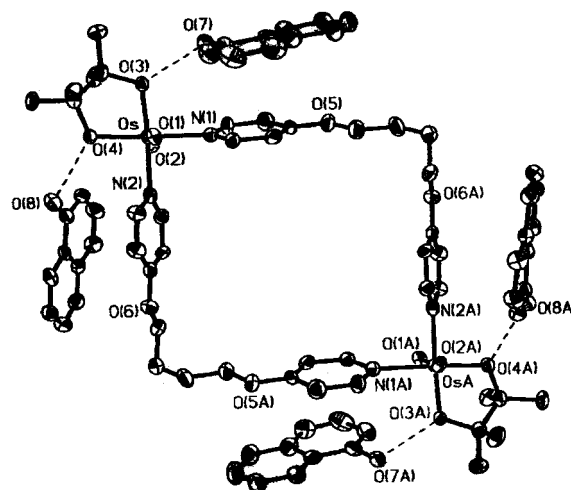
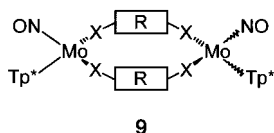


Figure 2. X-ray crystal structure of the 1-naphthol adduct of a dinuclear macrocycle with Os^{VI} metal centers. Reprinted with permission from ref. [36].

X-ray crystal structure of the 1-naphthol adduct of one such complex. Furthermore, Jeong et al. have prepared a macrocyclic receptor containing hydrogen-bonding groups on the interior of the cavity and have studied the binding of several guest molecules.^[36] The synthesis of molybdenum-containing dinuclear macrocycles **9** has been reported by Jones and co-workers.^[38–40] The synthetic procedure adopted for this preparation utilizes an octahedral Mo^{III} metal center with bulky Tp or Tp^* (Tp = hydrotris(pyrazol-1-yl)borate, Tp^* = hydrotris(3,5-dimethylpyrazol-1-yl)borate) and nitrosyl ligands as the directing groups which allow binding of the bridging anionic diol or dithiol ligands in the two *cis* coordination sites.

As demonstrated by the examples above, the directional-bonding approach can be employed to synthesize a variety of homodimetallic and heterodimetallic macrocyclic compounds

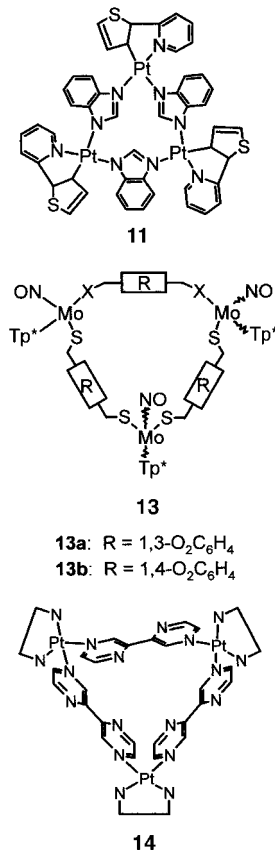
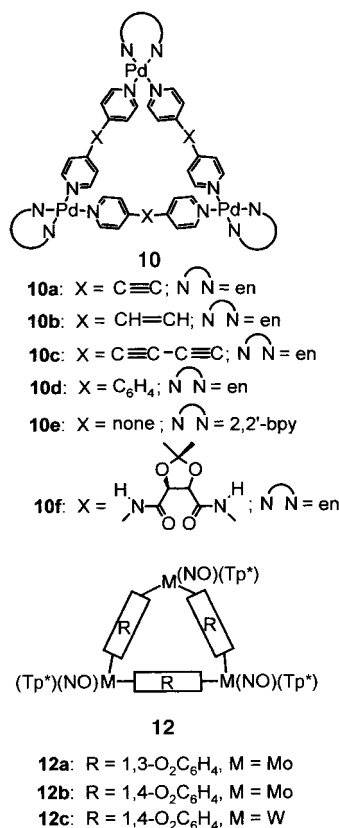


- 9a:** R = 1,3-CH₂(C₆H₄)CH₂; X = S
9b: R = 1,3-CH₂(C₆H₄)CH₂; X = O
9c: R = 1,4-CH₂(C₆H₄)CH₂; X = S
9d: R = 4,4'-(C₆H₄)CH₂(C₆H₄); X = O
9e: R = 2,7-C₁₀H₈; X = O

by selecting the proper transition metal complexes and ligands as starting materials. The synthetic strategy has been developed and generalized now by a large number of research groups to include a diverse set of metals and ligands. As discussed in Section 1, subtle changes in the protecting ligands on the transition metal center can lead to the formation of different molecular geometries, for example, trinuclear transition metal-containing molecular triangles, which will be considered next.

2.1.4. Molecular Triangles

The requirements for the formation of molecular triangles by the directional-bonding approach have been outlined in Section 2.1.1 and are illustrated in Scheme 1. Relatively few examples of trinuclear molecular triangles have appeared in the literature, for example, **10–14**. Fujita et al. have shown that molecular triangles **10** are formed in equilibrium with molecular squares.^[41] By varying the length of the ligand (see



10a–10d; en = ethylenediamine) and changing the protecting group on the metal starting material (see **10e**) this equilibrium can be adjusted in a predictable way. Additionally, Fujita et al. reported on dilution studies that support the thermodynamic balance they proposed exists between the enthalpically favored squares and the entropically favored triangles.^[41] Similar studies of the dynamic solution equilibrium of these systems have been carried out by Hong and co-workers utilizing ligand systems illustrated in structures **10b** and **10f**.^[23, 42]

The flexibility of the directional-bonding approach has been demonstrated by Chan and co-workers through the rational synthesis of two luminescent molecular triangles (**11**) that, in contrast to the complexes prepared by Fujita et al., incorporate ligands with a 150° bend and metal corners that have coordination sites at 90° to one another, instead of linear or pseudo-linear ligands and metal centers with distorted coordination sites at 60° to each other.^[43] Chan and co-workers chose deprotonated benzimidazolate as the edge units and 2-(2'-thienyl)pyridine (in **11**) or 7,8-benzoquinoline (not shown) as the protecting groups on the platinum(II) metal centers. These trimers have been prepared in high yields and are well characterized in solution, the gas phase, and the solid state. Other luminescent molecular triangles have been reported by Sun and Lees.^[44, 45] These systems incorporate 1,4-bis(4'-pyridylethynyl)-2,5-dihydroxybenzene as a ligand with rhenium(I) centers as the vertices of the structure (not shown). The molecular triangles are luminescent at room temperature in solution and show increasing structural features in the spectra at low temperatures.

Jones and co-workers have used Group 10 transition metal centers to expand the directional-bonding approach to a series of molybdenum- and tungsten-containing trinuclear metal-lomacrocycles (**12** and **13**).^[38, 39] These compounds exist as a mixture of structural isomers which differ with respect to the orientation of the protecting ligands relative to one another. The trimers have been well characterized, and the solid-state molecular structure of **12b** has been reported.^[38]

Recently, Lippert and co-workers have reported the synthesis of a novel class of trinuclear metallomacrocycles based on 2,2'-bipyrazine (bpz) as an edge group, ethylenediamine as the directing group, and platinum or palladium as the transition metal centers.^[46, 47] Significantly, it has been demonstrated that triangle **14** is the kinetic product of the reaction of [(en)Pd(H₂O)₂](NO₃)₂ with bpz; longer reaction times and elevated temperature lead to the formation of the mononuclear product [(en)Pt(bpz)](NO₃)₂.^[46] It is important to note that the ligand groups in **14** are oriented approximately perpendicular to the plane defined by the three metal atoms. This arrangement not only creates a larger interior cavity for possible host–guest interactions (anionic guests have been shown to bind inside this cavity), but it also orients the remaining coordination sites of the bpz ligands above and below the plane defined by the three metal centers. Rotation about the C–C single bond of the bpz ligand (from the conformation shown) allows for the chelation of three additional transition metals, thereby locking the structure into one conformation and resulting in a hexanuclear molecular triangle. Lippert and co-workers have also reported the

synthesis of the Pt_6 , Pd_6 , and Pt_3Pd_3 triangles as well as more complex structures which can be formed from them.^[47]

The triangular structures reviewed thus far are based on trinuclear species with single metal centers at each geometric vertex. The syntheses of molecular triangles where transition metal dimers form the corners also have been reported; Figure 3 depicts two such structures. These structures are

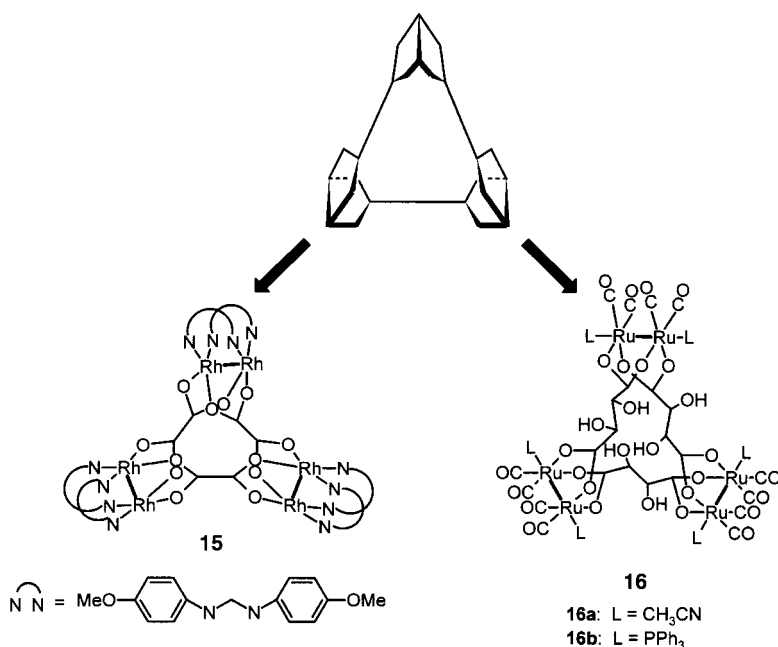


Figure 3. Simplified diagram (top) and molecular structures of molecular triangles **15** and **16**.

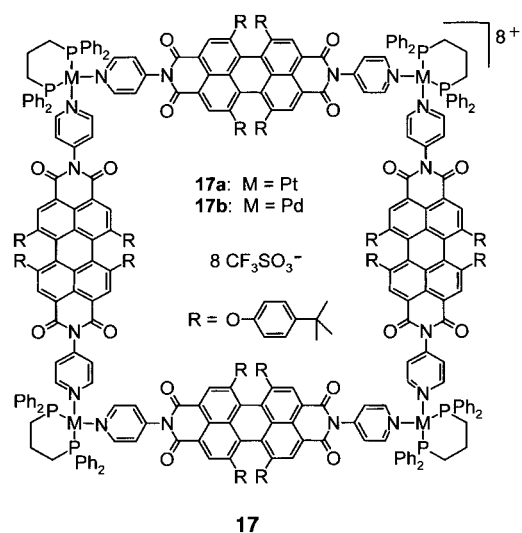
classified under the directional-bonding approach because the metal centers are introduced with directing groups present which predetermine the final molecular shape. It is important to note that despite being introduced as dimeric complexes, the metal centers maintain their role as the geometric cornerstones of the structures. Each metal center still has two available coordination sites which are oriented at the appropriate angles to form the desired geometric shape. The synthesis and characterization of complex **15** was reported by Cotton et al.^[48] Quantitative formation of **15** was achieved while attempting to construct the corresponding molecular square with rhodium dimer corners. Süss-Fink et al. have synthesized the trimeric structure **16**, which incorporates diruthenium complexes as the corners and tartaric acid as the edges of the triangle.^[49] The molecular triangle **16a** can be formed as three different isomers depending on which diastereomer of tartaric acid is used as the starting material. All of the isomers can be obtained in about 80% yield. The triphenylphosphane complex **16b** is synthesized by a ligand substitution reaction on the preformed triangle **16a**.

The synthesis of molecular triangles by the directional-bonding approach has been demonstrated by several research groups and represents the important link between enthalpic and entropic considerations when targeting discrete geometric shapes through the directed-assembly of edges and corners.

2.1.5. Molecular Squares

Of the geometric shapes accessible through the directional-bonding approach, squares have been the most widely reported. The requirements for the formation of a square metallocyclophane from molecular components has been outlined in Section 2.1.1 (see Scheme 1C and D). The formation of molecular squares over oligomeric or polymeric products in high yields is enthalpically driven in that the resulting shape is essentially strain free. Furthermore, the incorporation of a large number of ligand systems and transition metals is easily understood as a result of the relatively simple requirements for each. The ligands must be rigid, linear or pseudo-linear, difunctional, and capable of bridging, while the metal centers must have open coordination sites at either 90° or 180° to one another (*cis* square planar or octahedral metal centers). Many commercially available or easily synthesized compounds meet these requirements. Molecular squares made by the directional-bonding approach have been thoroughly reviewed elsewhere.^[8, 11–13, 50] Table 1 summarizes the molecular components used to assemble squares and the resulting properties that have been successfully imparted to the squares.

Notable structures that are outlined above include the final entry in Table 1; the construction of a molecular square with nanometer-scale dimensions in high yield (90–95%) from a perylenebisimide derivative and Pt^{II} and Pd^{II} corners.^[77] The resulting tetranuclear metallomacrocyclic **17** is significant for several reasons:



- 1) the square is exceptionally large, with a metal–metal diagonal length of 3.4 nm,
- 2) the dipyriddylerylene ligand retains its photophysical properties after being bound to the metal centers ($\Phi_F = 0.88$), and
- 3) the organic ligands also exhibit reversible electrochemistry in the final Pt^{II} complex.

Table 1. Components used in the formation of molecular squares by the directional-bonding approach.

Ligand(s)	Directing group(s)	Transition metal center(s)	P	Ref.
P(OPCH ₂) ₃ P	(CO) ₄	Cr and Mo, W and Mo		[51]
4,4'-bpy	en	Pd or Pt	1	[41, 52, 53]
	dppp	Pd or Pt		[54]
	crown ether bisphosphane	Pt		[29]
	calix[4]bisphosphane	Pt	4	[29]
	dppp and (CO) ₃ Cl	Pd and Re	5	[34]
	2,2'-bpz	Pd		[55]
	O ₂ (mes) ₂	Os		[56]
bis(4-pyridyl)acetylene	en	Pd		[41]
P-benzonitrile	dppp or PEt ₃	Pd and/or Pt		[57, 58]
diazapyrene	Et ₃ P	Pd or Pt		[59]
	1,1'-bis(diphenylphosphanyl)ferrocene	Pd or Pt	3	[27]
	crown ether bisphosphane	Pt		[29]
diazaperylene	Et ₃ P	Pd or Pt		[59]
dicyanobenzene	dppp	Pd		[59]
2,6-diazaanthracene	binap	Pd or Pt	2	[28, 60]
2,6-diazaanthracene-9,10-dione	binap	Pd or Pt	2	[28, 60]
[[[CC(C ₅ H ₄ N)](C ₆ H ₄)(PPh ₃) ₂ Pt] ₂]	dppp	Pt		[26]
5,15-dipyridylporphyrin (2H or Zn)	dppp or binap	Pd or Pt		[15, 33]
	(CO) ₃ Cl	Re	5, 6	[61, 62]
4-pyridyl acetate	dppp or PEt ₃	Pt and Ti		[63]
4-ethynylpyridine	dppp and/or PEt ₃	Pd and/or Pt	1	[58, 64]
	dppp and/or PEt ₃ and/or diop	Pd and/or Pt	2	[65]
1,2-C ₂ B ₁₀ H ₁₂ or 3-phenyl-1,2-C ₂ B ₁₀ H ₁₁	–	Hg	2	[66]
2-hydroxybenzoxazole	–	Al		[67]
functionalized zinc porphyrin	porphyrin	Zn		[68]
uracilate	en	Pt		[69]
4,4'-bpy, pyrazine, or 1,2-bis(4-pyridyl)ethylene	(CO) ₃ Cl	Re	5, 6, 1	[70, 71, 72]
cyanide	Cl/C ₁₀ H ₁₄	Rh and Co		[73]
1,3-dihydroxybenzene or 1,4-dihydroxybenzene	TP*/NO	Mo or W		[38]
butadiyne and bis(tri- <i>n</i> -butylphosphane)platinum	d(cy)pe	Pt		[74]
dibutadiyne				
<i>t</i> -dppen	(CO) ₂ bpy	Re	5	[75]
1,2-bis(4-pyridyl)ethylene	en	Pd	1	[41, 42]
	(CO) ₃ Cl	Re	5	[45]
	(CO) ₃ Cl and 1,1'-bis(diphenylphosphanyl)ferrocene	Re and Pd	5, 3	[45]
1,4-dipyridylbutadiyne	(CO) ₃ Cl	Re	5	[44, 45]
benzene-1,4-dicarboxylic acid	dicarboxylic acid and 4- <i>tert</i> -butylpyridine	Rh ₂		[76]
oxalate, tetrafluoroparaphthalate, or	DarF	Mo ₂		[48]
ferrocene-1,1'-dicarboxylate dianion				
perylenebisimide	dppp	Pt or Pd	3, 5	[77]

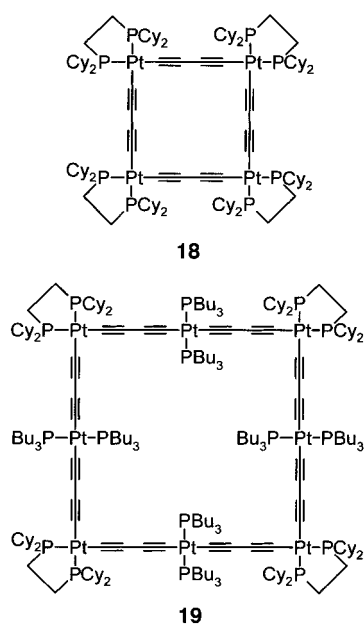
P = Properties the resulting square possesses. 1 = host – guest interactions, 2 = chiral, 3 = redox-active, 4 = molecular transport, 5 = luminescence, 6 = molecular separations. dppp = 1,3-bis(diphenylphosphanyl)propane, bpy = 2,2'-bipyridine, binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl, bpz = 2,2'-bipyrazine, diop = 4,5-bis(diphenylphosphanylmethyl)-2,2-dimethyl-1,3-dioxolane, dppen = 1,2-bis(diphenylphosphanyl)ethene, DarF = *N,N'*-diarylformamidinate anion, d(cy)pe = 1,2-bis(dicyclohexylphosphino)ethane.

These properties give complex **17** the potential to be used as a sensitive host for large functional guest molecules which can be monitored by electro- and photochemistry.

Additional structures have been reported by other groups which incorporate ethynyl groups and transition metals into the sides of the final square to provide binding sites for other metal atoms and ligands. Tessier, Youngs, and co-workers have reported the synthesis of a butadiyne linked/Pt^{II} molecular square **18** (Cy = cyclohexyl) and a derivative that introduces a platinum metal center into each side of the square (**19**).^[74] Both structures can be synthesized in good yield (80–98 %), and silver binding studies have been reported for compound **18**. Introduction of 1.5 equivalents of AgOTf to a solution containing square **18** results in the bonding of a silver atom across each corner of the square in a tweezer fashion. Additional structures containing ethynyl–

metal linkages and metal centers on the edges have been reported by Stang and co-workers.^[26] These structures incorporate diplatinum building blocks into the linear edges. The resulting squares are very large (4.3–4.8 nm on the diagonal) and also have been shown to bind silver atoms across the corners.

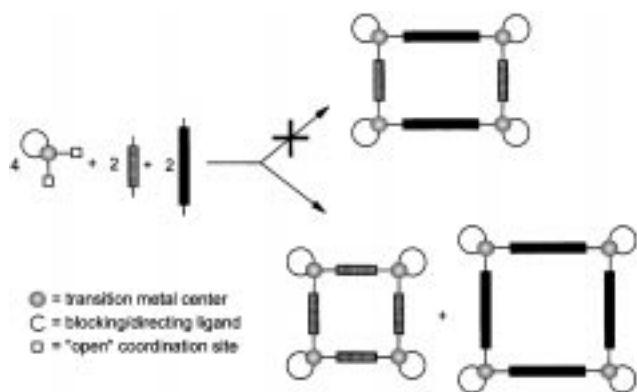
The synthesis of molecular squares by the directional-bonding approach has become a widely used technique for the high-yield formation of discrete tetranuclear metallocyclophanes, some with nanometer dimensions. The incorporation of functional organic groups into the interconnecting ligands has allowed the synthesis of squares with a wide range of desirable chemical and physical properties. However, the exploitation of these properties in the development of sensors and catalysts has yet to be demonstrated and represents an important frontier for those working with these types of complexes.



2.1.6. Molecular Rectangles

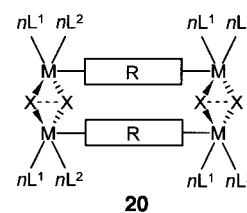
Molecular rectangles (tetranuclear metallocyclophanes constructed with two different lengths of bridging ligands) can be synthesized through a stepwise modification of the directional-bonding approach. While one of the advantages of this synthetic strategy for molecular squares is the spontaneous assembly of such structures from a mixture of ligands (edges) and metals (corners) in one step, the one-step synthesis of rectangles is not possible.

The strong enthalpic driving force, which makes possible the high-yield formation of squares over polymers and oligomers, also makes the statistical formation of rectangles from a mixture of two ligands and metal starting materials unfavorable. In fact, in studies aimed at evaluating the likelihood of the one-pot formation of molecular rectangles from a mixture of metal precursors and two rigid ligands which differ in length, only the two types of molecular squares formed rather than the molecular rectangles (Scheme 4).^[13, 78]



Scheme 4. From a mixture of metal-containing precursors and two rigid ligands of different length only the two molecular squares are formed, not the molecular rectangle.^[13, 78]

Hupp and co-workers have reported the preparation of a series of rhenium- and manganese-based molecular rectangles, which are synthesized in two steps. First, the shorter edge of the rectangle is assembled from a rhenium starting material and (a) bridging ligand(s), for example, sulfides, selenides, bipyrimidine (bpym), or bisbenzimidazole (BzIm). This dimer is then treated with a longer bridging ligand to form the target rectangles **20a–h** (see Table 2).^[78, 79] These rectangles can be prepared in moderate to



20: See Table 2.

Table 2. Molecular rectangles synthesized by the directional-bonding approach (see **20**).

20	M	L ¹	n	L ²	n	X	R
a	Re	CO	3	–	–	SCH ₂ CH ₂ CH ₃	4,4'-bpy
b	Re	CO	3	–	–	SCH ₂ CH ₂ CH ₃	pz
c	Re	CO	3	–	–	SC ₆ H ₅	4,4'-bpy
d	Re	CO	3	–	–	SeC ₆ H ₅	4,4'-bpy
e	Re	CO	3	–	–	bpym	4,4'-bpy
f	Re	CO	3	–	–	bpym	bpe
g	Re	CO	3	–	–	BzIm	4,4'-bpy
h	Mn	CO	3	–	–	BzIm	4,4'-bpy
i	Re	CO	3	–	–	OH	4,4'-bpy
j	Re	CO	3	–	–	OCH ₃	4,4'-bpy
k	Re	CO	3	–	–	OCH ₂ CH ₃	4,4'-bpy
l	Re	CO	3	–	–	OCH ₂ CH ₂ OH	4,4'-bpy
m	Ru	<i>p</i> -PriC ₆ H ₄ Me	1	–	–	C ₂ O ₄	4,4'-bpy
n	Re	CO	3	Br	1	pz	4,4'-bpy
o	Re	CO	3	Br	1	bpe	4,4'-bpy
p	Re	CO	3	Br	1	pz	bpe
q	Ir	Cp*	1	–	–	Cl	pz
r	Rh	Cp*	1	–	–	Cl	pz
s	Ir	Cp*	1	Cl	1	pz	CN(C ₆ H ₄)NC
t	Rh	Cp*	1	Cl	1	pz	CN(C ₆ H ₄)NC

good yields (50–80%) and have been well characterized in solution. Additionally, the solid-state X-ray crystal structure of rectangles **20a**, **20e**, and **20h** have been reported. Structurally similar molecular rectangles have also been reported by Sullivan and co-workers (**20i–l**).^[80] These structures utilize alkoxide bridging ligands to form the dimer on the shorter end of the rectangle. Complexes **20i–l** have been isolated in near-quantitative yield and are well characterized. Notably, rectangles **20i–l** show luminescence in the solid state and complexes **20g** and **20h** show luminescence both in solution and the solid state. These compounds are in contrast to the compounds initially reported by Hupp and co-workers which exhibit no luminescence in either solution or the solid state. Süß-Fink and co-workers have also reported the synthesis of a ruthenium molecular rectangle (**20m**) comprised of 4,4'-bpy and oxalate ligands with a *p*-cymene blocking ligand.^[81] Again, this complex was prepared in a step-wise fashion from the corresponding methanol dimer and 4,4'-bpy.

Two recent reports of the synthesis of molecular rectangles have appeared by Lu and co-workers and Yamamoto and co-

workers. Lu has reported the stepwise synthesis of neutral molecular rectangles that are luminescent in solution at room temperature. These complexes (**20n–p**) are constructed from rhenium metal centers and pyridyl bridging ligands.^[82] Finally, Yamamoto and co-workers have assembled rectangles **20q–t** from Cp^*MCl_2 ($\text{M} = \text{Rh}$ or Ir) building blocks and either pyrazine and/or diisocyanide bridging units.^[83] These simple two-step routes to molecular rectangles demonstrate the important control offered by the directional-bonding approach over the shape of the resulting complex.

2.1.7. Molecular Cages and Higher Order Structures

The directional-bonding approach has been extended to include the synthesis of more complex polynuclear three-dimensional structures. The simplest of these structures is the cagelike structure that results from the coordination of two tridentate bridging ligands to three transition metal centers (Figure 4A). These complexes have been reported by several

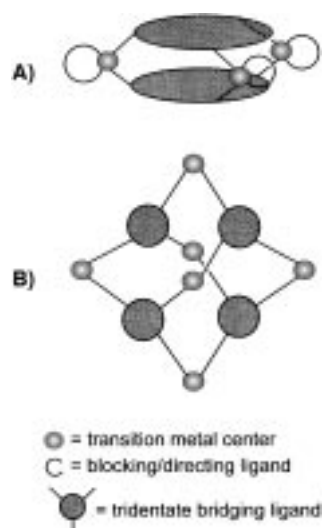


Figure 4. Molecular cages prepared by the directional-bonding approach.

groups and exhibit interesting host–guest properties.^[10, 11, 84–88] Fujita and co-workers have reported the synthesis of cage molecules based on palladium(II) ions and 1,3,5-tris(4-pyridylmethyl)benzene.^[84, 89] Interestingly, these trinuclear cages only form in high yields in the presence of a suitable guest molecule to template the reaction (namely, sodium *p*-methoxybenzoate). Fujita et al. have also reported the synthesis of trinuclear complexes with asymmetric tridentate ligands which assemble as two interlocked cages.^[88] Additional cage structures have been reported that incorporate novel functional groups into the tridentate ligand to enhance host–guest interactions. Shinkai and co-workers have synthesized a tridentate ligand which branches off a homooxalix[3]arene core.^[85, 90] The cage formation is based on N donor ligands and palladium(II) metal centers. The resulting molecular cage showed reversible inclusion of a C_{60} molecule in solution. Other research groups have formed molecular cages based on tridentate P donor ligands and transition metal centers. Lindner et al. have reported the

synthesis of 1,3,5-tris(4-diphenylphosphanylmethyl)-benzene and its cage complex with platinum(II) dichloride.^[86] The target complex was isolated in 38% yield, and underwent ligand substitution reactions at the transition metal center without significant decomposition. Finally, a tetranuclear cage molecule based on tetracyanocavitand and Pt^{II} and Pd^{II} metal centers has been synthesized by Jacopozi and Dalcanele.^[87] They demonstrated that the cages can be formed reversibly in quantitative yields through the addition of excess of N donor ligands which bind strongly to the metal centers.

The formation of structures such as that depicted in Figure 4B have been reported by several research groups.^[91–94] These cage molecules are assembled in solution from a mixture of ten components: six metal centers and four ligands. The ligands are based on 1,3,5-substituted arene rings with pendant pyridyl or pyrazole groups, and the transition metal centers are platinum or palladium(II) with *cis* coordination sites open for complexation. Fujita and co-workers have demonstrated the unique properties of these nanometer-scale cages, for example, reversible pH-dependent binding of a molecular guest,^[93] encapsulation of large neutral guests,^[92] selective binding of *cis* over *trans* isomers of azobenzene and stilbene molecules on the basis of cavity size and packing,^[94] synthesis of labile siloxanes,^[95] and as reverse phase-transfer reagents for aqueous-phase catalysis.^[96]

Other two- and three-dimensional shapes have been synthesized using the principles of the directional-bonding approach. They include hexagons,^[97] dodecahedra,^[98] cuboctahedra,^[99] hexahedra,^[100] rectangular boxes,^[101] compounds with an adamantane-type geometry,^[102] cubes,^[73, 103] tubes,^[104] bowls,^[105] and grids.^[106] The expansion of this synthetic strategy into the third dimension and the organization of complex structures through simple metal–ligand coordination bonds demonstrates a powerful ability to rationally design and synthesize complex nanoscale structures in high yield and represents an important aspect of supramolecular chemistry today.

2.2. The Symmetry-Interaction Approach

2.2.1. Preface

The symmetry-interaction approach has been developed as a transition metal templated, high-yield strategy for the rational design of high symmetry coordination clusters. In this strategy, multibranched chelating ligands are used in conjunction with sources of transition or main group metals which are free of strongly coordinating ligands. With this combination of starting materials, the formation of a given supramolecular shape is driven by the inherent symmetry of the coordination sites available on the metal center. Therefore, careful consideration must be given to the preferred coordination environment of the metal to be used and the binding mode of the chelating ligand. Additionally, the orientation of the multiple chelation sites with respect to one another within the ligand must be carefully chosen to ensure the closure of discrete clusters over formation of oligomers and polymers. The chelation effect of the ligands used in this approach

provides stronger overall binding constants to the metal centers than monodentate ligands, but the metal/ligand combinations must be chosen carefully in order to maintain coordinative lability. This approach, like the directional-bonding approach, targets the thermodynamic products of the reaction which makes thermal annealing of defect structures an important feature of the synthetic strategy. Finally, the symmetry interactions with which one must contend (for example, metal geometry, ligand orientation, and ligand–ligand steric interactions) when designing a supramolecular assembly utilizing this method can be considerably more complicated than the other two approaches presented in this Review. This added level of complexity has facilitated the extensive use of computer modeling to predict whether target architectures are possible products of a given combination of metals and ligands. Comprehensive reviews on this topic have recently been reported;^[12, 14] supramolecular shapes available through this approach will therefore only be highlighted briefly below.

2.2.2. Advantages and Limitations of the Symmetry-Interaction Approach

The symmetry-interaction synthetic strategy has granted researchers access to a variety of elegant shapes and architectures (for example, helicates, tetrahedra, and adamantoid structures) through the predictable coordination chemistry of multibranching chelating ligands with transition and main group metal centers. The added complexity that is inherent in this approach has, until recently, defined the synthesis of novel complexes as mostly resulting from trial and error. While Raymond et al. and Saalfrank et al., among others, have made significant strides towards developing a rational synthetic scheme, the subtle interactions driving the formation of these architectures is not fully understood.^[12, 14]

The compounds formed through this approach are, by definition, supramolecular clusters, the structure of which are usually relatively compact. While some host–guest interactions have been demonstrated by these complexes, the relatively small dimensions of the interior cavities typically prohibits the encapsulation of large guest molecules.

2.2.3. Dinuclear Structures

Dinuclear structures formed using the symmetry-interaction model have been classified into three categories for the purposes of this review: macrocycles formed with chelating ligands, helical structures, and dinuclear metallocryptands (Figure 5, **A**, **B**, and **C**, respectively). Although structure **C** is not formed with chelating ligands, it is still classified by the symmetry-interaction model as a consequence of the lack of blocking ligands present on the metal starting materials. The formation of the resulting structures is therefore driven by the coordination symmetry about the metal center. Dinuclear macrocycles which contain a variety of metal centers, such as Cu^[107–109] and Zn,^[108, 110, 111] have been reported (Figure 5, **A**). These structures possess desirable supramolecular properties, such as host–guest interactions,^[107, 110] and the ability to form

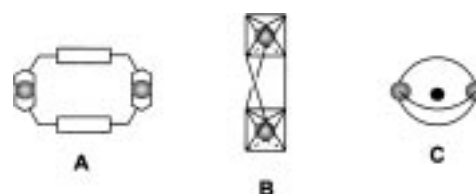


Figure 5. Dinuclear structures prepared by the symmetry-interaction approach.

more complex structures, such as catenanes^[110] has been reported (Figure 5). Homodimetallic helicates are the most widely reported dinuclear structures formed by this model. Several research groups have reported the synthesis of structures analogous to **B** (Figure 5). The most common ligands incorporated into these coordination clusters are based on catecholamide and hydroxamate units. The research groups of Albrecht,^[112] Stack,^[113] Raymond,^[114] Rice/Ward,^[115] Yoshida,^[116] James,^[117] Bünzli,^[118] and Lehn^[119] have reported dinuclear helicates assembled by utilizing the principles of the symmetry-interaction approach. Dinuclear metallocryptands (**C**, Figure 5) have also been reported. These structures are assembled with ligands which contain a central binding site which allows the encapsulation of a guest (usually an alkali earth metal cation) into the center of the final structure. Saalfrank et al. have reported such a complex based on iron(III) ions.^[120] This complex contains a pyridyl unit on the interior of the cage for guest binding. Similar structures which possess a dipyriddy binding site have also been reported.^[121] Catalano et al. have recently synthesized a series of structural analogues assembled from gold(I), silver(I), platinum(0), or palladium(0) ions and 2,9-bis(diphenylphosphanyl)-1,10-phenanthroline.^[122]

2.2.4. Three-Dimensional Structures

Two types of three-dimensional structures have most commonly been prepared utilizing the symmetry-interaction synthetic strategy. The first class of coordination clusters are molecular tetrahedra (Figure 6 **A**), such as those reported



Figure 6. Tetranuclear structures prepared by the symmetry-interaction approach.

by Raymond et al.^[123] These structures were synthesized from catecholamide or hydroxamate derivatives and aluminum(III), iron(III), or gallium(III) metal centers. Other examples of molecular tetrahedra have been reported by Saalfrank et al.^[124] and McCleverty, Ward, and co-workers.^[125]

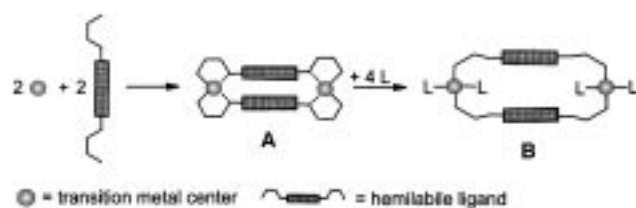
The second class of coordination clusters with adamantoid structures (Figure 6, **B**) have been reported by Saalfrank et al. A series of these structures has been prepared incorporating tetracarboxylate ligands and magnesium(II), manganese(II),

cobalt(II), iron(III), or nickel(II) centers.^[126] The redox properties of these complexes as well as their guest-encapsulation properties have been investigated. In addition to the three-dimensional structures highlighted here, other architectures prepared with this methodology include triangles,^[127] squares,^[128] cylindrical structures,^[129] molecular grids,^[130, 131] and circular helicates.^[132]

2.3. The Weak-Link Approach

2.3.1. Preface

The weak-link synthetic strategy for two- and three-dimensional structures offers one the ability to prepare supramolecular architectures from flexible ligands and transition metal starting materials free of directing ligands to yield structures with coordination sites that are available for further chemistry. In this approach, hemilabile ligands^[133] are used to bond to transition metal centers in a bidentate fashion in such a way that one of the metal–ligand bonds is stronger than the other, and formation of the dinuclear complex **A**, rather than mononuclear complex, is favored (Scheme 5). The formation



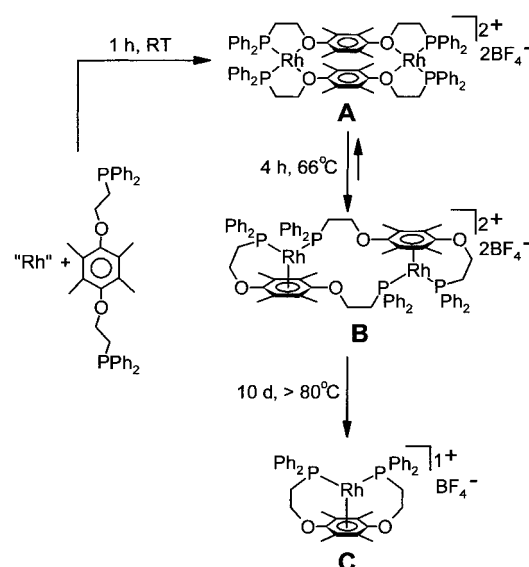
Scheme 5. The formation of the dinuclear complex **A** is favored by using hemilabile difunctional ligands.

of this intermediate is driven by the formation of favorable five- or six-member chelate rings, the chelation effect of the bidentate ligand which directs the formation of dinuclear structures, and the π – π interactions between the central bridging units (typically arenes) in the ligands. This intermediate structure is typically formed in high, if not quantitative, yield and often can be isolated and fully characterized. The target dinuclear metallocyclophane **B** (Scheme 5) is formed by introducing the condensed intermediate **A** to a ligand that preferentially binds to the metal center rather than the groups forming the weak links; this process results in the selective displacement of the weak links and, in most cases, quantitative formation of the desired product. It is important to note that this approach is conceptually different from the directional-bonding and symmetry-interaction approaches and yields structures that are not accessible by those approaches. Some of the notable differences are:

- 1) flexible metal-linking ligands can be used in place of rigid aromatic groups,
- 2) the metal centers in the condensed intermediate and, often, even in the metallocyclophane structures, have coordination sites that can be used for host–guest chemistry or the construction of more elaborate architectures, and

- 3) the reactions used in the weak-link approach are under kinetic rather than thermodynamic control; indeed, the 1:1 ligand:metal complex is typically the thermodynamic product, but because of large activation barriers it can be prohibited from forming through the careful choice of reaction conditions.

Mirkin and co-workers have recently reported the slow conversion, at elevated temperature, of a dirhodium intermediate (**A**) based on a 2,3,5,6-tetramethylbenzene (durene) ligand to the monomeric piano-stool species (**C**) via an arene–rhodium structure (**B**, Scheme 6).^[134] A preliminary



Scheme 6. At high temperature the dinuclear intermediate **A**, a dirhodium complex with durene ligands, is converted into monomer **C** via the arene–rhodium structure **B**.

conclusion has been made on the basis of these results that the bidentate chelating properties of the symmetrical hemilabile ligands used in the weak-link approach are essential for complexing the metal precursors and directing the formation of the condensed intermediate (**A**). Once formed, **A** can convert into other more-stable dinuclear forms (for example, **B**), but there is a relatively large energetic barrier to the formation of the mononuclear thermodynamic product (**C**). This process ensures the high-yield formation of a set of dinuclear intermediates that can be converted into a single macrocyclic product.

2.3.2. Advantages and Limitations of this Approach

The weak-link approach is a general synthetic strategy which grants access to sophisticated two- and three-dimensional supramolecular architectures through control over the coordination environment of transition metal centers with hemilabile ligands. Furthermore, the approach demonstrates the use of relatively subtle coordination chemistry principles to incorporate greater flexibility and impart utility to the metal centers in the final structure. The metal centers do not merely act as the corners of the structures but remain useful as dynamic building blocks for the construction of more-

complex architectures and for potential applications (for example, catalysis and host–guest chemistry). A significant attribute of this approach is the ability to perform ligand substitution reactions at the metal centers of the target macrocycles while maintaining the supramolecular structure (see Section 2.3.3). This ability allows one to control the electronic and steric properties of the metal centers contained within the supramolecular architectures in a systematic fashion.

In contrast to the directional-bonding approach, the weak-link approach can be used to incorporate structurally flexible ligands into supramolecular coordination complexes. By targeting the condensed intermediate discussed above, which is relatively rigid, the entropic cost of using flexible ligands is reduced in the initial organization of the molecular components. Upon expansion of the intermediate structure into an open macrocycle, the flexible portion of the ligand system is liberated from the metal and imparts flexibility to the entire metallocyclophane structure. This feature of the approach facilitates the synthesis of flexible supramolecular complexes with dynamic structural properties.

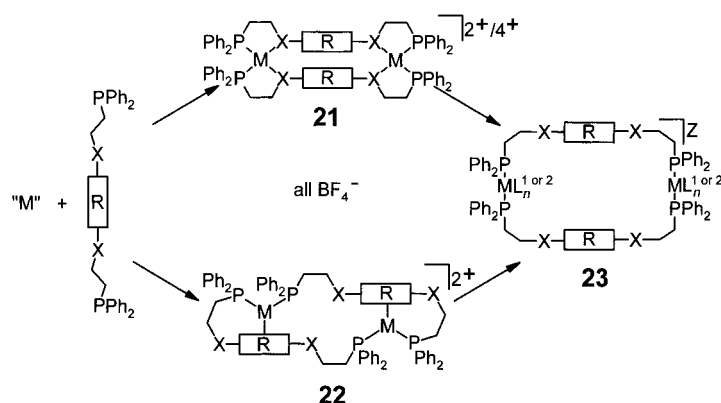
The coordinatively labile transition metal centers in the target supramolecular structures formed by the weak-link synthetic strategy offer the ability to tailor both the electronic and steric properties of the resulting host structure through simple coordination chemistry. In the case of Rh^I and Pd^{II} centers, reaction of the condensed intermediate with neutral ancillary ligands will result in formation of dinuclear macrocycles with 2+ and 4+ charges, respectively. The use of anionic ligands to open the condensed intermediates can be used to produce macrocycles of neutral or anionic charge. This tailorability of complex electronic properties in the final step of synthesis is an extremely useful feature of this approach. Additionally, like the directional-bonding approach, simple modifications of the ligand systems provide control over the macrocycle shape, size, and physical properties (for example, luminescence, redox activity, or chirality).

A potential disadvantage of this approach has been eluded to earlier. As discussed above, the condensed intermediate structures are the kinetic products of the reactions, with the mononuclear 1:1 metal:ligand complexes typically being the thermodynamic products. This, in principle, will result in some thermal instability of the supramolecular structures formed by this approach. However, for the systems studied thus far, the energy barrier for dimer to monomer conversion is exceptionally high and, therefore, product selection is relatively easy to control. Indeed, the desired products exhibit long-term stability over a moderate temperature range (RT to 100 °C).

2.3.3. Dinuclear Macrocycles

Mirkin and co-workers have utilized this synthetic strategy to produce a series of homodimetallic macrocyclic structures.^[134–139] The structures reported thus far have been prepared from hemilabile ligands derived from phosphanyl alkyl ether, thioether, and amine groups. These ligands bind to many late transition metal centers such as rhodium(I) and palladium(II) with the strong binding groups being the

phosphines and the weak binding groups being the ethers, thioethers, or amines. The initial structure prepared by this approach was synthesized from phosphanyl alkyl ether, **21a** containing a durenyl group (Scheme 7 and Table 3).^[135] This



- 21a:** R = 1, 4-C₆(CH₃)₄; X = O; M = Rh
21b: R = 9, 10-C₁₄H₈; X = O; M = Rh
21c: R = 1, 4-C₆H₄; X = S; M = Rh
21d: R = 1, 4-C₆H₄; X = N(CH₃); M = Rh
21e: R = 1, 4-C₆(CH₃)₄; X = O; M = Pd
21f: R = 1, 4-C₆H₄; X = S; M = Pd
22a: R = 1, 4-C₆H₄; X = O; M = Rh
22b: R = 4, 4'-(C₆H₄)₂; X = O; M = Rh
23: See Table 3.

Scheme 7. Preparation of macrocycles with homodinuclear metal centers starting from hemilabile ligands.

condensed intermediate was opened into a dinuclear 26-membered ring (**23a**) by treating it with carbon monoxide (1 atm; Scheme 7). This strategy has been expanded to include other aromatic groups such as benzene and 4,4'-biphenyl, with the latter resulting in a 34-membered ring.^[134] In both of these cases the stable intermediate structure formed is a “slipped” macrocycle in which the ether–rhodium weak links are replaced by arene–rhodium weak links (**22a** and **22b**, respectively, Scheme 7). Upon addition of a stronger

Table 3. Homodimetallic macrocycles prepared by the weak-link approach (see Scheme 7).

23	R	X	M	L ¹	n(L ¹)	L ²	n(L ²)	Z
a	1,4-C ₆ (CH ₃) ₄	O	Rh	CO	3	–	–	2+
b	1,4-C ₆ H ₄	O	Rh	CO	3	–	–	2+
c	4,4'-(C ₆ H ₄) ₂	O	Rh	CO	3	–	–	2+
d	9,10-C ₁₄ H ₈	O	Rh	CO	3	–	–	2+
e	1,4-C ₆ (CH ₃) ₄	O	Rh	CO	1	CH ₃ CN	1	2+
f	1,4-C ₆ H ₄	O	Rh	CO	1	CH ₃ CN	1	2+
g	4,4'-(C ₆ H ₄) ₂	O	Rh	CO	1	CH ₃ CN	1	2+
h	9,10-C ₁₄ H ₈	O	Rh	CH ₃ CN	2	–	–	2+
i	9,10-C ₁₄ H ₈	O	Rh	CH ₃ CN	1	2,6-(CH ₃) ₂ (C ₆ H ₃)NC	1	2+
j	9,10-C ₁₄ H ₈	O	Rh	CH ₃ CN	1	(CH ₃) ₃ CNC	1	2+
k	1,4-C ₆ H ₄	S	Rh	CO	1	Cl	1	0
l	1,4-C ₆ H ₄	O	Rh	CO	1	Cl	1	0
m	1,4-C ₆ (CH ₃) ₄	O	Rh	CO	1	Cl	1	0
n	1,4-C ₆ H ₄	S	Rh	CO	2	I	1	0
o	1,4-C ₆ H ₄	N(CH ₃)	Rh	CO	1	–	–	2+
p	1,4-C ₆ H ₄	N(CH ₃)	Rh	CO	1	CH ₃ CN	1	2+
q	1,4-C ₆ H ₄	O	Pd	CH ₃ CN	2	–	–	4+
r	1,4-C ₆ (CH ₃) ₄	O	Pd	CH ₃ CN	2	–	–	4+
s	1,4-C ₆ H ₄	O	Pd	CN	2	–	–	0
t	1,4-C ₆ (CH ₃) ₄	O	Pd	CN	2	–	–	0
u	1,4-C ₆ H ₄	S	Pd	CN	2	–	–	0

binding ligand such as carbon monoxide these rhodium–arene weak links have been selectively broken to form the analogous open structures **23b** and **23c**. Significantly, the incorporation of 4,4'-biphenyl into these structures demonstrates that the macrocycle size can be expanded by adjusting the size of the initial aromatic group in the ligand system. Ligand substitution reactions have also shown that the transition metal centers in the target macrocycle remain coordinatively labile towards incoming ligands, such as acetonitrile, as evidenced by the formation of the stable carbon monoxide/acetonitrile adducts **23e–g** (Scheme 7).^[134, 135]

Fluorescent aromatic units have also been incorporated into macrocyclic structures with this approach. Mirkin and co-workers have reported the synthesis of a dinuclear rhodium macrocycle that has an anthracene functionality in the backbone of the macrocycle (**21b** and **23h**, Scheme 7).^[136] Notably, the condensed intermediate **21b** exhibits fluorescence in solution which is significantly increased upon expansion to macrocyclic structures **23h–j** (Scheme 7). Also, the fluorescence signatures of these complexes are sensitive to molecules bound inside the macrocyclic cavity, thus pointing towards potential sensor applications (see Section 3.2).

Dinuclear macrocycles containing thioether weak links also have been prepared through this approach.^[137] Structure **21c** was prepared from a ligand derived from 1,4-benzenedithiol. Compound **21c** is an exceptionally stable condensed intermediate as a consequence of the stronger rhodium–sulfur bonds (compared to the rhodium–oxygen bonds in **21a** and **21b**). Consequently complex **21c** does not form open macrocycles when introduced to excess acetonitrile or even carbon monoxide. However, **21c** has been opened through a novel halide-induced ring-opening reaction which forms the neutral chloride/carbon monoxide complex **23k** (Scheme 7).^[137] The generality of this ring-opening reaction has been demonstrated by extending it to several analogous ether-containing ligand systems and other halides (**23l–n**, Scheme 7).

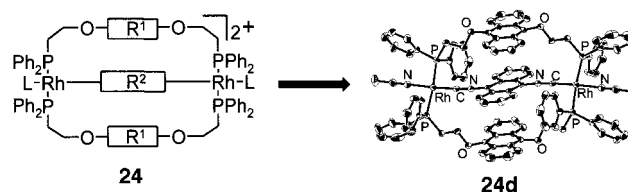
The incorporation of redox-active groups into this ligand system is straightforward and has been accomplished with the synthesis of a ligand based on Wurster's reagent (*N,N,N',N'*-tetramethyl-1,4-phenylenediamine).^[139] This ligand allows the templated synthesis of a homodimetallic macrocyclic structure which has sensitive indicators for the formation of inclusion complexes and the ability to precisely control the electronic environment of the internal cavity. The condensed structure **21d** is formed in quantitative yield, and the amine groups display the anticipated intermediate reactivity towards incoming ligands (relative to the ether and thioether systems). Specifically, reaction with CO alone forms structure **23o**, with one amine and one CO ligand about each metal center (displacement of only one amine from each rhodium center). Access to the fully “opened” macrocycle is accomplished by the addition of excess CH₃CN in the presence of CO to yield macrocycle **23p** (Scheme 7). This system holds promise for the electrochemical control of supramolecular host–guest chemistry, and its properties are currently being investigated.^[139]

The weak-link synthetic strategy has also been used to prepare isostructural macrocycles with two palladium(II) centers.^[138] These structures were formed in quantitative

yields by combining the hemilabile ligands discussed above with a source of “naked” palladium(II) ions ([Pd(CH₃CN)₄][BF₄]₂). Analogous intermediates, **21e** and **21f**, were isolated and characterized and these compounds exhibit similar reactivity to the dirhodium(II) complexes, thus allowing the formation of **23q** and **23r** (Scheme 7). Finally, the closed palladium(II) complexes react with cyanide ligands to produce neutral macrocycles **23s–u** (Scheme 7). Thus far, the generality of the weak-link approach for the synthesis of dinuclear macrocycles of varying size, physical property, and charge has been demonstrated. The coordinative unsaturation of the metal centers in the macrocycles makes this system ideal for designing receptor sites with tailorable molecular recognition properties and, perhaps, catalysts with size- and shape-dependent reactivities and selectivities.

2.3.4. Three-Tiered Metallocyclophanes

The dinuclear metallocyclophanes discussed above have the potential to be used as building blocks to form more complex supramolecular structures. For example, the coordinatively labile metal centers incorporated into the macrocycle skeleton allow arrays to be built up through simple coordination chemistry. Judicious choice of difunctional ligands of the appropriate length to span the interior cavity of the macrocycles can lead to the formation of three-tiered metallocyclophanes. Complexes **24a–d**, in which aryl diisocyanides or dinitriles have been used to bind across the center of the macrocycles have been reported (Figure 7).^[134–136] These structures form in quantitative yield from the corre-



- 24a:** R¹ = 1, 4-C₆(CH₃)₄, R² = 1, 4-(CN)₂C₆H₄, L = CH₃CN
24b: R¹ = 1, 4-C₆(CH₃)₄, R² = 1, 4-(NC)₂C₆H₄, L = CO
24c: R¹ = 9, 10-C₁₄H₈, R² = 1, 4-(CN)₂C₆H₄, L = CH₃CN
24d: R¹ = 9, 10-C₁₄H₈, R² = 1, 4-(CN)₂C₆H₄, L = CH₃CN

Figure 7. Three-tiered metallocyclophanes prepared by the weak-link approach (left). X-ray crystal structure of complex **24d** (right). Reprinted with permission from ref. [136].

sponding macrocycles and difunctional ligands. The aromatic groups of the incoming ligands and the dirhodium macrocycles align in a parallel-planar or cofacial fashion. The ability to place chromophores and fluorophores in such a well-defined geometric arrangement is appealing for the study of the chemical and photophysical interactions of these molecules. The fluorescent anthracene-containing macrocycle **23h** (see Section 2.3.3) binds 1,4-phenylene- and 9,10-anthracene-diisocyanide to form fluorescent triple-layered metallocyclophanes (**24c** and **24d**) in quantitative yield. These compounds exhibit charge-transfer behavior between the aromatic fluorophores (Figure 7).^[136] It is important to note that cyclo-

phanes containing anthracene units have been prepared through conventional stepwise organic synthesis, but these syntheses involve many steps and give extremely low overall yields (5–7 steps, 1–10 % yields).^[140] Additionally, organic triple-layered structures have been prepared by stepwise synthesis and their charge-transfer behavior studied, but none have incorporated three anthracene units and all suffer the same multiple-step synthetic pathways and low yields (5–8 steps, 10–40 % yields).^[141]

2.3.5. Molecular Cylinders

As discussed above, the transition metals in the homodimetallic structures accessed through the weak-link approach allow for further chemistry at the metal centers. For example, the triple-layered structures (**24**) were formed by reaction of difunctional ligands of the appropriate dimensions to span across the interior of the macrocycle. If a rigid difunctional ligand is used which is too large to fit in the interior of the macrocycles, then the ligand links two macrocycle building blocks to form a molecular cylinder (Figure 8). Two such

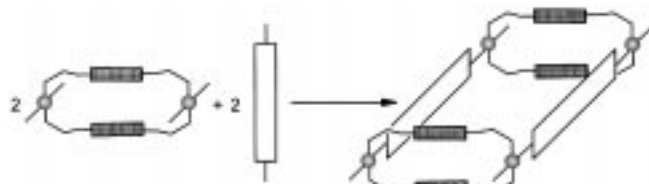


Figure 8. The joining of two macrocycles with rigid difunctional ligands to form a molecular cylinder.

structures, which were formed using 4,4'-biphenyldicarbonyl and -diisocyanide as the linker units, have been reported.^[142] The X-ray crystal structure analysis of one of these cylinders revealed an interior cavity of 1100 Å³. This structure, which has the complexity of a small protein, is a beautiful example of the versatility of the weak-link approach. The structure was assembled in three simple synthetic steps and formed in quantitative yield. The size and complexity of these structures, combined with the tailorability of their structural parameters, which are accessible by the weak-link approach makes it ideal for designing receptors for mesoscale substrates.

3. Summary and Outlook

The directed assembly of supramolecular arrays from discrete molecular building blocks is a topic of significant interest with tremendous potential in the areas of catalysis, molecular electronics, sensor design, and optics. As demonstrated in this Review, one is now able to design and synthesize a myriad of supramolecular coordination complexes with a great deal of control over the complex shape, size, physical properties, and internal cavity dimensions on the basis of the general principles of a few high-yielding reactions in coordination chemistry, which have been exploited in the outlined strategies. A goal of this field now lies in the realization of the promise these strategies offer for designing

and preparing structures with exquisitely tailorable recognition properties. While workers in this field have made major strides in the development of synthetic methods for complex structures, the realization of applications of such structures has lagged behind the progress made in reaction development. The recent advances in these areas towards some of the goals outlined above will be briefly discussed.

3.1. Supramolecular Catalysis

The area of supramolecular chemistry in general has potential to affect the field of catalysis, especially with regard to selective transformations of substrates in complex mixtures. The design and construction of large molecules with well-defined cavities opens the possibilities of host–guest and inclusion chemistry and, therefore, the ultimate goal of selective substrate activation and catalysis. While the synthesis of supramolecular structures, constructed by both covalent and coordination chemistry, has flourished over the past decade, the report of catalytic transformations performed by these systems has lagged behind such developments.^[143] There are some inherent limitations in supramolecular coordination chemistry which are to blame for this lack of progress. Namely, the majority of the complexes reported that have been assembled utilizing the principles of coordination chemistry have only taken advantage of the transition metal centers as building blocks. Therefore, such complexes often have coordinatively inert, saturated metal centers, which precludes their involvement in catalytic transformations without concomitant destruction of the supramolecular complex.

There are several examples in the recent literature where the internal cavity of covalently linked supramolecular structures has been exploited to arrange reactants and stabilize reactive intermediates involved in organic transformations.^[144] Notably, an example of a supramolecular coordination complex being used to facilitate a metal-mediated catalytic transformation was recently reported by Fujita and co-workers.^[96] In this report a cage structure was used as a reverse phase-transfer catalyst for the Wacker oxidation of olefins in aqueous media by free [Pd(en)(NO₃)₂]. While this work represents a significant advance, the long-standing goal of utilizing transition metal centers incorporated in the backbone of supramolecular coordination complexes as active catalytic species has not been realized.

3.2. Supramolecular Complexes as Sensors and Sieves

As described above, a wide range of chromophores, fluorophores, and redox-active functionalities have been successfully incorporated into supramolecular frameworks. When their physical properties are retained, these groups can act as sensitive indicators of guest binding and weak host–guest interactions within the supramolecular cavities. Combined with the rich host–guest chemistry demonstrated by many of these systems they are well-suited for sensing applications.

Initial work reported by Fujita and co-workers on shifts in the ^1H NMR spectra showed that electron-rich aromatic molecules have an affinity for the interior of di- and tetranuclear macrocyclic structures.^[17, 52] These first demonstrations, while not ideal for the design of sensing systems, led to more recent work in which guest binding is detected through luminescence^[13, 136] and/or electrochemistry.^[145, 146]

Both metal- and ligand-based luminescence have been exploited for this application. For example, host–guest interactions can be followed by changes in the emission profiles of molecular squares with rhenium corner fragments by monitoring shifts in the metal-to-ligand charge transfer (MLCT) bands.^[13] A series of dinuclear macrocycles have also been reported which can detect anion binding through the emission from a Ru-bpy group.^[145] If dipyritylporphyrin ligands are used as the walls of tetrarhenium squares then the photophysics of the resulting squares are dominated by the porphyrin chromophore and it can be used to report host–guest binding events.^[13] Ligand-based luminescence has also been used to detect guest inclusion which involves direct coordination of the guest molecule to the metal centers.^[136] While these systems provide proof-of-concept towards the design of sensors with supramolecular coordination compounds, practical sensor arrays based on this chemistry have not yet been demonstrated.

Beer and co-workers have prepared a series of homo- and heterodimetallic macrocycles which take advantage of both luminescence and electrochemical properties to detect the binding of anions inside the cavity.^[145, 146] The electrochemical response, as monitored by both cyclic and square-wave voltammetry, shows cathodic perturbations of the reporting redox-active groups upon binding of anionic guests. The shifts ranged from 10–125 mV depending on the host–guest combination.^[145]

The host–guest properties of supramolecular coordination compounds in the solid state have also been exploited in the design of molecular sieves and sensors. Hupp and co-workers have reported the synthesis of a series of rhenium-based molecular squares with cavity dimensions that depend on the bridging ligand employed (see Section 2.1.5). These squares can be cast into uniform mesoporous thin films which are stable in aqueous media.^[62, 71] X-ray crystal structure data show that, in the solid state, the squares stack on top of one another to generate pores which have the dimensions of the original square. By adjusting the size of the squares used, Hupp and co-workers have demonstrated the size-selective sieving of a mixture of redox-active molecules by electrochemical detection. Additionally, Hupp and co-workers have recently reported the use of these mesoporous thin films of molecular squares as selective sensors for volatile organic compounds in the gas phase.^[72] A quartz-crystal microbalance was utilized to detect the binding of analytes inside the molecular squares.

3.3. Towards Molecular Electronics

Molecular electronics, the miniaturization of electronic circuits to the molecular level, has been an ultimate goal of

supramolecular chemistry since its inception.^[4, 147] This area of application represents the most challenging of those discussed here. While the synthesis of supramolecular structures with variable physical properties has developed greatly, the construction of molecular circuits requires several key technological advances to be realized:

- 1) the synthesis of compounds and complexes which display changes in physical properties that can be precisely controlled through external stimuli,
- 2) the development of techniques to deposit these molecules, or supermolecules, with exact control over their position and orientation, and
- 3) the ability to address individual molecules, or even atoms, selectively.

The largest advances in this area have been towards the first goal, although recent advances in nanolithography for molecular systems look quite promising.^[148] The work of Stoddart and co-workers in this field has produced numerous examples of supramolecular systems prepared through covalent organic chemistry which display specific molecular motion which can be controlled by photochemical and electrochemical changes.^[149] Additionally, Lindsey, Bocian, and co-workers have reported the synthesis of porphyrin arrays that act as molecular optoelectronic gates.^[150] In this area, supramolecular coordination chemistry has produced few examples of complexes which demonstrate the required properties. A notable exception was recently reported by Lehn, Gütllich, and co-workers. The synthesis of a $\text{Fe}_4^{II} [2 \times 2]$ supramolecular grid which exhibits a spin-crossover that is triggered by temperature, pressure, or light, represents an important advance.^[131] This grid complex, synthesized by the principles of the symmetry-interaction approach, is constructed by the combination of 4,6-bis(2',2''-bipyrid-6'-yl)-2-phenylpyrimidine and $\text{Fe}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in acetonitrile at room temperature. The four iron atoms in the resulting molecular grid can be present in either a high-spin (HS) or low-spin (LS) state. The spin state of the iron atoms can be switched by several external perturbations including light, pressure, and temperature. The availability of three distinct magnetic levels (3HS/1LS, 2HS/2LS, and 1HS/3LS) makes this unique system a “multiply switchable multilevel device.”^[131] The application of supramolecular coordination complexes towards the goal of molecular electronics and information storage has great potential and will continue to be the focus of intense investigation.

3.4. Conclusions

The next decade will see rapid advances in the development and utilization of supramolecular coordination complexes as designer catalysts, small and intermediate-sized molecular receptors in sensor devices, molecular transport agents, new materials for molecular electronics, novel light-harvesting structures for solar energy conversion, and perhaps even molecular machines.^[151] The driving force behind the intense interest in the metal-directed synthesis of supramolecular compounds lies in the ease with which many of these structures can be prepared. Indeed, the basic chemical

principles of using metals with predetermined coordination numbers and angles as building blocks and functional units is generally appealing when compared to the tedious, multistep synthetic organic approaches. However, the relatively weak heteroatom bonds (compared to the strong covalent bonds of organic systems) are thermally labile and require additional considerations in order to assure the formation of stable products in high yield. These ideas have been refined into several distinct synthetic approaches. The directional-bonding, symmetry-interaction, and weak-link approaches now provide rational synthetic routes to supramolecular coordination compounds with tailorable physical dimensions, functionalities, substrate-binding capabilities, and chemical properties.

4. Addendum

Since the submission of this manuscript significant progress has been made in this rapidly expanding field. Two review articles of supramolecular coordination chemistry, its progress, and future directions have been recently published by Ward^[152] and Andrews and Raston.^[153] Other relevant work^[154–176] is listed in the Literature Section with keywords or referenced to the relevant section of this review.

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In Search of Practical Esterification

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Esterification is one of the most important reactions in organic synthesis.^[1] It has a long history in both laboratory work and industrial processes on account of its versatility. The simple condensation between a carboxylic acid and an alcohol is the most straightforward way to this end. Thus, numerous methods have been reported, yet they are not necessarily satisfactory from a practical point of view. The difficulty stems primarily from the equilibration of the condensation reaction. The commonest approach to bias the equilibrium in favor of the product side is either by the use of one reactant in excess over the other or the continuous removal of the water formed. The former treatment is not desirable in terms of “atom economy”^[2] since the excess reactant remains to be separated from the product mixture. On the other hand, the complete removal of water is not easy, but a variety of dehydration methods have been put forth. Azeotropy is most frequently invoked, while the addition of dehydrating agents is an alternative choice, although 100% conversion and, hence, 100% yield are, in general, not easy to achieve. Another problem emerges from the base or acid catalysts which are inevitably employed in this reaction. Under such conditions, the tolerance of a wide spectrum of functional groups that is often required in modern synthetic chemistry is not achievable.

It follows from these circumstances that the ultimate goal of esterification should meet the following requirements: 1) the relative amounts of reactant carboxylic acid and alcohol are regulated to the precise 1:1 ratio, 2) the catalyst is neutral, 3) no dehydration technology is necessary, and 4) both conversion and yield are 100%. The esterification by the simplest combination of carboxylic acid, alcohol, and catalyst alone met with success on some occasions, yet the employment of one of the reactants in excess was necessary to attain the satisfactory conversion.^[3] Therefore, a catalytic version that allows a 1:1 reactant stoichiometry has long been desired. Recently, two Japanese groups have come up with new protocols to overcome such difficulties (Table 1).

Yamamoto and co-workers disclosed, after the screening of various Lewis acids, that commercially available $\text{HfCl}_4 \cdot 2\text{THF}$

Table 1. Esterification by use of equimolar amounts of carboxylic acid and alcohol.

$\text{RCOOH} + \text{R'OH} \xrightarrow{\text{cat.}} \text{RCOOR'}$ 1 equiv 1 equiv	
Author	Conditions
Yamamoto	$\text{HfCl}_4 \cdot 2\text{THF}$ (0.2 mol %); Soxhlet extraction with 4-Å molecular sieves; toluene, <i>o</i> -xylene, mesitylene
Tanabe	$\text{Ph}_2\text{NH}_2^+\text{OTf}^-$ (1–10 mol %); toluene, 80 °C

was the most effective for the condensation between an equimolar mixture of carboxylic acid and alcohol.^[4] The reaction was run in refluxing toluene, *o*-xylene, or 1,3,5-mesitylene and furnished nearly quantitative yields of esters (91 to >99%). The catalyst activity is so high that only a 0.2 mol% loading is necessary to achieve high conversions. Sterically hindered secondary alcohols as well as primary alcohols were used, although the reaction with tertiary alcohols did not proceed. Even the condensation between benzoic acid and phenol, which usually proceeds sluggishly, was feasible by increasing the catalyst concentration to 1 mol%. This result is indicative of the broad applicability of the present protocol. The application was further extended to polyester formation by polycondensing ω -hydroxycarboxylic acids or equimolar amounts of aliphatic dicarboxylic acids and aliphatic diols. Despite these advantages, the present protocol seems to suffer from some inconvenience. Although no mention was made on the compatibility of the functional groups, acid-sensitive groups are probably not tolerated as a result of the acidic nature of the catalyst. Moreover, the reaction system is sensitive to water and thus the rigorous dehydration by Soxhlet extraction with 4-Å molecular sieves is indispensable.

Tanabe and co-workers reported another approach which demands no dehydration reagents or equipment.^[5] Diphenylammonium triflate, which is obtainable from diphenylamine and triflic acid, catalyzed the condensation of equimolar amounts of carboxylic acid and alcohol (Table 1). The reaction proceeded by heating the reactants in toluene at 80 °C without recourse to any dehydration technique. The products were isolated by column chromatography in substantially, but not perfectly, high yields (89–96%, except for one case (78%)). Primary and secondary alcohols were used and some functionalities such as ketone and cyclopropane were tolerated.

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In the above protocols the reaction mixture was contaminated by small amounts of starting materials, but the high yields enabled facile isolation of the pure product esters by column chromatography.^[6] There is no problem so long as the isolation of the esters is solely targeted. However, this is not the case in practical processes wherein the remaining reactants need to be recovered. The 1:1 stoichiometry is truly effective only if the 100% conversion is reached because otherwise the two components (recovered carboxylic acid and alcohol) should be separated from the product mixture, which is a less favorable situation than the reaction employing one of the reactants in excess. In this case, the recovery of only one reactant is necessitated on account of the more facile feasibility of the 100% conversion. As such, the 100% yield with equimolar amounts of the reactants which demands no purification step still remains a challenge. The levels of conversion and yield attained in the above studies are not satisfactory in such a strict sense. Nevertheless, these proto-

cols have no doubt made a big step forward along this line and, accordingly, these achievements are expected to pave the way to the ultimate goal.

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Recent Advances in High-Resolution Solid-State NMR Spectroscopy**

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It has long been known that NMR spectroscopy can yield precise information about the structure and dynamics of large biological molecules. The vast majority of NMR studies have been carried out on liquid solution samples owing to the good resolution, namely narrower peaks, as compared to solid samples. Even so, it is often necessary to study the solid state for insoluble biopolymers, such as aggregates or amyloids. There are also significant classes of materials whose properties lie between the solid and liquid states: Membranes and membrane-bound proteins are not strictly solid and may be more accurately described as liquid crystals, since they have a high degree of molecular alignment. Other examples would be extremely viscous liquids or gels, where the molecular mobility is slow or limited. For all of these systems, solid-state NMR investigations can be particularly useful. The question then is not whether to study the liquid or solid form, but how one can get the best information from solid-state NMR methods.

The difficulties of solid-state NMR are due to large anisotropic interactions, namely the through-space dipole–dipole coupling, more often called the dipolar coupling, and the orientational dependence of the chemical shift, called the chemical shift anisotropy (CSA). (Some nuclei possess an electric quadrupole moment, which creates yet another anisotropic interaction, but that will not be discussed further in this article.) Rapid molecular motion in the liquid state removes anisotropic interactions, except for their effects on relaxation. However, in solids these interactions are present at their full strength and they must be dealt with appropriately. There are different experimental approaches in solid-state NMR spectroscopy, depicted in Figure 1, which either circumvent or utilize these anisotropic interactions in order to investigate structures of biological systems.

MAS Solid-State NMR

One approach is to use magic-angle spinning (MAS) in combination with high-power radio-frequency decoupling to remove the chemical shift anisotropy and the dipolar couplings (Figure 1 a). MAS spectra of solids often exhibit sharp resonances at frequencies determined solely by the isotropic chemical shift. In this respect, they resemble NMR spectra of liquids, and the information content is at least qualitatively similar. For example, in multidimensional MAS spectra, chemical-shift correlations are measured, and these yield information about connectivity and proximity, just as in multidimensional NMR of solutions. In the past, MAS solid-

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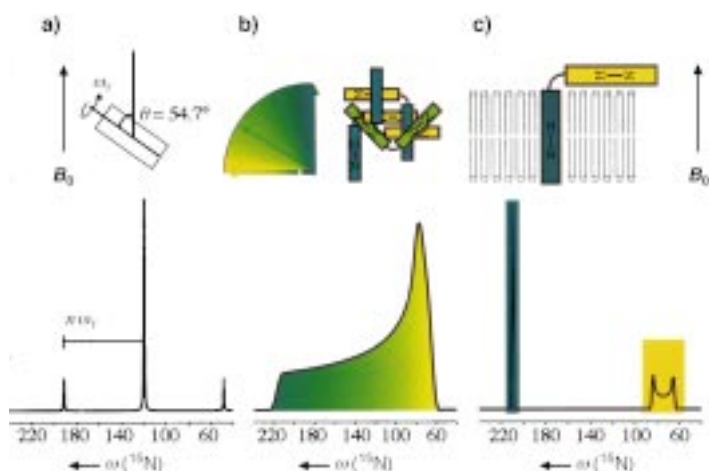


Figure 1. Three methods in solid-state NMR. Above are the experimental approaches, below are the matching ^{15}N NMR spectra. a) In magic-angle spinning (MAS) NMR, the sample is rotated with a rotation speed ω_r around an axis with an angle 54.7° ($=\theta \approx \cos^{-1} \sqrt{1/3}$) relative to the magnetic field B_0 . This leads to an averaging of anisotropic interactions such as dipolar couplings and chemical shift anisotropy. Additional peaks arise from spinning sidebands at multiples of the rotor frequency $n\omega_r$. b) In solid-state NMR of orientationally disordered samples, a broad frequency distribution is observed that reflects the orientational dependence of the chemical shift, the CSA. c) In solid-state NMR of samples oriented in lipid bilayers, the observed chemical shift depends on the orientation of a specific site relative to the bilayer normal. Experimentally, the bilayer normal axis is mechanically oriented parallel to the B_0 field.

state NMR experiments on biological systems have often been performed with samples that were labeled at specific sites with NMR-active isotopes, such as ^{13}C or ^{15}N . These studies have focused on the investigation of one specific structural question at a time and yielded, for example, selected internuclear distances with very high precision. However, selective-labeling schemes lack generality. Therefore, a number of recent reports of nearly complete resonance assignments in uniformly ^{13}C , ^{15}N -labeled proteins by MAS solid-state NMR have generated considerable excitement.

The groups of McDermott, Zilm, and Montelione^[1] have studied BPTI, a 6.5 kDa protein with 58 residues, and the groups of Baldus, de Groot, and Oschkinat^[2] have reported the ^{13}C , ^{15}N resonance assignments of an SH3 domain of 62 residues. Part of the success in both reports stems from the optimized sample preparation conditions that could be found, which yielded narrow line widths in the MAS solid-state spectra. For overexpressed BPTI, microcrystallites were obtained by dialysis methods. For the SH3 domain, different sample preparation methods were compared: a) lyophilization from an aqueous low-salt buffer, b) lyophilization retaining hydration water, c) lyophilization from a solution containing PEG-8000 and sucrose, and d) precipitation from a concentrated $(\text{NH}_4)_2\text{SO}_4$ solution.^[3] The differences in the spectral quality depending on the sample preparation are impressive: The observed line width could be reduced from 190 to 70 Hz for the precipitated SH3 (condition d). Pauli et al.^[2] then showed that, on having such systems in hand, almost complete resonance assignments in uniformly ^{13}C , ^{15}N -labeled proteins can be achieved by solid-state NMR spectroscopy. A representative spectrum, correlating nitrogen

amide backbone nuclei with side chain carbon nuclei from their report is shown in Figure 2.

The report of two uniformly labeled protein systems amenable to MAS solid-state spectroscopy allows optimization of assignment procedures under realistic conditions even for larger protein systems in the solid state. Based on previous methodological developments,^[4] Pauli et al. have used three different experimental schemes for solid-state spectra: The first correlation experiments, NCO and NCA, established connectivity between the amide nitrogen and the directly bound C' and C_α atoms, respectively. Such selective coherence transfers can be achieved in band-selective experiments.^[5] In the next two experiments, one additional transfer step is added to transfer coherence from the C' and C_α atoms into the inter- and intraresidual carbon network, respectively. Depending on the contact time used in these experiments, coherence transfer is predominantly observed to directly bound carbon or to remote carbon atoms.

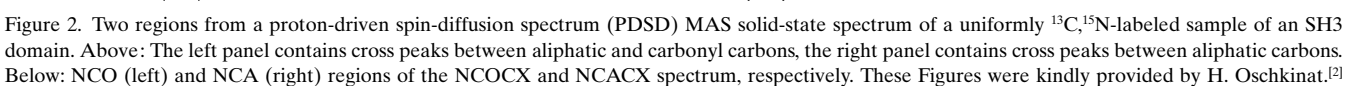
McDermott et al.^[1] commented that the resonance assignments in the solid state show that the isotropic chemical shifts in the solid state are similar to those in the liquid state for the majority of the observed cross peaks. This makes it feasible to transfer chemical shift assignments obtained in solution to the solid-state spectra. Such resonance assignment transfer is an attractive tool, if chemical shifts and their perturbation, such as in the presence of a ligand interacting with a target protein in a lipid environment, are to be compared. At the same time, methods are being developed to measure internuclear ^{13}C – ^{13}C and ^{13}C – ^{15}N distances^[6] as well as torsion angle restraints^[7] in uniformly labeled proteins, which holds promise for the structure determination of proteins in their solid state.

The investigations also underline the importance of high magnetic-field strengths, corresponding to 750 and 800 MHz proton resonance frequencies, for solid-state NMR spectroscopy. McDermott et al.^[1] clearly demonstrate that the resolution improvement at high field strengths will be essential to extend these studies to larger systems assembled in a membrane environment.

Solid-State NMR of Static Oriented Samples

When static spectra, those acquired without MAS, are measured in solids, the situation is much different. Orientation-dependent interactions, such as CSA and direct dipole–dipole coupling of nuclei one bond apart, such as between ^1H and ^{15}N , are then dominant, and multidimensional NMR spectra show the correlations between different anisotropic interactions. The appearance and usefulness of the spectrum depends on how the sample is oriented with respect to the magnetic field.

When the sample is highly oriented (Figure 1c), as a lipid bilayer might be, the spectrum consists of discrete resonances. The spectrum looks superficially like a MAS or solution-state NMR spectrum, but with the important distinction that the frequencies in each dimension depend on the molecular orientation with respect to the magnetic field. This property can be exploited to determine the direction of orientation of various parts of the molecule, and further analysis may reveal the overall structure of the molecule.



ment of cross peaks in order to draw conclusions about the secondary structure. For larger proteins, there is an increasing problem of spectral congestion and overlap, which makes it more difficult to assign the complete spectrum. However, there is a promising new method to alleviate this difficulty, by extending PISEMA into a third dimension based on the amide ^1H CSA.^[10]

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spectrum. Remarkably, this can reveal the presence of a helix and its tilt angle with respect to the bilayer and, after initial assignment, the angular displacement of one repetition unit relative to the next as well as the handedness of the helix. The dipolar coupling between ^1H and ^{15}N and the ^{15}N CSA can be described as tensors. While variations of the CSA may be significant and provide important structural and dynamic information, the two-dimensional signal $F(\omega_2, \omega_1)$ of the PISEMA experiment can be described to a good approximation using a fixed set of uniform values for the CSA tensor elements and their orientation within a peptide plane,^[13] as given by Equation (1). In Equation (1), $\sigma_{11} = 64$, $\sigma_{22} = 77$, and $\sigma_{33} = 217$ ppm and are the principal components of the ^{15}N CSA tensor; the dipole tensor and the σ_{33} component of the CSA tensor are at an angle of $\theta = 17^\circ$ (see Figure 3b). The term $\nu_{\parallel} = -10.4$ kHz is the dipolar coupling found for an amide site parallel to B_0 , τ defines the tilt of the helix axis relative to B_0 (and the bilayer normal), and ρ defines the rotational orientation of a specific site within the helix.

$$\begin{aligned}
 F(\omega_2, \omega_1) &= F(\text{CSA}(\rho, \tau), \text{dipole-dipole coupling}(\rho, \tau)) \\
 &= (\sigma_{11}(-0.828 \cos \rho \sin \tau - 0.558 \sin \rho \sin \tau - 0.047 \cos \tau)^2 \\
 &\quad + \sigma_{22}(0.554 \cos \rho \sin \tau - 0.803 \sin \rho \sin \tau - 0.220 \cos \tau)^2 \\
 &\quad + \sigma_{33}(-0.088 \cos \rho \sin \tau + 0.206 \sin \rho \sin \tau \\
 &\quad - 0.975 \cos \tau)^2, \nu_{\parallel}/2((-0.326 \cos \rho \sin \tau + 0.034 \sin \rho \sin \tau \\
 &\quad - 0.946 \cos \tau)^2 - 1))
 \end{aligned} \quad (1)$$

The cyclic regularity of a helical structure displaces amide NH bonds in a regular manner along the helix. This leads to roughly elliptical patterns of peaks in 2D PISEMA spectra. Figure 3a shows a simulation of the PISEMA spectra as a function of the tilt τ of the helix with respect to the bilayer and the orientation ρ of specific amino acids. The position and shape of the observed ellipsoid in the PISEMA spectrum reflects the helix tilt angle τ . For an angle $\tau = 15^\circ$, two sets of 18 peaks shifted to the downfield part of the ^{15}N spectrum are observed. The fine structure of each ellipsoid, 18 peaks for a regular α -helix, stems from the different amino acids within a helix. Their resonance positions reflect the rotational position of individual sites. The screw sense of the resonance pattern correlates with the helical handedness, as indicated by numbers for individual residues in Figure 3a. It is clear that from the spectral information, the handedness, the tilt, and the rotational displacement per residue (ideally 3.6 residues per turn) of the helices can be determined, and resonances can be assigned based on the position of their two-dimensional correlation peak in the PISEMA spectrum.

Solid-State NMR of Static, Orientationally Disordered Samples

Static (non-MAS) spectra of orientationally disordered solids (Figure 1b) are qualitatively very different from those of oriented samples. The distribution of molecular orientations with respect to the magnetic field leads to a distribution of frequencies, that is, the signal from each site is spread out into a so-called powder pattern. Undesirable spectral overlap is quite likely, unless the sample is labeled specifically at the sites of interest. In the multidimensional spectra of static samples, the signal is spread out in each dimension, typically

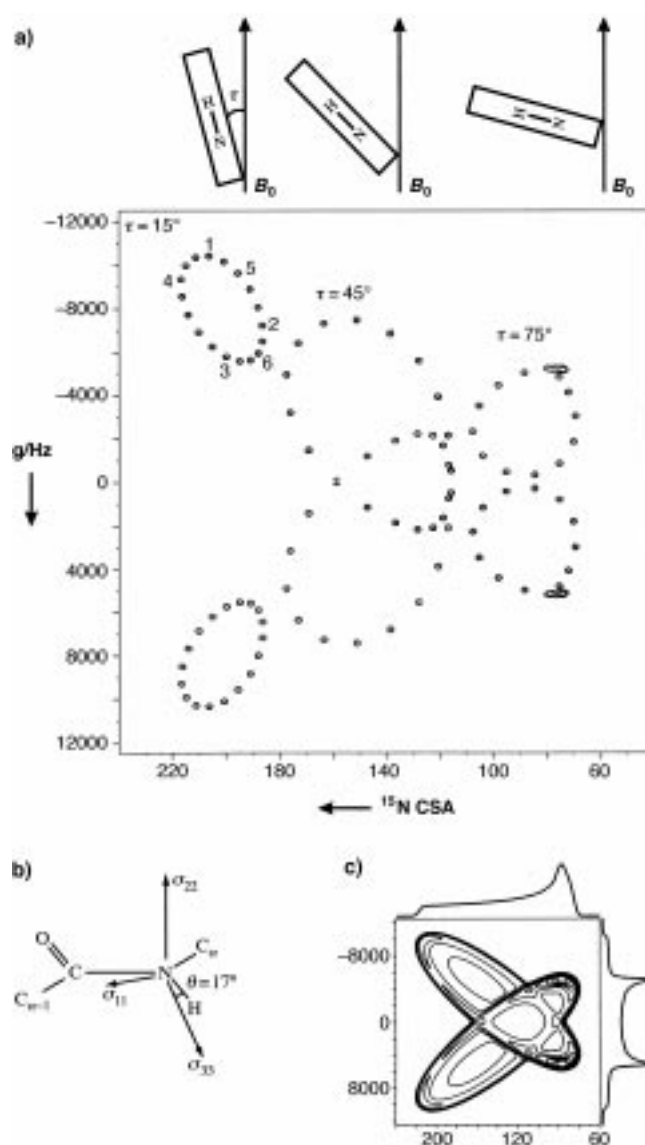


Figure 3. a) Simulation of the 2D PISEMA experiment for different orientations τ of the helix with respect to the bilayer normal. The simulations assume an ideal helix, standard bond angles for peptide planes, and standard values for the relative orientation of the dipole and chemical shift tensors. For each of the helical wheels, ρ (the rotation about the helix axis) was taken in 100° increments (namely, 3.6 residues per helix cycle) for 18 steps. Each peak within an ellipsoid represents a single amino acid residue in a regular helix oriented at an angle τ relative to the bilayer normal. The amino acid position along the helix is indicated for the tilt angle $\tau = 15^\circ$. A right-handed helix will lead to a clockwise positioning of the resonance peaks of the amino acids in the helix (1–6 for $\tau = 15^\circ$). b) Orientation of the ^{15}N CSA tensor elements in the peptide plane. c) Simulation of a dipolar–CSA correlation spectrum of an orientationally disordered sample. Projections along both dimensions reveal the CSA powder pattern (shown on the horizontal axis) and the dipolar Pake pattern (shown on the vertical axis). Parameters for the CSA and dipolar coupling were chosen as for Figure 3a, and an isotropic distribution within the powder was assumed.

forming a pattern of lobes and ridges that indicate the various anisotropic interactions and how they are correlated. A spectrum correlating ^1H – ^{15}N dipole–dipole couplings with the respective ^{15}N CSAs in a static, orientationally disordered sample is shown in Figure 3c; it can be understood as a weighted summation over all helix orientations τ and ρ in

Figure 3 a. These 2D powder patterns are usually analyzed by simulation and iterative fitting, and ultimately they are interpreted in terms of the relative orientations of dipolar and CSA tensors.

Another possibility is to correlate one CSA to another in the polypeptide chain. The group of Meier has used such an approach to determine the chain conformation of a silk protein. In their report, the chain conformation is revealed by examining correlations of ^{13}C CSAs between adjacent carbonyl sites in ^{13}C -labeled silk materials.^[14] This was accomplished by double-quantum/single-quantum correlation spectroscopy that excites double-quantum coherence of adjacent carbonyl nuclei in the first evolution period of the 2D correlation experiment (DOQSY).^[15] The orientation of the carbonyl CSA with respect to the C–O and C–N bonds is known from earlier work. With that, and other prior knowledge such as typical bond angles and distances, analysis of the DOQSY spectrum yields torsion angles of the protein backbone.

For a given pair of backbone torsion angles (ϕ, ψ) , a distinctive 2D powder pattern is observed, as shown in Figure 4. Given an experimental powder pattern, one could

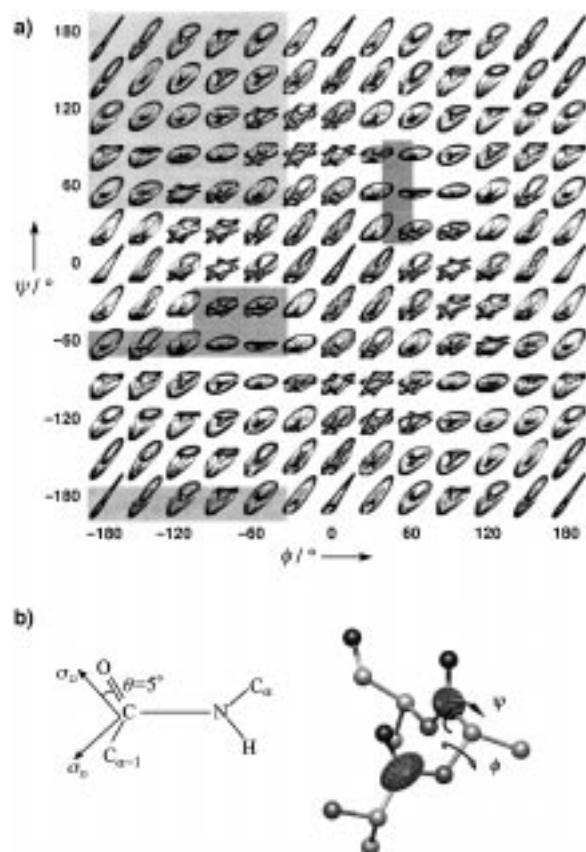


Figure 4. The (ϕ, ψ) dependence of DOQSY spectra in the two-spin approximation. a) Simulated DOQSY spectra as a function of (ϕ, ψ) . Energetically favorable areas of the Ramachandran diagram are marked by a gray background. Each pattern represents a entire ^{13}C DOQSY spectrum, covering a chemical shift range of approximately $\delta = 490$ to 180 ppm in the vertical (double quantum) dimension, and $\delta = 245$ to 90 ppm in the horizontal (single quantum) dimension. b) Molecular orientation of a polypeptide and orientation of the ^{13}C CSA tensor elements in the peptide plane. The following CSA values have been assumed: $\sigma_{33} = 244.8$, $\sigma_{22} = 194.7$, and $\sigma_{11} = 91.6$ ppm, and $\theta = 5^\circ$. The Figure is reproduced, with small alterations, with permission from *Nature*.

solve for the torsion angles by iterative fitting, namely by adjusting ϕ and ψ as parameters of a simulation until it closely matches the measured spectrum. Van Beek et al.^[14] performed a more sophisticated analysis that reconstituted the experimental 2D powder spectrum from simulated spectra weighted by the respective probability density $P(\phi, \psi)$.

Symmetry relations are evident in Figure 4. The patterns are identical for (ϕ, ψ) and $(-\phi, -\psi)$, and one consequence is that DOQSY itself cannot distinguish between left- and right-handed helices. In addition, spectra arising from torsion angle pairs (ϕ, ψ) and (ψ, ϕ) are similar. As van Beek et al.^[14] mention, the two conformations have similar CSA–CSA correlations, which leads to a similarity in the overall outline of the DOQSY pattern. However, there is a difference in the dipolar–CSA correlation, which influences the intensity distribution over the pattern. This breaks the symmetry and allows distinction between these torsion angle pairs.

The DOQSY experiment yields particularly unambiguous results when the protein is isotopically labeled at specific sites. For the silk protein study, this was achieved by feeding ^{13}C carbonyl-labeled alanine to silkworms, with the expectation that alanine–alanine pairs with ^{13}C labeling in adjacent sites would appear predominantly in polyalanine domains. The application of the DOQSY technique to other proteins will require labeling schemes which are similarly well chosen for the particular system at hand.

The mechanical properties of silk depend on the state of polyalanine domains, which form small crystallites embedded within the fiber.^[16] In natural silk fibers, the DOQSY spectrum indicates that the polyalanine domains exist in a β -sheet arrangement. In the same study,^[14] a “silk” solid film was prepared from fluid withdrawn directly from the silk gland, and the DOQSY spectrum revealed that the polyalanine domains were in the α -helical form. These experimental data suggest that the structure of the silk protein depends sensitively on the method of its preparation.

The few examples in this article demonstrate some of the recent excitement in solid-state NMR: It seems possible to assign uniformly labeled proteins in their solid state. Tensor correlations in oriented and in orientationally disordered samples allow the determination of secondary structure elements with high precision. In addition, the tensor-correlation experiments^[15] have considerable impact on new experiments in liquid NMR spectroscopy,^[17–19] so that two fields of NMR, distinct in the past, are now merging together.

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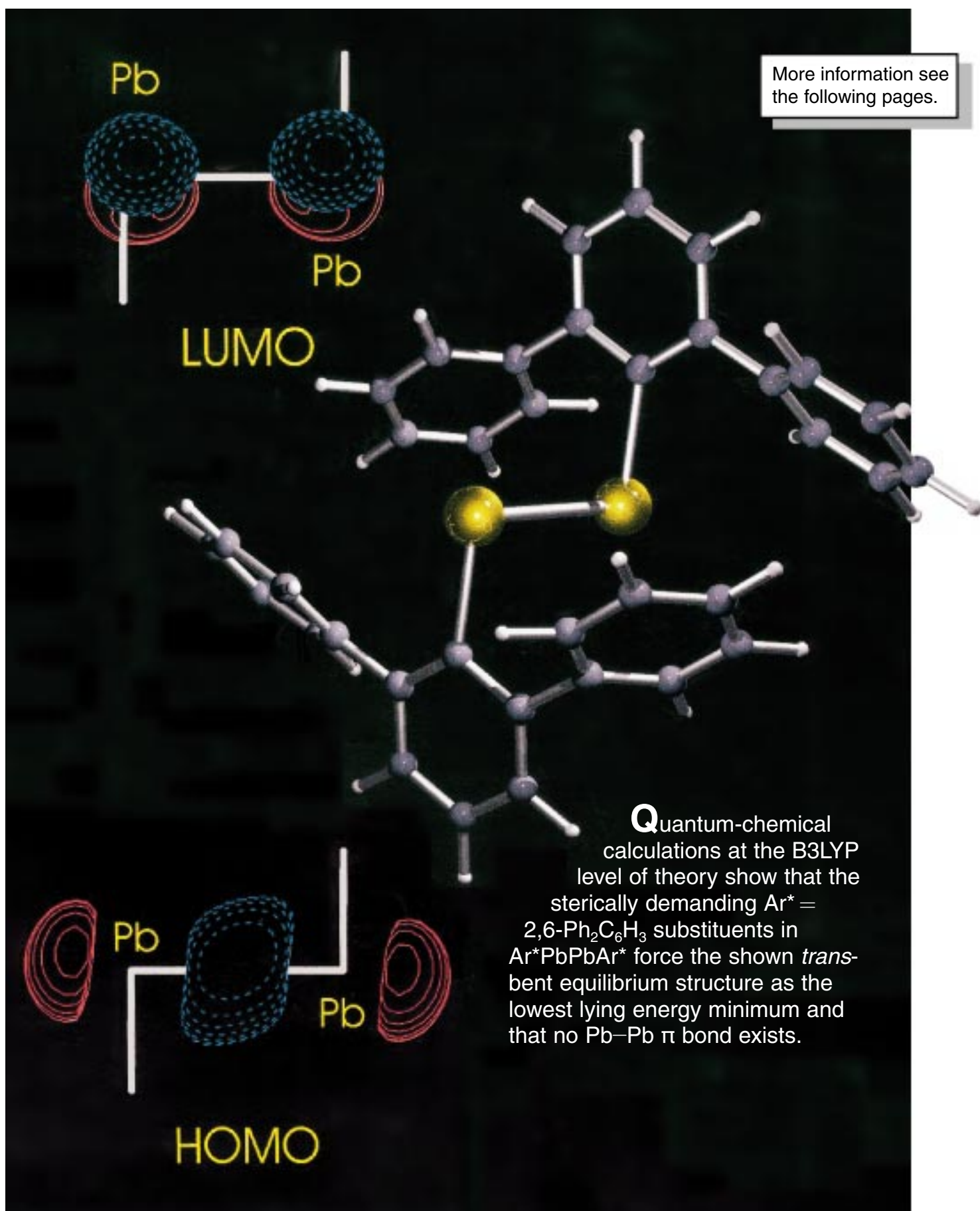
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Turning a Transition State into a Minimum— The Nature of the Bonding in Diplumbylene Compounds RPbPbR ($\text{R} = \text{H}, \text{Ar}$)**

Yu Chen, Michael Hartmann, Michael Diedenhofen,
and Gernot Frenking*

Much progress has been made recently in the synthesis of molecules with multiple bonds between heavier main group elements.^[1] Numerous compounds in particular of the Group 14 elements with the formula $\text{R}_2\text{E}=\text{ER}_2$ ($\text{E} = \text{Si}-\text{Pb}$; $\text{R} = \text{bulky alkyl groups}$) have been prepared and their geometries characterized by X-ray structure analysis.^[2] The structures and bonding of the heavier analogues $\text{R}_2\text{E}=\text{ER}_2$ differ strongly from those of the olefins $\text{R}_2\text{C}=\text{CR}_2$. The former species have a skeleton with a nonplanar geometry and the $\text{E}=\text{E}$ bonding is rather weak, which is evident from the fact that many compounds dissociate in solution.^[3] Much less is known about the heavier Group 14 analogues of alkynes REER . Theoretical studies predicted that the energetically lowest lying structures of Si_2H_2 and Ge_2H_2 are very different from the linear equilibrium geometry of acetylene (Figure 1).^[4]

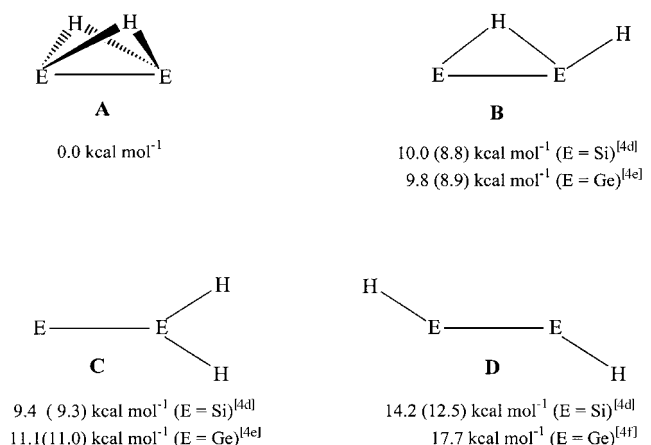


Figure 1. Theoretically predicted energy minima on the E_2H_2 ($\text{E} = \text{Si}, \text{Ge}$) potential energy surface.

The doubly bridged form **A** is calculated as the global minimum on the potential energy surface (PES) of Si_2H_2 and Ge_2H_2 . The singly bridged isomer **B** and the vinylidene form **C** are 9–11 kcal mol^{-1} higher in energy than **A**. The *trans*-bent

form **D**, which resembles most closely the geometry of acetylene, is the highest lying isomer of Si_2H_2 and Ge_2H_2 . The linear forms $\text{HSi}=\text{SiH}$ and $\text{HGe}=\text{GeH}$ are no minima but high-lying saddle points on the PES. They are about 40 kcal mol^{-1} higher in energy than **A**.^[4] Gas-phase spectroscopic investigations of Si_2H_2 have been reported which also suggest that the most stable isomers have the bridged geometries **A** and **B**.^[6] Until recently these were the only experimental studies about the heavier Group 14 analogues of alkynes. The doubly bridged form **A** has been calculated for Pb_2H_2 but the other isomers have not been investigated.^[5]

The recent report by Power and co-workers^[7] about the synthesis and X-ray structure determination of 2,6-Trip₂C₆H₃PbPb-2,6-Trip₂C₆H₃ (Trip = 2,4,6-*i*Pr₃C₆H₂) (**1Ar**) is a breakthrough in the chemistry of heavier Group 14 analogues of alkynes. The isolation of a stable compound with the formula RPbPbR is not only a great success experimentally, the unusual geometry of **1Ar** (Figure 2a) indicates that

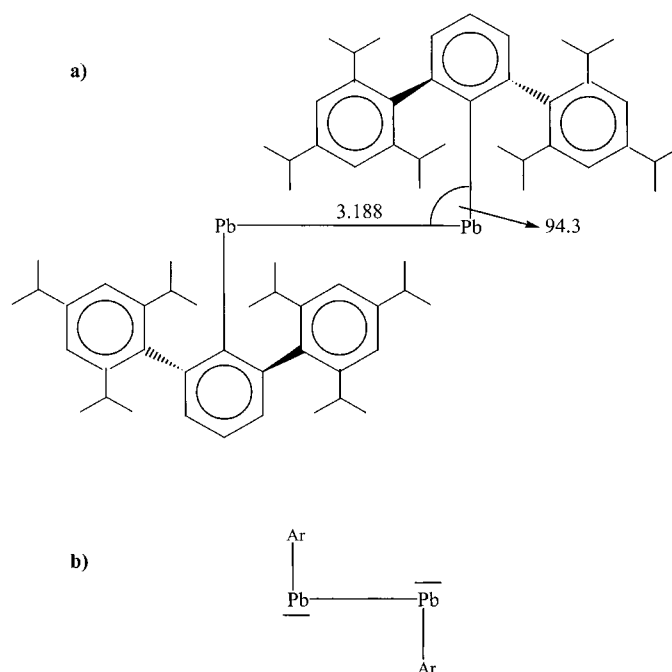


Figure 2. a) Graphical representation of the molecule 2,6-Trip₂C₆H₃PbPb-2,6-Trip₂C₆H₃ (Trip = 2,4,6-*i*Pr₃C₆H₂) (**1Ar**); the experimental Pb-Pb bond length [Å] and C-Pb-Pb bond angle [°] are taken from reference [7]. b) Proposed bonding for **1Ar**.

the bonding of the molecule is different from the $\text{E}-\text{E}$ bonding in the species **A–D** (Figure 1). The rather long Pb-Pb interatomic distance in **1Ar** (3.188 Å) and the small C-Pb-Pb angle (94.26°) led the authors to suggest that the molecule has only a Pb-Pb single bond.^[7] They proposed that the 6p(π) atomic orbitals at the lead atoms are empty and that the Pb-Pb and Pb-C bonds are formed from the remaining two valence p(σ) orbitals of each Pb atom without significant hybridization with the 6s orbital. The latter orbital accommodates a lone pair of electrons which is found at each Pb. Thus the lead atoms have an electron sextet in the valence shell (Figure 2b).

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The above-mentioned suggestion about the bonding in **1Ar** was made using Pauling's proposed correlation between bond angle and hybridization.^[8] However, it has been shown by Kutzelnigg^[9] that the correlation is not valid for heavier elements. The bonding shown in Figure 2b does not agree with the *trans*-bent structure **D** which has an out-of-plane π bond. To investigate the bonding in **1Ar** with quantum-chemical methods we carried out density functional theory (DFT) and ab initio calculations^[10] of the parent system Pb_2H_2 (**1H**) and the phenyl-substituted species Pb_2Ph_2 (**1Ph**). We also calculated the equilibrium structure and bonding of the model compound $\text{Ar}^*\text{PbPbAr}^*$ (**1Ar**) ($\text{Ar}^* = 2,6\text{-Ph}_2\text{C}_6\text{H}_3$).

The calculated structures of **1H** are shown in Figure 3. The doubly bridged form **1H(A)** is the theoretically predicted global minimum on the Pb_2H_2 PES. The calculated geometry is very similar to the theoretical structure which was reported by Han et al. using a relativistic Hartree–Fock method.^[5] The singly bridged form **1H(B)** is 15.6 kcal mol^{−1} higher in energy than **1H(A)**. However, **1H(B)** is not an energy minimum at the B3LYP level of theory.^[15] Calculation of the vibrational frequencies showed that **1H(B)** has one imaginary frequency and thus, is a transition state. The only other energy minimum

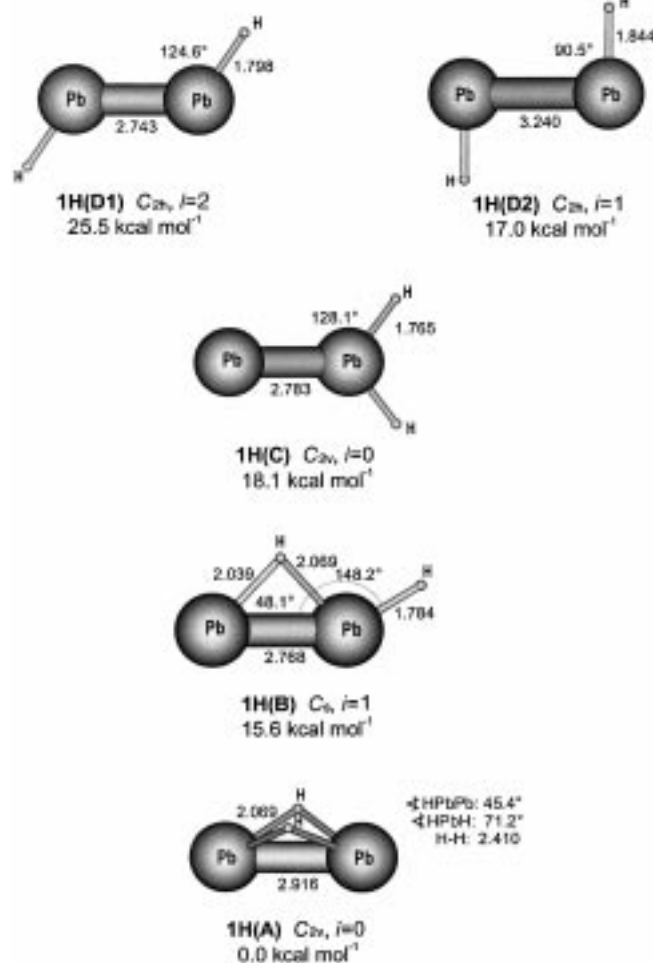


Figure 3. Calculated stationary points on the Pb_2H_2 singlet PES at the B3LYP level with information on the number of imaginary frequencies (i) and relative energies. Bond lengths in Å and bond angles in degrees.

form on the Pb_2H_2 singlet PES^[16] is the vinylidene analogue **1H(C)**. This isomer is 18.1 kcal mol^{−1} higher in energy than **1H(A)** (Figure 3).

We searched for *trans*-bent forms of Pb_2H_2 by using theoretical methods. Geometry optimizations with the constraint of planar symmetry yielded two structures **1H(D1)** and the energetically lower lying form **1H(D2)** (Figure 3). The former species is the lead analogue of the structure **D** which was found as a high-lying energy minimum on the Si_2H_2 and Ge_2H_2 PES.^[4] The H–Pb–Pb bond angle (124.6°) of **1H(D1)** is similar to the values which have been reported for the **D** forms of Si_2H_2 and Ge_2H_2 . Inspection of the calculated orbitals showed that **1H(D1)** has an occupied Pb–Pb π orbital as HOMO (Figure 4a). The second *trans*-bent form **1H(D2)**

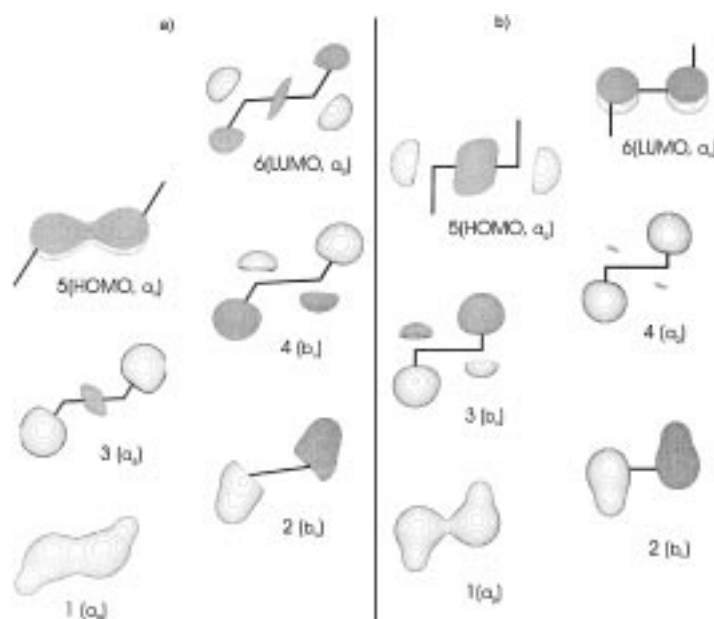


Figure 4. Plot of the valence orbitals of **1H(D1)** (a) and **1H(D2)** (b).

has a significantly longer Pb–Pb distance (3.240 Å) than **1H(D1)** (2.743 Å) and a smaller H–Pb–Pb bond angle (90.5°). Analysis of the electronic structure of **1H(D2)** showed that the HOMO is a σ orbital which can be described as a lone-pair orbital, while the Pb–Pb π orbital is the LUMO (Figure 4b). Thus, HOMO and LUMO of **1H(D1)** and **1H(D2)** are exchanged and the former species can be considered as the first excited singlet state of **1H(D2)** with the same symmetry (^1A_g). The lower energy of **1H(D2)** can be explained with the electronic structure of PbH in the doublet electronic ground state and with the doublet $\rightarrow$ quartet excitation energy. Figure 5 shows that the dimerization of PbH in the $^2\Pi$ ground state via coupling of the unpaired electrons directly leads to **1H(D2)**, while the $^4\Sigma^-$ excited state of PbH is the reference state for the higher lying π -bonded form **1H(D1)**. The calculations suggest that **1H(D1)** is higher in energy than **1H(D2)** because the $^2\Pi \rightarrow ^4\Sigma^-$ excitation energy of PbH is larger than the energy gain of the Pb–Pb π bond in the former isomer. Calculations at the B3LYP level show that the

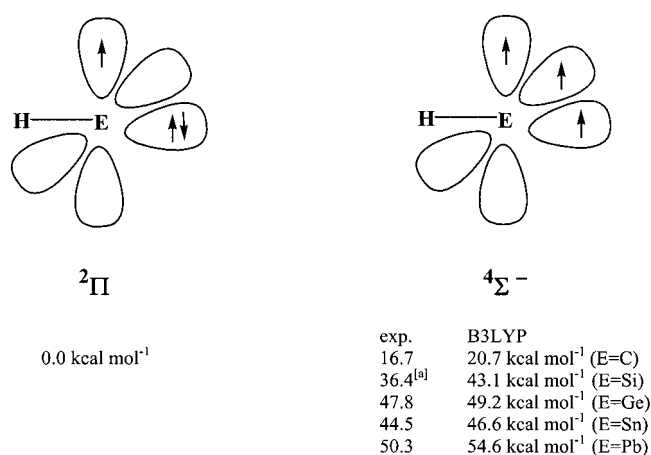


Figure 5. Schematic representation of the $^2\Pi$ electronic ground state and $^4\Sigma^-$ excited state of EH (E=C–Pb). Calculated $^2\Pi \rightarrow ^4\Sigma^-$ excitation energies at the B3LYP level. Experimental values were taken from ref. [19]. [a] The full configuration interaction estimate of SiH was taken from ref. [20].

$^2\Pi \rightarrow ^4\Sigma^-$ excitation energy of PbH is the highest among the Group 14 hydrides EH (Figure 5). Furthermore, the π -bond energy decreases for heavier atoms of the same group.^[9] The calculated excitation energies of EH are supported by the experimental values and high-level ab initio data which are also shown in Figure 5. The good agreement between theory and experiment indicates that the theoretical values should be quite reliable.

The calculated Pb–Pb distance and the H–Pb–Pb angle of **1H(D2)** agree very well with the experimental values of **1Ar**.^[7] However, **1H(D2)** is a high-lying transition state and not an energy minimum on the Pb₂H₂ PES. We investigated the question of whether the relative energies of structures **A** and **D** might be reversed for the phenyl-substituted system Pb₂Ph₂ (**1Ph**). Figure 6 shows the calculated geometry of **1Ph(A)**. The DFT calculations predict an unsymmetrical bridging of the lead atoms by the phenyl substituents, while the MP2 method gives a symmetrical structure with Pb–C distance of 2.579 Å. The Pb–C bond lengths at the B3LYP level are 2.467 and 2.780 Å. The calculations suggest that the isomer **1Ph(A)** is the global minimum on the Pb₂Ph₂ potential energy surface. The *trans*-bent forms **1Ph(D1)** and **1Ph(D2)** are 10.0 and 8.0 kcal mol⁻¹ higher in energy than **1Ph(A)**.

Inspection of the orbital structure showed that the Pb–Pb bonding of **1Ph(D1)** and **1Ph(D2)** is the same as in **1H(D1)** and **1H(D2)**, that is the former has a Pb–Pb π bond, while the latter has a lone pair of electrons at each lead atom. Note that **1Ph(D2)** is only 2.0 kcal mol⁻¹ lower in energy than **1Ph(D1)**, while **1H(D2)** is 8.5 kcal mol⁻¹ more stable than **1H(D1)**.^[17] The phenyl-substituted structures **1Ph(D1)** and **1Ph(D2)** are like the parent compounds **1H(D1)** and **1H(D2)** not minima on the PES. The calculations give one imaginary frequency for **1Ph(D2)** and two imaginary frequencies for **1Ph(D1)**. Thus, the experimentally observed stability of **1Ar** cannot be explained with electronic effects of the aryl substituents.

We finally calculated the model compound **1Ar*** which has bulky substituents (Ar* = 2,6-Ph₂C₆H₃) bonded to the lead

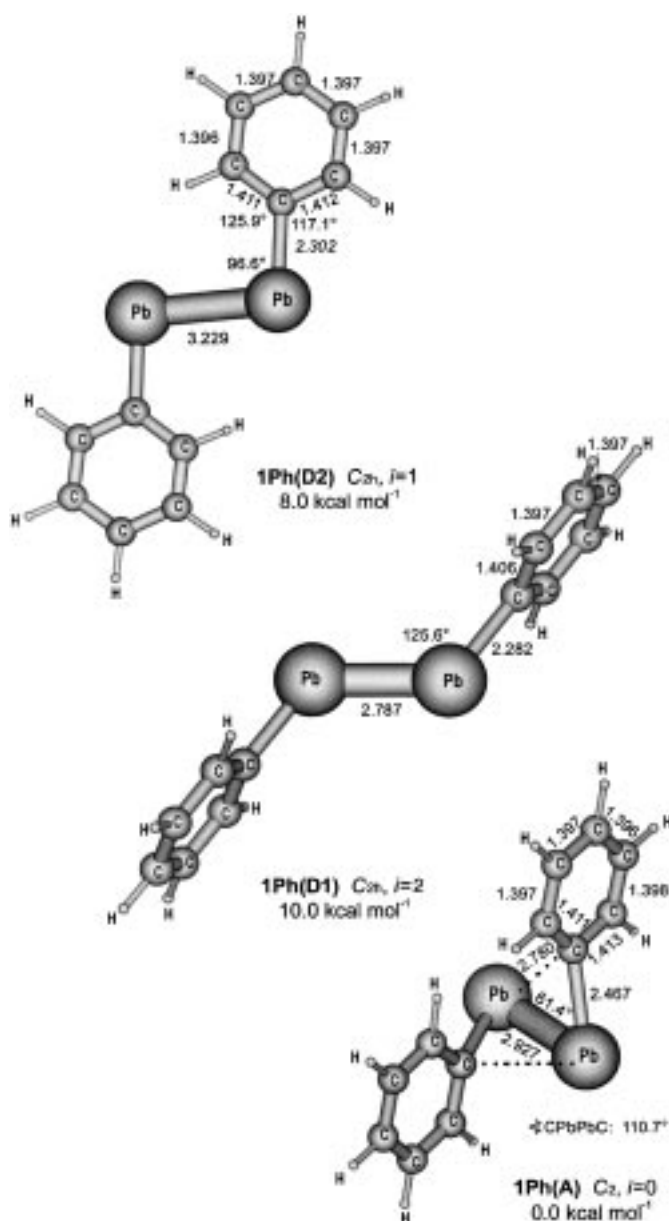


Figure 6. Calculated stationary points on the Pb₂Ph₂ singlet PES at the B3LYP level with information on the number of imaginary frequencies (*i*) and relative energies. Bond lengths in Å and bond angles in degrees.

atoms. The geometry optimization of a structure in which the Ar* groups are in a bridging position like in **1Ph(A)** failed because of steric repulsion between the large substituents. The calculations rather yielded the *trans*-bent form **1Ar*(D2)** (Figure 7). Calculation of the Hessian matrix showed that, unlike **1Ph(D2)**, **1Ar*(D2)** is an energy minimum. The orbital analysis revealed that there is no Pb–Pb π bond in **1Ar*(D2)**. The calculated Pb–Pb bond length (3.213 Å) and the C–Pb–Pb angle (91.2°) are very similar to the experimental data of **1Ar** (Figure 2a). They are also similar to the calculated values of **1H(D2)** and **1Ph(D2)**. However, the latter structures are transition states and not energy minima. It follows that the steric effect of the large aryl substituents Ar* not only stabilizes the *trans*-bent form **D2** relative to the other isomeric forms **A–C** energetically, it also contributes to **D2** becoming

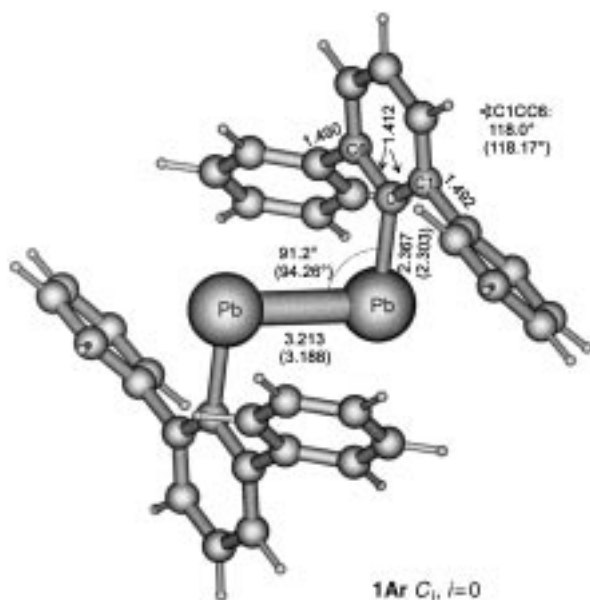


Figure 7. Calculated geometry of **1Ar*(D2)** at the B3LYP level. Bond lengths in Å and bond angles in degrees. Experimental values of **1Ar** are given in parentheses.

an energy minimum rather than a transition state. The lower energy of the six-valence-electron form **D2** compared with **D1** is an electronic effect which is already found in the parent system **1H(D)**.

The results presented here indicate that the lighter homologues of **1Ar** with E = Si – Sn might also be isolated. Recent experimental work has shown that the compound $\text{Si}_2(2,6\text{-Me}_2\text{C}_6\text{H}_3)_2$ (Mes = 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2$) is probably formed as an intermediate.^[18] Our calculations suggest that $\text{Si}_2(2,6\text{-Me}_2\text{C}_6\text{H}_3)_2$ should rather display bonding like that in **D1**, because the energetically lowest *trans*-bent form of Si_2H_2 has a π bond.^[21] We are currently investigating the structure and bonding of E_2R_2 (E = Si – Sn; R = H, Ar).

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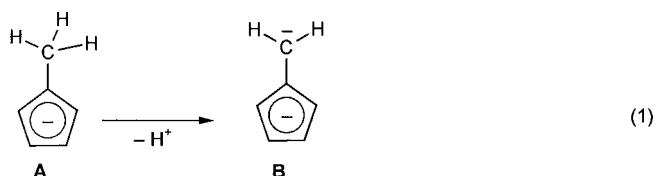
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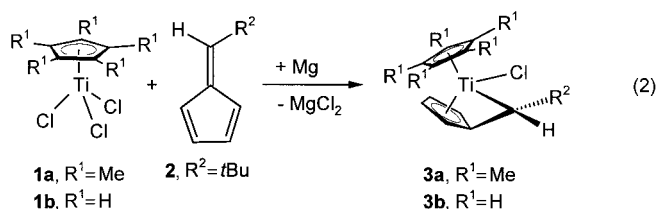
A Novel Route to Fulvene Complexes of Titanium—Diastereoselective Complexation of Pentafulvenes to Cyclopentadienyltitanium Fragments**

Rüdiger Beckhaus,* Arne Lützen, Detlev Haase, Wolfgang Saak, Jörg Stroot, Sigurd Becke, and Jürgen Heinrichs

Metallocene compounds dominate broad fields in organo-metallic chemistry.^[1] Particularly, the bent dicyclopentadienyl derivatives of titanium group metals have gained great importance as catalysts in olefin polymerization.^[2] It was already observed at an early stage that alkyl-substituted ligands such as $C_5Me_xH_{5-x}$ ($x = 1-5$) undergo spontaneous C–H activation under thermolytic conditions leading to fulvene complexes.^[3] Recently these so-called “tuck-in” complexes have attracted more and more interest not only with regard to their coordination chemistry^[3d, 4, 5] but also with regard to their catalytic properties.^[6] The conversion **A** $\rightarrow$ **B** can be discussed formally as deprotonation of an alkyl cyclopentadienyl ligand under formation of a fulvene dianion [Eq. (1)].^[7]



Herein we report on the first direct complexation of fulvenes to titanium(II) fragments.^[8] Treatment of a solution of the cyclopentadienyltitanium trihalides $[Cp^*TiCl_3]$ (**1a**) ($Cp^* = C_5Me_5$) or $[CpTiCl_3]$ (**1b**) ($Cp = C_5H_5$) in THF with magnesium in the presence of 6-*tert*-butylfulvene (**2**) (molar ratio 1:1:1) led to a color change from red (**1a**) and yellow (**1b**), respectively, to dark green in only one hour [Eq. (2)]. After



removal of the solvent, addition of *n*-pentane to the residue, and separation from insoluble $MgCl_2$ by filtration, **3a** and **3b** can be isolated as dark green, needle-shaped crystals. The complex formation proceeds in a highly diastereoselective manner (*de* > 98%).

The structures of **3a** and **3b** have been confirmed by X-ray structure analysis,^[9] and Figure 1 shows the structure of **3a** as an example.^[10] Comparable structural data have been found for **3b**, consequently both compounds are discussed together.

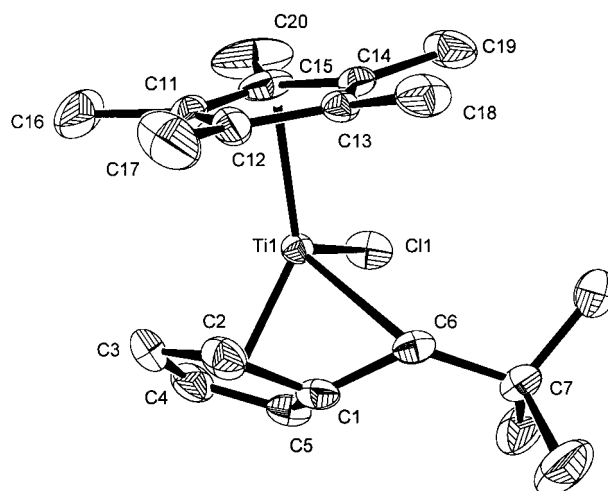
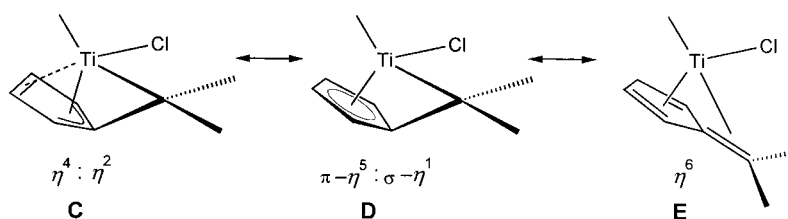


Figure 1. Structure of **3a** in the crystal (50% probability, without H-atoms). Selected bond lengths [Å] and angles [°] (values for **3b** in parentheses): Ti–C1 2.151(2) (2.155(2)), Ti–C6 2.355(2) (2.367(2)), Ti–C2 2.279(2) (2.286(2)), Ti–C5 2.293(2) (2.291(2)), Ti–C3 2.446(3) (2.443(2)), Ti–C4 2.452(2) (2.446(2)), Ti–C1 2.355(1) (2.354(1)), Ti–Ct2 1.993(2) (1.991(2)), Ti–Ct1 2.062(2) (2.045(2)), C1–C6 1.432(3) (1.434(3)), C1–C2 1.431(4) (1.443(3)), C1–C5 1.440(3) (1.440(3)), C2–C3 1.401(4) (1.395(3)), C4–C5 1.394(4) (1.400(3)), C3–C4 1.395(4) (1.405(3)); Ct1–Ti–Ct2 136.8 (138.3) (Ct1 = ring centroid of C11–C15, Ct2 = ring centroid of C1–C5).

Generally, the coordinated fulvene can be considered as a neutral olefinic (**E**, Ti^{II} complex) or as a dianionic ligand (**C**, Ti^{IV} complex; Scheme 1).

Compared to classical $[(\eta^5-Cp)_2Ti]$ derivatives, in **3a** and **3b** the normal from the metal center to the C1–C5 plane is shifted by 0.32 and 0.31 Å, respectively, from the ring centroid



Scheme 1. Coordination modes of fulvene ligands.

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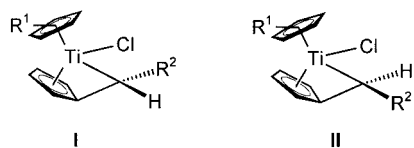
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

in the direction of C1. Hence, the Ti–C3 and Ti–C4 distances are considerably longer than the other Ti–C distances. The concurrent shortening of the C3–C4 bond (1.395(4) (3a), 1.405(3) Å (3b)) compared to that in free fulvenes (1.476,^[11a] 1.462(9) Å^[11b]) is an indication for a trimethylenemethane-like $\eta^4:\eta^2$ -coordination (C) as described for fulvene complexes with ansa-structure.^[4b, 12] The angle θ formed between the C1–C6 bond and the plane C1–C5 in 3a and 3b (35.6°) is in the expected range for this class of compounds (35(1)°^[5]). The distance Ti–C6 (2.355(2) Å 3a, 2.367(2) Å 3b) is longer than that in exocyclic unsubstituted fulvene complexes (2.281(14) Å^[5]). NMR data confirm the structural integrity of compounds 3a and 3b in solution. The proton signals in 3a and 3b are shifted upfield compared with those for 2, with large differences for the signal positions of the fulvene protons.^[10] Owing to the change of hybridization from C_{sp}² to C_{sp}³ expected for C and D, the H6 resonance signal experiences the strongest shift to high field (δ = 6.18 (2), 1.68 (3a), 2.04 (3b)). Contributions of mesomer E can be concluded, however, from the value of the C–H coupling constant for the exocyclic carbon atom C6 ($^1J(\text{C},\text{H})$ = 149.8 (2), 148.6 (3a), 144.0 (3b) Hz), which is in the olefinic region, and from the UV/Vis spectral data. Therefore, the green color of 3a and 3b results from a weak absorption ($\lambda_{\text{max}}(\epsilon)$ = 670 (150) (3a), 665 nm (150) (3b)) probably caused by d–d transitions. Thus, electron density remains at the titanium center and this corresponds with a lower oxidation state.

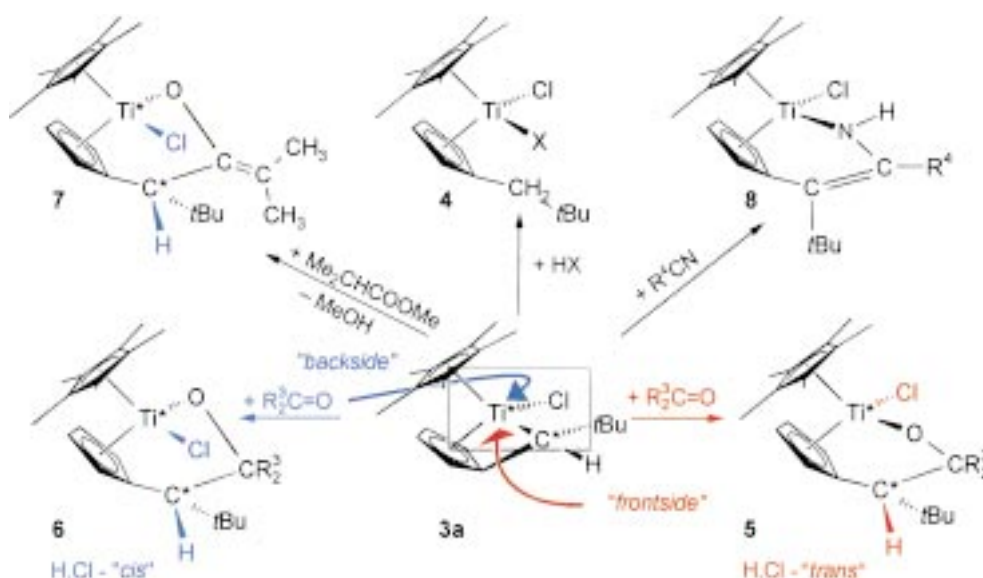
The high diastereoselectivity of the formation of 3a and 3b is caused by the comparatively high difference in energy between the diastereomeric pairs I and II (Scheme 2).^[16] Density functional theory (DFT) calculations with the



Scheme 2. Diastereomeric pairs I and II.

B3LYP functional show for 3a ($\text{R}^1 = \text{Me}$, $\text{R}^2 = t\text{Bu}$) preference for the diastereomer I over II by 29.1 kcal mol^{−1}. This difference in energy decreases on lowering the steric demands of the fulvene substituents. For $\text{R}^1 = \text{R}^2 = \text{Me}$ the difference is lowered to 4.5 kcal mol^{−1}. This behavior corresponds with the experimental results for the synthesis of $[(\text{C}_5\text{R}_1)(\text{C}_5\text{H}_4=\text{CR}^2\text{H})\text{TiCl}]$ complexes with different substituents: *de* = 98 % ($\text{R}^1 = \text{Me}$, $\text{R}^2 = i\text{Pr}$), 49 % ($\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$), 81 % ($\text{R}^1 = \text{H}$, $\text{R}^2 = i\text{Pr}$).^[17a]

Compared with the described dianionic character of the fulvene ligands, a change of reactivity is observed. Whereas free fulvenes undergo reactions with nucleophiles, due to the electrophilic character of the exocyclic carbon, the C6 position in the titanium–fulvene complexes becomes strongly nucleophilic. First examples of the reactivity are given in Scheme 3.^[17] Mixed substituted titanocene complexes 4 are formed with simple electrophiles (HX, X = OH, Cl, RO). Insertion reactions with ketones confirm the side differentiation during the primary attack according to the substrate (“frontside” and “backside” attack, respectively). Thus, the



Scheme 3. Selected subsequent reactions of 3a.

diastereomers 5 and 6 are formed in a reaction of 3a with benzophenone derivatives $\text{R}^3\text{C}=\text{O}$ ($\text{R}^3 = p\text{-XC}_6\text{H}_4$; X = H, F, Cl, Br, Me, MeO, Me₂N). These differ in the arrangement of the fulvene proton (H6) to the chlorine atom related to a plane formed by the diastereogenic centers and the O atom. The separation of the diastereomers can be achieved for the used benzophenones by selective crystallization, owing to the low solubility of 6 in *n*-hexane. The ratio of 5 to 6 is controlled by electronic and steric properties of the used ketones. With $\text{R}^3 = p\text{-NMe}_2\text{C}_6\text{H}_4$ the formation of 5 dominates, whereas with $\text{R}^3 = p\text{-FC}_6\text{H}_4$ the *cis* isomer 6 is preferred. Unlike the used benzophenones, camphor (bulky carbonyl compound) reacts exclusively to give 6. With isomethyl butyrate (less electrophilic carbonyl carbon atom) exclusively isomer 7 is isolated as a result of a primary “backside” attack, followed by thermal elimination of methanol. Insertion reactions with nitriles take place in a similar manner, but the stereochemical information is lost because of an imine–enamine rearrangement to give 8 ($\text{R}^4 = \text{C}_6\text{H}_5\text{-}p\text{-Cl}$).

The described fulvene complexes of titanium, easily available through the reported diastereoselective procedure, and their subsequent reactions have substantially enriched the access to substituted metallocene derivatives of early transition metals especially those with stereochemically, well-defined σ,π ligands.

Experimental Section

General remarks: The compounds **3a** and **3b** were prepared and handled in a nitrogen atmosphere with rigorous exclusion of oxygen (Schlenk technique). Solvents were thoroughly dried and saturated with nitrogen prior to use.

3a: A solution of **2** (1.356 g, 10.1 mmol) [13] in THF (20 mL) was added dropwise to a reaction mixture of **1a** (2.895 g, 10 mmol) [14] and Mg (0.255 g, 10.5 mmol) in THF (40 mL). After about 1 h the color of the solution turned from red to green. The reaction mixture was stirred at room temperature until the magnesium was consumed (8 h). After the THF had been removed, the residue was dissolved in *n*-pentane (60 mL), and separated from the insoluble MgCl₂ by filtration. The filtrate was evaporated to 10 mL and cooled to −20 °C. Compound **3a** was isolated as dark green, needle-shaped crystals (2.388 g, 68 %). M.p. 118 °C; ¹H NMR (500 MHz, C₆D₆, 300 K): δ = 1.15 (s, 9H; *t*Bu), 1.68 (s, 1H; H₆), 1.71 (s, 15H; Cp*), 3.17 (m, 1H; H₂), 4.76 (m, 1H; H₃), 5.96 (m, 1H; H₄), 6.60 (m, 1H; H₅); ¹³C NMR (125 MHz, C₆D₆, 300 K): δ = 13.1 (C₅(CH₃)₅), 33.6 (C(CH₃)₃), 35.6 (C(CH₃)₃), 115.7 (C₃), 119.2 (J(C,H) = 148.6 Hz, C₆), 119.7 (C₄), 120.2 (C₂), 121.8 (C₅(CH₃)₅), 126.1 (C₅), 129.6 (C₁); [15] MS (70 eV): *m/z* (%): 352 (6) [M⁺], 316 (100) [M⁺ − HCl], 218 (32) [M⁺ − C₁₀H₁₄]; IR (KBr): $\tilde{\nu}$ = 2947, 2903, 2863, 1481, 1452, 1377, 1360, 1248, 1217, 1049, 1024 cm^{−1}; UV/Vis (*n*-pentane): λ_{max} (ε) = 670 nm (150); C,H analysis calcd (%) for C₂₀H₂₉TiCl: C 68.09, H 8.29; found: C 68.57, H 8.03.

3b: Procedure analogous to that for **3a**, [CpTiCl₃] (2.194 g, 10 mmol), [13] Mg (0.255 g, 10.5 mmol), **2** (1.356 g, 10.5 mmol) [14] gave **3b** (1.362 g, 48 %). M.p. 92 °C; ¹H NMR (500 MHz, C₆D₆, 300 K): δ = 1.05 (s, 9H; *t*Bu), 2.04 (s, 1H; H₆), 3.25 (m, 1H; H₂), 4.80 (m, 1H; H₃), 6.17 (m, 1H; H₄), 6.61 (m, 1H; H₅), 5.84 (s, 5H; C₅H₅); ¹³C NMR (125 MHz, C₆D₆, 300 K): δ = 32.7 (C(CH₃)₃), 35.6 (C(CH₃)₃), 111.0 (C₅H₅), 111.4 (C₃), 116.5 (J(C,H) = 144.0 Hz, C₆), 117.2 (C₂), 121.5 (C₄), 127.3 (C₁), 127.5 (C₅); [15] MS (70 eV): *m/z* (%): 282 (2) [M⁺], 246 (95) [M⁺ − HCl], 148 (100) [M⁺ − C₁₀H₁₄]; IR (KBr): $\tilde{\nu}$ = 3102, 2959, 2905, 2866, 1466, 1454, 1387, 1362, 1252, 1215, 1194, 1159, 1055, 1022 cm^{−1}; UV/Vis (*n*-pentane): λ_{max} (ε) = 665 (150); C,H analysis calcd (%) for C₁₅H₁₉TiCl: C 63.74, H 6.78; found: C 63.70, H 7.00.

Subsequent products **4–8** were characterized spectroscopically and structurally, as well as by correct elemental analyses. Preparation of **5** and **6**: A solution of benzophenone (0.911 g, 5.0 mmol) (**a**) in *n*-hexane (10 mL) was added to a stirred solution of **3a** (1.764 g, 5.0 mmol) in *n*-hexane (20 mL) at room temperature. After 8 h, **5a** began to precipitate as a yellow nacreous deposit. After a total reaction time of 60 h, **5a** was isolated by filtration and drying (82 %). After evaporation to 10 mL and cooling to −20 °C, **6a** (12 %) was isolated from the filtrate as yellow-orange, cube-shaped crystals. (An analogous procedure was used for other benzophenone derivatives; reaction conditions for the reaction with camphor: 8 d 60 °C).

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Fabrication of Micro-Chain Mail by Simultaneous, Patterned Electrodeposition on a Plane and Multiple Cylinders**

Hongkai Wu, Sue Whitesides, and George M. Whitesides*

Herein we describe a method for forming complex three-dimensional (3D) microstructures by decomposing them into substructures to be patterned on separate substrates, then juxtaposing the patterned substrates, and joining the substructures to form the desired structures. The broad applicability of the method is demonstrated by the fabrication of micro-chain mail, the charm of the structure of which as a target has been noted by others.^[1, 2]

We decomposed the chain mail (H) shown in Figure 1 into two sets of curves and lines: one set was patterned onto a plane, and the other set was patterned onto several cylinders. The patterns on these cylinders joined the patterns on the plane, such that two neighboring lines in the center of the pattern on the plane connected to two curves on two neighboring cylinders to form an oval. This oval linked with four other ovals. The partial ovals at the sides of the pattern on the plane were completed similarly. The collection of ovals—connected in this fashion—formed the chain mail.

To fabricate this chain mail, we formed the 2D pattern (Figure 1) in photoresist on a gold-coated glass slide by photolithography, and the remainder of the patterns on cylinders as features in silver by microcontact printing (μ CP).^[3] The patterns on the cylinders were aligned with those on the plane so that they formed the required template. Isotropic electrodeposition of nickel metal onto areas defined by this template produced the chain mail with links that were continuous and interconnected; the electrodeposition welded the substructures together.^[4] Dissolving the substrates released the metal structure; the result was a free-standing, interlinked chain mail with a wire width of about 100 μ m (Figure 2).

Forming patterns on separate substrates, and joining these patterns by electrodeposition, can form 3D microstructures with complex topologies and topographies. The smoothness of the connections between the components is determined by the design of these patterns, and by the way the substrates contact each other (here, the cylinders contacted the planar substrate tangentially and the connections are smooth). Microstructures having different topologies and topographies can be

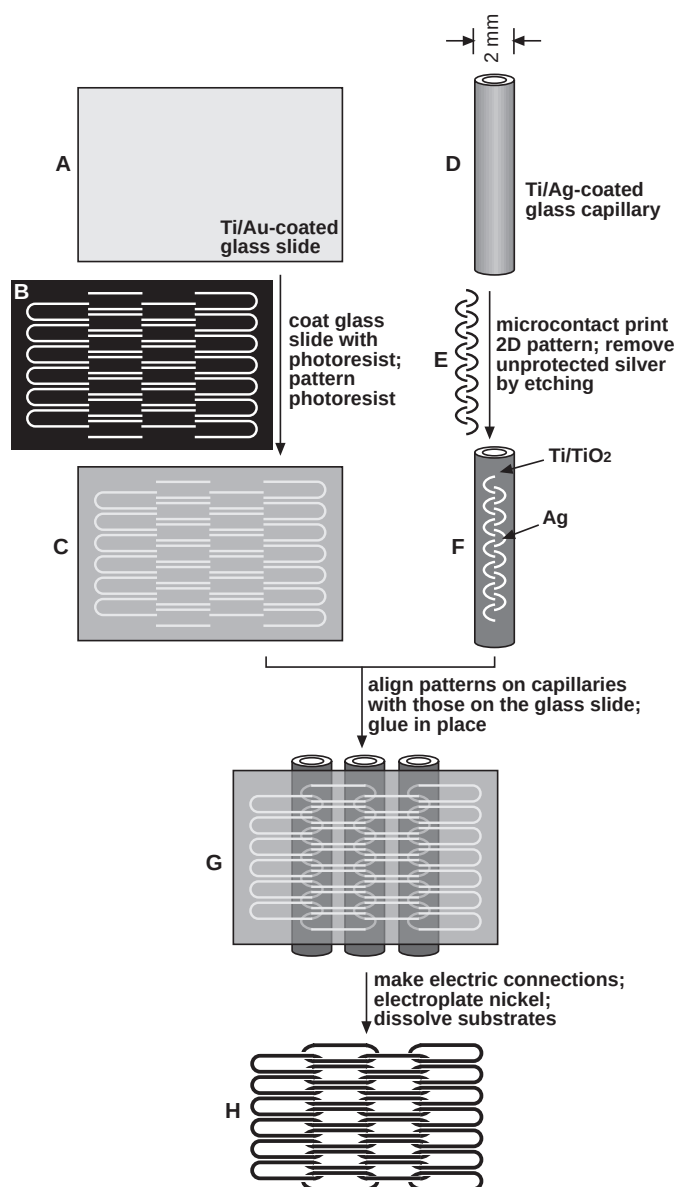


Figure 1. Schematic illustration of the fabrication of micro-chain mail using a planar substrate and multiple cylinders. The procedure begins with the deposition of a titanium adhesion layer as well as a gold layer on a glass slide. After the glass slide (A) had been coated with a positive photoresist, the pattern (B) was transferred into the photoresist by UV photolithography (C). Glass capillaries were coated in an ebeam evaporator with titanium and silver (D). Microcontact printing of hexadecanethiol with a polydimethylsiloxane stamp (with pattern E on its surface) formed a patterned, self-assembled monolayer on the capillaries (F). The surface of the titanium, when exposed to air, oxidized to a thin film, and electrodeposition did not occur on the exposed surface of the non-conductive Ti/TiO₂ film. The patterned glass slide and the capillaries were aligned so that the capillaries were in close proximity to the glass slide and their patterns matched to form a chain mail (G). Electrodeposition with nickel led to the formation of the wires of the chain mail, and the fully formed chain mail was released from the substrates (H).

generated by using the same procedure: In general, we can make any 3D wire structure that can be laid down in a plane so that all wire crossings occur on vertical lines in the plane; the number of cylinders required equals the number of vertical lines through the crossings.^[5]

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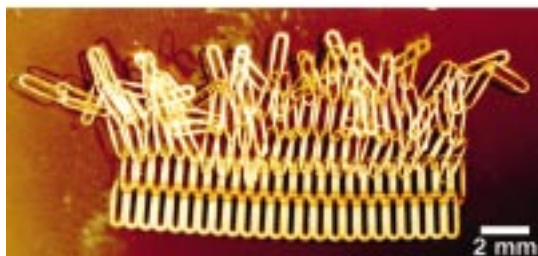
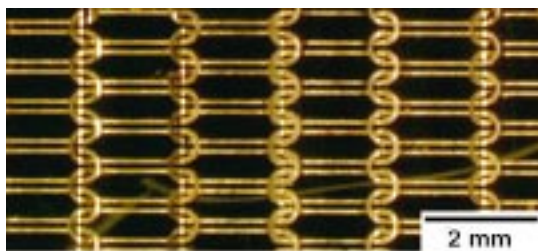


Figure 2. Top: A freely interlocked chain mail (5×24 ovals) fabricated by using one glass slide and five cylinders; bottom: a blow-up image of the chain mail.

Experimental Section

The masks for photolithography were produced with a rapid prototyping technique: we designed the patterns with a CAD program; the files containing these designs were sent to a commercial high-resolution printer (5010 dpi) and printed onto transparencies.^[3, 6] By UV photolithography, we transferred patterns into negative photoresist (NANO XP SU-8, MicroChem Corp., Newton, MA) on silicon wafers for microcontact printing, and patterns into positive photoresist (Shipley 1813, MicroLithography Chemical Corporation, Newton, MA) on a glass slide coated with a thin layer of gold by ebeam evaporation. The surface of these patterned silicon wafers was made more hydrophobic by exposing them to a vapor of perfluoro-1,1,2,2-tetrahydrooctyltrichlorosilane (United Chemical Technologies, Inc., Bristol, PA) in a vacuum desiccator; poly(dimethylsiloxane) (PDMS) prepolymer (Sylgard 184, Dow Corning, Midland, MI) was cast against the silanized silicon wafers and cured at 60 °C for about 3 h, and the elastomeric PDMS replica were peeled from the silicon wafers to be used as stamps for microcontact printing.^[3] We coated the glass slide with about 1.5 nm of titanium and about 15 nm of gold by ebeam evaporation; the capillaries were mounted on a stage that rotated about two orthogonal axes during the evaporation, and coated with about 50 nm of titanium and about 70 nm of silver.^[7] We used a laser-aligned arrangement of precision translation and rotation stages and hexadecanethiol (hexadecyl mercaptan, technical grade, 92 %, Aldrich) as an “ink” for microcontact printing patterns onto the capillaries.^[8] Subsequent wet-chemical etching was accomplished by immersing the printed substrates in an aqueous ferri-/ferrocyanide bath ($0.001\text{M K}_4[\text{Fe}(\text{CN})_6]$, $0.01\text{M K}_3[\text{Fe}(\text{CN})_6]$, $0.1\text{M Na}_2\text{S}_2\text{O}_3$) for about 30 s to remove the underivatized silver. We aligned the patterns on the substrates manually under a stereoscope and immobilized them by applying 5-min epoxy at the ends of the capillaries and the glass slide. After making electrical connections to the metal with silver epoxy (SPI Supplies, West Chester, PA), we electroplated nickel onto the areas defined by the photoresist on the slide and the silver patterns on the cylinders from a nickel sulfamate-based plating bath (Techni-Nickel “S”, Technic Inc., Providence, RI) at 45 °C for about 4 h at a current density of about 20 mA cm^{-2} until the matched ends on different substrates were welded. We released the fully formed chain mail from the substrates by dissolving the photoresist in acetone and dissolving the titanium and glass in concentrated HF solution. **Caution:** concentrated HF is highly corrosive to skin, tissues and bones; avoid exposure. The thin layer of gold was removed by sonication for about 1 min.

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Color-Tuned Electroluminescence from Columnar Liquid Crystalline Alkyl Arenecarboxylates**

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Columnar liquid crystals consisting of a polycyclic aromatic core surrounded by flexible side chains combine the good charge-transport properties of aromatic single crystals with the good film-forming properties of viscous liquids.^[1] Thus, thin films made of large well-aligned monocrystalline domains can be obtained at room temperature after annealing the material in the liquid crystalline state at elevated temperature. The columns generally align perpendicular to the surface. Thus, the direction of maximum charge mobility, which is along the column axis due to the proximity of the aromatic cores of neighboring molecules, is normal to the plane of the film.

Such semiconducting materials may be used in light-emitting diodes,^[2] where an organic film or a stack of organic layers is confined between an anode with high work function (usually formed from transparent indium–tin oxide) and a cathode with low work function (for example, Al or Mg).^[3] In devices containing only a single organic layer, the fluorescent organic material needs to exhibit both sufficient hole and electron affinity to allow injection of charges of both signs into the organic layer. It is useful to prepare multilayer devices^[4] in order to efficiently confine the recombination of charges in

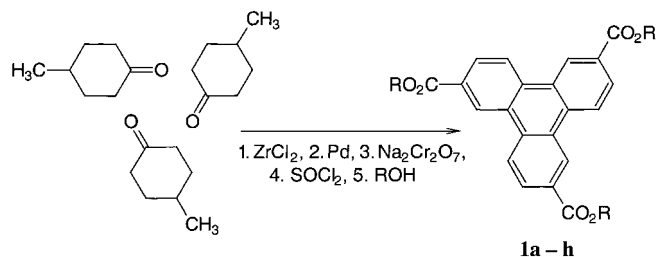
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the interior of the device, near the interface of a hole-transporting layer (HTL) with an electron-transporting layer (ETL). Appropriate stacks of several emitting layers may be used to achieve white electroluminescence through additive color mixing.^[5]

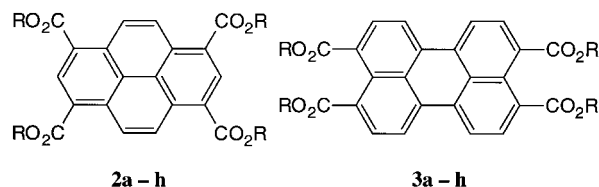
We have developed liquid crystalline aromatic esters which show luminescence in different wavelength ranges between the violet and the red end of the visible spectrum, to combine the excellent charge-transport and film-forming properties of columnar liquid crystals with the ability to emit light.

We prepared alkyl esters of triphenylene 2,6,10-tricarboxylic acid **1a–h** (Scheme 1) to obtain luminescence in the violet–blue range. In contrast to well-known electron-rich



Scheme 1. Synthesis of the triphenylene derivatives **1a–h** ($R = C_nH_{2n+1}$).

(hole-transporting) hexaethers and hexathioethers of triphenylene,^[2] these compounds contain weakly electron-withdrawing alkoxy carbonyl groups that diminish the electron density of the aromatic system and, thus, enable electron transport. For emission at longer wavelengths, we made the liquid crystalline (LC) and nonmesomorphic alkyl esters of pyrene 1,3,6,8-tetracarboxylic acid **2a–h** and perylene 3,4,9,10-tetracarboxylic acid **3a–h** ($R = C_nH_{2n+1}$). Dilute



solutions of the pyrene derivatives emit in the blue region, while the pure compounds show a green to yellow emission due to the formation of oligomolecular aggregates. The emission colors of the perylene derivatives are green for solutions and orange to red for the pure compounds, respectively. Appropriate mixtures between the derivatives of triphenylene and pyrene or triphenylene and perylene show fluorescence in a broad spectral range.

Triphenylene 2,6,10-tricarboxylic acid and its trialkyl esters **1a–h** (Scheme 1) were synthesized by a) dehydrating cyclotrimerization of 4-methylcyclohexanone with $ZrCl_2$ (12 h reflux, 50% yield; a simplification of the procedure of Shirai et al.^[6]); b) dehydrogenation with Pd/C ; c) oxidation in aqueous $Na_2Cr_2O_7$ under pressure;^[7] and d) treatment with thionyl chloride followed by treatment with the appropriate alcohol. The ethyl derivative **1b** (NMR data are shown in Table 2) shows a monotropic columnar LC phase, the *n*-

propyl and *n*-butyl esters **1c** and **1d** are monotropic nematic, the *rac*-2-ethylhexyl derivative **1h** exhibits an enantiotropic columnar LC phase, and the other derivatives (methyl, *n*-pentyl, *n*-hexyl, *n*-octyl) are not mesomorphic (Table 1). The monotropic mesophases of **1b** and **1c** are metastable against

Table 1. Phase-transition temperatures [$^{\circ}C$] of the three series of compounds (on heating).^[a]

R	1a–h	2a–h	3a–h
methyl (a)	cr-258-i	cr-266-[col-262]-i	cr-322-i
ethyl (b)	cr-161-[col-135]-i	cr-190-col-204-i	cr-244-col-313-i
<i>n</i> -propyl (c)	cr-137-(<i>n</i> -82)-i	cr-181-i	cr-193-col-287-i
<i>n</i> -butyl (d)	cr-86-[<i>n</i> -59]-i	cr-101-i	cr-161-col-242-i
<i>n</i> -pentyl (e)	cr-111-i	cr-101-i	cr-114-col-203-i
<i>n</i> -hexyl (f)	cr-101-i	cr-104-i	cr-72-col-177-i
<i>n</i> -octyl (g)	cr-77-i	cr-88-i	cr-62-col-132-i
<i>rac</i> -2-ethylhexyl (h)	cr-111-col-124-i	col-94-i	col-240-i

[a] cr = crystalline, col = columnar liquid crystalline, n = nematic liquid crystalline, i = isotropic liquid.

crystallization (glassy) at room temperature. Crystallization sets in upon heating to about $60^{\circ}C$. The nematic phase of **1d** gives way to crystals upon standing at ambient temperature. Most interestingly, the crystalline phase of **1h**, which forms when cooling an aligned sample below the liquid crystal–crystal transition temperature, is sufficiently similar in its lattice parameters to the mesophase to make the transition nearly undetectable in the polarizing microscope. This made us expect that the columnar structure of the liquid crystal is unusually well maintained in the crystal, and no significant reorientation or formation of grain boundaries (which both would impair the charge-transport properties of the film) takes place in thin films. This assumption of an isomorphic columnar crystalline structure is confirmed by powder X-ray diffraction measurements; these show that the main reflection in the LC phase, which corresponds to the spacing of a hexagonal columnar lattice, is maintained nearly unchanged in the crystalline state (Figure 1). This new family of triphenylene esters offers, in the ethyl and *rac*-2-ethylhexyl homologues **1b** and **1h**, two compounds that are well suited for use in semiconducting thin films because they form solid phases (glassy and crystalline, respectively) at room temperature that maintain the uniform alignment obtained when cooling through the phase transition.

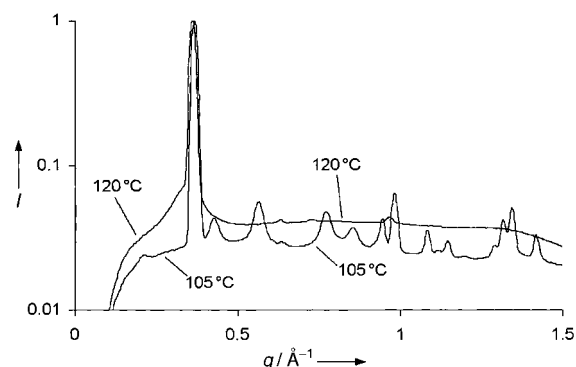


Figure 1. Powder X-ray diffraction study of compound **1h** at $120^{\circ}C$ and at $105^{\circ}C$. q = wave vector, I = intensity.

Pyrene 1,3,6,8-tetracarboxylic acid was synthesized following the procedure of Vollmann et al.^[8] and esterified with SOCl_2/ROH . We again made the methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-octyl, and *rac*-2-ethylhexyl esters, **2a–h** (NMR data of **2b** are shown in Table 2). The methyl, ethyl, and *rac*-2-ethylhexyl homologues **2a**, **2b**, and **2h** are

Table 2. ^1H NMR data for ethyl esters **1b**, **2b**, and **3b** (300 MHz, Me_4Si , CDCl_3).

	$\delta(\text{CH}_3)$	$\delta(\text{CH}_2)$	$\delta(\text{ArH})$
1b	1.52 (t, $J = 7$ Hz, 9H)	4.52 (q, $J = 7$ Hz, 6H)	8.33 (dd, $J = 9, 1.5$ Hz, 3H), 8.75 (d, $J = 9$ Hz, 3H), 9.32 (d, $J = 1.5$ Hz, 3H)
2b	1.56 (t, $J = 7$ Hz, 12H)	4.62 (q, $J = 7$ Hz, 8H)	9.20 (s, 2H), 9.37 (s, 4H)
3b	1.46 (t, $J = 7$ Hz, 12H)	4.41 (q, $J = 7$ Hz, 8H)	7.82 (d, $J = 8$ Hz, 4H), 7.85 (d, $J = 8$ Hz, 4H)

columnar liquid crystalline, while the other compounds are not mesogenic. Compound **2a** is monotropic, and **2b** and **2h** are enantiotropic. Both **2a** and **2b** crystallize with loss of the homeotropic alignment, whilst **2h** does not crystallize and is a mesomorphic fluid at room temperature.

Perylene 3,4,9,10-tetracarboxylic esters **3a–h** were obtained from the dianhydride by treatment with K_2CO_3 in a 1:1 mixture of RI and ROH (3 days at approximately 80°C ; NMR data for **3b** are given in Table 2). The mesomorphic behavior of the *n*-alkyl series has been published previously.^[9] In addition, we made the *rac*-2-ethylhexyl homologue **3h**, which does not crystallize and is a columnar liquid crystalline fluid over a very large temperature range (from room temperature to the liquid transition at 240°C). Columnar LC room temperature glasses can be obtained by mixing different short-chain *n*-alkyl homologues (for example, **3b/3e** in a 1:1 ratio).

The photoluminescence wavelengths of the compounds presented here are distributed over the entire visible spectrum, and the respective chromaticity coordinates make a nearly uninterrupted arc of points through the chromaticity diagram from blue to red (Figure 2). This allowed us to prepare electroluminescent samples with a wide range of colors.

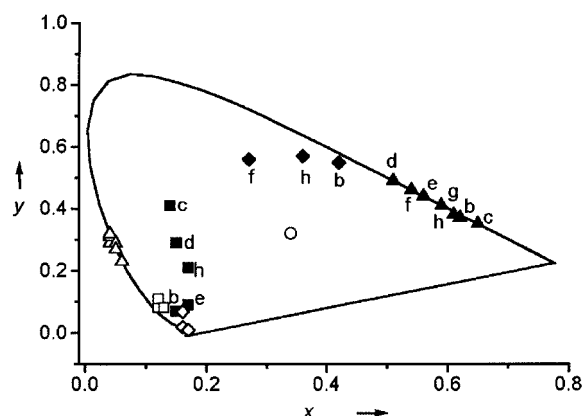


Figure 2. Chromaticity coordinates ($x = \text{red}$, $y = \text{green}$) for the photoluminescence of solutions (open symbols) and thin films (closed symbols) of the triphenylene (squares), pyrene (diamonds), and perylene (triangles) derivatives. The open circle in the center represents the panchromatic point (white).

We prepared light-emitting diodes consisting of a glass substrate coated with an indium–tin oxide (ITO) electrode layer, one to three organic layers, and an aluminum layer serving as the negative electrode. The perylene derivatives **3a–h** show a strong electroluminescence even in single-layer samples (Figure 3). They were made by deposition of a layer

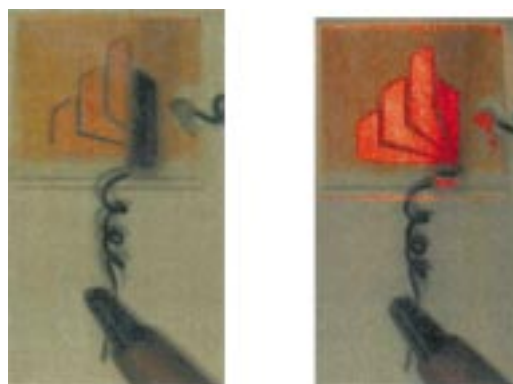


Figure 3. Photograph of a light-emitting diode that contains compound **3b**, without (left) and with (right) applied voltage.

(about 50 nm thick) on top of the ITO substrate by thermal evaporation under high vacuum, followed by evaporation of a thin (approximately 100 nm) Al electrode on top of the organic layer. Compounds **1a–h** and **2a–h** were used in two-layer samples containing an HTL (approximately 50 nm; produced by spin coating) such as poly-3,4-ethylene dioxythiophene (Baytron P, Bayer AG) or *N,N'*-diphenyl-*N,N'*-bis(3-methylphenyl)-1,1'-biphenyl-4,4'-diamine (TPD, SynTec) between the ITO and the emitting layer. The HTL serves to improve the charge-carrier injection at the ITO anode. Subsequently, the emitting layer (20–50 nm) consisting of the aromatic ester and then the Al top electrode (100 nm) were evaporated onto the HTL. In addition, we prepared and tested three-layer devices that contained an HTL and two emitting layers, in order to combine the emission of different compounds and, thereby, broaden the emission spectra towards a nearly white appearance.

Measurements of the current and the emission intensity versus voltage show typical diode characteristics for the prepared devices, with a threshold voltage where the current starts rising abruptly and where electroluminescence sets in. For example, bilayers with **2b** and **2f** as the emitting ETL show electroluminescence if the voltage exceeds a threshold value of about 5–6 V. For a single-layer light-emitting diode of **3b** with a film thickness of about 50 nm, we observed emission above a threshold of 7–8 V, and the maximum luminance was 100 cd cm^{-2} at a voltage of 20 V. By subsequent evaporation of **3b** on top of a bilayer of HTL and **1b**, light emission in a wide spectral range could be obtained. The corresponding three-layer diode appears nearly panchromatic (Figure 4). Most of the samples can be operated in air under laboratory conditions for several hours at about 10 V.

In conclusion, the compounds presented here prove to be very useful for preparing organic light-emitting devices of different colors, including red, green, blue, and almost white. The color-tuning towards white emission, the color stability,

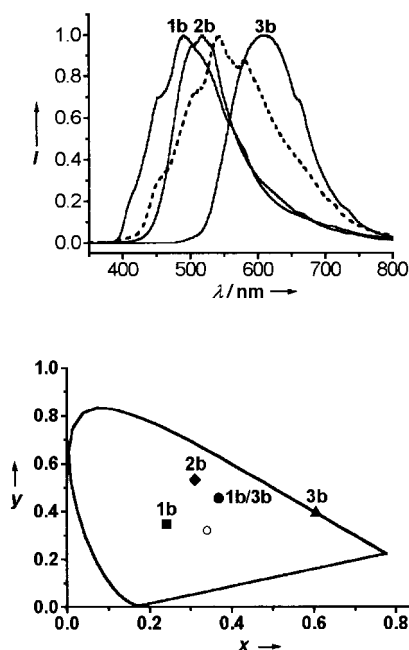


Figure 4. Top: Electroluminescence spectra of diodes (solid lines) that contain an emitting layer of the compounds **1b**, **2b**, and **3b**, and a light-emitting diode that contains two emitting layers made of compound **1b** and compound **3b** (dashed line). Bottom: Chromaticity coordinates of the electroluminescence for **1b**, **2b**, **3b**, and a sample with two emitting layers made of **1b** and **3b**. The open circle in the center represents the panchromatic point (white).

and the lifetime of the device may be improved by simultaneous codeposition of several of these compounds of presumably very similar electro- and photochemical stability. The extent to which the self-organization of the liquid crystalline mesophase can be used, through annealing or similar procedures, to further improve the uniformity of the films and thus the efficiency of these materials, is the subject of forthcoming investigations.

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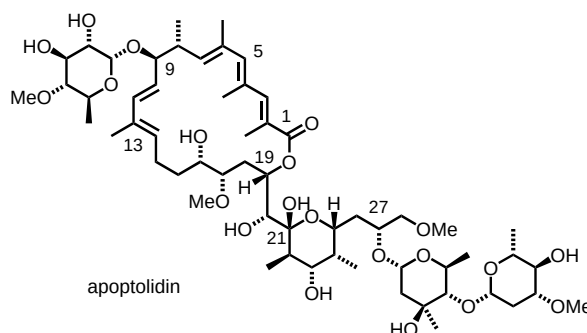
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Synthesis of Apoptolidinone**

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Programmed cell death or apoptosis is a basic biological process that regulates, for example, the homeostasis and morphogenesis of organisms.^[1] One very promising application of apoptosis control is in tumor therapy.^[2] Apoptolidin, a natural product isolated from *Nocardiopsis sp.*, induces apoptosis in rat glioma cells transformed with the E1A oncogene ($IC_{50} = 11 \text{ ng mL}^{-1}$), but not in untransformed cell lines.^[3] Khosla and co-workers identified the mitochondrial F_1F_0 ATPase as one possible target to explain the biological action.^[4] Apoptolidin is a 20-membered macrolide with a side chain at C19 containing a 6-membered cyclic hemiketal. A disacchar-



ide from D-oleandrose and L-olivomycose is located at C27, while 6-deoxy-4-O-methyl-L-glucose is attached at C9. Here we report on the synthesis of apoptolidinone, the aglycon of apoptolidin.^[5]

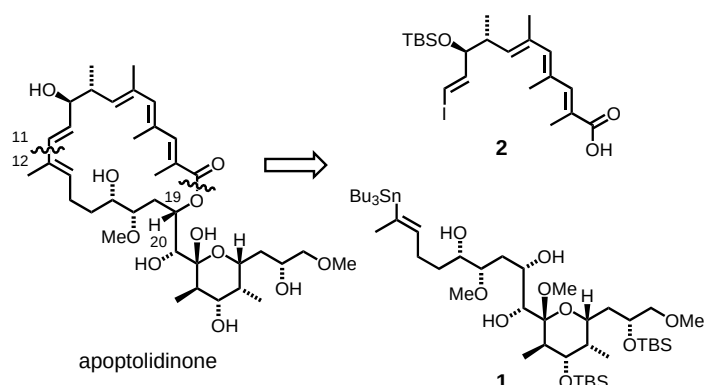
Our retrosynthetic analysis of apoptolidinone is based on a macrolactonization and a disconnection between C11 and C12

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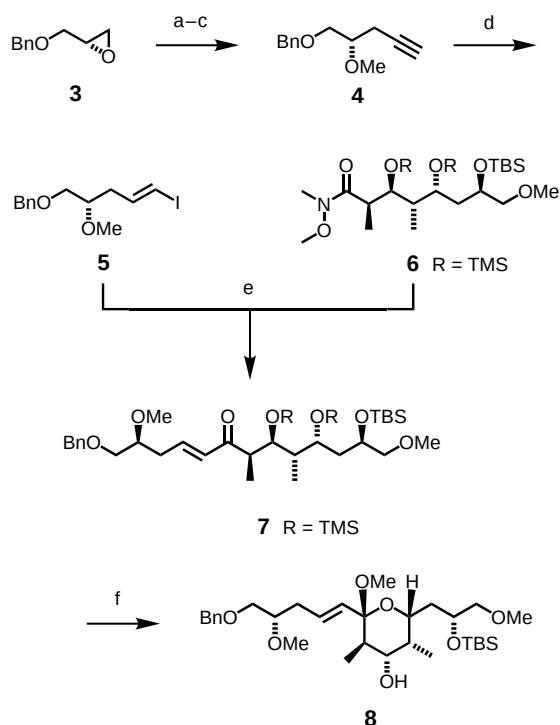
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(Cu^I coupling; Scheme 1). This leads to a “southern” half **1** and a “northern” half **2**. No protective group differentiation between the hydroxy functionalities at C19 and C20 was chosen, because a size-selective macrolactonization^[6] was expected based on model inspections.



Scheme 1. Retrosynthetic analysis of apoptolidinone. TBS = *tert*-butyldimethylsilyl.

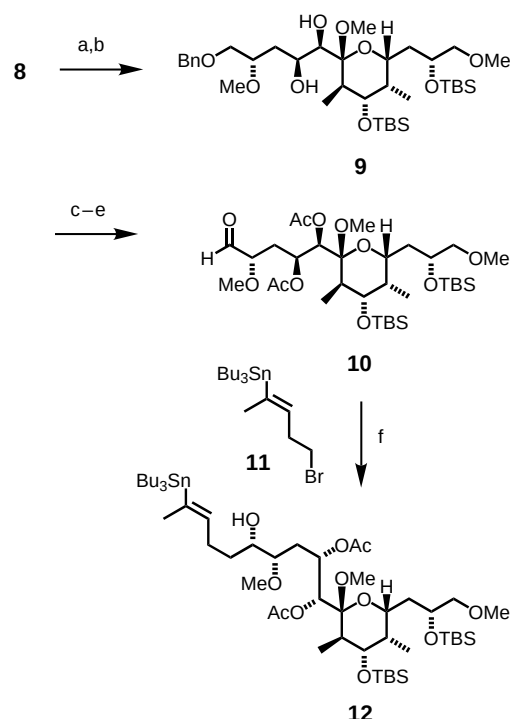
The synthesis of the southern half started with an epoxide opening of compound **3**, the benzyl-protected (*R*)-glycidol^[7] (Scheme 2). Subsequent *O*-methylation and removal of the trimethylsilyl group gave the alkyne **4**, which was transformed through hydrosilyzirconation/iodination^[8] into the *E*-alkenyl



Scheme 2. Synthesis of the southern half, part I. a) LiCCSiMe₃, BF₃·OEt₂, THF, −78 °C; b) 3.0 equiv LiHMDS, 7.0 equiv MeI, THF, 0 → 20 °C; c) Bu₄NF, THF, 0 °C, 88% (3 steps); d) 2.0 equiv [Cp₂ZrCl₂], 2.0 equiv LiEt₃BH, 2.2 equiv NIS, THF, 20 °C, 88%; e) **5**, *t*BuLi, Et₂O, −78 °C, then **6**; f) PPTS, MeOH/CH₂Cl₂ (1:1), 0 °C, 1.5 h, 87% (2 steps). Bn = benzyl, LiHMDS = lithium hexamethyldisilazide, NIS = *N*-iodosuccinimide, PPTS = pyridinium *p*-toluenesulfonate, TMS = trimethylsilyl.

iodide **5** (77% yield from **3**). Compound **5** was converted by an iodine–lithium exchange into the corresponding organo-lithium compound, which was allowed to react with Weinreb amide **6**^[5a] to yield the ketone **7**. Protodesilylation of the two TMS ether groups in MeOH/CH₂Cl₂ and a spontaneous cyclization led to the ketal **8** (87% yield from **6**).

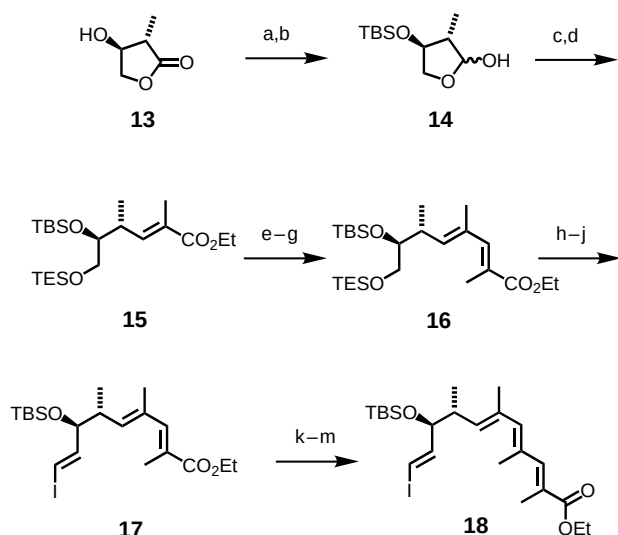
The hydroxy group at C23 was protected and a subsequent dihydroxylation (*ds* = 6:1) gave the diol **9** (Scheme 3). The stereochemical outcome of this reaction was assigned by



Scheme 3. Synthesis of the southern half, part II. a) *t*BuMe₂SiOTf, 2,6-lutidine, CH₂Cl₂, −78 °C, 2 h, 98%; b) K₂OsO₂(OH)₄, NMO, *t*BuOH/H₂O, 20 °C, 9 d, 78%, *ds* = 6:1, chromatographic separation of the diastereomers in the following step; c) Ac₂O, pyridine, DMAP, 40 °C, 3 h, 69% of the main diastereomer; d) H₂, Pd(OH)₂/C, EtOAc, 20 °C, 1 h, 97%; e) Dess–Martin periodinane, pyridine, CH₂Cl₂, 91%; f) **11**, Mg, 1,2-dibromoethane, Et₂O, 20 °C, then −78 °C, **10**, 58%, *ds* = 93:7. DMAP = 4-dimethylaminopyridine, NMO = 4-methyl morpholine *N*-oxide, Tf = triflate = trifluoromethanesulfonyl.

comparison of the ¹³C NMR spectrum with that of a model compound.^[5a] Compound **9** was diacetylated and converted into the aldehyde **10** by a standard sequence. Compound **10** was allowed to react with the Grignard reagent prepared from **11**^[9] to give the complete diacetylated southern half **12** (*ds* = 93:7, determined by HPLC; chelation control^[10]). The compatibility of the organotin and the organomagnesium group is noteworthy.

The starting point for the northern half was the β -hydroxy lactone **13**,^[11] which was protected as its *tert*-butyldimethylsilyl ether and subsequently reduced to the lactol **14** (Scheme 4). The twofold use of an *E*-selective Wittig reaction with commercially available Ph₃P=C(CH₃)COOEt led via **15** to the diene **16**. Selective deprotection of the triethylsilyl ether in **16** followed by a Dess–Martin oxidation^[12] gave an aldehyde that could be converted by a Takai reaction^[13] into the *E*-



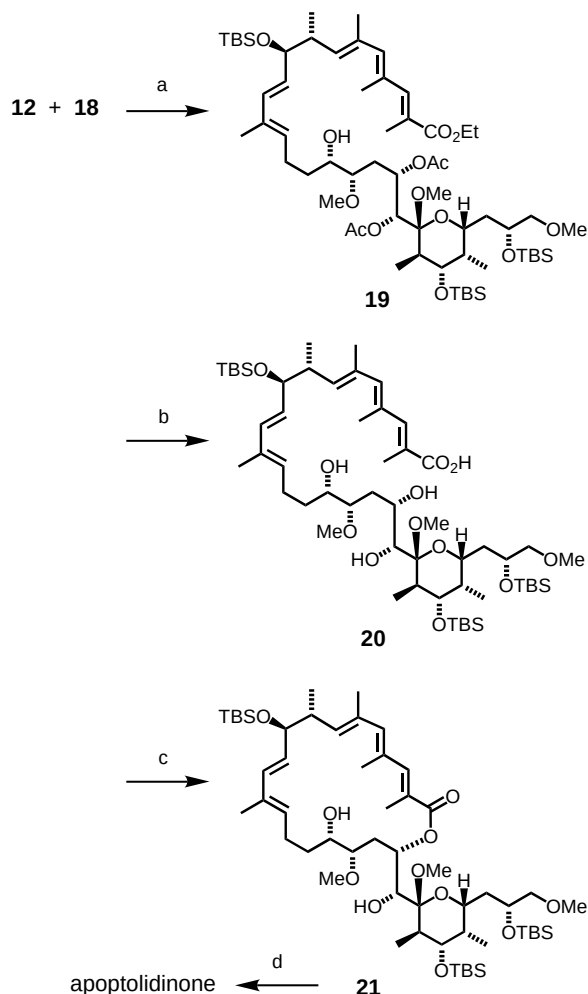
Scheme 4. Synthesis of the northern half. a) $t\text{BuMe}_2\text{SiOTf}$, 2,6-lutidine, CH_2Cl_2 , 0°C , 30 min, 90%; b) DIBAH, CH_2Cl_2 , -78°C , 15 min, 95%; c) $\text{Ph}_3\text{P}=\text{CCH}_3\text{CO}_2\text{Et}$, toluene, 110°C , 12 h; d) Et_3SiCl , imidazole, CH_2Cl_2 , 0°C , 82% (2 steps); e) DIBAH, toluene, -78°C , 15 min; f) MnO_2 , CH_2Cl_2 , 40°C , 30 min; g) $\text{Ph}_3\text{P}=\text{CCH}_3\text{CO}_2\text{Et}$, toluene, 110°C , 86% (3 steps); h) camphorsulfonic acid, $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (1:2) 0°C , 15 min, 95%; i) Dess–Martin periodinane, pyridine, CH_2Cl_2 , 20°C ; j) CrCl_2 , CHI_3 , cat. hydroquinone, THF, dioxane, 20°C , 12 h, 69% (2 steps); k) DIBAH, n -hexane, -78°C , 1 h, 80%; l) MnO_2 , CH_2Cl_2 , 20°C , 2 h; m) $\text{Ph}_3\text{P}=\text{CCH}_3\text{CO}_2\text{Et}$, toluene, 100°C , 12 h, 60% (2 steps). DIBAH = diisobutylaluminum hydride, TES = triethylsilyl.

alkenyl iodide **17**. After transformation of the ester group into an aldehyde, another Wittig reaction produced the complete northern half ethyl derivative **18**. Compound **18** was found to be light sensitive^[14] and all steps beyond **16** were carried out under yellow light.

The final sequence of the synthesis focused on the coupling of the southern and the northern half, as well as on the macrolactonization (Scheme 5). Attempts for a Pd^0 -catalyzed Stille coupling^[15] between **12** and **18** were disappointing (<30% yield at prolonged reaction times and 60°C). In contrast, the use of two equivalents of Cu^{I} -thiophene carboxylate^[16] gave **19** in 80% yield under very mild conditions (-10°C , 1 h). Treatment of **19** with LiOH gave the trihydroxycarboxylic acid **20**. The macrolactonization of **20** according to the modified Yamaguchi procedure^[17] produced the 20-membered macrolide **21** in 74% yield (100-mg scale). The ring-size selectivity of this step is remarkable. No 21-membered lactone could be identified. Deprotection of **21** with HF/pyridine gave the target compound apoptolidinone^[18] in 2.8% yield for the longest linear sequence (19 steps).^[5a]

The preferred conformation of the 20-membered macrolide is an important aspect of the bioactive conformation of apoptolidin. The analysis of the ROESY NMR spectrum of **21** is summarized in Figure 1. The ROESY crosspeaks that were found support a conformation that is in agreement with the conformation described by Hayakawa and co-workers for apoptolidin.^[3a]

The synthesis of the apoptolidin aglycon described here provides, for the first time, synthetic access to this molecular



Scheme 5. Coupling of **12** and **18** and completion of the synthesis. a) Cu^{I} -thiophene-2-carboxylate, N -methylpyrrolidinone, -10°C , 1 h, 80%; b) LiOH, THF/MeOH/ H_2O (2:1:1), $25 \rightarrow 40^\circ\text{C}$, 40 h, 87%; c) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, 18 h, 25°C , then DMAP, toluene, 80°C , 6 h, 74%; d) HF/pyridine, THF, $0 \rightarrow 25^\circ\text{C}$, 24 h, 55%.

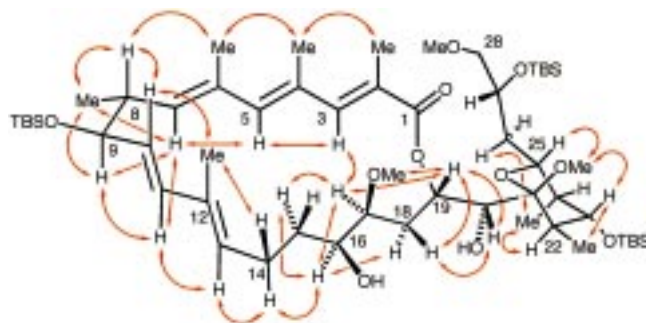


Figure 1. Conformation of **21** in C_6D_6 , as determined from selected ROESY NMR spectroscopic data. ROESY cross signals are indicated with double-ended arrows.

framework with a very promising antitumor bioactivity. It forms the basis for the attachment of the sugar residues at C9 and C27. Our convergent strategy allows access to synthetic derivatives of the natural product, which will be of interest for further pharmacological developments.

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Carbon Nanofilaments in Heterogeneous Catalysis: An Industrial Application for New Carbon Materials?*

Gerhard Mestl, Nadezhda I. Maksimova, Nicolas Keller, Vladimir V. Roddatis, and Robert Schlögl*

The direct dehydrogenation of ethylbenzene to styrene is one of the ten most important industrial processes. In this process a potassium-promoted iron catalyst is used at temperatures between 870 and 930 K.^[1] However, this method is thermodynamically limited and, because of the required excess of steam, very energy consuming.^[2, 3] The oxidative dehydrogenation (ODH) of ethylbenzene could be a promising alternative in which the hydrogen generated is directly oxidized making the overall process exothermic.

Mechanistic studies of the dehydrogenation of ethylbenzene on single-crystal model surfaces provide fundamental information about the role of the active K–Fe phase.^[4–7] This surface is evidently well suited to generate a graphitic carbon deposit. Therefore, it is possible that these carbon deposits are actually the catalytically active phase.

Transition metal oxides^[8] and phosphates^[9, 10] as well as polymers^[11] have been described as active and selective catalysts for the ODH of ethylbenzene. The carbon deposits^[12] detected on such catalysts again point to an active role of carbon in this reaction. Accordingly, catalytic activity in the ODH was demonstrated for activated charcoals,^[13, 14] their commercialization however, is impossible because of their low oxidation resistance.^[15] Graphite, on the other hand, exhibits activity in the ODH of methanol.^[16] Thus, graphitic carbon materials, that is, nanofilaments with high surface area, are promising candidates for dehydrogenation catalysts in the presence of oxygen.

We have tested the catalytic properties of lamp soot, graphite, and nanofilaments for the ODH of ethylbenzene to styrene. Figure 1 displays the catalytic properties of the investigated carbon materials with time on stream *t*. The higher activity of nanofilaments relative to soot and graphite is evident. While the catalytic activity of soot decreases during the induction period because of burn-off, that of graphite and the nanofilaments increases with time. This behavior can be correlated with the stability toward combustion. Nanofilaments show a higher activity, selectivity, and yield relative to graphite. The catalytic properties of the three investigated carbon materials after 7 h operation are given in Table 1. Again the superiority of the nanofilaments over graphite is evident. Although the specific activity of nanofilaments is somewhat lower, they exhibit comparable selectivity and

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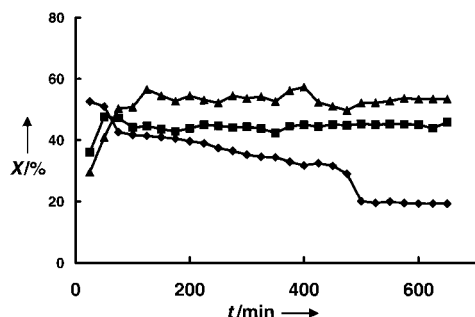


Figure 1. The styrene yield from soot (◆), graphite (■), and nanofilaments (▲) with time on stream in the oxidative dehydrogenation of ethylbenzene at 820 K.

Table 1. Comparison of the specific activities, selectivities, and yields of styrene, and the specific surface areas of lamp soot,^[a] graphite, and nanofilaments after 7 h reaction.

Catalyst	Lamp soot ^[a]	Graphite	Filaments
Spec. activity [10^{-7} mol m ⁻²]	(14.40)	3.66	3.03
Selectivity [%]	(65)	80	85
Spec. yield [10^{-7} mol m ⁻²]	(9.32)	2.93	4.67
Spec. surface area [m ² g ⁻¹]	(19)	69	47

[a] Values in parentheses indicate that Lamp soot quantitatively combusts under the reaction conditions.

hence a 37% higher specific yield of styrene. After 7 h operation, soot still shows good performance but with extended time on stream burns up completely under these reaction conditions.

Figure 2 displays two high resolution transmission electron micrographs of nanofilament walls before and after the reaction. The fresh nanofilament walls (Figure 2a) are built

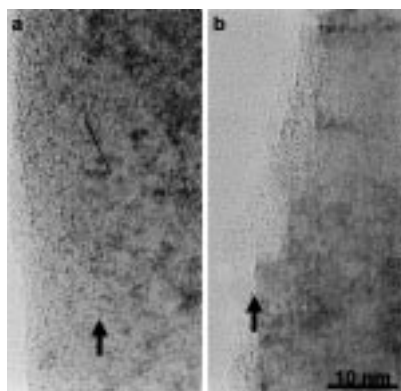


Figure 2. High resolution TEM images of the walls of carbon nanofilaments before (a) and after (b) the oxidative dehydrogenation of ethylbenzene. Arrows mark the boundary layer between the conical graphite layers and the outer shell.

up by two different layers. The inner layer is formed by conical graphite layers with an angle of 26° to the filament axis. The interlayer distance of 0.348 nm is comparable to that of normal graphite. The outer nanofilament shell is formed by ill-defined carbon layers which are oriented parallel to the filament axis. The mean layer distance is about 0.388 nm. After the catalytic reaction, the nanofilaments have an altered wall structure (Figure 2 b): the outer shell of ill-defined carbon

layers is combusted and a thin layer of polymeric carbon deposits covers the outer surface of the conical graphite layers. This carbon deposit can be seen especially at the step edges between the conical layers. Additionally, the ends of the conical layers seem to be partially oxidized. These partially oxidized prism faces presumably play an important role in the catalytic reaction.

The purity and composition of the test materials was characterized prior to catalysis by X-ray photoemission spectroscopy (XPS) and energy dispersive X-ray spectroscopy (EDX). The ratio of graphitic to aliphatic carbon was determined to be 0.13:1 for soot, 0.19:1 for graphite, and 0.15:1 for the nanofilaments. Hence, within the experimental error, this ratio is the same for all samples. The oxygen content was determined by EDX to be 10–20 wt % for all samples. Thus within the experimental error no difference in the oxygen content of the samples could be determined. The remaining iron-catalyst particles in the nanofilaments were always completely covered by carbon and clearly could not play an active part in the reaction.

Figure 3 displays the O(1s) XP spectrum of the nanofilament catalyst after ODH. Among others a very weak signal can be seen at 530.2 eV^[17] which points to the presence of

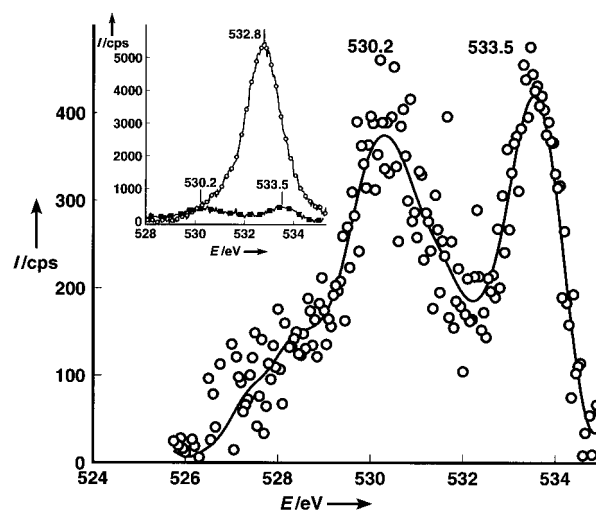
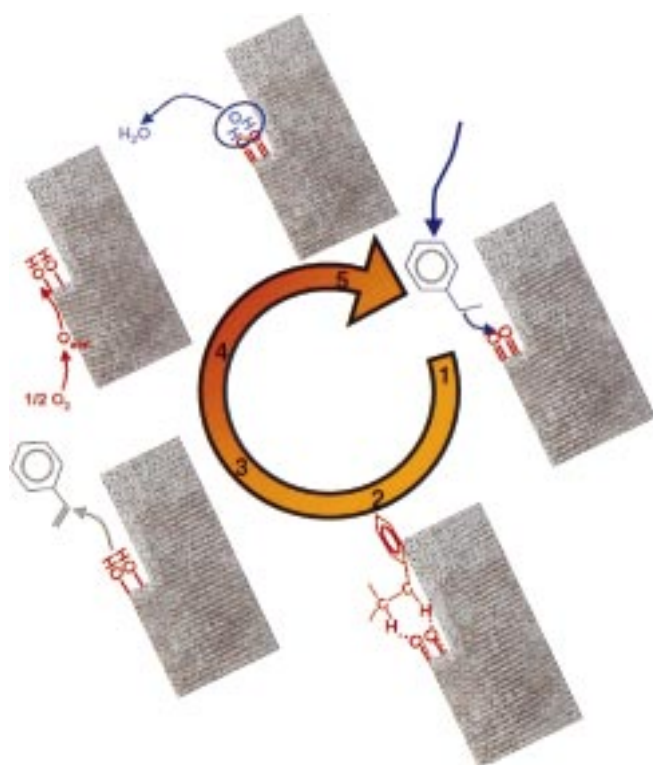


Figure 3. O(1s) XP spectrum of the carbon nanofilaments after oxidative dehydrogenation of ethylbenzene. The inset shows a comparison of the spectra before (○) and after (■) the catalytic reaction.

strongly basic surface oxygen groups,^[17] for example, quinoidic groups.^[18] Another weak signal at 533.6 eV is attributed to adsorbed water.^[19] The detection of strongly basic groups after the catalytic reaction indicates the important dehydrogenating function these groups have during the catalytic process.

A possible reaction mechanism of the ODH of ethylbenzene over nanofilaments is shown in Scheme 1. Strongly basic, adjacent (quinoidic) oxygen centers dehydrogenate ethylbenzene to styrene under the formation of surface OH groups.^[3, 9, 20] Gas-phase oxygen is dissociated on the basal planes of the graphite layers^[16] and diffuses to the hydroxyl groups, which then react under reformation of the quinoidic groups and the desorption of water.



Scheme 1. Mechanism of the catalytic oxidative dehydrogenation over carbon nanofilaments, 1) adsorption of ethylbenzene, 2) dehydrogenation at basic centers, 3) desorption of styrene, 4) adsorption of oxygen and reaction with OH groups, 5) desorption of water.

Catalytic ODH giving good yields seems to be possible over carbon catalysts. Carbon nanofilaments in particular display a high stability toward oxidation; their recently reported cheap synthesis by catalytic decomposition^[21] seems to make a first industrial application of carbon nanofilaments plausible. Rational design of experiments on the basis of a functional analysis of industrial catalysts with the aid of surface-science methods resulted, in a short time, in a high-temperature stable, active, and selective catalyst for the ODH of ethylbenzene.

Experimental Section

Soot (Lamp soot 101, Degussa), graphite (HSAG, TIMCAL) and commercial carbon nanofilaments (Applied Science) were used as catalysts for the oxidative dehydrogenation of ethylbenzene to styrene. The reaction was carried out in a tubular quartz reactor, inner diameter 4 mm, length 200 mm. The catalysts (0.02 g) were held in the isothermal oven zone by quartz wool plugs. He and O₂ were fed in by mass flow controllers. Ethylbenzene (EB) was evaporated at 35 °C (2.16 kPa) in a flow of He and mixed with the O₂ flow to obtain different EB:O₂ ratios (0:1, 1:1, 2:1). The reaction was carried out at 820 K in a total flow of 10 mL min⁻¹ (LHSV (liquid hourly space velocity): 0.5 h⁻¹). The reaction products were analyzed on-line by gas chromatography (hydrocarbons with a 5% SP-1200/1.75% Bentone 34 packed column and flame ionization detector (FID); permanent gases with a Carboxen 1010 PLOT column/thermal conductivity detector).

The ethylbenzene conversion (X_{EB}), the styrene yield (Y_{ST}) and the selectivity to styrene (S_{ST}) were calculated according to the standard reaction engineering Equations (1)–(3).

$$X_{EB} = \frac{n_{EB_{in}} - n_{EB_{ex}}}{n_{EB_{in}}} \quad (1)$$

$$S_{ST} = \frac{n_{ST}}{n_{EB_{in}} - n_{EB_{ex}}} \quad (2)$$

$$Y_{ST} = \frac{n_{ST}}{n_{EB_{in}}} \quad (3)$$

To calculate the specific activity, X_{EB} was divided by the catalyst mass and its specific surface area. The specific styrene yield was obtained analogously by dividing Y_{ST} by the catalyst mass and its specific surface area. Transmission electron microscopy was carried out on a Phillips CM200-FEG at an acceleration voltage of 200 kV. Photoelectron spectra were recorded on a modified Leybold Heraeus spectrometer (LHS12 MCD) with MgK α radiation (1253.6 eV) and a power of 240 W. The bandpass energy was set to 50 eV. X-ray satellites and Shirley background was subtracted. The Brunauer–Emmett–Teller (BET) surface area of the catalysts was determined by N₂ adsorption at 77 K.

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Linear Polymeric C_{70}^{2-} Ions**

Holger Brumm, Eva Peters, and Martin Jansen*

*Dedicated to Professor Hans Georg von Schnering
on the occasion of his 70th birthday*

Two of the most obvious characteristics of the fullerenes are their ease of reduction and the large number of negative charges that they can accept. The ions C_{60}^- to C_{60}^{12-} ^[1] and C_{70}^- to C_{70}^{9-} have been detected.^[2] Naturally such anions are mainly obtained in compounds with electropositive metals and provide a great diversity of structural and electronic phenomena in solid-state chemistry. The fulleride anions may be present as isolated units,^[1] as dimers,^[3] or as polymers.^[4] Fullerides of alkali and alkaline earth metals can be non-conductors, semiconductors, or metallic conductors.^[1] Some become superconducting with remarkably high transition temperatures, 40 K, for example.^[5] Fullerides derived from C_{60} have received the most attention. Most of the studies of C_{70} have concerned the formation of compounds with alkali metals^[2] and preliminary investigations have been carried out with the Ba/C_{70} system.^[6] It is disappointing that none of the C_{70}^{n-} phases identified so far become superconducting on cooling.

A logical interpretation of the large range of experimental results obtained to date is restricted by the conspicuous lack of reliable structural information. A complete structure solution with refinement of all the atomic positions has not been possible for any of the linked fullerides reported. Nevertheless, from the experimental data gathered, it appears that the existence of polymeric and oligomeric $(C_{60}^{n-})_x$ ions has been verified. However, doubts still remain concerning the type of linkage. Above all, the available information does not offer a reliable basis for an analysis of the extent of the localization of charges in polymeric fullerides. Only a few structural determinations have been made with single crystals of fullerides that contain completely ordered and isolated C_{60}^{2-} ions,^[7] which could be used to verify the theoretically developed models for the expected Jahn–Teller distortion.^[1]

In expanding our studies of fullerides to systems including C_{70} we were able to synthesize the first linear polymeric C_{70}^{2-} species (Figure 1) as a barium salt, $[Ba(NH_3)_9]C_{70} \cdot 7NH_3$ (**1**), and to determine its structure by single-crystal X-ray analy-



Figure 1. Structure of the linear polymeric $(C_{70}^{2-})_n$ ion. The bond length of each of the bridging C–C single bonds is 1.53(2) Å. The smallest intermolecular distance between the centers of mass of two fullerenes is 10.11 Å, the smallest intramolecular distance is 10.47 Å.

sis.^[8] Compound **1** is obtained from the reduction of C_{70} with barium in liquid ammonia. The product precipitates from liquid ammonia at room temperature in the form of black needles which decompose above -33°C under normal pressure with loss of ammonia.

In **1**, barium is coordinated to nine ammonia molecules and the coordination geometry is a strongly distorted, tricapped trigonal prism (Figure 2). The lengths of the bonds between the barium and the nitrogen atoms vary between 2.89(2) and 3.09(2) Å, which is in agreement with literature values.^[7b, 9] Seven of the nine ammonia ligands are each coordinated to a further ammonia solvent molecule that is not bonded to barium (N–N bond lengths of 2.98(5) to 3.69(4) Å).

All the carbon atoms of the fullerene cage could be localized and refined. The fullerene units are linked together in linear chains by bonds between carbon atoms located in each of the two opposing five-membered rings through which the fivefold rotational axis of the neutral C_{70} runs. This type of linkage causes a slight zigzagging in the (001) plane. The angle between the lines connecting the centers of mass of three neighboring fullerene cages is 151° . The length of the bridging bond is 1.53(2) Å, which corresponds to a single C–C bond. This bond length and the bond angle at the bridging carbon atoms show that these atoms have sp^3 hybridization.

Within the chains, the smallest separation between the center of mass of two fullerenes is 10.47 Å. The fulleride chains are ordered along [100] with hexagonal close pack of rods (Figure 3); this is supported by the ratio between the lengths of the *b* and *c* axes of approximately $\sqrt{3}$. The smallest intermolecular distance between the centers of mass of a fullerene within a chain and its six neighbors is 10.11 Å. This distance corresponds to van der Waals contact and thus does not indicate any significant bonding interactions.

Because of the one-dimensional linkage and the resulting formation of two sp^3 -hybridized carbon atoms, the point symmetry of the C_{70} unit is lowered from D_{5h} for the uncharged fullerene to C_2 (positional symmetry: C_1 ; Figure 4). This point symmetry, which usually covers only the general topology of one unit of the $(C_{70}^{2-})_n$ polymer with respect to the arrangement of the five- and six-membered rings as well as the two quaternary carbon atoms, also covers, within the limits of error, the variations in bond lengths which result from the localization of charges (Figure 5). Moving away from the bridging sites there is a general tendency for the alternation of the bond lengths to become less pronounced. Thus the five-membered ring and both six-membered rings which include the sp^3 -hybridized carbon atom, have “diene

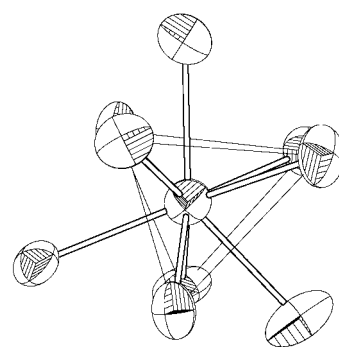


Figure 2. Structure of the cationic unit (anisotropic thermal ellipsoids set at the 50% probability level). In the first sphere nine NH_3 molecules coordinate the Ba^{2+} ion in a strongly distorted, tricapped trigonal prism geometry.

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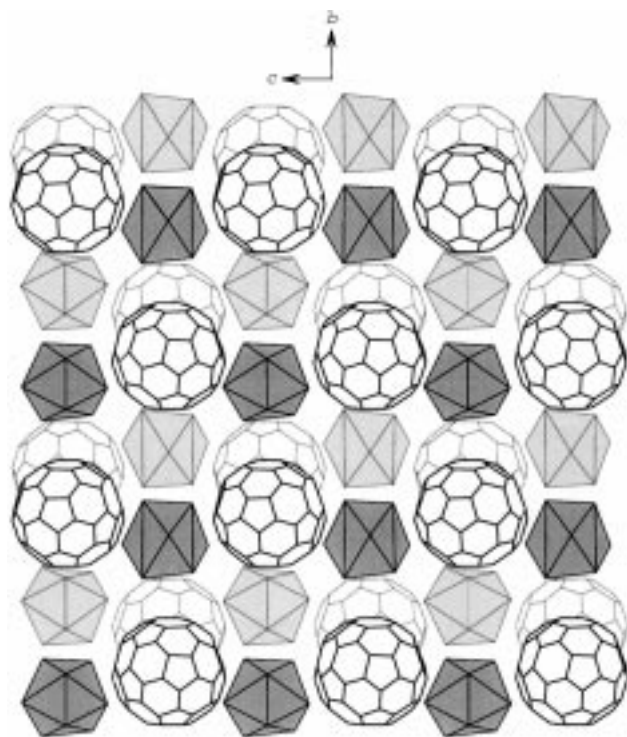


Figure 3. The molecular structure of **1** viewed along the (C_{70}^{2-}) chains which are ordered as a hexagonal close pack of rods.

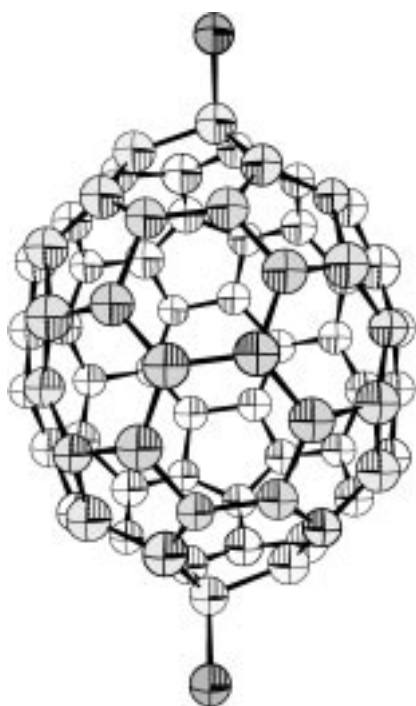


Figure 4. The molecular structure of a C_{70}^{2-} unit viewed along the noncrystallographic twofold rotation axis (isotropic thermal ellipsoids set at the 50% probability level).

character” while the delocalization of the π electrons increases towards the middle of the fulleride. Therefore, there are no indications of a localization of the negative excess charges on particular carbon atoms.

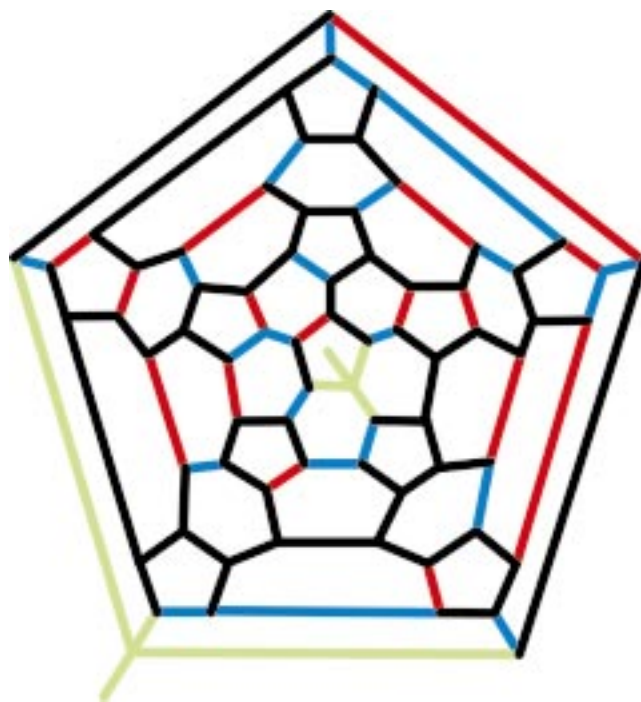


Figure 5. Schlegel diagram of a C_{70}^{2-} unit. Color coding of the bond lengths [Å]: blue < 1.39, black 1.39–1.47, red 1.47–1.52 Å, green > 1.52. The average standard deviation of the bond lengths is 0.02 Å, the maximum standard deviation is 0.03 Å.

Experimental Section

Under argon, Ba (4.0 mg, 2.91×10^{-5} mol) and C_{70} (25.1 mg, 2.99×10^{-5} mol), previously purified by sublimation, were added to an ampoule ($\varnothing=8$ mm) fused onto the base to a oven dried Schlenk vessel. The Schlenk vessel was subsequently evacuated and ammonia introduced by condensation. This mixture of starting materials was frozen solid with liquid nitrogen and the glass ampoule was sealed. After three weeks at -33°C , the solution which was initially blue had changed color to red-brown. Subsequently, the ampoule was carefully warmed to room temperature and then stored for ca. 4 months. During this period, shiny black needles formed on the bottom and on the glass walls. The ampoule was refrozen with liquid nitrogen and opened under argon. At -78°C , the thawed ammonia and the crystals were transferred under inert gas into degassed and cooled perfluoropolyether oil (Galden HT230). A crystal suitable for single-crystal X-ray analysis was removed from the oil with a glass capillary attached to a preadjusted goniometer head. The crystal was immediately cooled with liquid nitrogen and placed in the diffractometer.

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Orthogonal Photolysis of Protecting Groups**

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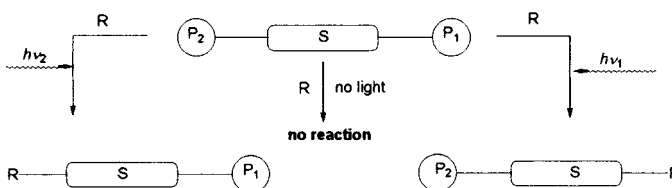
Dedicated to Professor Barry M. Trost
on the occasion of his 60th birthday

One of the major challenges in the chemistry of protecting groups is orthogonality, that is, the possibility of selectively removing one group in the presence of others in any chronological sequence.^[1] Photolabile protecting groups form an attractive subclass of these groups, since they are essentially cleaved without the need for any reagent, which thus increases compatibility with other functionalities.^[2, 3] How-

ever, orthogonality between such protecting groups has never been observed. We recently published our preliminary results on the possible use of monochromatic light to differentiate photolabile groups,^[4] and we wish to disclose here the first orthogonal photochemical protection/deprotection of polyfunctional molecules.

Before considering applying a strategy such as that shown in Scheme 1, several critical issues have to be addressed:

- The intrinsic stability of each protecting group should be very different at various wavelengths.
- The energy transfer between an excited chromophore and its ground-state neighbor should be suppressed.
- The cleavage at high energy (for example, at 254 nm) should be very fast, to avoid photodegradation of otherwise sensitive groups.



Scheme 1. General strategy for photochemical orthogonal deprotection of functional groups. S = substrate; P₁, P₂ = groups which are photoactivatable at ν_1 or ν_2 ; R = reacting species (for example, H).

Among the known photolabile protecting groups, the 3',5'-dimethoxybenzoin esters attracted our attention since they were found to be equally reactive in nonabsorbent solvents and in neat piperylene (1,3-pentadiene).^[5] This suggested the absence of quenching by the solvent and a very short-lived excited state. This feature, combined with the very high quantum yield ($\phi = 0.64$) makes this ester an ideal candidate for an orthogonal protecting group. On the other hand, the nitrobenzyl derivatives are known to be less reactive, but with sensitivity to much longer wavelengths (up to 420 nm).^[3] These differences in wavelength sensitivity are clearly illustrated by the UV spectra of **1** and **2** (Figure 1).

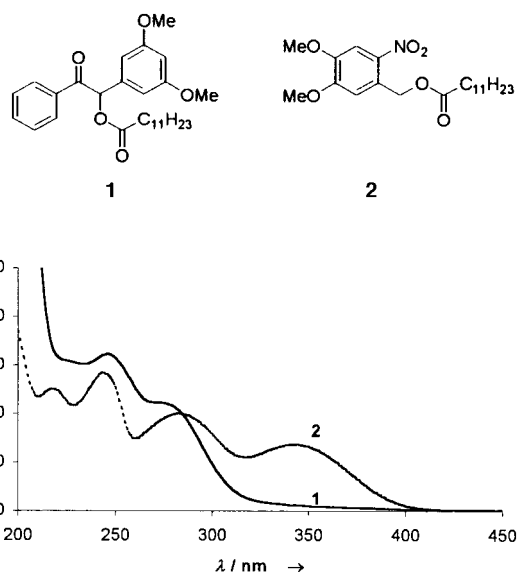


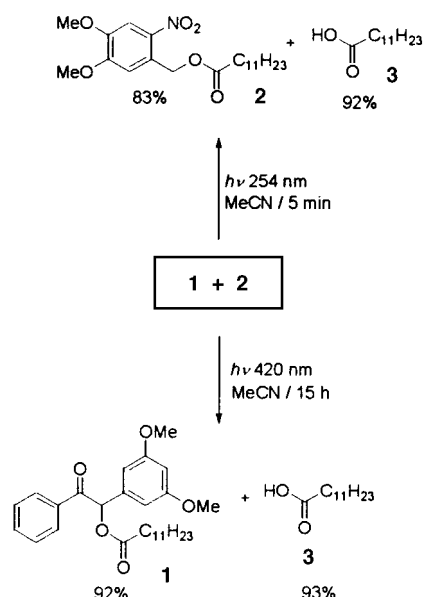
Figure 1. UV spectra of benzoin ester **1** and benzyl ester **2**.

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We first exposed an acetonitrile solution of the lauryl ester **1**^[6] to UV light with a wavelength of 254 nm. The half-life was determined as less than 5 minutes, which is significantly shorter than that for the nitrobenzyl ester **2** (97 minutes). On the other hand, **1** was totally unreactive at 420 nm, even for a prolonged time (24 hours), whereas **2** was quantitatively cleaved under these conditions.^[7]

With these encouraging differential reactivities^[8] established, we then submitted a 1:1 mixture of **1** and **2** to UV light with a wavelength of 254 nm. After irradiation for 5 minutes, 83 % of **2** was “intact” and 92 % of the acid **3** was detected (by ¹H NMR spectroscopy). The same experiment at 420 nm gave 93 % of **3** and 92 % of intact benzoin ester **1**, after 14 hours (Scheme 2). Figure 2 shows the ¹H NMR spectra of the initial 1:1 mixture of **1** and **2** and of the mixture after irradiation at different wavelengths. The signals around $\delta \approx 2.5$ arise from the methylene group adjacent to the carboxyl groups and clearly show the complementary behavior at the two wavelengths.



Scheme 2. Orthogonal stability of photolabile esters **1** and **2**.

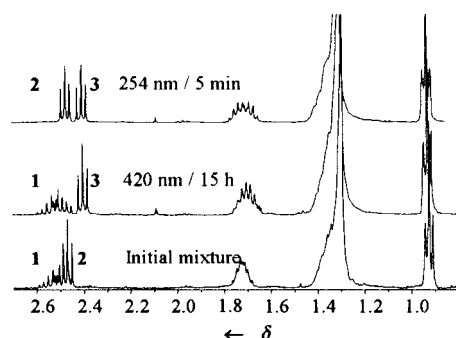
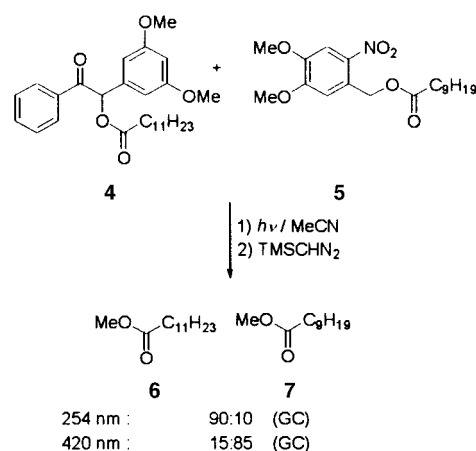


Figure 2. ¹H NMR spectra before and after irradiation of a mixture of esters **1** and **2**.

We prepared a mixture of the two esters **4** and **5**, which bear saturated aliphatic chains of different length, to check further the orthogonality. Photolysis at 254 nm for 5 minutes led to a mixture of two carboxylic acids in 82 % yield; these were

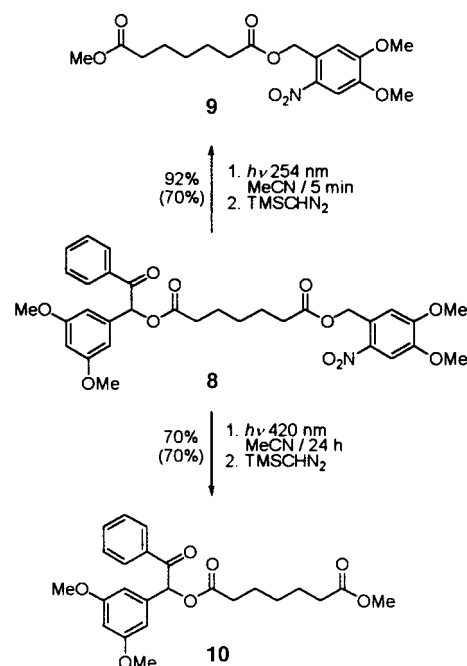
converted, by esterification with trimethylsilyldiazomethane,^[9] into the methyl esters **6** and **7** in a 90:10 ratio (as determined by GC analysis). A similar mixture, when irradiated at 420 nm for 24 hours, gave a 15:85 mixture in 91 % yield (Scheme 3).



Scheme 3. Photochemical cleavage of orthogonal protecting groups from different esters. TMS = trimethylsilyl.

This experiment clearly shows the absence of the intermolecular energy transfer that was observed with 3,5-dimethoxybenzyl alcohol derivatives.^[4] The overall result is that it was possible to activate individual components in a mixture by using an external influence.

Intramolecular energy transfer was also found to be absent in this system (Scheme 4). The mixed diester **8** bearing a dimethoxybenzoin ester at one terminus and a nitrobenzyl derivative at the other was photolyzed at 254 nm for 5 minutes and the crude mixture was treated with trimethylsilyldiazo-



Scheme 4. Intramolecular photochemical cleavage of orthogonal protecting groups.

methane. The diester **9** was isolated in 70% yield after chromatography (92% by ^1H NMR spectroscopy). The same experiment at 420 nm cleanly gave the diester **10** in 70% yield (70% by ^1H NMR spectroscopy). In other words, it was possible to perform a photochemical orthogonal deprotection of a bifunctional substrate.

In conclusion, we have shown that chromatic orthogonality is indeed possible, in both inter- and intramolecular cases. This new strategy could be successfully applied to orthogonal deprotection of bifunctional molecules and to wavelength-selective photorelease of compounds. We are currently investigating the possibility of adding a third dimension to the set, as well as testing applications in solution- and solid-phase organic synthesis.

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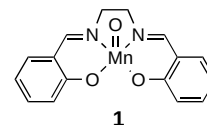
Rate Enhancement and Enantioselectivity of the Jacobsen–Katsuki Epoxidation: The Significance of the Sixth Coordination Site**

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The oxygenation of olefins by high-valent transition metal oxo complexes is one of the most useful and elegant techniques for the functionalization of organic substrates. A breakthrough was the introduction of chiral manganese–salen catalysts by Jacobsen and co-workers,^[1] with a similar system developed by Katsuki and co-workers.^[2] The Jacobsen–Katsuki reaction is universally recognized as one of the most useful and widely applicable methods for the epoxidation of unfunctionalized olefins.^[3, 4]

Despite the synthetic utility of this catalytic transformation, the origin of its high selectivity is not well understood. The key problems that mechanistic studies of the catalytic reaction cycle need to address are: 1) the nature of the oxygen-transferring species; 2) the mechanism of oxygen transfer to the olefinic substrate; and 3) the highly efficient stereochemical communication between catalyst and substrate. By electrospray tandem mass spectrometry, we were able to show that the reaction proceeds via an oxomanganese(v) complex as catalytically active species,^[5] but the remaining questions are still open despite numerous experimental^[6] and computational studies.^[7]

Herein, we report on the results of a high-level computational study^[8] of oxomanganese(v)–salen complexes of type **1** bearing different axial ligands. Axial ligation of the salen catalyst is known to have a favorable influence on the asymmetric induction. This has been explained by a shortening of the Mn–O bond length and a decrease of the reactivity of the oxo species upon axial coordination.^[3d] We have recently shown experimentally that axial coordination of an *N*-oxide ligand at the oxomanganese(v) complex raises the oxygen transfer reactivity of the catalyst dramatically.^[5d] The question arises why it is possible in this specific case of asymmetric catalysis to raise the



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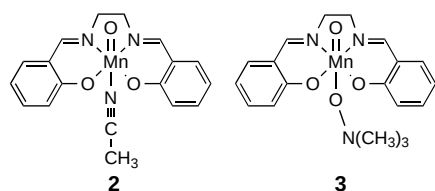
[**] This work was made possible through generous allocation of computer resources by the OIT at Notre Dame, the National Computational Science Alliance and the Competence Center for Computational Chemistry at ETH Zürich.



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

reaction rates as well as the enantioselectivities by axial coordination. We will show herein that the axial ligands have a profound effect on the conformation of the basal salen ligand, leading in the case of a strongly binding ligand to two steplike and one cup-shaped conformation.

In the absence of another ligand, the free binding site at the metal center is occupied by a solvent molecule. We studied this type of complexation for the case of the experimentally observed^[5a,b] oxomanganese(v)–salen acetonitrile complex **2**.



To model the stronger binding *N*-oxide ligands commonly used as additives to enhance both reactivity and selectivity of the epoxidation,^[3d, 9] we calculated the oxomanganese(v)–salen trimethylamine *N*-oxide complex **3**. All species were calculated by using the B3LYP hybrid functional in combination with a triple-zeta basis set. It was shown previously^[5b, 7] that this functional yields qualitatively reasonable results, even though several of the species discussed here deviate significantly from the expected $\langle S^2 \rangle$ values.^[10]

The structure of the oxomanganese(v)–salen complex **1** in its triplet and quintet state has been discussed previously.^[5b] Contrary to the results of a recent study of a smaller model system,^[7a] the singlet state of the oxomanganese(v)–salen complex, **1**, is found to be 0.9 kcal mol^{−1} lower in energy than **3** (Table 1). The axial Mn=O bond is calculated to be 0.05 Å shorter than in the previous studies, due to the larger triple-bond character, which needs a sufficiently flexible basis set for the description of the interaction of the 2p orbitals on the oxygen center with the 3d_π and the 3d_δ orbitals on the manganese center.

Introduction of a weakly binding ligand shows the following effects. Whereas no binding occurs in the singlet state, the solvent in the triplet state **2** is weakly bound with a bond length of 2.46 Å (see Figure 1). This, and the fact that the

partial charge on the manganese center in the three spin states of **1** is virtually identical, indicates that the solvent ligand is weakly bound by the p-donation of a free electron pair of the solvent into an empty orbital at the manganese center rather than by an electrostatic interaction as implied by previous studies using a chloride ligand complexed to the metal.^[7b,c] This interaction is stronger in **2**, leading to a bond length of only 2.23 Å. The effect of the ligand binding on the geometry of the manganese–salen moiety is relatively minor. The axial Mn=O bond is 0.02 Å longer than that in **1**. The metal center, which is positioned above the plane of the four basal heteroatoms in **1**, moves into the plane and the salen ligand is slightly distorted towards a steplike, transoid conformation.

The much stronger binding of the acetonitrile ligand in **2** does, however, have a strong effect on the relative energies of the spin states. The already small energy difference between the triplet and the quintet states in **1** is almost completely overcome by the additional binding energy of the solvent ligand, leading to virtually degenerate triplet and quintet states in **2**.

These trends are even more pronounced for a stronger axial ligand as shown for **3**. While, in contrast to **1**, the structure of a ligand-bound singlet state **3** could be located, it is quite high in energy and was not considered further. The deviations from the planar structure and bond lengths of **1** are relatively small for **3**. However, strong deviations from a planar structure were obtained for the triplet and quintet states **3** and **3**, leading to the *cis* and *trans* forms of **3** and **3** shown in Figure 1.

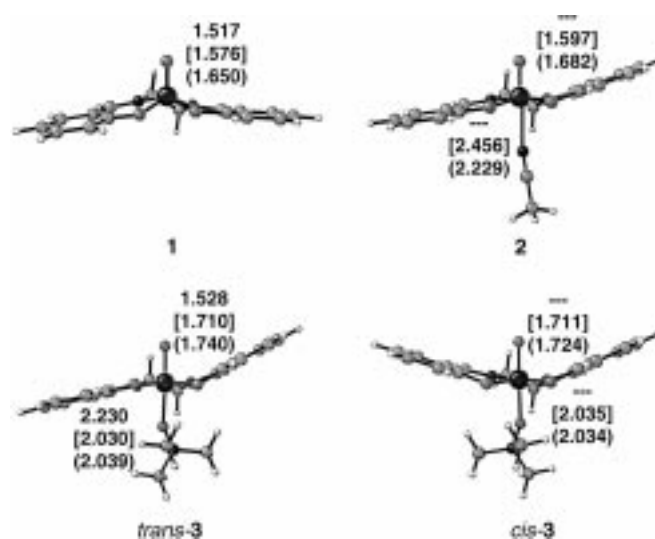


Figure 1. Structures of **1**, **2**, *trans*-**3**, and *cis*-**3** calculated at the B3LYP/6-311G* level. Bond lengths for singlet states are given without brackets, for triplet states in square brackets, and for quintet states in parentheses.

Table 1. Calculated relative energies and dihedral angles for singlet, triplet, and quintet states of **1**–**3**.

Compound	E_{rel} [kcal mol ^{−1}]	$\langle S^2 \rangle$	Dihedral angle 1 [°] ^[a]	Dihedral angle 2 [°] ^[a]
1	−0.9	—	175.8	170.3
3	0.0	2.0973	170.4	174.1
5	6.8	6.0545	175.1	173.3
2	—	—	—	—
3	0.0	2.2118	162.1	174.4
5	0.5	6.0523	170.0	175.6
<i>trans</i> - 3	10.8	—	166.1	169.6
<i>trans</i> - 3	0.0	2.8122	153.3	167.0
<i>cis</i> - 3	1.5	2.8164	154.6	162.9
<i>trans</i> - 5	3.0	6.0488	153.5	170.9
<i>cis</i> - 5	3.9	6.0455	165.6	162.9

[a] Defined as angle between the plane of the phenyl ring and the plane of the four heteroatoms.

The axial bond lengths in these four structures for **3** and **5** are very similar. The Mn=O bond in **3** is approximately 0.1 Å longer than that in **2**, whereas the manganese–ligand bond is approximately 0.42 and 0.2 Å shorter in the triplet and quintet state, respectively. The triplet–quintet gaps are with 3.0 and 2.4 kcal mol^{−1} for *trans*-**3** and *cis*-**3**, respectively, again small. Although these energy differences are on the order of the

accuracy that can reasonably be expected from the method used, an analysis of the geometry suggests that the triplet–quintet gap is slightly larger than in the case of **2** because **53** does not benefit from increased binding of the ligand in the quintet state. Steric repulsion cannot be the reason for the ligand bending as the bulky trimethylamine *N*-oxide ligand is far away from the salen moiety of the molecule. The energy difference between the *trans* and the *cis* conformer in **3** and **53** is only 1.5 and 0.9 kcal mol^{−1}, respectively. This indicates that the stronger bonding of the ligand corresponds to a weakening of the Mn=O bond.

These results provide a structural basis to test several of the hypotheses that have been put forward to explain the high degree of asymmetric induction by manganese–salen complexes. The calculated structures of the hexacoordinate complexes **2** and **3** support the hypothesis of a family of nonplanar, enantiomeric conformations that are in rapid equilibrium. For both spin states of **3**, we find in addition to the *trans* conformation, which would be equivalent to the stepped conformation proposed earlier,^[3a, 11] an energetically slightly higher *cis* conformation. As shown in Table 1, the distortion is stronger in the triplet than in the quintet state. These findings, together with the fact that the distortion from planarity correlates with the donor ability of the ligand, suggest that this effect is electronic rather than steric in nature.^[12]

Further corroboration for the presence of nonplanar conformations of axially ligated oxomanganese–salen complexes comes from electrospray MS experiments with authentic epoxidation catalyst mixtures. When spraying an in situ mixture of Jacobsen's catalyst ((*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III)triflate), *p*-CN-*N,N*-dimethylaniline *N*-oxide, and iodosobenzene, the oxomanganese(V) complex, but no dinuclear μ -oxo-bridged manganese(IV)–salen complex were detected. This observation is in striking contrast to the behavior of solutions of the arene-unsubstituted salen complexes used in our previous studies, where conproportionation of oxomanganese(V) and manganese(III) complexes plays a crucial role for parking the catalyst in a more persistent form. Inspection of a model of the μ -oxo-bridged manganese(IV) complex with the arene-substituted Jacobsen ligand in a planar conformation shows no apparent steric overcrowding as a possible reason for the failure to observe the μ -oxo-bridged species. This leads us to the conclusion that in the case of salen complexes bearing sterically demanding substituents the existence of highly nonplanar conformations precludes the conproportionation to dinuclear μ -oxomanganese complexes.

trans-**33** can exist in two enantiomeric forms, which can be transferred into diastereomers with the help of chiral axial ligands (e.g. *N*-oxides).^[13] While the *cis* conformation will be destabilized by the approaching olefin or the epoxide product, the *trans* conformation will be destabilized by a large axial ligand. This could potentially be the origin of the observed lower enantioselectivity obtained with bulky *N*-oxides.^[13] The geometry of *trans*-**33** also suggests that a side-on approach of the olefin might most favorably occur from the salicylaldehyde ring rather than from the imine portion,^[2b] which would be hindered by the axial substituents on the ethylene bridge.

In addition to the influence on the conformation of the salen, the axial ligand decreases the triplet–quintet gap and lowers the energy of the open-shell states, making the triplet the ground state of **2** and **3**. Contrary to an earlier proposal,^[3d] stronger binding of the ligand leads to a weaker Mn=O bond, which should increase the reactivity for an oxygen transfer.

The importance of the triplet to quintet spin crossing, which has been shown to occur after the rate-determining transition state along the reaction pathway, has been pointed out earlier.^[7a] Although an explicit calculation of the spin transition probability is not feasible for a system of this size,^[14] it can be assumed that a decrease in the triplet–quintet gap leads to a stronger interaction between the states and a higher spin transition probability. This would lead to the drastic rate enhancement for epoxidation observed in the gas phase as well as in solution.

The results presented here provide new insights into the origin of the reactivity and selectivity of the oxomanganese(V)–salen complexes based on hybrid density functional calculations using triple-zeta basis sets on the complete chemical system. The effect of the axial ligand on the rate enhancement and enantioselectivity of the Jacobsen–Katsuki reaction should be quite general as all published epoxidation protocols contain potential axial ligands in the form of additives, counterions, or solvents. The structures obtained could help in the design of new and more effective asymmetric catalysts and additives for this and related reactions catalyzed by transition metal salen complexes.

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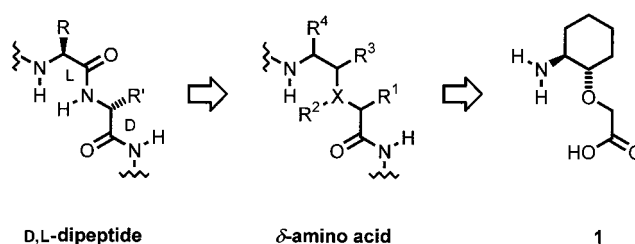
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Cyclohexylether δ -Amino Acids: New Leads for Selectivity Filters in Ion Channels**

Hans-Dieter Arndt, Andrea Knoll, and Ulrich Koert*

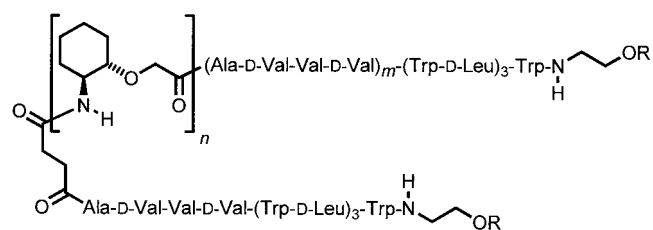
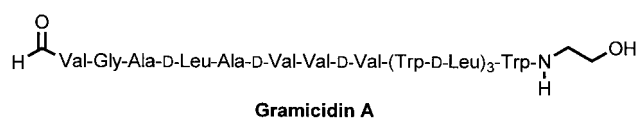
Biological ion channels are key molecules for cellular regulation and communication. They couple (bio)molecular events to electric signals.^[1] This property of natural pore-forming substances has been utilized in engineering biosensors.^[2] In order to use synthetic channel structures^[3] as sensors or implants in biological systems, they have to meet requirements in two areas: ion selectivity^[3e, 4] and gating.^[5] We report here on novel oligomers made from δ -amino acids that led to H^+ - and NH_4^+ -selective ion channels.

On substituting the central amide bond of a dipeptide, a δ -amino acid is obtained (Scheme 1).^[6] Besides offering structural diversity at four positions, a δ -amino acid allows incorporation of a heteroatom in the continuous backbone.^[7] If one chooses an oxygen and constricts the degrees of conformational freedom with a cyclohexane ring, the ether amino acid (AA) **1** results.



Scheme 1. From D,L-dipeptides to the stereoequivalent δ -amino acid **1**, a new building block for cation channels.

The selectivity filters of biological K^+ and Ca^{2+} channels are lined with backbone atoms.^[8a,b] In the ion channel active, but weakly selective, $\beta^{6,3}$ -helical dimer of the D,L-peptide gramicidin A (gA) only backbone amides are exposed towards the



2 ($n = 2$, $m = 1$)

3 ($n = 4$, $m = 1$)

4 ($n = 6$, $m = 0$)

$R = t\text{BuPh}_2\text{Si}$

interior.^[8c] The incorporation of δ -AA **1** with its ether oxygens should offer additional binding sites for a cation in the lumen.^[9] Our target compounds **2–4** were chosen by combining di-, tetra-, and hexameric δ -AA segments with functionally important sequences from gA to yield structures with the approximate total length of the gA dimer.^[10, 11]

The synthesis of the compounds incorporating δ -AA **1** starts from cyclohexene epoxide **5**, which was transformed to the azido alcohol according to the method of Jacobsen and co-workers^[12] (94 % yield, 93 % *ee* under optimized conditions, Scheme 2). Alkylation with *tert*-butylbromoacetate using phase-transfer catalysis^[13] gave masked δ -AA monomer **6** (95 %; $R = t\text{Bu}$),^[14] which was homodimerized to **9** via a mixed anhydride ($R = \text{COCMe}_3$; formed from **7** (step e in Scheme 2)). Dimer **9** could be obtained isomerically pure by crystallization (*n*-hexane/ Et_2O (7:1), Figure 2). After elongation with a succinate building block, the resulting diester **10** was connected at both termini with the α -peptide **11**^[11] to yield the target compound **2**. Compounds **3** and **4** were similarly synthesized (see Supporting Information).^[14]

The compounds **2–4** were then examined for their ion channel forming activity.^[15, 16] The compounds with tetra- and hexameric δ -peptide units, **3** and **4**, did not form detectable cation channels. But they induced short-lived proton channels when applied in concentrations above 100 nM (Figure 1 a, b). Probably, a bottleneck conformation permits only protons to pass.^[17]

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

A 2',4'-Bridged Nucleic Acid Containing 2-Pyridone as a Nucleobase: Efficient Recognition of a C·G Interruption by Triplex Formation with a Pyrimidine Motif**

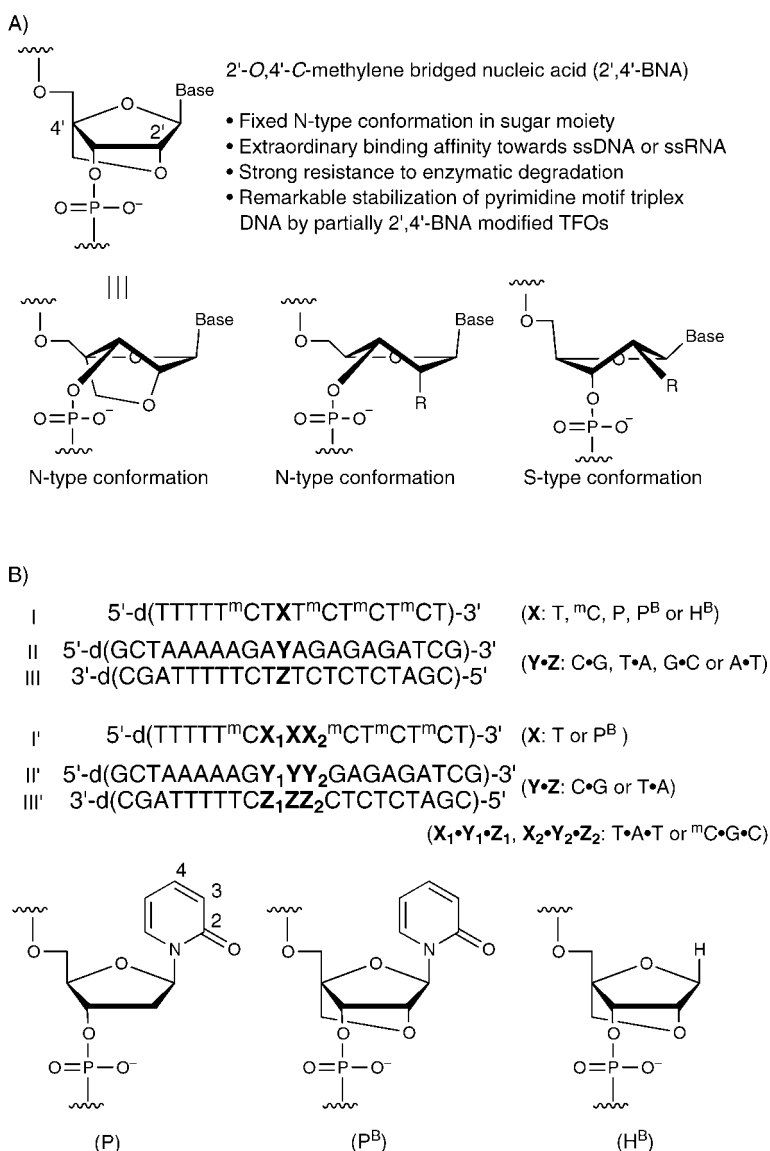
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Triplex formation between duplex DNA and a triplex-forming oligonucleotide (TFO) has been noted in practical applications of antigene methodology and in genomic analysis. In the triplex DNA formed with the pyrimidine motif, the homopyrimidine TFO binds to the homopurine tract of the target duplex DNA in a sequence-specific manner through the formation of Hoogsteen hydrogen bonds to form T·A·T and C⁺·G·C triads. Interruption of the homopurine sequence of the target duplex DNA by a pyrimidine nucleotide causes destabilization of the triplex. Chemical modification of the TFOs in the nucleobase moiety has been reported to give efficient recognition of a pyrimidine·purine base pair, such as a C·G or T·A base pair.^[1,2] However, development of practical TFOs for recognition of general duplex DNA sequences is still pending.

We recently achieved the first synthesis of a novel nucleoside with a fixed N-type conformation (C-3'-endo),^[3] namely, 2'-O,4'-C-methylenribonucleic acid (2'-O,4'-C-methylene Bridged Nucleic Acid 2',4'-BNA; Scheme 1A)^[4,5] and found that pyrimidine oligonucleotides with partial 2',4'-BNA modification exhibited strong triplex-forming abilities at neutral pH values.^[6-9]

From the fact that T or C moderately interacts with a C·G base pair in homopurine·homopyrimidine double-stranded DNA (dsDNA),^[10-12] we considered that the 2-carbonyl oxygen atom of T or C plays an important role in the recognition of a C·G base pair. Therefore, we selected the 2-pyridone group,^[13,14] which has only a 2-carbonyl group and lacks the 3-nitrogen atom and a 4-carbonyl or amino group of thymine or cytosine (Scheme 1B), as a nucleobase to interact with a C·G base pair. Here, we report the synthesis of the novel 2',4'-BNA monomer **1** bearing a 2-pyridone group, and its application to the efficient recognition of C·G interruption in homopurine·homopyrimidine dsDNA.

The synthetic route to **1** is shown in Scheme 2. The starting material **2**,^[15] which was easily prepared from D-glucose, was

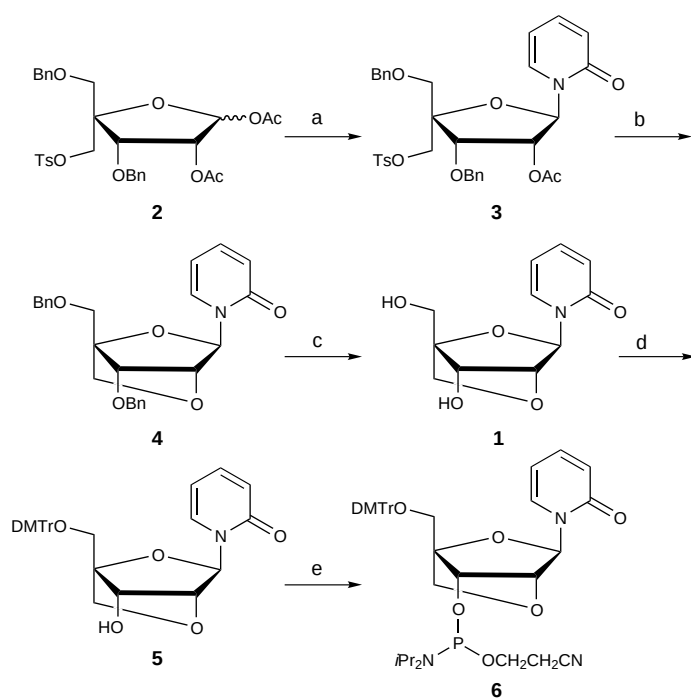


Scheme 1. A) Structure and characteristics of 2',4'-BNA. B) The oligonucleotides used in this study.

treated with 2-pyridone, *N,O*-bis(trimethylsilyl)acetamide (BSA), and trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloroethane to give **3**. Bicyclic nucleoside **4** was obtained upon exposure of **3** to potassium carbonate in methanol. Next, hydrogenolysis of **4** afforded the desired compound **1**. The structure of 2',4'-BNA monomer **1** was confirmed by X-ray crystallographic analysis (Figure 1),^[16] which revealed that the sugar moiety in **1** was fixed in an N-type conformation (pseudorotation phase angle *P* is 16.7°), the same as that in the 2',4'-BNA uracil monomer (*P* is 17.4°).^[4] The phosphoramidite **6**, the suitable building block for DNA synthesis, was obtained by dimethoxytritylation (**1**→**5**) and phosphitylation (**5**→**6**), and then incorporated into TFOs I and I' (Scheme 1B) by a standard phosphoramidite protocol on a DNA synthesizer. The purity of the modified TFOs was verified by using reversed-phase HPLC, and the compositions were determined by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS.^[17]

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Scheme 2. Synthesis of 2',4'-BNA-pyridone monomer **1** and its phosphoramidite derivative **6**. a) 2-pyridone, BSA, TMSOTf, dichloroethane, reflux, 74%; b) K_2CO_3 , MeOH, RT, 100%; c) 20% $Pd(OH)_2/C$, cyclohexene, EtOH, reflux, 95%; d) DMTrCl, pyridine, RT, 96%; e) 2-cyanoethyl N,N,N',N' -tetraisopropylphosphorodiamidite, diisopropylammonium tetrazolide, MeCN/THF, RT, 98%. Bn = benzyl, Ac = acetyl, Ts = toluene-4-sulfonyl, DMTr = dimethoxytrityl.

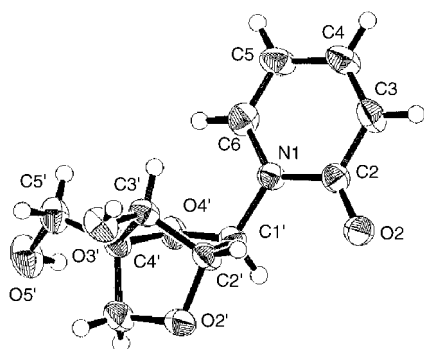


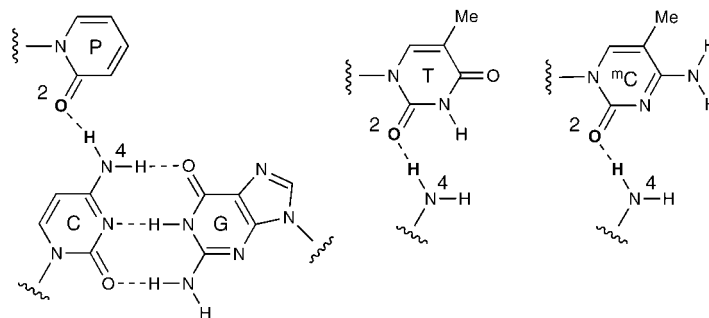
Figure 1. X-ray structure of 2',4'-BNA-pyridone monomer **1**.

The melting temperatures (T_m) for the triplexes formed by TFO I containing the 2',4'-BNA-2-pyridone monomer (P^B) were compared with those of triplexes where TFO I contained a natural nucleobase (T or mC), a DNA-2-pyridone monomer (P),^[14] or the 2',4'-BNA abasic monomer (H^B , Table 1).^[7, 18] At first, it was found that the triplex I·II·III containing a $P \cdot C \cdot G$ triad was as stable as the triplexes I·II·III containing a $T \cdot C \cdot G$ or $mC \cdot C \cdot G$ triad, which indicates the great importance of the 2-carbonyl oxygen atom of T, mC , and P in the recognition of a $C \cdot G$ base pair.^[19] Furthermore, as we expected, the TFO I containing P showed high sequence selectivity, while that containing T or mC preferentially recognizes an A·T or G·C base pair. The proposed hydrogen-bonding pattern for the $P \cdot C \cdot G$ triad is shown in Scheme 3.

Table 1. T_m values [$^{\circ}C$] of the triplex formed between TFO I and the target duplex II·III.^[a]

X	Y·Z			
	C·G	G·C	T·A	A·T
T	25	20	17	44
mC	25	43	16	18
P	24	16	15	15
P^B	33	19	14	23
H^B	24	20	20	16

[a] UV melting profiles were measured in 7 mM sodium phosphate buffer (pH 7.0) containing 140 mM KCl and 10 mM $MgCl_2$ at a scan rate of $0.5 K min^{-1}$ at 260 nm. The oligonucleotide concentration used was $1.5 \mu M$ for each strand.



Scheme 3. Proposed structures of the $P \cdot C \cdot G$, $T \cdot C \cdot G$, and $mC \cdot C \cdot G$ triads.

Triplex formation between TFO I ($X = P^B$) and the target duplex II·III was also found to be sequence selective, with the triplex I·II·III containing a $P^B \cdot C \cdot G$ triad being the most stable in the triplexes I·II·III with a $P^B \cdot X \cdot Y$ triad (Figure 2A). Moreover, the thermal stability of the triplex I·II·III containing a $P^B \cdot C \cdot G$ triad is preferable to that of the triplex I·II·III containing a $T \cdot C \cdot G$ triad (Figure 2B). Comparison of the T_m values of the triplexes with $P^B \cdot C \cdot G$ ($33^{\circ}C$) and $P \cdot C \cdot G$ triad ($24^{\circ}C$) demonstrates that the level of triplex stabilization induced by the 2',4'-BNA modification of the 2-pyridone derivative for recognition of the $C \cdot G$ interruption ($\Delta T_m = +9 K$) is comparable to that caused by the 2',4'-BNA modification of thymidine or 5-methylcytidine in the fully matched triplexes.^[7]

To confirm the general applicability of this result, the ability of P^B to recognize the $C \cdot G$ interruption in other dsDNA targets was also studied (Table 2). Replacement of an A·T base pair by a G·C base pair at the neighboring sites of the $C \cdot G$ interruption caused a decrease in the T_m values as a result of the low stability of a $mC \cdot G \cdot C$ triad under neutral conditions. However, the TFOs I' ($X = P^B$) preserved the reasonable triplex-forming ability towards the corresponding target duplex ($Y \cdot Z = C \cdot G$). Furthermore, the triplexes I'·II'·III' containing a $P^B \cdot C \cdot G$ triad had much superior thermal stability than any other triplexes I'·II'·III' having a $P^B \cdot T \cdot A$, $T \cdot C \cdot G$, or $T \cdot T \cdot A$ triad.

To the best of our knowledge, P^B is one of the best nucleic acid analogues for recognizing a $C \cdot G$ base pair since it gives a significant increase in binding affinity without loss of selectivity. Considering that the TFO I containing the 2',4'-BNA abasic monomer (H^B) had only a slight effect on the triplex

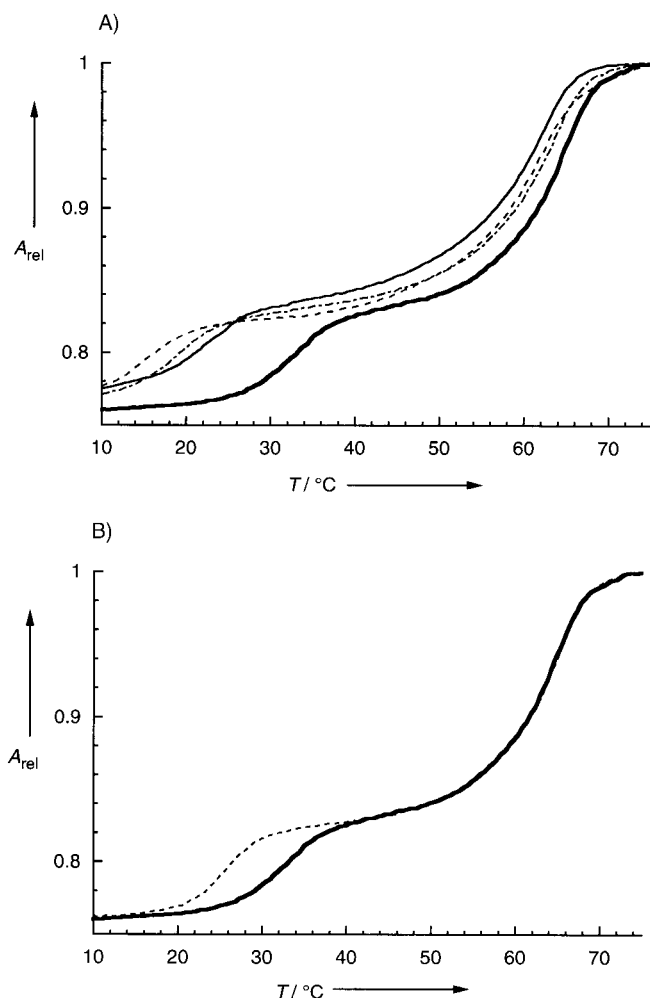


Figure 2. T_m profiles of triplex I·II·III containing a A) $P^B \cdot C \cdot G$ (—), $P^B \cdot T \cdot A$ (---), $P^B \cdot G \cdot C$ (·-·-), or $P^B \cdot A \cdot T$ (— · —) triad and B) a $P^B \cdot C \cdot G$ (—) or $T \cdot C \cdot G$ (---) triad.

Table 2. T_m values [°C] of the triplex formed from the TFO I' and the target duplex II'·III'.^[a]

X_1-X-X_2	Y·Z		X_1-X-X_2	Y·Z	
	C·G	T·A		C·G	T·A
T-T- ^m C	16	ca. 10	^m C- P^B -T	21	— ^[b]
T- P^B - ^m C	27	ca. 10	^m C-T- ^m C	— ^[b]	— ^[b]
^m C-T-T	13	ca. 10	^m C- P^B - ^m C	16	— ^[b]

[a] See captions in Table 1. [b] Typical hyperchromicity for the triplex dissociation was not observed.

stabilization, the unprecedented C·G recognition ability of P^B would be attributable to the 2'-O,4'-C-methylene bridged ribofuranose moiety coupled with an appropriate hydrogen bond between the 2-carbonyl oxygen atom in P^B and the 4-amino group in C.

The results presented here demonstrate that the 2-carbonyl oxygen atoms of pyridone and pyrimidine nucleobases play an important role in the recognition of a C·G base pair. In contrast to T or ^mC, the 2-pyridone derivative (P) has a reasonable C·G selectivity because of the lack of a 3-nitrogen atom and a 4-carbonyl or amino group which are crucial for hydrogen bonding with other base pairs. The combination of

2-pyridone and the 2'-O,4'-C-methylene bridged sugar moiety significantly enhances the binding affinity with a C·G base pair, without loss of selectivity. The application of the present findings to the regulation of gene expression is currently under way.

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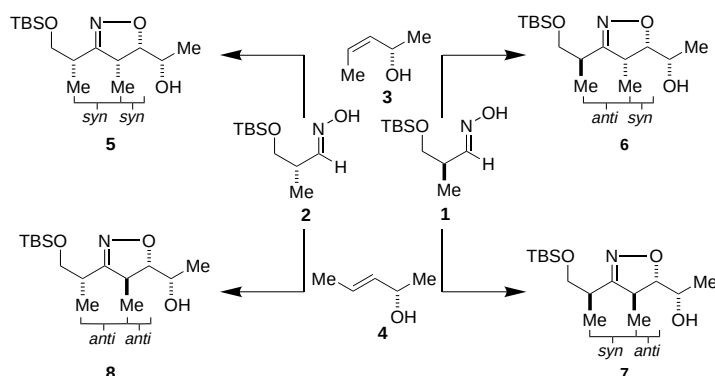
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A General Solution to the Modular Synthesis of Polyketide Building Blocks by Kanemasa Hydroxy-Directed Nitrile Oxide Cycloadditions**

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The abundance, structural diversity, and significant biological activity of polyketide-derived natural products has placed at the forefront of chemistry and biology the identification and development of processes permitting their expeditious synthesis.^[1, 2] Of particular interest are methods which allow the convergent assembly of stereochemically defined building blocks as well as those which are readily tailored to provide the full spectrum of stereochemical permutations and functional group diversity inherent to these structures. Although the most widely used methods towards this goal employ carbonyl additions reactions,^[3–7] numerous alternatives have been advocated.^[8] One of the most intriguing proposals is Curran's and Torssell's recognition that the products of nitrile oxide cycloadditions with alkenes, namely isoxazolines, are latent aldol adducts.^[9]

Herein we disclose the general, stereo- and regioselective cycloaddition of chiral nitrile oxides and allylic alcohols to provide enantiomerically pure isoxazolines. We demonstrate that this strategy permits the modular preparation of all possible protected dipropionate diastereomers with the same set of reagents and a single reaction protocol affording complex, densely functionalized polyketide building blocks **5–8** (Scheme 1).



Scheme 1. Single-step preparation of all possible diastereomers of latent dipropionates. TBS = *t*BuMe₂Si.

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

The use of isoxazolines as masked β -hydroxy carbonyl compounds offers considerable advantages over alternative processes for the construction of aldol adducts. These include: the ability to carry out convergent syntheses through the coupling of complex olefin and nitrile oxide fragments;^[10] the ease of preparation and stability of the reaction partners; the use of isoxazolines as masked aldol – adducts avoiding superfluous protecting group manipulations; the ability of this heterocycle to function as a platform for stereoselective transformations;^[11, 12] and the highly stereospecific nature of the cycloadditions. Despite intense efforts in this field, however, the lack of regio- and stereochemical control in the typical nitrile oxide cycloaddition reaction, the inability to successfully employ substituted olefins, and the lack of a general procedure permitting the preparation of isoxazolines in enantiomerically pure form have to date precluded the widespread adoption of this method in polyketide synthesis.^[12]

The basis for the strategy we disclose for the preparation of enantiomerically pure latent dipropionate stereotetrads is the seemingly unnoticed report by Kanemasa et al. on Mg^{II}-directed nitrile oxide cycloadditions with allylic alcohols.^[13] Although these studies documented the ability of magnesium alkoxides to promote significant rate acceleration and diastereoselectivity in cycloaddition reactions, this study was limited to the use of benzonitrile oxide. Aliphatic nitrile oxides, which are considerably more capricious than their aromatic counterparts, were not investigated. Consequently, at the onset of our own efforts it was unclear whether this process would be amenable to the use of functionalized aliphatic nitrile oxides of interest to achieve a general surrogate for convergent aldol-equivalent reactions.

In the course of our studies to establish this protocol for a wide range of cycloaddition partners, we have developed convenient, broadly applicable reaction conditions for highly diastereoselective cycloadditions. This protocol permits the use of otherwise problematic aliphatic nitrile oxides by preparation of the corresponding hydroximinoyl chlorides with *t*BuOCl at -78°C and direct reaction of this solution with an allylic magnesium alkoxide. Under these conditions nitrile oxides otherwise prone to dimerization or decomposition can be employed successfully as substrates. The magnesium alkoxides, which are unwieldy to prepare as isolated salts, are conveniently generated in situ from the allylic alcohol and a Grignard reagent. The use of isopropanol as an additive improves reaction times and yields otherwise diminished by the ethereal solvent.^[14] The operationally simple and remarkably versatile reaction procedure that results is tolerant of a wide range of functionality and olefin substitution [Eq. (1)]. As shown in Table 1, these conditions routinely afford the desired cycloadducts in good yields and high diastereoselectivities. Additionally, we have found this protocol to be amenable to preparative-scale syntheses (>25 mmol).

Optically active oximes **1** and **2** are conveniently and readily prepared from (*R*)- and (*S*)-3-hydroxy-2-methylpropionic acid methyl esters which are commodity chemicals available at <1 \$g⁻¹.^[15] Each of these oximes reacts smoothly with enantiomerically pure *cis*-allylic alcohol^[16] **3** to give the

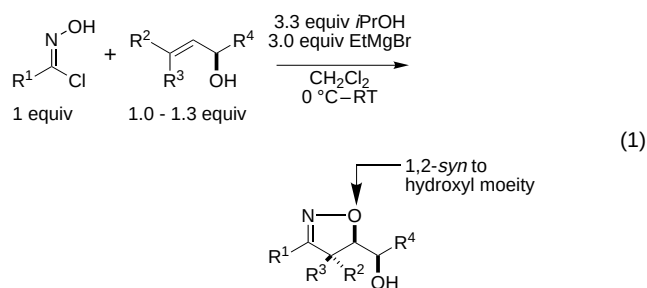


Table 1. Polypropionate building by hydroxy-directed nitrile oxide cycloadditions.^[a]

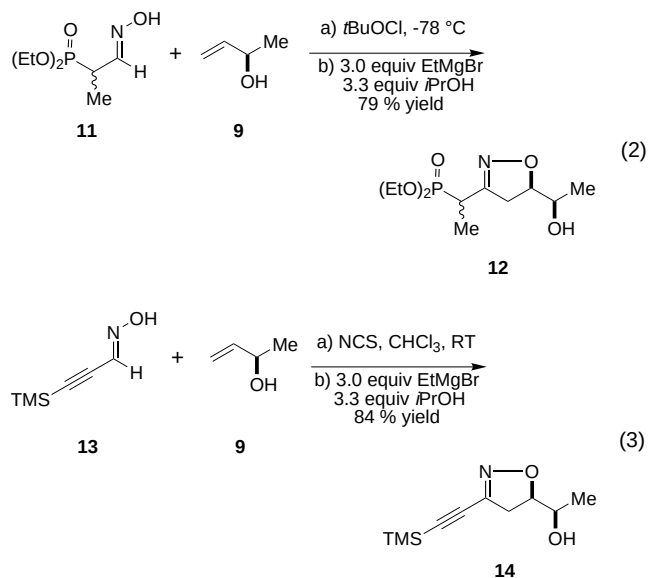
Entry	Oxime	Allylic alcohol	Cycloadduct ^[b]	Yield [%]
1				82
2 ^[c]				87
3				68
4				73
5				83

[a] All reactions were performed by chlorination of the oxime with 1.0 equivalents of *t*BuOCl at -78°C followed by addition of this solution to a mixture of the allylic alcohol (1.0–1.3 equiv), isopropanol (3.3 equiv), and EtMgBr (3.0 equiv) in CH_2Cl_2 and stirring 12 h at room temperature. [b] All cycloadducts were regiochemically and stereochemically pure by ^1H and ^{13}C NMR analyses. [c] The structure of a derivative of this cycloadduct was confirmed by X-ray diffraction analysis.

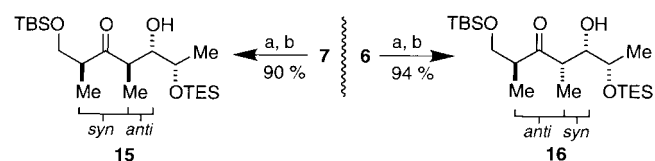
corresponding cycloadducts with complete regio- and stereo-selectivity (Table 1, entries 1, 2), affording 4,5-*syn* adducts.^[17] Likewise, the use of the *trans*-allylic alcohol **4** provides direct access to the complementary stereochemical family of 4,5-*anti* products (Table 1, entries 3, 4). In all cases the isoxazolines were isolated as single compounds without detectable amounts of other diastereomers or regioisomers (^1H and ^{13}C NMR analyses). In contrast to carbonyl addition methodologies, we did not observe any complications due to mismatched stereochemistries of the reaction partners. Equally noteworthy is the facile application of this nitrile oxide cycloaddition to the synthesis of the methyl ketone aldol equivalents (**10**, Table 1, entry 5) which in general are particularly onerous to accomplish by carbonyl addition methodologies. The ability to selectively prepare all eight of the possible stereoisomers^[18] from the same set of reagents (*cis*- or *trans*-allylic alcohols and nitrile oxides) and under a

single set of reaction conditions offers great potential for the development of a general synthesis of polyketide structures.^[19, 20]

Preliminary results on the use of highly functionalized nitrile oxides and olefins additionally highlight the unique features of this protocol. Despite potential complications due to its C–H acidity, phosphonate oxime **11** cleanly affords the cycloadduct **12** [Eq. (2)]; importantly, the presence of a phosphonate in the product facilitates functionalization and synthetic elaboration. Additionally, the previously unreported C-alkynyl nitrile oxides can successfully participate in the cycloaddition, giving adducts amenable to a wide range of transformations [Eq. (3); TMS = Me_3Si].^[21]



Although the optically active isoxazoline cycloadducts are in themselves useful synthetic intermediates, we have carried out their conversion to the corresponding hydroxy ketones without loss of stereochemical integrity (Scheme 2). Isoxazolines **6** and **7** undergo N–O bond cleavage and imine

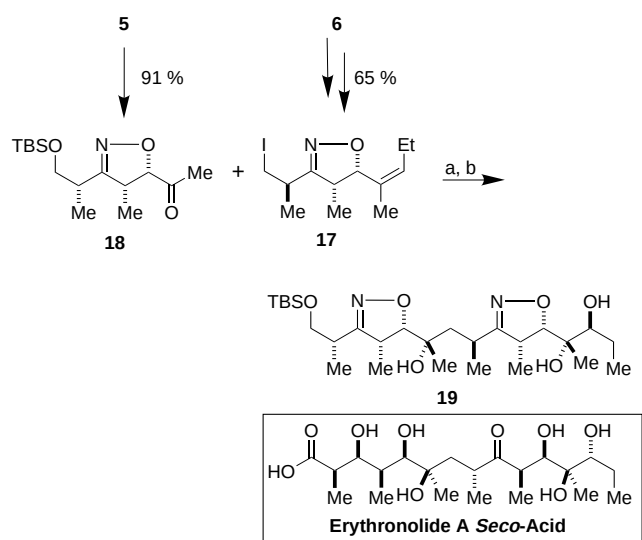


Scheme 2. Facile conversion of isoxazolines **6** and **7** to β -hydroxy ketones. a) TESCl, NEt_3 , CH_2Cl_2 ; b) W2 Ra-Ni, $\text{B}(\text{OH})_3$, H_2 , $\text{MeOH}-\text{H}_2\text{O}$. TES = Et_3Si .

hydrolysis upon exposure to Curran's conditions (Raney-Ni, $\text{B}(\text{OH})_3$),^[22] furnishing β -hydroxy ketones related to those typically used for the synthesis of complex polypropionates.^[23]

The free alcohol present in the cycloaddition products provides a convenient synthetic handle for further transformation to more elaborate structures. The unique ability of the enantiomerically pure isoxazolines to function as protecting groups as well as a stereochemical controlling element is one of the strengths of this method, enabling the rapid and

highly convergent assembly of complex polyketide structures through diastereoselective fragment couplings. This is illustrated with the use of **5** and **6** (Table 1) in the expeditious assembly of a representative polypropionate. Diastereoselective coupling of **17** and **18** (d.r. > 10:1) followed by reagent-controlled catalytic dihydroxylation affords **19**, which contains the dense stereochemical array found in *ent*-erythronolide A (Scheme 3).^[24]



Scheme 3. The rapid, convergent, and diastereoselective assembly of the erythronolide A stereochemical array. a) *t*BuLi, MgBr₂, -78 °C; then **14**, THF, -78 °C, 50%; b) AD-Mix β, CH₃SO₂NH₂, 65%.

In conclusion, we have described the preparation of enantiomerically pure, protected β-hydroxy ketones. The nature of this approach allows the modular preparation of the entire spectrum of functionalization and stereochemical permutations found in polyketide-derived structures. Importantly, the building blocks obtained possess the appropriate functionality for elaboration and stereoselective fragment coupling necessary for the rapid assembly of complex natural and unnatural polyketides.

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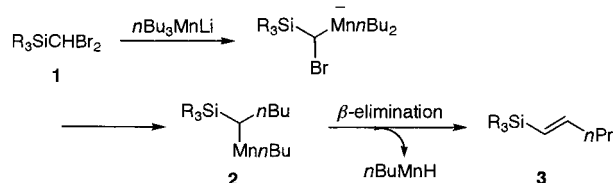
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Alkylative Preparation of α -Silylalkylmagnesium from $R_3SiCHBr_2$ Using a Magnesate Reagent**

Junichi Kondo, Atsushi Inoue, Hiroshi Shinokubo, and Koichiro Oshima*

The Peterson olefination reaction utilizing α -silylalkylmetals has been established as a highly stereoselective method to prepare alkenes.^[1] Therefore, α -silylalkylmetal species have gained importance as reagents for organic synthesis.^[2] Methods for the preparation of α -silylalkylmetals are usually based on 1) deprotonation,^[3] 2) halogen–metal exchange with metals (Li or Mg) or organometallic compounds (BuLi or $RMgX$),^[4] or 3) addition of an organometallic species to vinylsilanes.^[5] Deprotonation methods require strong bases (typically $tBuLi$) and are not effective for the deprotonation of alkylsilanes which lack an activating group (such as a carbonyl group). The requisite α -haloalkylsilanes for halogen–metal exchange reactions are not readily available; the most efficient method for their preparation is the addition of an organometallic species to a vinylsilane.

Metal carbenoid species are well-known to undergo alkylation by the action of alkylmetals.^[6] Therefore, the alkylation of silyl-substituted carbenoids could be an attractive route to α -silylalkylmetals. We have previously reported the synthesis of 1-alkenylsilanes **3** from dibromomethylsilanes **1**^[7] via manganese carbenoids (Scheme 1).^[8] The α -silylalkylmanga-



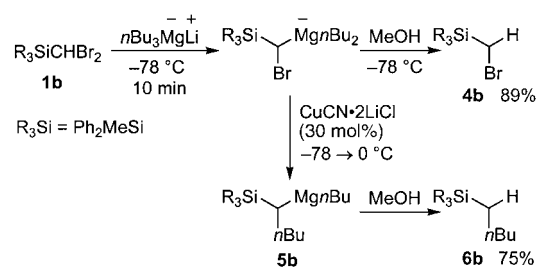
Scheme 1. Reaction of dibromomethylsilanes **1** with tributylmanganate.

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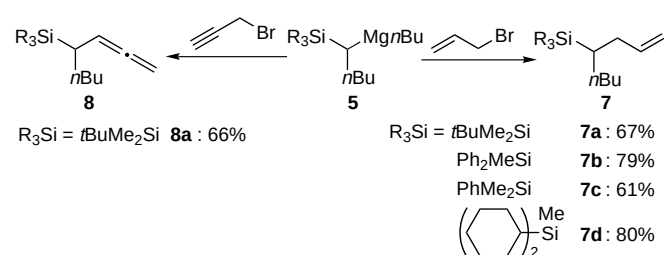
nese **2** formed in this reaction cannot be trapped with electrophiles because of its rapid conversion into alkenylsilane **3** by β -hydride elimination. We then investigated alternative methods to generate α -silylalkylmetallic compounds. Herein we report a copper-catalyzed alkylative preparation of α -silylalkylmagnesium compounds via trialkylmagnesium ate complexes and its application to the synthesis of α -silyl ketones.

We examined the reaction of dibromomethylsilane **1** with trialkylmagnesate (Scheme 2).^[9,10] Tributylmagnesate (nBu_3MgLi) was easily prepared by mixing butyllithium



Scheme 2. Bromine–magnesium exchange and the subsequent migration of an alkyl group.

(2.0 equiv) and butylmagnesium bromide (1.0 equiv) in THF at 0 °C. Treatment of dibromomethylsilane **1** with a magnesium ate complex induced clean bromine–magnesium exchange to provide bromomethylsilane **4** upon quenching with methanol at -78 °C.^[11] Warming the reaction mixture to room temperature before quenching resulted in the migration of the butyl group to yield α -silylpentylmagnesium **5**.^[12,13] This migration was facilitated by a copper salt.^[14] The addition of $CuCN \cdot 2LiCl$ (30 mol%) to the reaction mixture induced smooth migration of the butyl group at lower temperatures (-30 °C for **1a** and 0 °C for **1b**) to afford **5** in good yield. The use of butyllithium or $nBuMgBr$ instead of tributylmagnesate also induced the metalation and the subsequent butylation. Under these conditions, however, the yields of the desired products were quite low. The α -silylpentylmagnesium **5** could be trapped with allyl bromide to give **7** in good yield (Scheme 3). The reaction with propargyl bromide furnished exclusively the allenylated product **8**.



Scheme 3. Reaction of α -silylalkylmagnesium compounds **5** with allyl or propargyl bromide.

α -Silyl ketones are quite useful intermediates in organic synthesis.^[15] Therefore, we undertook the preparation of α -silyl ketones using this new methodology.^[16] The reaction of α -silylalkylmagnesiums **5** with various acyl chlorides was

examined (Table 1).^[17] The addition of acyl chlorides to the resulting solution of **5** furnished the corresponding α -silyl ketones **9** in good yields. 1,3-Dimethyl-2-imidazolidinone (DMI) proved to be an effective additive for the formation of α -silyl ketones. The yield of the product decreased when DMI was not used (entry 7).

Table 1. Synthesis of α -silyl ketones from dibromomethylsilanes.^[a]

$ \begin{array}{c} \text{R}_3\text{SiCHBr}_2 \xrightarrow[2) \text{ cat. CuCN}\cdot 2\text{LiCl}]{1) \text{R}^1_3\text{MgLi}} \text{R}_3\text{Si}-\text{CH}(\text{R}^1)-\text{MgR}^1 \xrightarrow[\text{DMI}]{\text{R}^2\text{COCl}} \text{R}_3\text{Si}-\text{CH}(\text{R}^1)-\text{C}(=\text{O})\text{R}^2 \\ \mathbf{1} \qquad \qquad \qquad \mathbf{5} \qquad \qquad \qquad \mathbf{9} \end{array} $						
Entry	Substrate	R ₃ Si	R ¹	R ²	Product	Yield [%]
1	1a	<i>t</i> BuMe ₂ Si	<i>n</i> Bu	CH ₃	9a	60
2				<i>c</i> Pr	9b	56
3				Ph	9c	66
4				(<i>E</i>)-CH ₃ CH=CH-	9d	53
5				(<i>E</i>)-PhCH=CH-	9e	51
6	1b	Ph ₂ MeSi	<i>n</i> Bu	CH ₃	9f	63
7				<i>n</i> Pr	9g	49
8 ^[b]				<i>n</i> Pr	9g	74
9 ^[b]				<i>i</i> Pr	9h	63
10 ^[b]				<i>c</i> Pr	9i	69
11 ^[b]				Ph	9j	77
12 ^[b,c]				<i>n</i> C ₆ H ₁₃	<i>n</i> Pr	9k
13 ^[c]			Ph	9l	70	

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

Dieter Lentz* and Stefan Willemsen

It is often extremely difficult to synthesize fluorinated analogues of ligands frequently used in organometallic chemistry,^[1] such as cyclopentadienyl and propenyl (allyl) ligands. After many unsuccessful attempts pentafluorocyclopentadiene was synthesized and deprotonated;^[2] however, no C_5F_5 complex could be prepared thereof. The synthesis of pentamethylcyclopentadienyl(pentafluorocyclopentadienyl)-ruthenium by vacuum pyrolysis of pentamethylcyclopentadienyl(pentafluorophenoxy)ruthenium with elimination of carbon monoxide at 750 °C demonstrates that fluorinated enyl complexes are not generally unstable,^[3] but suitable synthetic methods are often missing. As the C–F bond is the strongest element–carbon bond ($D(C-F) = 109–130$ kcal mol^{–1}) and C–F activation is gaining increasing importance,^[4] we are looking for methods to construct more complex ligands directly at metal complexes from simple, readily available fluoroorganic starting materials.

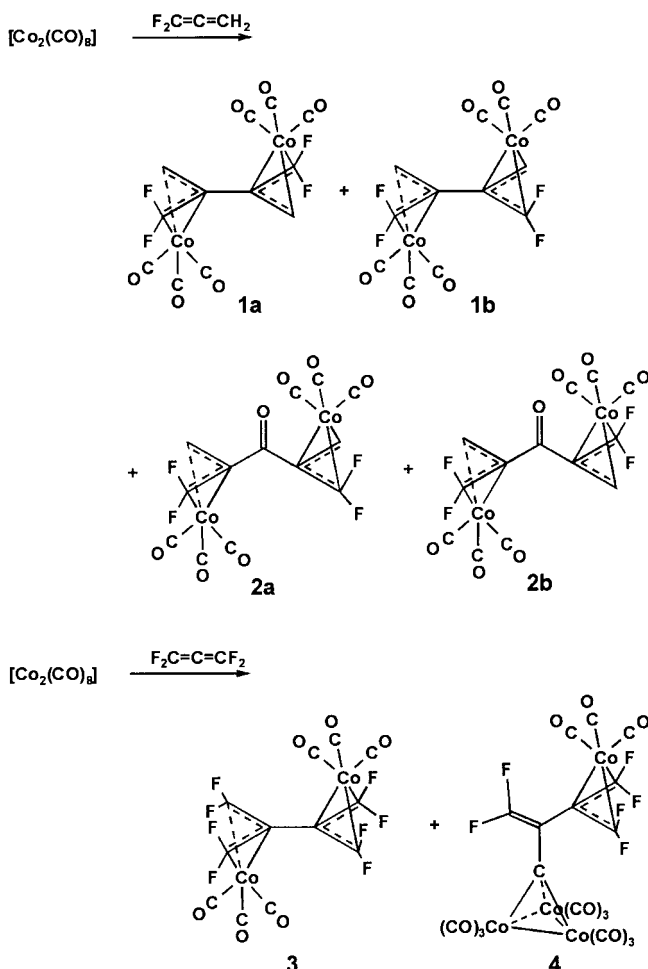
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We started our investigations by studying the ligand properties of fluorinated allenes, which turned out to be very strong π -acceptor ligands; thus, stressing the importance of π backbonding as shown also by theoretical calculations.^[6]

We expected to be able to construct new ligands by metal-induced dimerization of 1,1-difluoroallene and tetrafluoroallene on manganese and cobalt complex fragments, as reactions of allenes with decacarbonyldimanganese^[7] and octacarbonyldicobalt^[8] resulted in new ligand systems through C–C coupling. Furthermore the dimerization is the first step of a polymerization reaction which is not a metal-catalyzed process in the case of fluorinated alkenes. The polymerization of fluorinated alkenes to technically important products, such as polytetrafluoroethene (PTFE) and fluorinated ethylene propylene copolymer (FEP), is generally achieved by free radical polymerization.^[9] In the presence of radical trapping agents, such as terpenes, fluorinated alkenes yield [2+2] cycloaddition products.^[10] Tetrafluoroallene polymerizes to give a not fully characterized polymer and dimerizes in the presence of α -terpinene to give perfluoro-1,2-methylenecyclobutane.^[11]

Reaction of 1,1-difluoroallene and tetrafluoroallene with octacarbonyldicobalt yielded the dinuclear cobalt complexes **1** and **3**, respectively (Scheme 1). The reaction with 1,1-



Scheme 1. Reactions of octacarbonyldicobalt with 1,1-difluoroallene and with tetrafluoroallene.

difluoroallene additionally yields the dinuclear complex **2**, in which a CO unit is inserted between the two C₃ fragments, in the reaction with tetrafluoroallene small amounts of the cluster compound **4** were isolated. The NMR spectra of **1** exhibit two sets of signals, which are attributed to the presence of a C_i (**1a**) and a C₂-symmetrical isomer (**1b**). Crystals of both isomers were isolated and the structures of both were determined by X-ray crystallography^[12] (Figure 1). The two isomeric cobalt

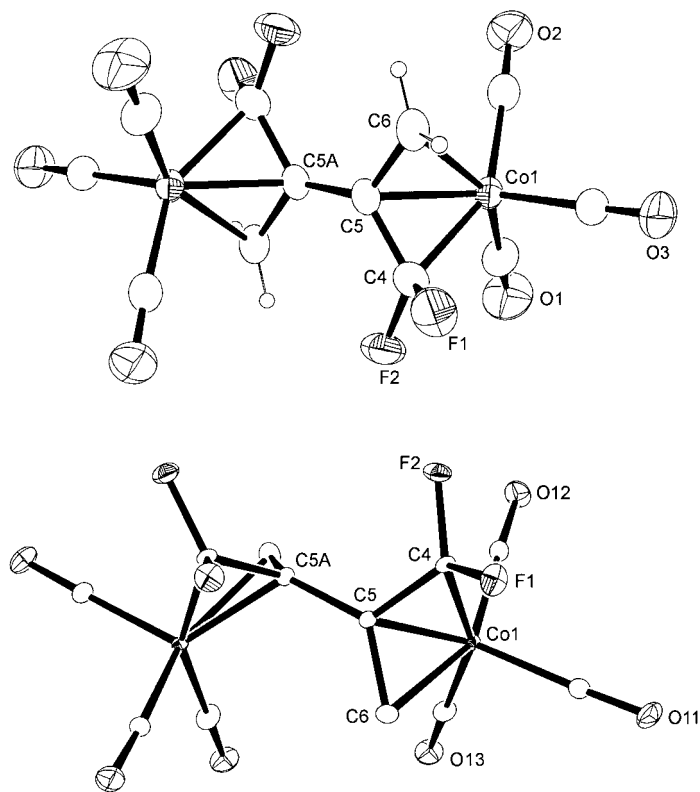


Figure 1. Molecular structures of **1a** (top, ORTEP^[17]; 30% ellipsoids) and **1b** (bottom, ORTEP^[17]; 50% ellipsoids; measurement temperature 20 K). Selected bond lengths [Å] and torsion angles [°] for **1a/1b**: Co1–C4 1.9632(19)/1.951(4), Co1–C5 2.0107(16)/1.996(4), Co1–C6 2.0706(18)/2.103(4), C4–C5 1.437(3)/1.446(5), C5–C6 1.419(2)/1.420(6), C5–C5A 1.478(3)/1.494(8); C4–C5–C5A–C4A –180.0(2)/–96.8(2).

complexes have very similar metal–carbon distances to the 2,3-dimethylenebuta-1,4-diyl ligands; the distances to the fluorine-substituted carbon atoms are about 0.1 Å shorter than those to the hydrogen-substituted ones. The distances to the central carbon atoms lie somewhere in between. Consequently the fluorine-substituted C–C bond is more elongated than the other one. Significant differences between the structures of the isomers **1a** and **1b** are observed for the C5–C5A distance (1.478(3) and 1.494(8) Å, respectively) and the torsion angles C4–C5–C5A–C4A (–180 and –96.8°, respectively). An isomerization of **1a** and **1b** would require that the [Co(CO)₃] fragment would migrate from one side of the allyl ligand to the other or that the coordination mode would change from η^3 to η^1 . Both were not observed in the temperature range from –100 to 50 °C by NMR spectroscopy. Interestingly, the chemical shift values of one these isomers shows a strong temperature dependence not observed for the

other one. Compound **3** crystallizes orthorhombic in the space group *Pcan* (no. 60, conventional *Pbcn*) with 1.5 molecules in the asymmetric unit. One of the molecules (molecule **2**) possesses crystallographic C₂ symmetry (Figure 2), whereas

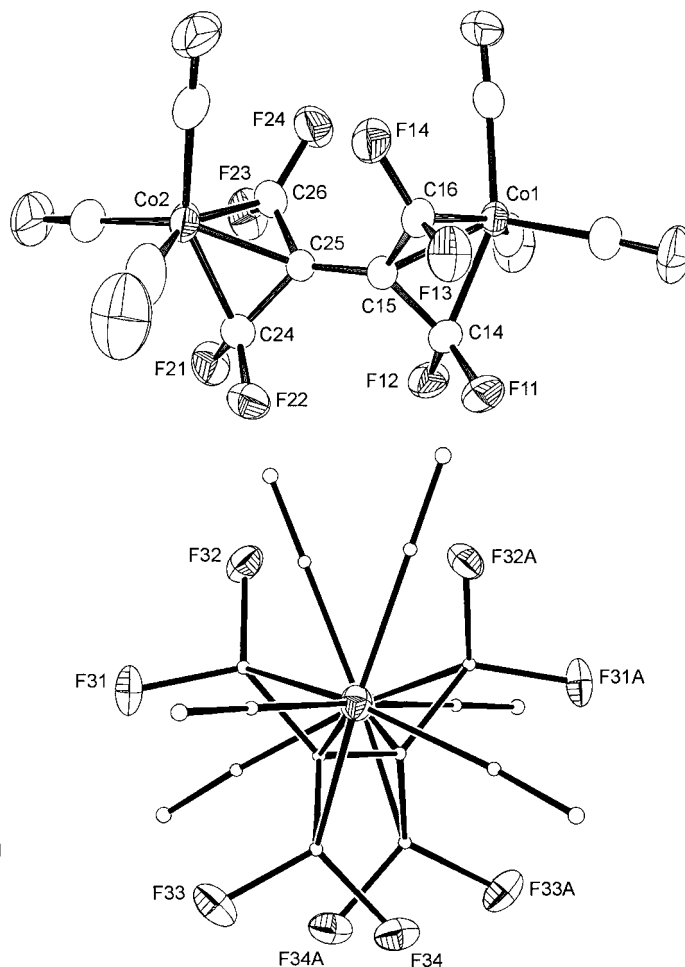


Figure 2. Molecular structures of **3** (ORTEP^[17]). Top: molecule **2** (30% ellipsoids), bottom: molecule **1** with view along the Co–Co axis to demonstrate the C₂ symmetry of the molecule. Selected bond lengths [Å] and torsion angles [°]. Co–CF₂ 1.955(3)–1.971(3), Co–C_{central} 1.988(3)–2.015(3), C–C_{allyl} 1.410(5)–1.425(5), C–C 1.483(4)–1.485(6); C14–C15–C25–C26 –116.5(3), C34–C35–C35A–C36A –132.4(3).

the other (molecule **1**) has only approximately C₂ symmetry. Major differences between the molecules are observed only for the torsion angles (C14–C15–C25–C26 –116.5°, C34–C35–C35A–C36A –132.4°). The metal–carbon distances to the CF₂ groups lie between 1.955(3) and 1.971(3) Å and are slightly shorter than those to the central carbon atom. According to the C₂ symmetry the ¹⁹F NMR spectrum of **3** should consist of two AB patterns for the four inequivalent fluorine atoms, as observed in the low-temperature spectrum at –60 °C. On raising the temperature the signals coalesce and only one AB pattern is found at ambient temperature, which can be explained by rapid rotation around the central C–C bond.

NMR studies of **2** show that this compound consists of a mixture of two isomers in the ratio 1:7; however, as above the spectrum does not allow an assignment of the signals to the

specific isomers **2a** and **2b**. The bond lengths and angles of **2b** (Figure 3, top) do not differ significantly from those of **1** besides the presence of an additional carbonyl group between the two allyl groups.

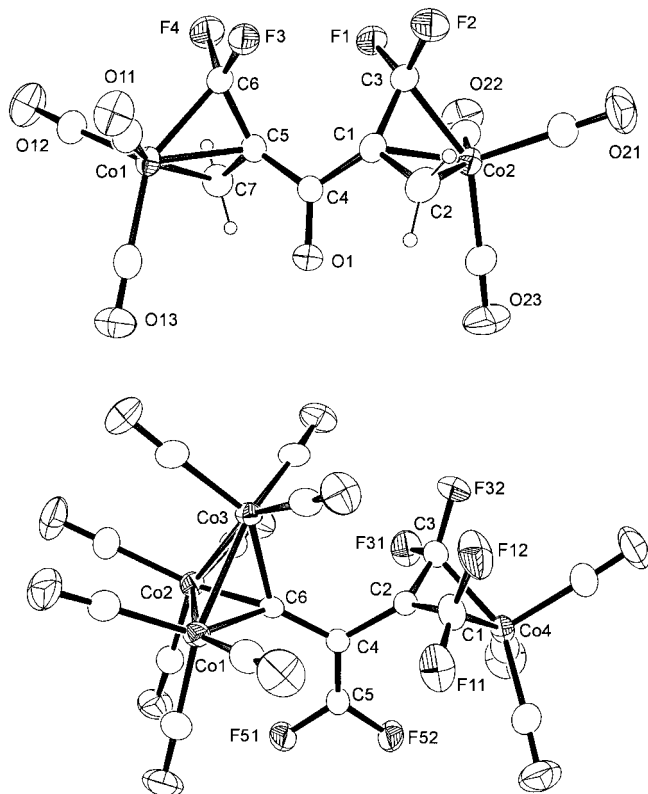
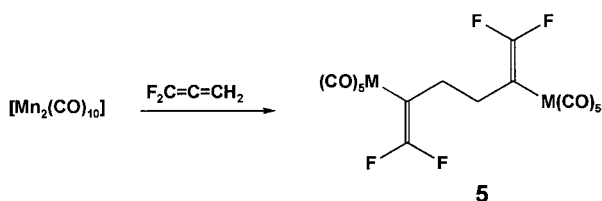


Figure 3. Molecular structures (ORTEP,^[17] 30% ellipsoids) of **2** (top) and **4** (bottom). Selected bond lengths [Å]: **2**: Co–CF₂ 1.966(4)–1.969(4), Co–C_{central} 1.980(3)–1.992(3), Co–CH₂ 2.058(4)–2.077(4), C–CF₂ 1.422(5)–1.433(5), C–CH₂ 1.402(5)–1.403(5); **4**: Co–C6 1.913(3)–1.916(3), Co4–C1 1.966(3), Co4–C2 2.002(3), Co4–C3 1.964(3), C1–C2 1.418(4), C2–C3 1.417(4), C2–C4 1.500(4), C4–C6 1.466(4), C4–C5 1.320(4), C5–F 1.313(3)–1.316(3), C3–F 1.347(4)–1.348(4).

The cluster compound **4** results from a fluoride abstraction from one CF₂ group in the reaction with octacarbonyldicobalt under formation of an alkylidyne ligand. The tetrafluoroallyl cobalt unit (Figure 3, bottom) shows the same structural characteristics as already observed in **3**. The alkylidyne carbon atom C6 forms a μ_3 bridge to three tricarbonylcobalt fragments, as observed in numerous alkylidyne cluster compounds of cobalt.^[13]

The reaction of 1,1-difluoroallene with decacarbonyldimanganese yields the dimer **5**, in which the ligand bridges two pentacarbonyl manganese fragments (Scheme 2). During this



Scheme 2. Reaction of decacarbonyldimanganese with 1,1-difluoroallene.

C–C coupling reaction the new bond is formed between the two CH₂ groups instead of at the central carbon atom, and the 1,1,6,6-tetrafluoro-1,5-hexadiene-2,5-diyl ligand is $\eta^1:\eta^1$ coordinated to the pentacarbonyl manganese fragments. The centrosymmetric molecule crystallizes triclinic (space group *P* $\bar{1}$) with half a molecule within the asymmetric unit. The metal atoms are almost octahedrally coordinated by five carbonyl ligands and the carbon atoms C6 and C6A of the 1,1,6,6-tetrafluoro-1,5-hexadiene-2,5-diyl ligand (Figure 4). The metal–carbon distances to the *trans* carbonyl ligand is significantly shorter than those to the *cis* carbonyl ligands.

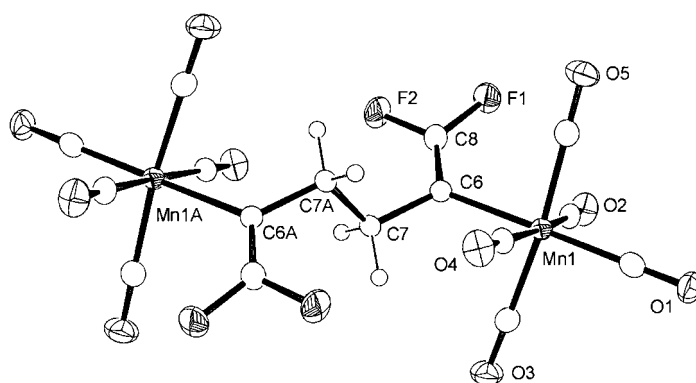


Figure 4. Molecular structure of **5** (ORTEP,^[17] 50% ellipsoids). Selected bond lengths [Å] of **5**: Mn–C1 1.847(2), Mn–C2 1.863(2), Mn–C6 2.108(2), C6–C7 1.524(2), C6–C8 1.309(2), C7–C7A 1.543(3), C–F 1.348(2)–1.350(2).

The products of the metal-induced dimerization of fluorinated allenes strongly depends on the metal complex used and they are completely different to those obtained in a “metal-free” dimerization reaction.

Experimental Section

Hexacarbonyl- μ -($\eta^3:\eta^3$ -1,1,5,5-tetrafluoro-2,3-dimethylenebuta-1,4-diyl)dicobalt (**1**) and hexacarbonyl- μ -($\eta^3:\eta^3$ -1,1,5,5-tetrafluoro-2,4-dimethylene-3-oxopenta-1,5-diyl)dicobalt (**2**): Octacarbonyldicobalt (**2**, 5.86 mmol) was dissolved in *n*-pentane (60 mL). 1,1-Difluoroallene (18.3 mmol) was condensed onto the solution by using a glass vacuum system. The reaction mixture was stirred for 48 h. The solvent was removed under vacuum and the residue was purified by column chromatography (*n*-pentane/silica, 45 $\times$ 3 cm²). The first fraction contained compound **2**, which, after removal of the solvent, was sublimed under vacuum at 40 °C/10^{−3} mbar onto a receiver cooled to −25 °C. Compound **2** (1172 mg, 43%) was obtained as yellow crystals as a mixture of two isomers in the ratio 1:7 (isomer 2: isomer 1). M.p. 77–78 °C. ¹H NMR (CDCl₃, −50 °C): δ = 2.17 (s, 1 H; CH₂, isomer 2), 2.21 (s, 1 H; CH₂, isomer 1), 2.58 (s, 1 H; CH₂, isomer 2), 2.99 (s, 1 H; CH₂, isomer 1); ¹⁹F NMR (CDCl₃): δ = −77.55 (d, ²J_{FF} = 84.0 Hz, 1 F; CF₂, isomer 2), −79.30 (d, ²J_{FF} = 89 Hz, 1 F; CF₂, isomer 1), −90.80 (d, ²J_{FF} = 89.5 Hz, 1 F; CF₂, isomer 1), −91.10 (d, ²J_{FF} = 84 Hz, 1 F; CF₂, isomer 2); ¹³C{¹H} NMR (CDCl₃): δ = 197.7 (s; CO), 190.5 (s; CO), 142.0 (dd, ¹J_{CF} = 318, 335 Hz; CF₂), 63.9 (s; C–CF₂), 45.5 (s; CH₂); ¹³C{¹⁹F} NMR (CDCl₃): isomer 1: δ = 197.7 (s; CO), 190.5 (s; CO), 142.0 (s; CF₂), 63.9 (s; C–CF₂), 45.6 (t, ¹J_{HC} = 167 Hz; CH₂); isomer 2: δ = 197.8, 189.1, 143.0, 65.6 and 44.0. IR (KBr): $\tilde{\nu}$ = 3098 w, 3074 w, 2321 w, 2093 vs (CO), 2053 vs (CO), 2031 vs (CO), 1997 s (CO), 1666 s (CO), 1491 w, 1452 m, 1400 s, 1346 s, 1162 s, 1099 s, 1017 s, 962 w, 884 m, 827 m, 808 w, 749 w, 712 m, 668 s, 610 m, 551 s, 534 s, 500 s, 490 s, 477 m, 454 m, 440 w, 419 m, 368 w, 345 m, 302 w cm^{−1}; IR (*n*-pentane): $\tilde{\nu}$ = 2094 vs (CO), 2045 vs cm^{−1}; MS (70 eV): *m/z* (%): 466 (1) [*M*⁺], 438 (15) [*M*⁺ − CO], 410 (70) [*M*⁺ − 2 CO], 382 (20) [*M*⁺ − 3 CO], 354 (17), [*M*⁺ − 4 CO], 326 (10) [*M*⁺ − 5 CO], 298 (100) [*M*⁺ − 6 CO]; elemental analysis calcd (%) for C₁₅H₄F₄O₇Co₂ (466.03): C 33.50, H 0.87; found: C 33.40, H 1.29. Compound **1** (386 mg, 15%) was isolated from the second fraction

after sublimation under vacuum ($40^{\circ}\text{C}/10^{-3}$ mbar) as yellow crystals which consist of two isomers in the ratio 4:5. M.p. 66°C (decomp); ^1H NMR (CDCl_3): $\delta = 2.87$ (s, 2H; CH_2 , isomer 1), 2.95 (s, 2H; CH_2 , isomer 2), 3.10 (s, 2H; CH_2 , isomer 2), 3.35 (s, 2H; CH_2 , isomer 1); ^{19}F NMR (CDCl_3): $\delta = -82.42$ (d, $^2J_{\text{FF}} = 94$ Hz, 2F; CF_2 , isomer 1), -84.17 (d, $^2J_{\text{FF}} = 88$ Hz, 2F; CF_2 , isomer 2), -86.01 (d, $^2J_{\text{FF}} = 88$ Hz, 2F; CF_2 , isomer 2), -91.51 (d, $^2J_{\text{FF}} = 94$ Hz, 2F; CF_2 , isomer 1); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 198.6$ (s; CO), 143.1 (dd, $^1J_{\text{CF}} = 318$, 349 Hz; CF_2), 142.3 (dd, $^1J_{\text{CF}} = 318$, 345 Hz; CF_2), 68.9 (s; C- CF_2 isomer 2), 65.2 (s; C- CF_2 , isomer 1), 46.2 (s; CH_2 , isomer 2), 45.1 (s; CH_2 , isomer 1); $^{13}\text{C}\{^{19}\text{F}\}$ NMR (CDCl_3): $\delta = 198.6$ (s; CO), 143.1 (s; CF_2 , isomer 1), 142.4 (s; CF_2 , isomer 2), 68.9 (s; C- CF_2 , isomer 2), 65.2 (s; C- CF_2 , isomer 1), 46.2 (dd, $^1J_{\text{CH}} = 166$ Hz; CH_2 , isomer 2), 45.7 (dd, $^1J_{\text{CH}} = 166$ Hz; CH_2 , isomer 1); IR (KBr): $\tilde{\nu} = 3120$ w, 2512 w, 2340 w, 2319 w, 2082 vs (CO), 2024 vs (CO), 1943 s (CO), 1464 w, 1409 w, 1387 w, 1339 s, 1232 w, 1146 s, 1053 s, 961 w, 824 m, 801 m, 757 w, 721 w, 664 m, 592 s, 540 s, 519 m, 510 m, 491 m, 475 m, 445 m, 415 m, 366 w, 317 w cm^{-1} ; IR (*n*-pentane): $\tilde{\nu} = 2097$ s (CO), 2083 vs (CO), 2034 vs (CO), 2002 w (CO) cm^{-1} ; MS (70 eV): m/z (%): 438 (1) [M^+], 410 (24) [$M^+ - \text{CO}$], 382 (53) [$M^+ - 2\text{CO}$], 354 (7) [$M^+ - 3\text{CO}$], 326 (20) [$M^+ - 4\text{CO}$], 298 (21) [$M^+ - 5\text{CO}$], 270 (100) [$M^+ - 6\text{CO}$]; elemental analysis calcd (%) for $\text{C}_{12}\text{H}_4\text{F}_4\text{O}_6\text{Co}_2$ (438.02): C 32.90, H 0.92; found: C 32.82, H 1.41. If the reaction was carried out under a carbon monoxide atmosphere the yields of both compounds increased: **1** 19.7%, **2** 53.5%. Unexpectedly under these conditions the ratio of the products **1** and **2** does not change in favor to product **2**.

Hexacarbonyl- μ -(η^3 -1,1,4,4-tetrafluoro-2,3-bisdifluoromethylenebuta-1,4-diyldicobalt (**3**): Octacarbonyldicobalt (2 g, 5.86 mmol) was dissolved in *n*-pentane (60 mL). Tetrafluoroallene (18.3 mmol) was condensed onto the solution using a glass vacuum line. The reaction mixture was stirred for 48 h at ambient temperature. The solvent was removed under vacuum and the residue was purified by column chromatography (*n*-pentane/silica, 45×3 cm ^{2}). The first fraction was sublimed under vacuum at $40^{\circ}\text{C}/10^{-3}$ mbar to yield **3** (670 mg, 22%) as yellow crystals. M.p. 53 – 54°C ; ^{19}F NMR ($[\text{D}_8]\text{toluene}$, 20°C): $\delta = -78.59$ (d, $^2J_{\text{FF}} = 90$ Hz, 4F; CF_2), -80.47 (d, $^2J_{\text{FF}} = 90$ Hz, 4F; CF_2); ^{19}F NMR ($[\text{D}_8]\text{toluene}$, -60°C): $\delta = -77.34$ (d, $^2J_{\text{FF}} = 94$ Hz, 2F; CF_2), -79.75 ($^2J_{\text{FF}} = 90$ Hz, 2F; CF_2), -81.02 (d, 2F; CF_2), -81.25 (d, 2F; CF_2), the coupling constants cannot be determined due to overlap of two signals; ^{13}C NMR (CDCl_3): $\delta = 194.3$ (s; CO), 136.3 (dd, $^1J_{\text{CF}} = 307$, 350 Hz; CF_2), 30.9 (s; C- CF_2); IR (KBr): $\tilde{\nu} = 2126$ s (CO), 2111 vs (CO), 2065 vs (CO), 1772 w, 1695 w, 1635 w, 1358 s, 1208 m, 1192 s, 1183 s, 1117 m, 974 m, 930 s, 918 m, 893 s, 774 m, 768 m, 707 m, 668 w, 649 m, 623 m, 595 m, 569 s, 534 m, 502 m, 478 m, 463 m, 420 w, 398 w, 351 w, 337 w, 281 w cm^{-1} ; IR (*n*-pentane): $\tilde{\nu} = 2121$ (CO), 2108 (CO), 2067 (CO) cm^{-1} ; MS (70 eV): m/z (%): 510 (4) [M^+], 482 (29) [$M^+ - \text{CO}$], 454 (34) [$M^+ - 2\text{CO}$], 426 (68) [$M^+ - 3\text{CO}$], 398 (29) [$M^+ - 4\text{CO}$], 370 (27) [$M^+ - 5\text{CO}$], 342 (100) [$M^+ - 6\text{CO}$], 186 (18) [CoC_3F_5^+], 59 (24) [Co^+]; elemental analysis calcd (%) for $\text{C}_{12}\text{F}_8\text{O}_6\text{Co}_2$ (509.98): C 28.26; found: C 27.61. Compound **4** (40 mg, 0.9%) was obtained from the second fraction by crystallization at -30°C as black crystals. ^{19}F NMR (CDCl_3): $\delta = -78.3$ (d, $^2J_{\text{FF}} = 92$ Hz, 1F; CF_2), -77.05 (d, $^2J_{\text{FF}} = 93$ Hz, 2F; allyl CF_2), -78.92 (d, $^2J_{\text{FF}} = 92$ Hz, 2F; allyl CF_2), -79.9 (d, $^2J_{\text{FF}} = 93$ Hz, 1F; CF_2). MS (70 eV): m/z (%): 758 (1) [$M^+ - \text{CO}$], 730 (1) [$M^+ - 2\text{CO}$], 702 (3) [$M^+ - 3\text{CO}$], 673 (2), 646 [$M^+ - 5\text{CO}$], 617 (1), 571 (47), 543 (47), 515 (10), 488 (8), 460 (46) [$\text{CFCO}_3(\text{CO})_6^+$], 432 (100) [$\text{CFCO}_3(\text{CO})_8^+$], 404 (34) [$\text{CFCO}_3(\text{CO})_7^+$], 376 (28) [$\text{CFCO}_3(\text{CO})_6^+$], 348 (27) [$\text{CFCO}_3(\text{CO})_5^+$] and smaller fragment ions.

Decacarbonyl- μ -(η^1 -1,1,6,6-tetrafluoro-1,5-hexadien-2,5-diyldimanganane (**5**): Decacarbonyldimanganane (430 mg, 1.1 mmol) was dissolved in *n*-pentane in a photo reactor. 1,1-Difluoroallene (9.2 mmol) was condensed onto the solution using a glass vacuum line. The reaction mixture was irradiated for 4 h resulting in an orange solution containing a pale yellow precipitate. The precipitate was collected by filtration and dried under vacuum. Concentration of the filtrate under vacuum yielded additional substance. Column chromatography (silica, 45×3 cm ^{2}) using *n*-pentane/dichloromethane in the ratio 2:1 as eluent yielded **5** in the fraction with the largest R_f value. Compound **5** (85 mg, 14%) was isolated by crystallization at -30°C as pale yellow crystals. M.p. 110 – 111°C (decomp); ^1H NMR (CDCl_3): $\delta = 2.31$ (s, 4H; CH_2); ^{19}F NMR (CDCl_3): $\delta = -69.23$ (d, $^2J_{\text{FF}} = 66$ Hz, 2F; CF_2), -77.48 (d, $^2J_{\text{FF}} = 66$ Hz, 2F; CF_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 209.5$ (s; CO_{cis}), 207.2 (s; CO_{trans}), 150.9 (dd, $^1J_{\text{CF}} = 266$, 304 Hz; CF_2), 76.3 (dd, $^2J_{\text{CF}} = 46$, 10 Hz; C- CF_2), 37.3 (s; CH_2); $^{13}\text{C}\{^{19}\text{F}\}$ NMR (CD_2Cl_2): $\delta = 209.5$ (s; CO_{cis}), 209.1 (s; CO_{trans}), 150.8 (s; CF_2), 76.3 (s; C- CF_2), 37.3 (t, $^1J_{\text{CH}} = 130$ Hz; CH_2); IR (KBr): $\tilde{\nu} = 2968$ w, 2925 w, 2873 w, 2122 m (CO),

2040 s (CO), 2003 vs (CO), 1668 m (C=CF₂), 1460 w, 1262 w, 1196 w, 1155 m, 1072 w, 906 m, 805 w, 747 w, 646 s, 582 w, 527 w, 458 w, 438 w, 408 w, 325 w cm^{-1} ; IR (*n*-pentane): $\tilde{\nu} = 2122$ m (CO), 2030 vs (CO), 1999 m (CO) cm^{-1} ; MS (70 eV): m/z (%): 402 (5) [$M^+ - 5\text{CO}$], 346 (3) [$M^+ - 7\text{CO}$], 318 (4) [$M^+ - 8\text{CO}$], 290 (34) [$M^+ - 9\text{CO}$], 262 (100) [$M^+ - 10\text{CO}$]; elemental analysis calcd (%) for $\text{C}_{16}\text{H}_4\text{F}_4\text{O}_{10}\text{Mn}_2$ (542.07): C 35.45, H 0.74; found: C 35.16, H 1.32.

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- [12] Crystal structure analyses: Structure solution by direct methods and full-matrix least-squares refinement (SHELX97^[14]). **1a**: triclinic, space group $P\bar{1}$, $a = 6.6750(10)$, $b = 6.886(2)$, $c = 8.514(2)$ Å, $\alpha = 92.77(2)^{\circ}$, $\beta = 101.55(2)^{\circ}$, $\gamma = 100.05(2)^{\circ}$, $V = 376.12(15)$ Å ^{3} , $Z = 1$, $\rho_{\text{calcd}} = 1.934$ Mg m $^{-3}$, $T = 293$ K, 2593 measured, 2193 crystallographically unique, and 1955 reflections with $I > 2\sigma(I)$, $\text{MoK}\alpha$, $\lambda = 0.71069$ Å, $2\theta_{\text{max}} = 30^{\circ}$, empirical absorption correction (PSI scan)^[15] ($\mu = 2.276$ mm $^{-1}$), $R(F_o) = 0.0228$, $wR(F^2) = 0.0629$ (all data), 117 parameters, anisotropic thermal parameters, H atoms isotropic. **1b**: tetragonal, space group $P4_32_12$, $a = 6.3056(9)$, $c = 36.614(8)$ Å, $V = 1455.8(4)$ Å ^{3} , $Z = 4$, $\rho_{\text{calcd}} = 1.998$ Mg m $^{-3}$, $T = 20$ K, 7333 measured, 3579 crystallographically unique, and 2890 reflections with $I > 2\sigma(I)$, $\text{AgK}\alpha$, $\lambda = 0.56087$ Å, $2\theta_{\text{max}} = 56.2^{\circ}$, no absorption correction ($\mu = 1.223$ mm $^{-1}$), $R(F_o) = 0.0756$, $wR(F^2) = 0.1708$ (all data), 109 parameters, anisotropic thermal parameters, no hydrogen positions. **2**: monoclinic, space group $P2_1/a$, $a = 12.648(4)$, $b = 10.679(3)$, $c = 12.697(3)$ Å, $\beta = 102.84(2)^{\circ}$, $V = 1672.1(8)$ Å ^{3} , $Z = 4$, $\rho_{\text{calcd}} = 1.851$ Mg m $^{-3}$, $T = 293$ K, 4179 measured, 3644 crystallographically unique, and 2609 reflections with $I > 2\sigma(I)$, $\text{MoK}\alpha$, $\lambda = 0.71069$ Å, $2\theta_{\text{max}} = 27^{\circ}$, no absorption correction ($\mu = 2.059$ mm $^{-1}$), $R(F_o) = 0.0422$, $wR(F^2) = 0.1155$ (all data), 251 parameters, anisotropic thermal parameters, H atoms isotropic. **3**: orthorhombic, space group $Pcan$ (no. 60), $a = 11.3290(13)$, $b = 12.7359(10)$, $c = 34.826(3)$ Å, $\alpha = 92.77(2)^{\circ}$, $\beta = 101.55(2)^{\circ}$, $\gamma = 100.05(2)^{\circ}$, $V = 5024.8(8)$ Å ^{3} , $Z = 12$, $\rho_{\text{calcd}} = 2.022$ Mg m $^{-3}$, $T = 293$ K, 11502 measured, 7328 crystallographically unique, and 3227 reflections with $I > 2\sigma(I)$, $\text{MoK}\alpha$, $\lambda = 0.71069$ Å, $2\theta_{\text{max}} = 30^{\circ}$, empirical absorption correction (PSI scan)^[15] ($\mu = 2.093$ mm $^{-1}$), $R(F_o) = 0.0411$, $wR(F^2) = 0.0992$ (all data), 379 parameters, anisotropic thermal parameters. **4**: triclinic, space group $P\bar{1}$, $a = 8.0018(12)$, $b = 11.6060(18)$, $c = 13.7106(18)$ Å, $\alpha = 75.120(11)^{\circ}$, $\beta = 86.160(11)^{\circ}$, $\gamma = 76.020(12)^{\circ}$, $V = 1194.1(3)$ Å ^{3} , $Z = 2$, $\rho_{\text{calcd}} = 2.108$ Mg m $^{-3}$, $T = 293$ K, 4797 measured, 4214 crystallographically unique, and 3397 reflections with $I > 2\sigma(I)$, $\text{MoK}\alpha$, $\lambda = 0.71069$ Å, $2\theta_{\text{max}} = 25^{\circ}$, empirical absorption correction (PSI scan)^[15] ($\mu = 2.838$ mm $^{-1}$), $R(F_o) = 0.0243$, $wR(F^2) = 0.0657$ (all data), 361 parameters, anisotropic thermal parameters. **5**: triclinic, $P\bar{1}$, $a = 6.1860(6)$,

$b = 6.9912(7)$, $c = 12.3635(12)$ Å, $\alpha = 84.686(2)$, $\beta = 78.684(2)$, $\gamma = 68.044(2)^\circ$, $V = 486.16(8)$ Å³, $Z = 1$, $\rho_{\text{calc}} = 1.852$ Mg m⁻³, $T = 133$ K, 5719 measured, 2771 crystallographically unique, and 2771 reflections with $I > 2\sigma(I)$, $\text{MoK}\alpha$, $\lambda = 0.71069$ Å, $2\theta_{\text{max}} = 30^\circ$, empirical absorption correction (SADABS)^[16] ($\mu = 1.390$ mm⁻¹), $R(F_o) = 0.0320$, $wR(F^2) = 0.0785$ (all data), 153 parameters, anisotropic thermal parameters, H-atoms isotropic. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-156869–CCDC-156874. 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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Classification of Terpenoids according to the Methylerythritolphosphate or the Mevalonate Pathway with Natural ¹²C/¹³C Isotope Ratios: Dynamic Allocation of Resources in Induced Plants**

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*Dedicated to Professor Ernst-G. Jäger
on the occasion of his 65th birthday*

Plant volatiles, whose biosynthesis is induced by feeding insects, may serve as markers to allow the parasites of the herbivores to find their hosts.^[1, 2] Thus, they benefit the plant indirectly, and have been called the “plant’s cry for help”.^[3] Major constituents of such induced volatile blends include terpenoids, aromatic compounds, and degradation and transformation products derived from fatty acids. Mono- and diterpenoids are produced in the plastids from isopentenyl diphosphate (IDP) formed through the methylerythritol phosphate pathway (MEP pathway), while the IDP for

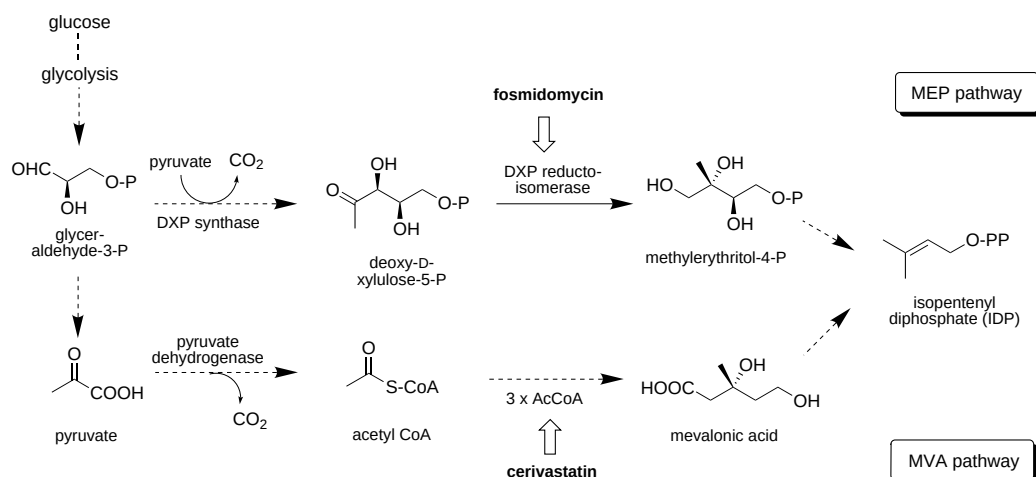
sesquiterpenoids is assembled by the well-known mevalonic acid pathway (MVA pathway) in the cytosol (Scheme 1).^[4–6] However, this classical allocation of terpenoids to pathways is not completely strict. While administration of deuterium-labeled 5-deoxy-D-xylulose, an early precursor of IDP in the MEP pathway, in principle confirmed the normal allocation of pathways in herbivore-induced biosynthesis, the ¹H/²H isotope signature of 4,8-dimethylnona-1,3,7-triene (DMNT, **4**; Figure 1) demonstrated a significant contribution from both pathways.^[7] In another example, the incorporation of ¹³C-labeled glucose into sesquiterpenes from chamomile resulted in an isotope signature that required contributions from both pathways.^[8] Moreover, careful analysis of sitosterol (isolated from cell cultures of *Catharanthus roseus*), which is assembled from two units of farnesyl diphosphate, clearly demonstrated a contribution (approximately 6%) from the mevalonate-independent MEP pathway.^[9] This classification of pathways, based on externally added precursors, is open to criticism, as administration may affect the natural balance of the cellular intermediates and result in shifted mass fluxes through the complex interacting pathways. Even the use of physiologically neutral precursors, such as glucose, has an impact on the metabolic network. Phototrophic organisms need to be kept under heterotrophic conditions to avoid dissipation of this valuable precursor into unwanted anabolic activities.^[5] An alternative to precursor-based approaches is provided by analysis of the isotope ratio of relevant compounds, at natural abundance level, using isotope-ratio mass spectrometry (IRMS).^[10] By linking an isotope-ratio mass spectrometer to a gas chromatograph, with online combustion of the eluting compounds to CO₂ and H₂O (GC-C-IRMS), analysis of the isotopic signature of individual compounds of complex mixtures is possible.^[11]

Owing to thermodynamic and kinetic isotope effects, the natural abundance of carbon isotopes exhibits minor local and temporal shifts from a global average value. In the biosphere these shifts are related to the isotope effects of the reactions catalyzed by enzymes involved in the physiological processes. Prominent examples exhibiting very high discrimination of carbon isotopes were reported for the different modes of CO₂ fixation by C₃ and C₄ plants, which utilize ribulose diphosphate carboxylase or phosphoenolpyruvate carboxylase.^[12] Further metabolism may additionally affect the isotope ratio, but in general these effects are less pronounced. Here we report that the different groups of terpenoid volatiles also exhibit significant differences in their ¹²C/¹³C ratio, which depend upon whether the universal building block IDP is produced predominantly from the MVA or MEP pathway (Scheme 1).

The isotope ratios of monoterpenes as $\delta(^{13}\text{C})$ values (see Experimental Section for definition) have already been determined by others, mainly to evaluate the origin and authenticity of compounds, and were observed within the range –26 to –30‰.^[13, 14] The value for ocimene (**2**; Figure 1), which is released from leaves of the lima bean (*Phaseolus lunatus*, used here as a model plant), was measured by us to be –29.0‰, a value that fits perfectly into the expected range (Figure 2). In contrast, the value of –37.4‰ for DMNT (an oxidative degradation product of the sesquiterpenoid ner-

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Scheme 1). The thiamine-dependent pyruvate dehydrogenase prefers the lighter isotopomers, producing acetyl CoA that is ¹³C depleted.^[16] Although a thiamine-dependent decarboxylation of pyruvate is also involved in the biosynthesis of 5-deoxy-D-xylulose-5-phosphate (DXP) along the MEP pathway,^[17] the assembly of the carbon skeleton of DXP requires only a single decarboxylation of pyruvate. In contrast, mevalonic acid originates from three molecules of acetyl CoA, which therefore eventually contribute to the biosynthesis

of IDP. Owing to this exclusive use of acetyl CoA, the MVA pathway should produce sesquiterpenoids that are significantly depleted in ¹³C isotopomers. Since the carbonyl carbon atoms of glyceraldehyde and pyruvate possess, due to their origin from glucose, a higher level of ¹³C isotopomers,^[18] the incorporation of intact glyceraldehyde-3-P into DXP additionally enhances the difference in the isotopic ratio of compounds produced along either of the two pathways.

The δ(¹³C) values for ocimene (MEP pathway) and DMNT (MVA pathway; Figure 2) clearly confirm the expected trend. The δ(¹³C) value of −37.4‰ for DMNT is close to that of −40.2‰ observed for hexenyl acetate. The latter should display a low ¹³C level due to its exclusive origin from acetyl CoA. A comparable discrimination of carbon isotopes in fatty acids and products of the MEP pathway was reported by Schouten et al. for algal lipids from marine or fresh water environments. The δ(¹³C) value of palmitic acid was about 2–5‰ lower than that of phytol (MEP pathway).^[19]

Previous findings from precursor studies with deuterium-labeled 5-deoxy-D-xylulose have to be considered to estimate the significance of the δ(¹³C) value of DMNT.^[7]

These data clearly showed the potential for mixed origin. Accordingly, the δ(¹³C) value of DMNT (Figure 2) should vary, if one of the two pathways is blocked by inhibitors. This was demonstrated by pretreatment of the lima bean leaves, prior to induction of volatile biosynthesis, with cerivastatin (**7**), a highly efficient inhibitor of HMGCoA reductase in the MVA pathway.^[20] The MEP pathway is blocked by fosmidomycin (**8**), which inhibits the DXP

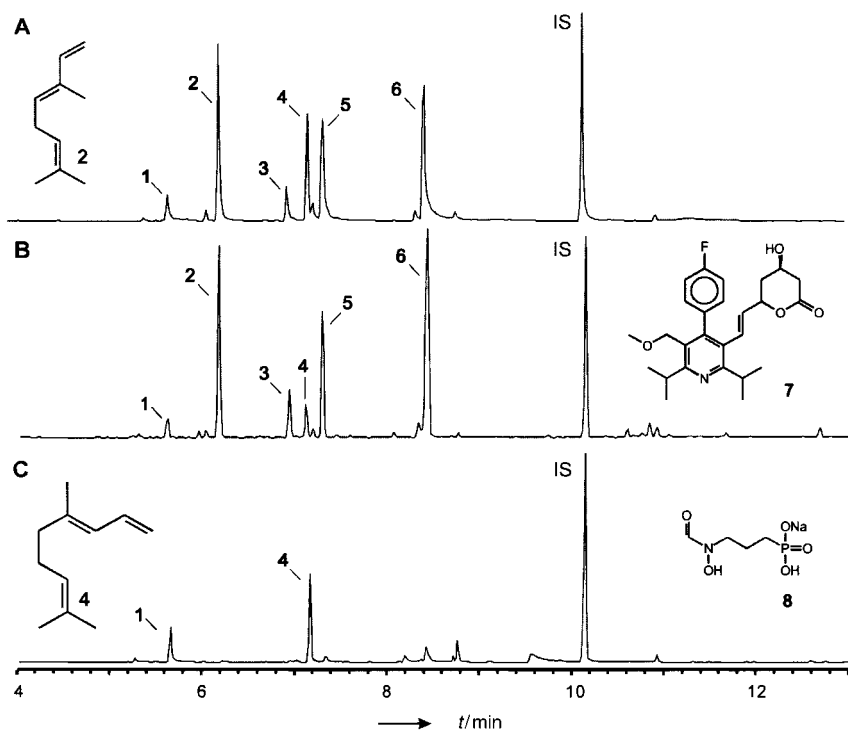


Figure 1. Chromatographic separation of volatiles produced by *Phaseolus lunatus* after induction with jasmonic acid (JA). A) JA-induced blend of volatiles without inhibitor pretreatment. B) JA-induced blend of volatiles after inhibition of the MVA pathway by cerivastatin (**7**). C) JA-induced blend of volatiles after inhibition of the MEP pathway by fosmidomycin (**8**). Compounds: (3Z)-hex-3-enyl acetate (**1**), ocimene (**2**), linalool (**3**), 4,8-dimethylnona-1,3,7-triene (DMNT, **4**), C₁₀H₁₄ (**5**), C₁₀H₁₆O (**6**); IS = internal standard (1-bromodecan). Linalool coelutes with a contaminant, which prevents exact determination of its isotope ratio.

olidol),^[15] displays a significant depletion of the ¹³C isotope. As the sesquiterpenoids are produced by the MVA pathway, while monoterpenoids originate from the MEP pathway, the difference in the isotopic signatures of ocimene and DMNT is explained by the different modes of the biosynthesis of their common intermediate IDP. A pronounced discrimination of isotopes has been reported for the production of acetyl CoA from pyruvate by decarboxylation (MVA pathway,

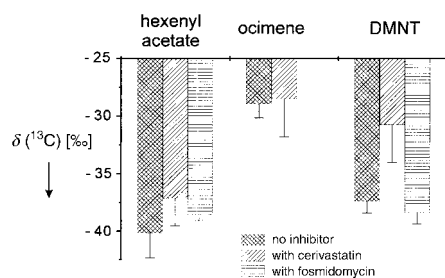


Figure 2. $\delta(^{13}\text{C})$ values of selected volatiles after induction with jasmonic acid. Average values from three samples are given.

reductoisomerase (Scheme 1).^[21] As shown in Figure 1 B and C a single inhibitor is not able to suppress the biosynthesis of DMNT.^[7] The efficiency of the fosmidomycin treatment is demonstrated by the almost complete lack of the monoterpenes (compounds **2**, **3**, **5**, and **6**; Figure 1 C), while application of cerivastatin reduces the biosynthesis of DMNT by approximately 70% relative to that of the noninhibited plant (Figure 1 C). Only the simultaneous application of both inhibitors completely suppresses the production of DMNT.

After inhibition of the MVA pathway by cerivastatin, the emitted DMNT displays a $\delta(^{13}\text{C})$ value of -30.8‰ , which is close to that of ocimene (-28.5‰) produced along the MEP pathway (Figure 2). On the other hand, if the MEP pathway is inhibited, the $\delta(^{13}\text{C})$ value of DMNT (-38.4‰) approaches the typical value of acetogenins such as hexenyl acetate. The $\delta(^{13}\text{C})$ value of ocimene remains unchanged after inhibition of the MVA pathway. Since the late steps of the biosynthesis of DMNT are identical in both inhibitor experiments, the observed differences in the $^{12}\text{C}/^{13}\text{C}$ ratios can be unequivocally attributed to the early steps of the MVA or MEP pathway.

Interestingly, treatment of the lima bean with different elicitors may channel the biosynthesis of DMNT through the MEP or the MVA pathway. Stimulation of leaves with the fungal elicitor alamethicin provides such an example.^[22, 23] With this pretreatment the $\delta(^{13}\text{C})$ value for DMNT (-30.7‰) is close to that of ocimene and, hence, suggests the predominant utilization of the MEP pathway.

Similar shifts in the isotope ratios of DMNT are observed if the volatile biosynthesis is triggered by feeding insects (Figure 3). Again, application of the individual inhibitors does not completely suppress the biosynthesis of DMNT. As seen from the $\delta(^{13}\text{C})$ values of DMNT (-39.0‰), herbivory preferentially stimulates the cytosolic MVA pathway (compare Figures 2 and 3).^[23] If this pathway is blocked, by pretreatment with cerivastatin, the MEP pathway compensates and the $\delta(^{13}\text{C})$ value for DMNT (-34.4‰) is raised. The

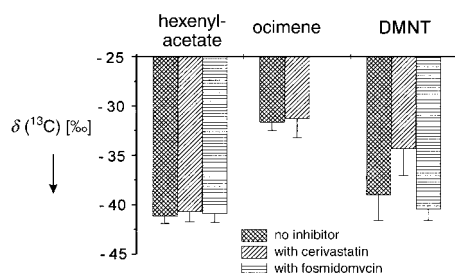


Figure 3. $\delta(^{13}\text{C})$ values of selected volatiles after induction by feeding insects (*Spodoptera frugiperda*). Average values from three samples are given.

data suggest that natural induction processes may also benefit from a dynamic allocation of both pathways.^[7]

Experimental Section

For induction of volatile biosynthesis, freshly cut stems of the lima bean (12–14 days old with two fully developed primary leaves) were placed in an aqueous solution of jasmonic acid (JA; 1 mM). After 12 h the plants were transferred into a closed system (desiccator, 3 L) and the emitted volatiles were collected over a period of 48 h on a small charcoal pad.^[24] For selective inhibition of the MVA or MEP pathway, the excised plants were placed for 24 h into solutions of the inhibitors cerivastatin or fosmidomycin ($3 \times 10^{-5}\text{ M}$ each), prior to the elicitation of volatile biosynthesis with JA (1 mM), alamethicin (10 μM), or herbivore feeding (four larvae of *Spodoptera frugiperda* per excised plant).

Analysis and separation of volatiles was achieved on a fused silica capillary column (DB-5-MS ITD, Alltech, dimensions: 30 m $\times$ 0.25 mm, film thickness: 0.25 μm ; conditions: 50 $^{\circ}\text{C}$ (2 min isotherm), then temperature rise at 5 $^{\circ}\text{C min}^{-1}$ to 220 $^{\circ}\text{C}$). The eluting compounds were combusted online at 940 $^{\circ}\text{C}$ with a catalyst system of CuO/NiO/PtO and the resulting CO_2 was transferred into an Delta^{plus} XL isotope-ratio mass spectrometer (Thermoquest, Egelsbach, Germany). An aliquot of the injected sample (10%) was split after separation and transferred into a normal mass spectrometer (GCQ, Thermoquest) for identification of the eluting compounds. All isotope ratios are given as $\delta(^{13}\text{C})$ values: $\delta(^{13}\text{C})[\text{‰}] = [(R_{\text{sample}}/R_{\text{standard}}) - 1] \times 10^3$. R corresponds to the $^{13}\text{C}/^{12}\text{C}$ ratio of the sample and the standard (Vienna Pee Dee Belemnite).

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New Transmembrane Polyene Bolaamphiphiles as Fluorescent Probes in Lipid Bilayers**

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The former view of the cell lipid membrane as a somewhat random and disordered distribution of lipids and proteins has given way to one characterized by a complex lateral organization, with nm-sized domains in which specific lipids and proteins are assembled to carry out a particular process.^[1] The study of the morphology, composition, regulation, and persistence time of these structures is an experimental challenge that has been taken up by fluorescence probe methods. In the case of lipid–lipid and lipid–protein interactions, the dependence of the resonant transfer of electronic excitation on the proximity of donor and acceptor probe molecules can provide very useful information in the 10-nm range.^[2] We have previously developed a series of fluorescent fatty acids that contain five conjugated double bonds at the end of a flexible linear chain.^[3] These probes accurately report the changes in order and dynamics of the lipid environment in artificial and natural membranes. Furthermore, the large spectral overlap of the polyene absorption with the tryptophan fluorescence from membrane proteins and peptides is very convenient for energy-transfer experiments. However, the mobility of the energy-accepting polyene group in fluid bilayers may introduce some uncertainty into the distance evaluation. This would also be the case in other possible applications of the probes, such as the detection of oxidizing radicals by fluorescence quenching. To restrict the mobility of the chromophore, a linear structure with two polar terminal groups, that is, a bolaform amphiphile similar to the membrane lipids of *Archaeobacteria*^[4] would be ideal, with the additional advantage of precisely locating the sensing group of the probe in the bilayer. Bolaamphiphiles can be constructed with the appropriate length to reach both external membrane surfaces with the distal polar groups, and with a sensitive group in the lipophilic central part of the molecule.^[5] Some transmembrane bolaamphiphiles have been produced previously for altering specific membrane properties: for example, compounds with *p*-benzoquinone or anthraquinone groups to change the redox behavior,^[6] or conjugated polyenes derived from the natural product bixine to modify the charge-transfer rate across the bilayer.^[7]

Furthermore, bolaamphiphiles that contain photochemically reactive benzophenone^[8] or diazirine^[9] groups, or emitting fluorene^[10] or anthracene groups,^[11] have been also synthesized. A different but interesting fluorescent bolaform structure was also produced by linking two rhodamine 101 dye molecules with a C₃₂ linear chain.^[12]

Herein we describe the synthesis of symmetrical bolaamphiphiles with four, five, or six conjugated double bonds in the center of the molecule, with terminal methyl ester (**4**) or carboxylic acid (**5**) groups (Scheme 1), and with the appropriate length for spanning the lipid bilayer (Figure 1). The intermediates in the synthesis of the former compounds are conjugated polyenediynes diesters **3** that might also be useful transmembrane probes as such or in the form of free acids.

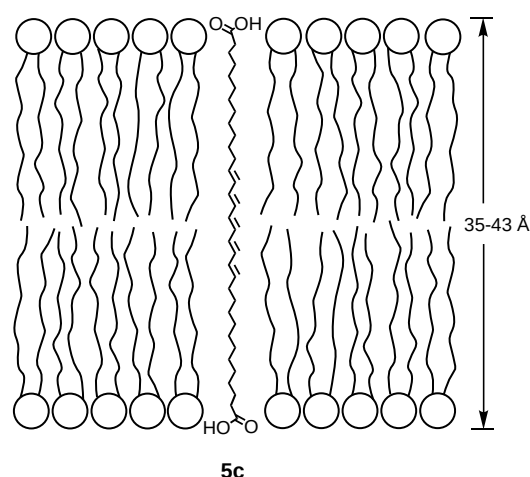
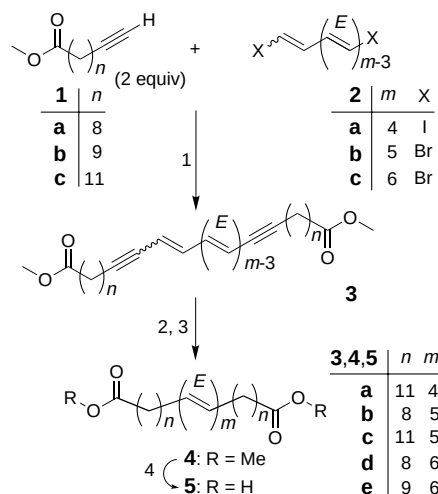


Figure 1. Schematic representation of the fluorescent polyene bolaamphiphile **5c** in a phospholipid bilayer.

Probes **5** were synthesized in four steps (Scheme 1), each with a yield of 95 % or higher: 1) Sonogashira–Hagihara double cross-coupling^[13] between the terminal acetylene



Scheme 1. 1) 1/2 3:1 (mol), [Pd(PPh₃)₂Cl₂] (10 mol %), CuI (20 mol %), Et₃NH, THF, Ar, room temperature, 3 h, >95 %; 2) Zn(Cu/Ag), MeOH/H₂O 1:1, room temperature, 24 h, >95 %; 3) I₂ (trace), hexane, Ar, reflux, 15 min, >95 %; 4) KOH (10 equiv), EtOH (95 %), Ar, reflux, 5 h; then 0 °C, HCl (5 %), >95 %.

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group of methyl esters **1** and conjugated 1, ω -dihalopolyenes **2** with two, three, or four double bonds to give the polyenediynes **3**; 2) partial reduction of the triple bonds of **3** with activated Zn^[14] to yield the corresponding polyene diesters with two more *Z* double bonds; 3) isomerization of the resulting polyenes with iodine to form the corresponding all-(*E*) isomers **4**; and 4) alkaline hydrolysis of **4** to yield the diacids **5**. As the cross-coupling of **1** and **2** does not change the stereochemistry of the double bonds in **2**, *E/Z* mixtures of polyenes **2** produced the same mixtures of isomeric products **3**.

This sequence produces the diacids **5** with good overall yields ($\geq 80\%$) and can be applied to the synthesis of analogues with different chain lengths, numbers of conjugated double bonds, or stereochemistries. The key steps in the sequence, namely the cross-coupling followed by the partial reduction with Zn (the acetylene approach) have been previously used with success to obtain arachidonic acid metabolites,^[15] 11-*cis*-retinoids,^[16] and other nonsymmetrical polyenes.^[17]

Compounds **3**, **4**, and **5** are thermally stable for several months if kept in a cool, dark place and their solubility in EtOH or dimethylsulfoxide is in the range of 1–10 μM . These probes have been designed to span typical lipid bilayers, that is, with a maximum expanded length of 35–43 Å,^[18] so that the carboxy groups can reach the two opposite membrane surfaces, and the polyene chromophore is located just in the center of the bilayers. Furthermore, much shorter molecules without saturated spacer chains (not shown) have also been obtained by using the methods described above. In this last case, the electronic interaction between the polyene and the carbonyl end group suppresses the fluorescence.

The large absorption coefficients ($\approx 10^5 \text{ M}^{-1} \text{ cm}^{-1}$) of these bolaamphiphiles facilitate their use in very low concentrations (Figure 2). The fluorescence quantum yields are modest—the highest are those of the compounds with the pentaene group (≈ 0.1). On the other hand, the orientation of the absorption

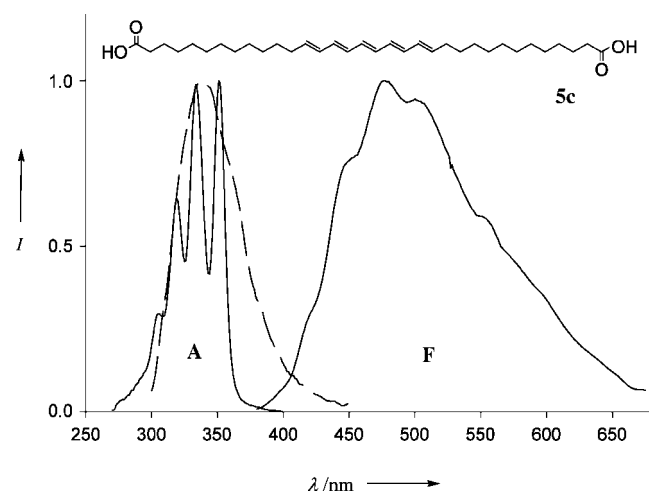


Figure 2. Corrected fluorescence excitation (A) and emission (F) spectra of the pentaene **5c** in large unilamellar vesicles of DMPC (1,2-dimyristoyl-*sn*-glycerophosphatidylcholine) ($\lambda_{\text{em}} = 468 \text{ nm}$, $\lambda_{\text{ex}} = 347 \text{ nm}$, [**5c**] = 10^{-7} M ; probe/lipid 1:5000). The tryptophan fluorescence (---) from the membrane peptide α -melanocyte-stimulating hormone (α -MSH) in lipid vesicles is overlaid.

and emission transition electronic moments along the long molecular axis is clearly defined and emission takes place in the visible region, thus facilitating the intended applications. The spectra of Figure 2 show the range of absorption and emission wavelengths available from the pentaene diacid **5c** when incorporated into vesicles of pure phospholipids, as well as the large spectral overlap with the tryptophan protein emission, with a donor–acceptor distance at which the transfer efficiency is 50 % (R_0) of $\approx 35 \text{ Å}$. The nonfluorescent bolaamphiphiles that lack the saturated spacer chain present a continuous π -electron cloud that might be of utility as a molecular wire in nanoscale devices.

A key point is the extent to which these probes orientate themselves parallel to the lipid chains in a bilayer. The recently developed polarized two-photon fluorescence microscopy of giant unilamellar vesicles allows the direct observation of the emission transition moment orientation of fluorescence probes in bilayers.^[19] Preliminary experiments in which this technique was applied to the diester probes **4c** and **4d** in the giant unilamellar vesicles of POPC show that the long molecular axis of both compounds is indeed aligned with the phospholipid acyl chains (Figure 3).

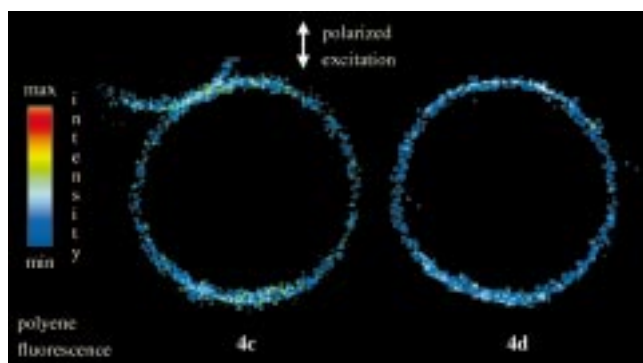


Figure 3. The fluorescence images of giant unilamellar vesicles (diameter 30 μm) of POPC (1-palmitoyl-2-oleoyl-*sn*-glycerophosphatidylcholine) containing the diesters **4c** and **4d** show the two probes aligned preferentially parallel to the phospholipid acyl chains. Two-photon linearly polarized laser excitation (720 nm) oriented as indicated (for details, see ref. [19]).

Experimental Section

1a: Obtained by esterification ($\text{MeOH}/\text{SOCl}_2$) of the corresponding acid; **1b,c**: prepared from 9-dodecyn-1-ol and 3-tetradecyn-1-ol, respectively, by triple bond zipper isomerization to the terminal position,^[20] Jones oxidation to the corresponding carboxylic acid,^[21] and esterification as above ($> 60\%$ overall yield).

(1*E*,3*E*)-**2a**: Obtained from acetylene;^[22] **2b** (1*E*,3*E*,5*E*)/(1*Z*,3*E*,5*E*) 1:4: obtained as described in ref.[23]; **2c** (1*E*,3*E*,5*E*,7*E*)/(1*Z*,3*E*,5*E*,7*E*) 1:4: (2*E*,4*E*)-5-bromo-2,4-pentadienal was treated with triethyl phosphonoacetate in aqueous K_2CO_3 (10 M)^[24] to yield ethyl all-(*E*)-7-bromo-2,4,6-heptatrienoate, which was reduced to the allyl alcohol with DIBAL in toluene/ CH_2Cl_2 at -78°C . The alcohol was then oxidized to the all-(*E*) aldehyde^[23a] with activated MnO_2 . The aldehyde was treated at -50°C with the ylide generated by the treatment of (bromomethyl)triphenylphosphonium bromide with *t*BuOK in THF to give **2c**.

Data of the representative compounds **3c**, **4c**, and **5c**:

3c (*E,E,E*)/(*Z,E,E*) 1:4: Yield 96%; the isomers were separated by precipitation of the all-(*E*) isomer with pentane; (*Z,E,E*)-**3c** is a waxy

oil; all-(*E*)-**3c**: m.p. 76–78 °C (decomp); ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 6.50 (ddd, 2H, ³J(H,H) = 7.0 and 15.2, ³J(H,H) = 3.0 Hz; H16, H19), 6.25 (dd, ²J(H,H) = 7.0, ³J(H,H) = 3.0 Hz, 2H; H17, H18), 5.63 (dt, ²J(H,H) = 15.2, ⁴J(H,H) = 2.4 Hz, 2H; H15, H20), 3.66 (s, 6H; 2 × CH₃), 2.33 (dt, ²J(H,H) = 7.2, ⁴J(H,H) = 2.4 Hz, 4H; H12, H23), 2.30 (t, ²J(H,H) = 7.6 Hz, 4H; H2, H32), 1.61 (quint, ²J(H,H) = 7.2 Hz, 4H; H3, H32), 1.52 (quint, ²J(H,H) = 7.6 Hz, 4H; H11, H24), 1.37 (quint, ²J(H,H) = 7.2 Hz, 4H; H10, H25), 1.27 (m, 24H, H4 to H9 and H26 to H31); ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 174.3 (2 × CO), 140.1 (C16, C19), 133.2 (C17, C18), 113.1 (C15, C20), 95.2 (C13, C22), 80.2 (C14, C21), 51.4 (2 × CH₃), 34.1 (C2, C33), 29.5, 29.5, 29.4, 29.2, 29.14, 28.9, 28.7 (C4 to C11 and C24 to C31), 24.9 (C3, C32), 19.8 (C12, C23); FT-IR (KBr) (only strong bands): $\tilde{\nu}$ = 2919, 2848, 2222, 1741, 1167 cm⁻¹; UV/Vis (CHCl₃): λ_{max} (ϵ) = 312.0 (45 000), 326.5 (74 000), 343.0 nm (77 000); MS (70 eV): *m/z* (%): 552 (90) [*M*⁺], 521 (17), 353 (29), 339 (22), 183 (32), 169 (62), 155 (100), 141 (63), 129 (63), 117 (29), 105 (15).

4c: A methanolic solution (0.5 mL) of the isomeric mixture of **3c** (0.10 mmol) was treated at room temperature in MeOH/water 1:1 (3 mL) with a slurry of freshly activated Zn powder (9 mmol, < 10 μm).^[14] After 24 h, the subsequent work-up afforded a 1:4 mixture of the pentaene isomers (*Z,E,E,E,Z*) and (*Z,Z,E,E,Z*) in 95 % yield. The pure (*Z,E,E,E,Z*) isomer was obtained by using all-(*E*)-**3c**. The isomeric mixture (0.1 mmol) in hexane (200 mL) was heated at reflux for 15 min with iodine-saturated hexane (60 μL) and the solution was filtered through silica gel while hot. The solvent was evaporated to 5 mL and **4c** (all-(*E*) isomer) was separated from the cooled (–20 °C) residual solution by filtration in 95 % yield. Highly pure samples were obtained by crystallization from acetone at –20 °C. M.p. 86–89 °C (decomp); ¹H NMR (400 MHz, CDCl₃, 30 °C, TMS): δ = 6.19 (m, 6H; H15 to H20), 6.05 (m, 2H; H14, H21), 5.69 (dt, ²J(H,H) = 7.2 and 14.2 Hz, 2H; H13, H22), 3.66 (s, 6H; 2 × CH₃), 2.29 (t, ²J(H,H) = 7.5 Hz, 4H; H2, H33), 2.09 (dt, ²J(H,H) = 7.2 and 7.2 Hz, 4H; H12, H23), 1.60 (quint, ²J(H,H) = 7.4 Hz, 4H; H3, H32), 1.37 (quint, ²J(H,H) = 7.2 Hz, 4H; H11, H24), 1.25 (brs, 28H; H4 to H10 and H25 to H31); ¹³C NMR (100 MHz, CDCl₃, 30 °C): δ = 174.3 (2 × CO), 135.8 (C13, C22), 133.0, 132.4, 130.9, 130.6 (C14 to C21), 51.4 (2 × CH₃), 34.1 (C2, C33), 32.9 (C12, C23), 29.55, 29.47, 29.43, 29.3, 29.24, 29.20, 29.16 (C4 to C11 and C24 to C31), 25.0 (C3, C32); IR (KBr) (only strong bands): $\tilde{\nu}$ = 3400, 2970, 2880, 2705, 1720, 1420, 1155, 970 cm⁻¹; UV/Vis (CHCl₃): λ_{max} (ϵ) = 305.8 (29 000), 319.8 (60 000), 335.1 (95 000), 353.1 nm (92 000); MS (70 eV): *m/z* (%): 556 (100) [*M*⁺], 525 (11), 357 (19), 343 (45), 145 (32), 131 (60), 117 (65), 105 (39), 91 (51).

5c: Yield 95 %, purified by crystallization in toluene at –20 °C; m.p. 141–143 °C (decomp); ¹H NMR (300 MHz, [D₆]DMSO, 70 °C, TMS): δ = 6.22 (m, 6H; H15 to H20), 6.10 (m, 2H; H14, H21), 5.72 (dt, ²J(H,H) = 7.2 and 13.8 Hz, 2H; H13, H22), 2.17 (t, ²J(H,H) = 6.9 Hz, 4H; H2, H33), 2.07 (dt, ²J(H,H) = 6.3 and 6.3 Hz, 4H; H12, H23), 1.50 (quint, ²J(H,H) = 6.9 Hz, 4H; H3, H32), 1.36 (quint, ²J(H,H) = 6.9 Hz, 4H; H11, H24), 1.25 (brs, 28H; H4 to H10 and H25 to H31); ¹³C NMR (75 MHz, [D₆]DMSO, 70 °C): δ = 173.8 (2 × CO), 134.8 (C13, C22), 132.5, 132.0, 130.5, 130.3 (C14 to C21), 33.4 (C2, C33), 31.5 (C12, C23), 28.5 (×2), 28.44, 28.40, 28.37, 28.3, 28.2 (C4 to C11 and C24 to C31), 24.1 (C3, C32); IR (KBr) (only strong bands): $\tilde{\nu}$ = 3390, 2880, 2710, 1690, 1450, 980, 695 cm⁻¹; UV/Vis (CHCl₃): λ_{max} (ϵ) = 305.8 (26 000), 319.8 (53 000), 335.1 (88 000), 353.1 nm (85 000); MS (70 eV): *m/z* (%): 528 (95) [*M*⁺], 343 (13), 329 (44), 145 (37), 131 (82), 117 (100), 105 (62), 91 (93).

The length of dicarboxylic acids **5** was estimated with MOPAC93 (Chem3D Pro 4.5 program, Cambridge Soft) by minimizing the energy with MM2 and AM1 successively down to a gradient of < 0.01 kcal mol⁻¹ Å⁻¹. Solvent effects were not taken into account. Distance OH–OH [Å]: **5a** 40.5, **5b** 35.0, **5c** 42.5, **5d** 37.1, **5e** 40.2.

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Nanoscale Push–Push Dihydrophenanthrene Derivatives as Novel Fluorophores for Two-Photon-Excited Fluorescence**

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Molecular two-photon absorption (TPA)^[1] has gained interest over recent years owing to its applications in various fields, including spectroscopy, optical data storage,^[2] optical power limitation,^[3] and microfabrication.^[4] Among these, two-photon-excited fluorescence (TPEF) has gained widespread popularity in the biological community and has given rise to the technique of two-photon laser scanning fluorescence microscopy.^[5] In standard fluorescence microscopy, molecular excitation is caused by the absorption of a single photon. Molecular excitation by the simultaneous absorption of two photons, however, presents several advantages including a capacity for a highly confined excitation and intrinsic three-dimensional resolution, and the possibility of imaging at an increased penetration depth in tissue, with reduced photo-damage and background fluorescence.^[5b] TPEF microscopy was initially developed by using conventional fluorophores whose TPA characteristics were not optimized and thus led to the necessity of high laser intensities and/or fluorophore concentrations. It has become clear that the development of TPEF microscopy would greatly benefit from the design of novel fluorophores specifically engineered for efficient TPEF. Key features for such a purpose are large TPA cross sections σ_2 and a high fluorescence quantum yield Φ . We present herein the design, synthesis, and potential applications for membrane imaging of a series of novel fluorophores that demonstrate enhanced TPEF cross sections in the visible-red or near-IR region.

It has been observed recently that symmetrical conjugated molecules that bear two electron-donating D (or electron-withdrawing A) end groups can display high nonlinear absorption characteristics^[3] and large σ_2 values.^[6] Such behavior is correlated to an intramolecular charge redistribution that occurs between the ends and the center of the molecule. Enhancing this quadrupolar charge transfer, either

in D-AA-D or A-DD-A derivatives,^[7] or by lengthening the conjugated system,^[6b,c] can lead to significant increases in σ_2 . Unfortunately, this often leads to a decrease in the fluorescence quantum yield. Based on these observations, our aim has been to design elongated systems that display large σ_2 in the visible-red/NIR region (700–900 nm), while maintaining high fluorescence quantum yields. Our molecular-engineering strategy is based on the push–push (e.g. bis-donor) functionalization of a semirigid nanoscale conjugated system. The structure is built from the symmetrical grafting of two elongated rods that bear a donating end group on a rigid conjugated core (Figure 1).

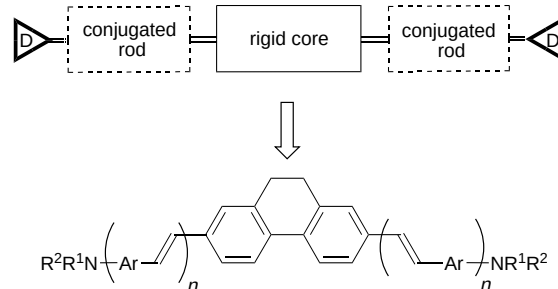


Figure 1. Molecular engineering of push–push fluorophores with high two-photon absorptivity. Based on earlier work,^[6a] the dihydrophenanthrene moiety was chosen as the central building block. The extending rods were built from arylene–vinylene oligomers which were expected to ensure electronic conjugation and maintain acceptable fluorescence quantum yields. The di(*n*-alkyl)amino substituents act both as donors and as solubilizing end groups.

Based on this strategy, we have prepared push–push molecules with a conjugation length that varies from 23 Å to 44 Å (Scheme 1). These compounds were synthesized from symmetrical reagents derived from dihydrophenanthrenes **1** and **2**. Push–push molecule **3** was readily obtained in one step from bisaldehyde **1**^[8] in 70% yield by means of a double Wittig reaction. Push–push molecules **4**–**6** were prepared from bisphosphonate **2** in yields of 71%, 94%, and 64%, respectively, by means of a double Wittig–Horner condensation with conjugated aldehydes **7**–**9**. The conjugated aldehyde **7** was prepared by treating 2,5-thiophenebiscarboxaldehyde with one equivalent of phosphonium reagent **10**. Similarly, **8** was obtained from terephthalaldehyde *mono*-(diethyl acetal) and one one equivalent of **11**, while the reaction of bisaldehyde **1** and **10** afforded the conjugated aldehyde **9**. The core reagent **2** was synthesized from dihydrophenanthrene in a two-step procedure by double bromomethylation^[8] followed by a Michaelis–Arbusov reaction.

The TPA cross sections of molecules **3**–**6** were determined by comparing their TPEF to that of fluorescein.^[9, 10] This procedure provides the TPEF action cross section, defined by $\sigma_2\Phi$. The corresponding σ_2 values can be derived by independently determining the fluorescence quantum yield Φ from standard fluorescence measurements (Table 1).^[11] Molecules **3**–**6** indeed combine very large two-photon absorption cross sections in the visible-red region and high fluorescence quantum yields. All new fluorophores outperform the standard fluorophore fluorescein by more than one or two orders

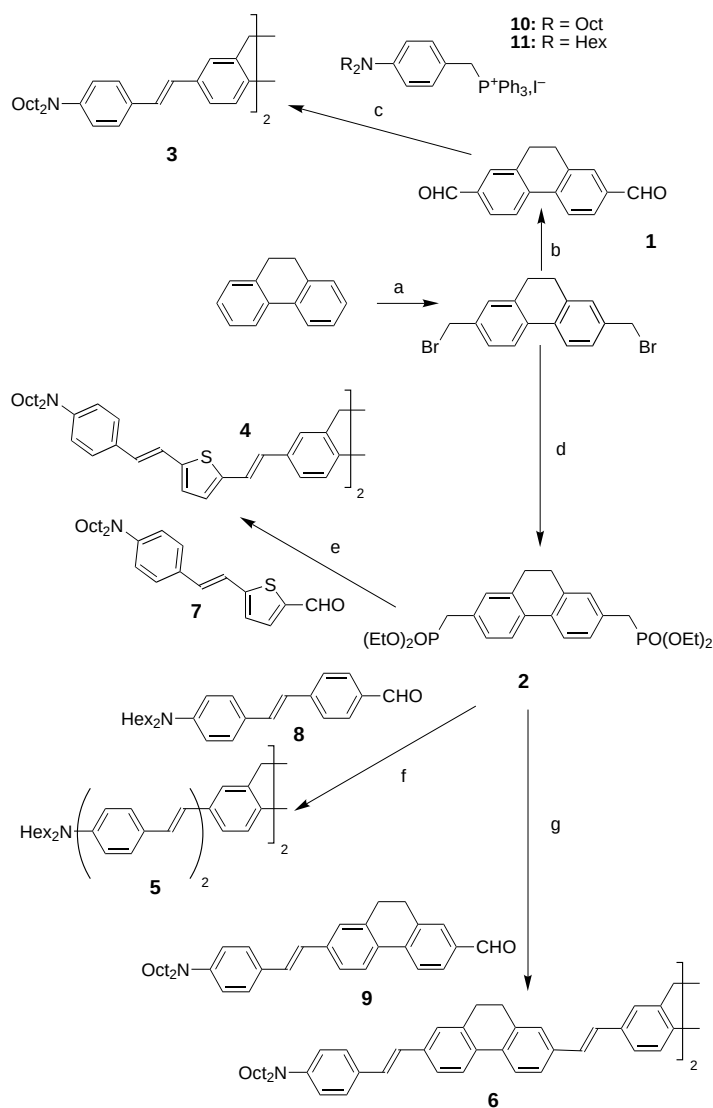
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 1. a) $(\text{CH}_2\text{O})_3$, HBr, H_3PO_4 , 24 h, 90 °C; b) NaHCO_3 , DMSO, 4 h, 115 °C; c) **10** (2.1 equiv), *t*BuOK (3 equiv), [18]crown-6, CH_2Cl_2 , 5 h, RT; d) $\text{P}(\text{OEt})_3$ (3 equiv), 6 h, 150 °C; e)–g) **7**, **8**, or **9** (2.1 equiv), NaH (3 equiv), [18]crown-6, THF, 16 h, RT.

Table 1. One-photon and two-photon absorption and fluorescence properties of molecules **3**–**6** in solution.

	<i>l</i> nm ^[a]	$\lambda_{\text{max}}(\text{abs})$ nm ^[b]	$\lambda_{\text{max}}(\text{em})$ nm ^[c]	Φ^{d}	$\sigma\Phi$ [GM] ^[e]	σ_2 [GM] ^[e]
Fluorescein		490	514	0.9 ^[11]	27 ^[10]	30 ^[10]
3 ^[f]	2.3	410	456	0.86	1490	1730
4 ^[f]	3.4	465	521	0.52	1330	2560
5 ^[f]	3.5	428	477	0.82	1870	2270
5 ^[g]	3.5	428	522	0.60	1980	3310
6 ^[g]	4.4	422	514	0.66	2480	3760

[a] Length of the push–push extended system evaluated by molecular mechanics calculation of the maximum distance between the nitrogen atoms of the donating end groups. [b] Absorption maxima. [c] Emission maxima. [d] Fluorescence quantum yield determined relative to fluorescein. [e] Values given at 740 nm in GM; 1 GM = $10^{-50} \text{ cm}^4 \text{ s photon}^{-1}$. [f] In toluene. [g] In chloroform.

of magnitude. As indicated by the comparison of molecules **3** and **5**, an increase in the length of the phenylene-vinylene oligomeric extending rods results in a noticeable increase in the TPA cross section while maintaining a nearly constant

quantum fluorescence yield. As a result, a net increase in the TPEF action cross section in the visible-red region is obtained. The effect of increasing length is also observed when a phenylene unit is substituted by a dihydrophenanthrene unit in the arylene-vinylene oligomers: fluorophore **6** combines a larger TPA cross section and quantum fluorescence yield than fluorophore **5**, while being slightly blue-shifted. As a result, fluorophore **6** shows both large TPA (with $\sigma_2 = 4200 \times 10^{-50} \text{ cm}^4 \text{ s photon}^{-1}$ at 710 nm) and TPEF cross sections in the visible-red region. An increase in the conjugation length also induces a significant broadening of the TPEF spectra in the NIR region (Figure 2a). Whereas molecule **3** shows a steeply declining TPEF cross section above 750 nm, fluorophores **5** and **6** maintain high TPEF cross sections in the 750–850 nm region (Figures 2a and b). The lowest energy TPA peaks are observed at higher energy than twice that corresponding to one-photon absorption maxima (Table 1). This is consistent with a higher lying TPA-allowed electronic excited state responsible for high

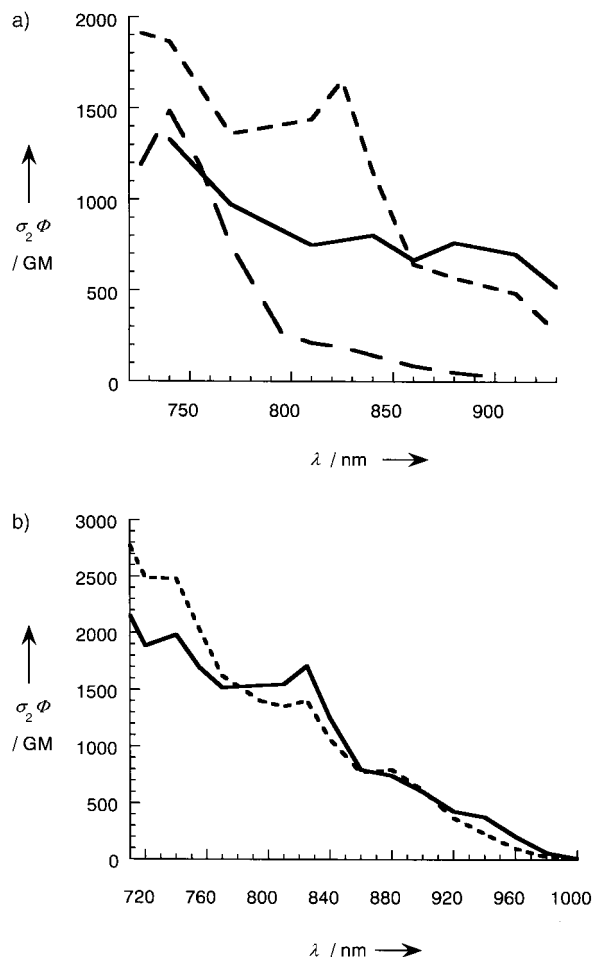


Figure 2. a) TPEF action cross sections of fluorophores **3**–**5** in toluene: **3** (---), **4** (—), **5** (---). b) TPEF action cross sections of fluorophores **5**–**6** in chloroform: **5** (—), **6** (---). Solutions of fluorophores **3**–**6** diluted to a final concentration of approximately 100 μM were used. TPEF measurements were calibrated relative to the absolute TPEF action cross section for fluorescein in water (pH 11).^[9,10] For each data point, an additional control was performed by comparing with the TPEF action cross section of rhodamine B in methanol.^[9,10] The experimental uncertainty amounts to $\pm 15\%$.

TPA, as already observed for other quadrupolar systems and predicted by calculations.^[7a, 12, 13]

The nature of the conjugated chain also plays a crucial role. We note that although fluorophore **4** is slightly shorter than fluorophore **5**, it still shows a slightly higher TPA cross section at 740 nm (Table 1), seemingly correlated with the lower aromaticity of the thienyl ring and the concomitant lower energy cost associated with intramolecular charge transfer.^[12] This effect is, however, counterbalanced by a significant decrease in the quantum fluorescence yield. Consequently, fluorophore **4** shows a significantly smaller TPEF action cross section than does fluorophore **5** in the visible red region. Nonetheless, fluorophore **4** becomes more effective in the NIR region ($\lambda > 850$ nm), owing to a combined broadening and red shift of the TPEF spectrum (Figure 2a).

The TPA characteristics of the bis-donor fluorophores can also be strongly affected by the molecular environment, as indicated by the different behavior of fluorophore **5** in toluene and chloroform (Table 1). Its TPA cross section is almost 50 % larger in the more polar solvent, probably correlated with a stabilization of the intramolecular charge transfer. This underlines the influence of the environmental parameters on the TPA responses of quadrupolar fluorophores, as was the case for the quadratic nonlinear optical responses of dipolar chromophores.

Finally, the potential applications of these novel fluorophores for the imaging of biological membranes has been investigated by designing derivatives that combine the TPEF features of fluorophore **3** and slightly amphiphilic features (i.e. an extended hydrophobic central part and two hydrophilic end groups). The incorporation of fluorophore **12** in a model membrane of giant unilamellar vesicles made up of pure lipid in water can be imaged by TPEF microscopy (Figure 3).

Multiphoton microscopy is currently a blooming field, owing to the advantages it provides in biological imaging. Besides the ongoing development of optical systems, the design of novel fluorophores with optimized characteristics is of timely importance. This calls for the development of new molecular systems and the determination of general structure–property relationships, an approach that has already proved successful for quadratic nonlinear optics but is only emerging in the field of multiphoton absorption. The novel series of push–push fluorophores derived from an extended dihydrophenanthrene core actually demonstrates large TPEF cross sections in the visible-red or NIR region, a spectral window of particular interest for the imaging of biological tissues. Furthermore, by adjusting the length and nature of the conjugated extensor, both amplification and spectral tuning of TPA cross sections can be obtained. The enhanced performance of these molecules promises to be of particular importance in biological imaging applications.

Experimental Section

The TPEF excitation spectra of molecules **3–6** were measured according to the experimental protocol established by Xu and Webb,^[9] by using a mode-locked Ti/sapphire laser that delivers 80-fs pulses at 80 MHz. The quadratic dependence of the fluorescence intensity on the excitation intensity was verified for every data point, indicating that our measurements were

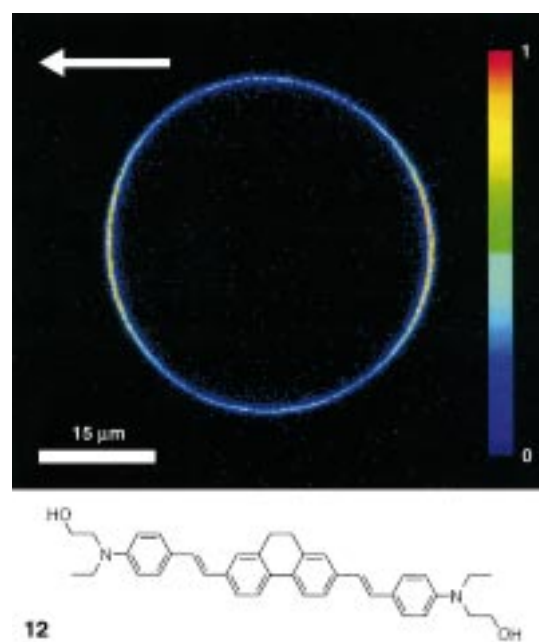


Figure 3. TPEF image of a giant unilamellar vesicle labeled with fluorophore **12**, excited at 750 nm with less than 1-mW excitation power. The vesicles were prepared from 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) and externally perfused with 40 μ M of fluorophore **12** in DMSO by using a protocol similar to that used in ref. [14]. Fluorescence anisotropy is observed when using a linearly polarized beam and selecting the corresponding parallel component of TPEF radiation (directed along the white arrow). This suggests a preferential transmembrane incorporation of derivative **12** whose total length approximately matches the width of the DOPC bilayer at room temperature.

carried out in intensity regimes in which saturation or photodegradation of fluorophores did not occur.

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Remote Stereocontrol in Carbonyl Additions Promoted by Vinylstannanes**

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 Diego Galisteo, and Henar Martínez-García

The search for highly stereocontrolled routes for the preparation of chiral compounds is an important goal in organic chemistry.^[1, 2] The asymmetric addition of nucleophiles to carbonyl groups is a cornerstone of organic synthesis and as such has been extensively reviewed.^[3] Although asymmetric induction by stereogenic centers adjacent to carbonyl groups has been widely studied, more remote inductions are less well known.^[1–3]

Thomas and co-workers reported the potential of the allylstannane moiety in the construction of chiral compounds, and showed many examples of remote asymmetric induction by allylic tin reagents and oxocompounds.^[4] Other outstanding reactions that involve chiral allylstannanes were reviewed by Marshall.^[5]

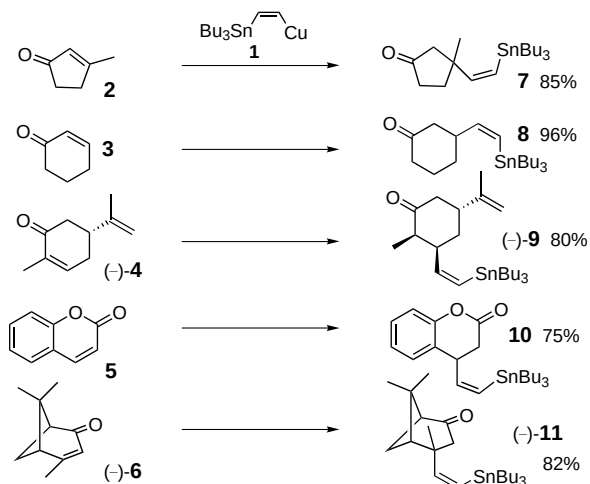
Herein we report a highly efficient stereocontrolled addition of organometallic reagents to carbonyl groups in the presence of a (*Z*)- β -stannylvinyl group. The remote stannyl group induces a highly stereoselective attack from the same face on which the tin center is found. To the best of our knowledge, the long-distance control effected by the vinyltin moiety has not been observed before. The role of the tin center, the influence of the Sn–CO bond separation, and a hypothetical mechanistic pathway that leads to this remarkable stereocontrol are discussed herein.

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The introduction of a vinylstannyl unit β to a carbonyl group was achieved by stannylcupration of acetylene, followed by treatment with α,β -unsaturated ketones. The stannylcupration of allenes^[6] and acetylenes^[7] has emerged as an important tool in the synthesis of allyl- and vinylstannanes.^[8, 9]

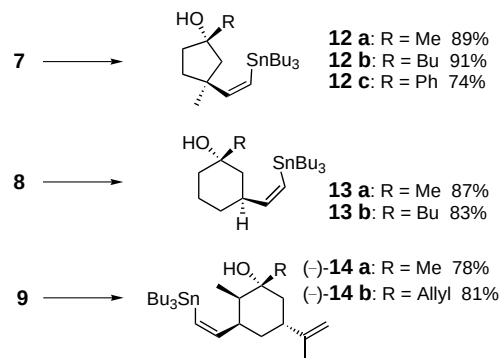
cis-2-(Tributylstannyl)vinyl cyanocuprates **1**^[7] react with enones **2–6** to give, after conjugate addition, *cis*- β -(tributylstannyl)vinyl ketones **7–11** in good yield (Scheme 1). The



Scheme 1. Reaction of enones **2–6** with cuprate **1**. Reagents and conditions: 1) **1** (1.0 equivalent), $\text{BF}_3 \cdot \text{Et}_2\text{O}$, THF, -78°C , 30 min; 2) $-78 \rightarrow 0^\circ\text{C}$, 1 h; 3) $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$, 0°C .

addition of one to two equivalents of BF_3 to the cuprate prior to the addition to the ketone increases the final yield significantly.^[10] $(-)\text{-}(5R)\text{-Carvone}$ (**4**) and $(-)\text{-}(1S,5S)\text{-verbenone}$ (**6**) underwent stereoselective conjugate addition to give the optically active ketones $(2R,3R,5R)\text{-9}$ and $(1S,4S,5R)\text{-11}$, respectively.^[11a]

The behavior of **7–9** toward typical organolithium reagents shows that addition occurs with a high degree of stereocontrol. The reaction of **7–9** with MeLi , BuLi , allyllithium, and PhLi in THF at -78°C affords diastereoselectively the tertiary alcohols **12–14** (Scheme 2), respectively, in which the addition of the alkyl or phenyl groups takes place *syn* to the



Scheme 2. Stereoselective addition of organolithium reagents to β -stannylvinyl ketones **7**, **8**, and **9**. Reagents and conditions: 1) RLi (1.2 equivalents), THF, -78°C , 30 min; 2) MeOH , -78°C .

vinyltin moiety. The *de* values in all the studied examples is greater than 98 % (GC-MS), except for the addition of PhLi which in some experiments also gave up to 10 % of the other diastereomer.

An indication of how this reaction might be applied to asymmetric synthesis is shown in the successive conversion of **4** → **9** → **14a**^[11b], in which new stereogenic centers of defined configuration are formed consecutively, starting from a chiral building block.

The stereochemistry assigned to the resulting alcohols **12**–**14** was confirmed by both physical (NOE, X-ray) and chemical^[12] methods. X-ray analysis of the phenylurethane derivative of **13b** (Figure 1) reveals that the butyl and the vinyltin groups are on the same side of the molecule in a *cis* diequatorial arrangement.^[13]

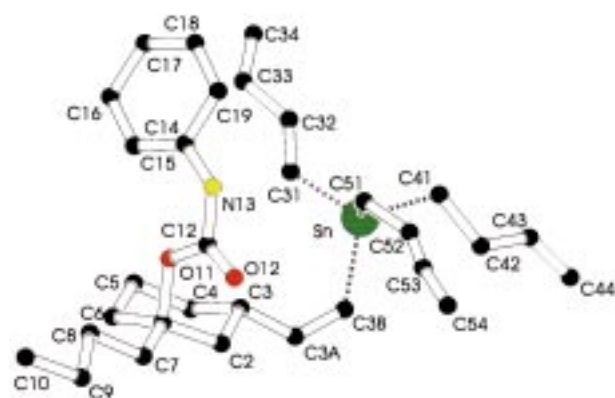
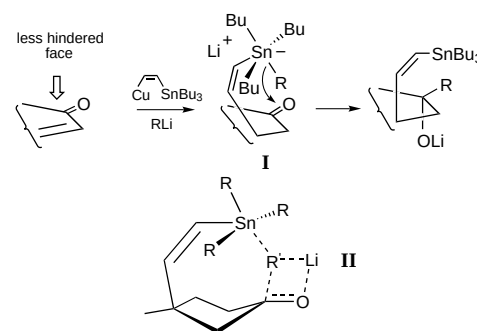


Figure 1. X-ray crystal structure of the phenylurethane derivative of **13b**.

Although the stereoselectivity observed in the reactions of ketones **7** and **8** could be explained without the mediation of the tin group, the diastereocontrol associated with ketone **9**, in which addition occurs from the same face as the tin center, cannot be easily explained without the assistance of the vinyltin group. Thus, in the case of ketones **7** and **8**, torsional strain and steric factors may lead to the observed high levels of stereocontrol.^[14] However, the conformationally rigid ketone **9**, which has the bulky stannylvinyl group in the axial position,^[15] also shows selective nucleophilic transfer from the face on which the tin center is found, when equatorial attack *anti* to the stannylvinyl group should be favored. This latter observation could be evidence for the participation of tin in the stereochemical course of the reaction.

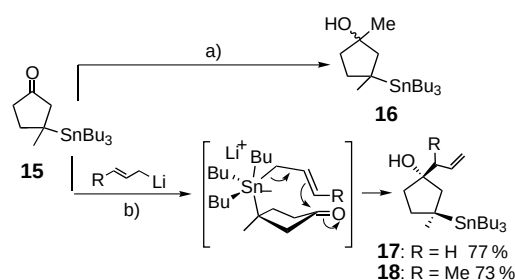
The stereoselectivity of these reactions could be interpreted if we assume that there exists a clear preference for the organometallic group to approach from the face on which the tin group is found. The high stereocontrol observed might then indicate that the reactive species is an intermediate pentacoordinate stannate anion **I** (Scheme 3), which delivers the alkyl or phenyl group by means of an intramolecular reaction. The *Z* stereochemistry of the stannylvinyl unit could favor the proposed intramolecular nucleophilic transfer. This directing effect, which is promoted by the remote tin center, has not been reported before.

The reaction of ketone **15** (readily available from stannylcupration of **2**) with organolithium reagents is significant.



Scheme 3. Directing effect of the stannate moiety in the proposed mechanism.

Compound **15** does not show any selectivity toward the attack of methylolithium and gives an almost equimolar mixture of diastereomeric alcohols **16** (Scheme 4). However, when

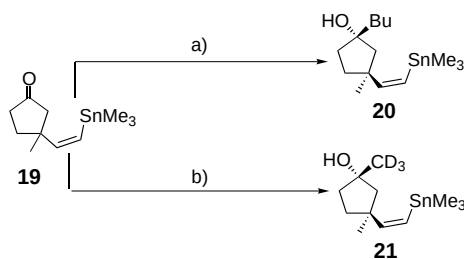


Scheme 4. Reaction of ketone **15** with organolithium compounds. Reagents and conditions: a) MeLi, THF, -78°C , 86 %; b) THF, -78°C .

allyllithium is used, the same selectivity and mode of addition is observed again, affording the alcohol **17**. Moreover, the reaction of **15** with 2-butenyllithium takes place apparently with complete allyl inversion to give **18** (Scheme 4). The lack of selectivity in the reaction of **15** with MeLi could be a result of the long spatial distance between the tin center and the carbonyl groups which does not favor intramolecular delivery. On the contrary, the three-carbon chain of the allyl or butenyl group could compensate for that distance, thus favoring the selective addition *syn* to the tin center. The allylic rearrangement supports this hypothesis of an intramolecular pathway (Scheme 4).

Although the proposed intermediate **I** explains the observed stereoselectivity well, the absence of scrambling reactions when the organolithium reagent is not BuLi is surprising. Similarly, treatment of the trimethyltin analogue **19**^[7] with BuLi gives the 1-butylalcohol (trimethyltin derivative) **20** as the only product (Scheme 5). Moreover, reaction of ketone **19** with deuterated MeLi leads to the alcohol **21**, which results from the selective addition of the deuteromethyl group from the same face as the tin center (Scheme 5). We were not able to detect scrambled methyl- and deuteromethylalcohols. Evidently, intermediate **I** fails to explain the lack of scrambling. Also, the chemoselectivity observed in the deuterium-labeling experiment is not consistent with a model as simple as the one initially proposed.

It is feasible that the high diastereoselectivity found in these processes could be ascribed to some kind of chelating effect



Scheme 5. Reagents and conditions: a) BuLi, THF, -90 °C, 30 min, 78%; b) CD₃Li (1.2 equivalents), THF, -90 °C, 30 min, 75%.

with the tin and carbonyl groups anchoring the RLi in between them. The results may be better rationalized if instead of a tight complex such as **I**, we assume a chelation-control model such as **II** (Scheme 3), in which the Sn–R and Sn–R' bonds have different strengths. The allyl inversion observed in **18** could thus arise from this anchoring effect.

To support theoretical evidence of the proposed mechanism, an ab initio molecular-orbital analysis of the reaction of ketone **19** with MeLi was performed by using Gaussian98,^[16] and two transition states (TS_s and TS_a) for the *syn* and *anti* addition (relative to Sn) were localized (Figure 2). The energies for the transition states when a methyl anion approaches **19** were estimated and it was found that *syn* addition is favored over the *anti* reaction by 10.7 kcal mol⁻¹.

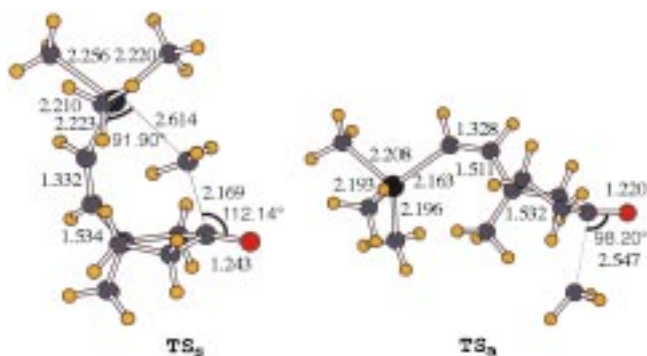


Figure 2. The calculated structures of TS_s and TS_a.

Work in progress shows that high levels of stereocontrol are also obtained when Grignard reagents are used instead of organolithium compounds.

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- [12] Chemical confirmation of the stereochemistry assigned to **12a** was obtained as follows: a diastereomeric mixture of 1,3-dimethyl-3-vinylcyclopentan-1-ol was obtained by adding lithium divinyl cuprate to **2**, and reacting the resulting ketone with MeLi. The two diastereomeric cyclopentanol compounds were separated: the 1-methyl/3-vinyl *syn* cyclopentanol is identical to that obtained from protodestannylation (HI/THF) of **12a**, whereas the other cyclopentanol (1-methyl/3-vinyl *anti*) was converted into the bicyclic lactone 1,4-dimethyl-3-oxa-bicyclo[2.2.1]heptan-2-one by ozonolysis followed by oxidation (PCC/CH₂Cl₂) of the resulting hydroxyaldehyde.
- [13] 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-139911. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [14] The pseudo-axial position of the methyl group in ketone **7** should favor the attack of the organometallic reagent from the less hindered side, *anti* to the methyl group and hence *syn* to vinyltin group. Similarly, for the ketone **8**, equatorial attack would be favored which could explain the diastereoselectivity observed.
- [15] Ab initio analysis of cyclohexanone **9** predicts equatorial positions for methyl and isopropenyl groups and an axial position for the stannylvinyl group. Coupling constants and NOE data from NMR spectroscopic analysis corroborate this.
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Detection of TNT and Picric Acid on Surfaces and in Seawater by Using Photoluminescent Polysiloles**

Honglae Sohn, Rebecca M. Calhoun, Michael J. Sailor,* and William C. Trogler*

Polysilanes exhibit high hole mobility and high nonlinear optical susceptibility in the UV region which makes them efficient photoemission candidates for a variety of optoelectronics applications.^[1] These properties arise from σ - σ^* delocalization of σ electrons along the Si-Si backbones and confinement of the conjugated electrons along the backbone. Polysiloles, such as poly(2,3,4,5-tetraphenyl-1-silacyclopenta-2,4-diene), also possess a Si-Si backbone, but the unsaturated five-membered ring of the silole shifts their optical absorption and emission spectra into the visible spectral region.^[2] Thus polysiloles have been examined as materials for organic light-emitting diodes (LED's).^[3] The most characteristic feature of siloles is a low reduction potential and a low-lying lowest unoccupied molecular orbital (LUMO). These features result from the σ^* - π^* conjugation arising from the interaction between the σ^* orbital of the silicon chain and the π^* orbital of the butadiene moiety of the five-membered ring.^[4, 5]

Polytetraphenyl-1,1-silole, $(C_4Ph_4Si)_n$, which was used in this study, has a helical structure along the Si-Si backbone^[6] and a highly conjugated ring system in the side chains. It also exhibits a high luminescence quantum yield.^[7] Recently Yang and Swager showed that highly π -conjugated, porous organic polymers can be used to detect vapors of electron-deficient chemicals.^[8, 9] Electron delocalization in these polymers provides a means of amplification, since interaction of an analyte molecule at any position along the polymer chain is communicated throughout the chain. A similar means of amplification is available to quantum-confined semiconductor nanocrystallites, where the electron and hole wave functions are delocalized throughout the nanocrystal.^[10]

Most methods for the detection of explosives are only applicable to air samples as a consequence of interference problems encountered in complex aqueous media. Sensing 2,4,6-trinitrotoluene (TNT) and 2,4,6-trinitrophenol (picric acid) in groundwater or seawater is important for the detection of buried unexploded ordnance and for locating underwater mines.^[11, 12] There are also environmental applications for characterizing soil and groundwater contaminated with toxic TNT at military bases as well as at munitions production and distribution facilities.^[13] Here we report an inexpensive and highly efficient inorganic polymer sensor that can detect nitroaromatic compounds, such as picric acid,

nitrobenzene, 2,4-dinitrotoluene (DNT), and TNT in air or seawater. The sensor employs a thin film of photoluminescent polysilole, which is stable to air, water, acids, common organic solvents, and even seawater-containing bioorganisms.

Polytetraphenylsilole^[14] was coated as a thin film on substrates such as commercial filter paper, borosilicate glass cover slips, porous silicon chips,^[15] and silicon wafers. Samples were prepared by soaking the substrates in a toluene solution of polysilole after filtration through a 0.2- μ m PTFE filter. Thin films of polysilole were also deposited on glass or silicon wafer substrates by spin coating. These samples were dried in a vacuum before use. Samples were then placed either in a cylindrical quartz flow cell ($d = 2.5$ cm, $h = 2.0$ cm) under flowing air or in a quartz cell ($1.5 \times 1.5 \times 2.5$ cm³) filled with seawater that contained the analyte for the detection experiment.

The detection method involves measuring the quenching of the photoluminescence of the polysilole by the analyte (by using a Perkin-Elmer LS 50B fluorescence spectrometer, 340 nm excitation wavelength). The fluorescence spectra of a toluene solution of the polysilole were obtained upon successive addition of aliquots of TNT. The quenching of the photoluminescence of the polysilole in toluene solutions of nitrobenzene, DNT, TNT (prepared from DNT^[16]), and picric acid were measured. A linear Stern-Volmer relationship was observed in the first three cases, but not for picric acid (Figure 1; $(I_0/I) - 1 = K[\text{analyte}]$). This latter observation may result from slight irreversibility in the case of picric acid. The fluorescence spectra of polysilole from either toluene solutions or thin polymer films displayed no shift in the maximum of the emission wavelength. This observation suggests that neither π stacking of the polymer chains nor excimer formation occurs with the polysilole.

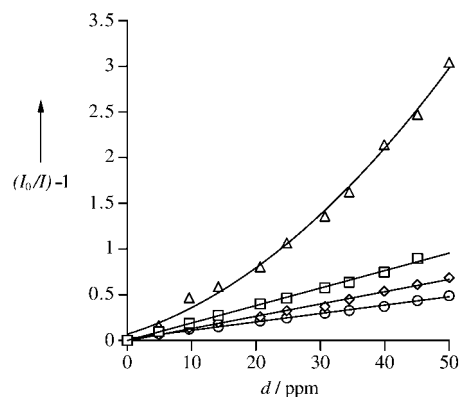


Figure 1. Stern-Volmer plots for the quenching of polysilole luminescence by nitrobenzene (○), DNT (◇), TNT (□), and picric acid (△).

The relative efficiencies of photoluminescence quenching of polysilole are 3.8:2.2:1.0 for TNT, DNT, and nitrobenzene (NB), respectively, as indicated by the values of K determined from the slopes of the steady-state Stern-Volmer plots. The quenching efficiency of photoluminescence for picric acid is 77 % greater than that for TNT at 50 ppb. Figure 2 shows that a plot of $\lg K$ versus the reduction potential of the analytes exhibits a linear relationship, which indicates that the

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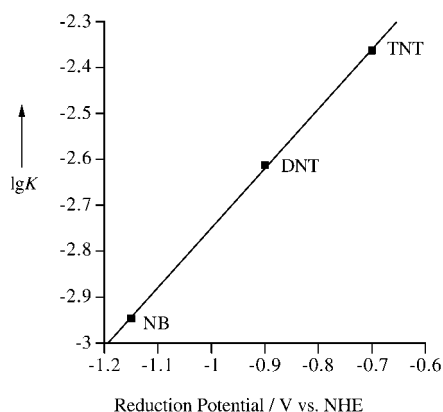


Figure 2. Plot of $\lg K$ versus the reduction potential of the analytes.

mechanism of quenching is attributable to electron transfer from the excited polysilole to the LUMO of the analyte. Since the reduction potential of TNT (-0.7 V versus the normal hydrogen electrode (NHE))^[9] is less negative than that of either DNT (-0.9 V versus NHE) or nitrobenzene (-1.15 V versus NHE), it is detected with high sensitivity.

Photoluminescence quenching of the oligomeric tersilole, $\text{Cl}(\text{C}_6\text{H}_4\text{Si})_3\text{Cl}$, by TNT was also measured. The K value of $(4.34 \pm 0.12) \times 10^3 \text{ M}^{-1}$ for a polysilole, which has about 15 repeat units,^[14] is 38 % greater than that for the oligomer tersilole ($K = (3.14 \pm 0.04) \times 10^3 \text{ M}^{-1}$). This result suggests that polysilole produces an excited state that is delocalized over many repeat units. The sensitivity of the photoluminescence quenching technique for the detection of analytes by organic polymers depends not only on the molecular weight of the polymer but also on the diffusion length of excitation.^[17]

An important aspect of the inorganic polymer sensors is their insensitivity to common interferents. Control experiments using thin films of polysiloles (deposited on glass substrates) with oxygenated air displayed no change in the photoluminescence spectrum. Similarly, exposure to organic solvents such as toluene, tetrahydrofuran, and methanol or the aqueous inorganic acids H_2SO_4 and HF produced no significant decrease in the photoluminescence intensity. However, 4 ppb of TNT vapor in air (air stream flowing at a rate of 100 mL min^{-1}) was detected as an 8.2 % decrease in the photoluminescence intensity within 10 min.

The detection of TNT and picric acid in seawater (collected off Scripps Pier, La Jolla, CA) was measured using thin films of polysilole. No quenching of the photoluminescence was observed until the seawater was spiked with 50 ppb of TNT. Quenching was detected instantly and the amount of quenching was stable with time. The efficiency of the photoluminescence quenching by picric acid is greater than that for TNT and we obtained a 6 ppb detection limit for picric acid in seawater using the thin films. Ionic oxidants, such as aqueous CrO_4^{2-} , are inefficient electron transfer quenchers of the hydrophobic polymer luminescence under similar conditions.

The effect of TNT exposure on polysilole-coated substrates is readily visible to the naked eye when the samples are illuminated with a small ultraviolet (UV) lamp. Thus, polysilole can be used as a convenient indicator reagent for TNT

residues. Trace amounts of TNT deposited by a glove that was used to handle TNT, and then wiped clean, show up as an easily viewed change in the photoluminescence (Figure 3).



Figure 3. TNT residue hand print visualized as quenched luminescence on paper developed with polysilole and illuminated with an ultraviolet light. The left hand (nitrile gloved) had been rubbed with about 0.1 g of TNT, and the glove was brushed to remove all visible TNT particles before being pressed onto the paper sheet. The right hand (nitrile gloved) was not exposed to TNT and serves as a control. The paper was then lightly coated with a fine mist of polysilole (0.1 mm in toluene) from an airbrush. The image taken under ultraviolet light demonstrates the utility of polysiloles for visualizing trace residues of TNT.

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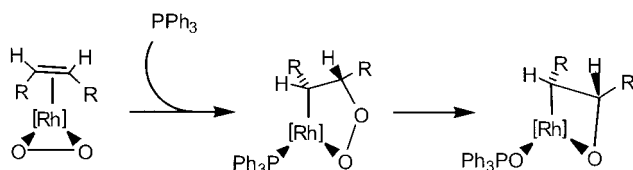
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3-Rhoda-1,2-dioxolanes through Dioxygenation of a Rhodium–Ethene Complex by Air**

Monique Krom, Ruud G. E. Coumans, Jan M. M. Smits, and Anton W. Gal*

3-Metalla-1,2-dioxolanes (κ^2C^1,O^2 -2-peroxyethyl metal complexes) have been proposed as intermediates in the catalytic oxidation of olefins by Group VIII metals.^[1] These reactions include epoxidation^[1d] and oxidation to ketones.^[1a,c]

Read has invoked contraction of 3-rhoda-1,2-dioxolanes to 2-rhodaioxetanes by O atom transfer to triphenylphosphane in catalytic co-oxygenation of olefins and triphenylphosphane (Scheme 1).^[1b]



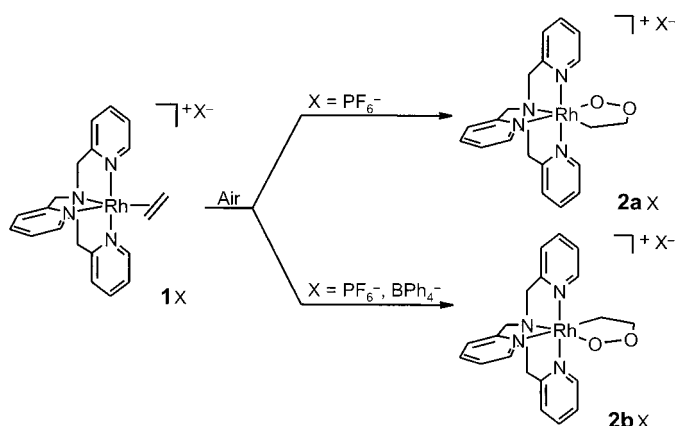
Scheme 1. 3-Rhoda-1,2-dioxolane and 2-rhodaioxetane intermediates in the co-oxygenation of triphenylphosphane and an olefin.^[1b]

We have previously obtained the stable 2-rhodaioxetanes, $[(tpa)Rh(\kappa^2C^1,O-CH_2CH_2O)]^+$ and $[(Metpa)Rh(\kappa^2C^1,O-CH_2CH_2O)]^+$, by mono-oxygenation of the corresponding ethene complexes, $[(tpa)Rh(CH_2CH_2)]^+$ and $[(Metpa)Rh(CH_2CH_2)]^+$, with H_2O_2 .^[2] In these reactions an unsubstituted 2-rhodaioxetane fragment, $[Rh(\kappa^2C^1,O-CH_2CH_2O)]^+$, is stabilized by the nitrogen donor ligands tpa and Metpa.^[3] Analogous 3-metalla-1,2-dioxolanes, containing an unsubstituted 3-metalla-1,2-dioxolane fragment $[M^n(\kappa^2C^1,O^2-CH_2CH_2OO)]^{(n-2)+}$, have not been reported to date. Tri- and tetrasubstituted 3-platina-1,2-dioxolanes, with β -carbon substituents that prevent β -hydrogen transfer, have been structurally characterized. They were obtained from the reaction of $[(PPh_3)_2Pt(\eta^2-O_2)]$ with compounds containing tetrasubstituted electron-deficient double bonds.^[4]

We now report the formation of a stable 3-metalla-1,2-dioxolane by dioxygenation of a metal olefin complex. The rhodium(i)-ethene fragment, $[Rh(CH_2CH_2)]^+$, stabilized by tpa, is found to be selectively dioxygenated by air to an unsubstituted 3-rhoda-1,2-dioxolane fragment. The structure of this dioxolane fragment has been determined by X-ray diffraction (see Figure 1).

The ethene complex $[(tpa)Rh(CH_2CH_2)]PF_6$ (**1**PF₆, Scheme 2) was synthesized according to a literature procedure.^[2b] Oxidation of a solution of **1**PF₆ with air at room

temperature results in loss of ethene from **1**⁺ and formation of as yet unidentified products. In marked contrast, exposure of solid **1**PF₆ to air results in a mixture of the products **2a**PF₆ and **2b**PF₆ in an approximate ratio of 1:1.



Scheme 2. Oxidation of **1**⁺ to 3-rhoda-1,2-dioxolanes. X = PF₆[−] (**1**, **2a**, **2b**), BPh₄[−] (**1**, **2b**).

Compounds **2a**PF₆, **2b**PF₆, and **2b**BPh₄ (see below) proved sensitive towards visible light and therefore had to be manipulated in the dark. The nature of their photochemical reaction products will be subject of a forthcoming publication.

Electrospray ionization mass spectrometry (ESI-MS) and ¹H NMR spectra of the mixture of **2a**PF₆ and **2b**PF₆ in CD₃CN indicate that **2a**⁺ and **2b**⁺ are the two isomeric 3-rhoda-1,2-dioxolanes shown in Scheme 2. The base peak at $m/z = 453$ in the ESI-MS spectrum is consistent with the presence of $[(tpa)Rh(CH_2CH_2) + O_2]^+$. The couplings $^3J(H_\alpha, H_\beta)$ of the $RhCH_2CH_2-$ fragments in **2a**⁺ and **2b**⁺ (6.1 Hz, Table 1) suggest them to be part of a five-membered ring: $^3J(H_\alpha, H_\beta)$ decreases from 7.5 Hz for the four-membered 2-rhodaioxetane ring in **3a**⁺,^[2a,b] to 6.1 Hz for the five-membered ring in **2a**⁺ and **2b**⁺, to only 5.6 Hz for the six-membered ring in rhodium 2-(acetimidoyloxy)ethyl complex **4a**⁺ (Scheme 3).^[2a] The nuclear Overhauser enhancement (NOE) interactions in **2a**⁺ and **2b**⁺ are consistent with their proposed structures: isomer **2b**⁺ shows NOE interactions between $RhCH_2CH_2-$ and one proton each of the two equivalent $Rh-N_{amine}-CH_2-$ units, and between $RhCH_2CH_2-$ and the two equivalent pyridyl (py) H6 centers; isomer **2a**⁺ shows NOE interactions between $RhCH_2CH_2-$ and all three pyridyl H6 centers, and between $RhCH_2CH_2-$ and the two equivalent pyridyl H6 centers.

In an attempt to selectively obtain one of the two isomeric 3-rhoda-1,2-dioxolanes **2a**⁺ and **2b**⁺, we changed the counterion of **1**⁺ from PF₆[−] to BPh₄[−].^[5] Upon reaction of solid **1**BPh₄ with air only **2b**BPh₄ was formed, as confirmed by the ¹H NMR and ESI-MS spectra. Possibly, different packings in (microcrystalline) **1**BPh₄ and **1**PF₆ have resulted in a different accessibility of O₂ to the ion **1**⁺. Remarkably, from the oxidation of **1**⁺ by hydrogen peroxide only the 2-rhodaioxetane **3a**⁺, the analogue of isomer **2a**⁺, has been obtained

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(Scheme 3). Thus far, a 2-rhodaioxetane analogue of isomer **2b**⁺ has not been obtained.

The structure of complex **2b**BPh₄, as determined by X-ray diffraction, is shown in Figure 1.^[6] The 5-membered ring has the envelope conformation and occurs in two almost mirrored, but crystallographically independent, conformations (**2bA**⁺ and **2bB**⁺). The bond Rh–N_{amine} (N1–Rh1) in 3-rhoda-1,2-dioxolane **2b**⁺ is shorter than that found in an analogue of 2-rhodaioxetane **3a**⁺ (Scheme 3; 2.056(2) Å vs. 2.132(8) Å av.);^[2a,b] as expected, the *trans* influence of a 3-rhoda-1,2-dioxolane O_α is smaller than that of a 2-rhoda-ioxetane C_α. The puckering of the 3-rhoda-1,2-dioxolane ring in the cations **2bA**⁺ and **2bB**⁺ is virtually the same as found in the α-dicyano-β-dimethyl substituted 3-platina-1,2-dioxolane ring.^[4a,7] The average O1–O2 bond in **2bA**⁺ and **2bB**⁺ (1.481(17) Å) is normal when compared to the O–O bond in

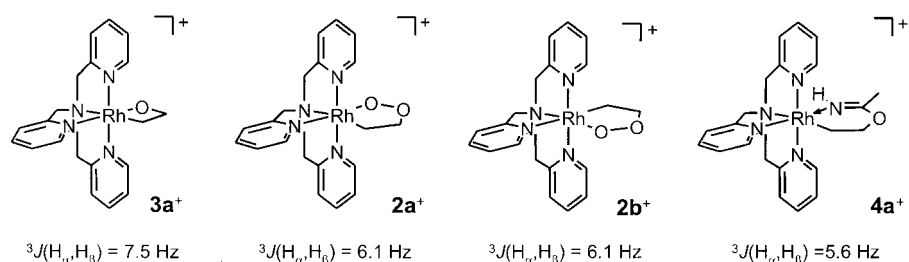
the 3-platina-1,2-dioxolane (1.482(15) Å)^[4a] and other M–O–O–C compounds (1.40–1.52 Å).^[8] The average distance O2–C2 for **2bA**⁺ and **2bB**⁺ (1.438(11) Å) is similar to the O–C distances in the 3-platina-1,2-dioxolane (1.407(19) Å) and in other M–O–O–C compounds (1.40–1.47 Å).^[9]

We have thus for the first time selectively oxidized a metal–ethene complex with air to a stable 3-metalla-1,2-dioxolane. Selective dioxygenation of **1**⁺ was successful only for **1**⁺ in a crystalline matrix. The observed formation of stable isomeric 3-rhoda-1,2-dioxolanes from a rhodium–ethene complex lends support to the involvement of 3-rhoda-1,2-dioxolanes as intermediates in rhodium-catalyzed oxygenation of olefins to ketones, as proposed by Mimoun et al.^[1a] and Read.^[1b] Both the mechanism of the observed selective oxidation in the solid state and the reactivity of the resulting 3-rhoda-1,2-dioxolanes are currently under investigation.

Table 1. Chemical shifts (ppm) and coupling constants (Hz) of the RhCH₂CH₂O– fragments in CD₃CN.

	δ(RhCH ₂)	δ(CH ₂ O)	³ J(H,H)	² J(H,Rh)	δ(RhCH ₂)	δ(CH ₂ O)	¹ J(C,Rh)
3a ⁺	2.24(dt)	4.88(t)	7.5	2.5	1.3(d) ^[a]	78.7(d)	18.4 ^[a]
2a ⁺	3.55(dt)	3.41(t)	6.1	2.4	44.8(d)	72.8(s)	28.8
2b ⁺	2.57(dt)	3.25(t)	6.1	2.4	35.0(d)	70.2(s)	25.0

[a] [D₆]Acetone.



Scheme 3. Decrease of ³J(H_α, H_β) with increasing ring size.

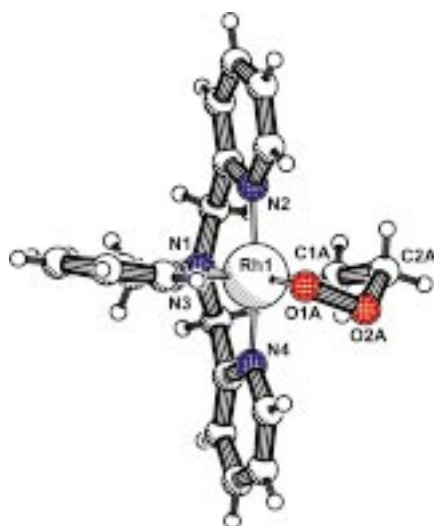


Figure 1. X-ray structure of **2b**BPh₄; only one of the two independent cations is shown (**2bA**⁺, but data for **2bB**⁺ are also listed). Selected bond lengths [Å]: Rh1–N1 2.056(2), Rh1–N2 2.015(2), Rh1–N3 2.144(3), Rh1–N4 2.025(2), Rh1–C1A 2.05(3), Rh1–C1B 2.06(4), Rh1–O1A 1.99(3), Rh1–O1B 2.00(3), O1A–O2A 1.481(17), O1B–O2B 1.481(16), O2A–C2A 1.431(11), O2B–C2B 1.445(11), C1A–C2A 1.548(13), C1B–C2B 1.531(15).

Experimental Section

NMR experiments were carried out on Bruker DPX200, Bruker AC300, and Bruker AM500 spectrometers. Solvent shift references for NMR are: CD₃CN δ(¹H) = 1.94, δ(¹³C) = 118.1. ESI-MS spectra were recorded on a Finnigan MAT 900S mass spectrometer.

Compounds [(tpa)Rh(CH₂CH₂)₂]BPh₄/PF₆,^[2b] [(CH₂CH₂)₂RhCl]₂,^[10] and tpa^[11] were prepared according to literature procedures.

2aPF₆/**2b**PF₆: **1**PF₆ was powdered with a mortar and exposed to air at room temperature and in the dark for 2 days at atmospheric pressure. A mixture of **2a**PF₆ and **2b**PF₆ in an approximate ratio of 1:1 was obtained in >90% yield, as determined by ¹H NMR. The data for **2a**PF₆ are: ¹H NMR (500 MHz, CD₃CN, 298 K): δ = 8.86 (d, 1H, ³J(H,H) = 5.4 Hz, py_a-H6), 8.56 (d, 2H, ³J(H,H) = 5.4 Hz, py_b-H6), 7.83 (dt, 2H, ³J(H,H) = 7.8 Hz, ⁴J(H,H) = 1.4 Hz, py_b-H4), 7.63 (t, 1H, ³J(H,H) = 7.3 Hz, py_a-H4), 7.48 (d, 2H, ³J(H,H) = 7.8 Hz, py_b-H3), 7.35 (t, 2H, ³J(H,H) = 6.6 Hz, py_b-H5), 7.25 (m, 1H, py_a-H5), 7.14 (d, 1H, ³J(H,H) = 7.8 Hz, py_a-H3), 5.12 (d[AB], 2H, ²J(H,H) = 15.6 Hz, NCH₂-py_b), 5.00 (d[AB], 2H, ²J(H,H) = 15.6 Hz, NCH₂-py_b), 4.80 (s, 2H, NCH₂-py_a), 3.55 (dt, 2H, ³J(H,H) = 6.1 Hz, ²J(H,Rh) = 2.4 Hz, RhCH₂CH₂O), 3.41 (t, 2H, ³J(H,H) = 6.1 Hz, RhCH₂CH₂O); ¹³C[¹H] NMR (50 MHz, CD₃CN, 300 K): δ = 164.6 (py_b-C2), 162.7 (py_a-C6), 152.5 (py_b-C6), 150.5 (py_b-C6), 139.7 (py_b-C4), 138.7 (py_a-C4), 125.9 (py_b-C3), 125.5 (py_a-C3), 124.6 (py_b-C5), 122.6 (py_a-C5), 72.8 (RhCH₂CHO), 67.9 (NCH₂-py_b), 65.4 (NCH₂-py_a), 44.8 (d, ¹J(C,Rh) = 28.8 Hz, RhCH₂CH₂O); ESI-MS (CD₃CN): 453 [M – PF₆]⁺, 425 [M – C₂H₄ – PF₆]⁺, 409 [M – C₂H₄O – PF₆]⁺, 393 [M – C₂H₄O₂ – PF₆]⁺, 391 [M – C₂H₄O₂ – H₂ – PF₆]⁺.

2bBPh₄: **1**BPh₄ was powdered with a mortar and exposed to air at room temperature and in the dark for 2 days at atmospheric pressure. **2b**BPh₄ was obtained in >90% yield, as determined by ¹H NMR spectroscopy. ¹H NMR (300 MHz, CD₃CN, 297 K): δ = 8.75 (d, 1H, ³J(H,H) = 5.4 Hz, py_a-H6), 8.66 (d, 2H, ³J(H,H) = 5.5 Hz, py_b-H6), 7.81 (dt, 2H, ³J(H,H) = 7.8 Hz, ⁴J(H,H) = 1.7 Hz, py_b-H4), 7.69 (dt, 1H, ³J(H,H) = 7.8 Hz, ⁴J(H,H) = 1.7 Hz, py_a-H4), 7.40 (d, 2H, ³J(H,H) = 8.0 Hz, py_b-H3), 7.35 (m, 3H, py_a-H5 and py_b-H5), 7.28 (m, 8H, BAr-H2), 7.16 (dt, 1H, ³J(H,H) = 7.8 Hz, ⁴J(H,H) = 0.9 Hz, py_a-H3), 6.99 (t, 8H, ³J(H,H) = 7.4 Hz, BAr-H3), 6.84 (t, 4H, ³J(H,H) = 7.3 Hz, BAr-H4), 4.88 (d[AB], 2H, ²J(H,H) = 15.6 Hz, NCH₂-py_b), 4.71 (d[AB], 2H, ²J(H,H) = 15.1 Hz, NCH₂-py_b), 4.57 (s, 2H, NCH₂-py_a), 3.25 (t, 2H, ³J(H,H) = 6.1 Hz, RhCH₂CH₂O), 2.57 (dt, 2H, ³J(H,H) = 6.1 Hz, ²J(H,Rh) = 2.4 Hz, RhCH₂CH₂O); ¹³C[¹H] NMR (75 MHz, CD₃CN, 297 K): δ = 164.6 (q, ¹J(C,B) = 49.5 Hz, BAr-C1), 162.7 (py_b-C2), 158.6 (py_a-C2), 150.1 (py_b-C6),

149.5 (py_a-C6), 139.4 (py_a-C4), 139.3 (py_b-C4), 136.5 (BAR-C2), 126.4 (q, ³J(C,B) = 2.8 Hz, BAR-C3), 125.5 (py_b-C3), 125.4 (py_a-C3), 124.2 (py_b-C5), 122.6 (BAR-C4), 121.9 (py_a-C5), 72.9 (NCH₂-py_a), 70.2 (NCH₂-py_b and RhCH₂CH₂O), 35.0 (d, ¹J(C,Rh) = 25.0 Hz, RhCH₂CH₂O); ESI-MS (CD₃CN): 453 [M-BPh₄]⁺, 425 [M-C₂H₄-BPh₄]⁺, 409 [M-C₂H₄O-BPh₄]⁺, 393 [M-C₂H₄O₂-BPh₄]⁺, 391 [M-C₂H₄O₂-H₂-BPh₄]⁺.

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- [5] NaBPh₄ was used instead of KPF₆ to precipitate the ethene complex.
- [6] Transparent yellow crystals of **2bBPh₄** were obtained by slow diffusion of diethylether into a 1,2-dichloroethane/acetonitrile solution. The X-ray diffraction data were collected at 150(2) K on an Enraf-Nonius CAD4 diffractometer with rotating anode and CCD area detector using graphite monochromatized MoK_α radiation (λ = 0.71073 Å). The structure was solved by the PATTY^[12] option of the DIRDIF^[13] program system. Crystal data: C₄₈H_{50.50}BClN_{4.50}O_{2.50}Rh, M_r = 879.60, monoclinic, space group C2/c, a = 35.8999(8), b = 10.7567(3), c = 24.2379(5) Å, β = 116.4699(12), V = 8378.6(3) Å³, Z = 8, ρ_{calcd} = 1.395 Mg m⁻³. All non-hydrogen atoms that could be located were refined with anisotropic temperature factors. The hydrogen atoms were placed at calculated positions and refined isotropically in riding mode. The 5-membered dioxolane ring has the envelope form and occurs in two conformations. As expected there is considerable positional overlap for some of the atoms (C1A and C1B, C2A and C2B, O1A and O1B). Therefore some geometrical constraints had to be applied: the two conformations were "SAMED" and the anisotropic thermal displacement parameters were tied. Calculations (PLATON, Spek 1995)^[14] showed two distinct voids, one of 228 Å³, containing 68 electrons, around a two-fold axis (position 4e, 0, y, 1/4; y = -0.037), and one of 151 Å³, containing 51 electrons, around an inversion center (position 4b: 1/2, 0, 0). Based on the synthetic route and evidence from NMR spectroscopy it is assumed that these electron densities possibly stand for one molecule diethylether (C₄H₁₀O, 42 electrons) plus one molecule acetonitrile (CH₃CN, 22 electrons) in the first void (64 electrons, 28.5 Å³/atom), and one molecule dichloroethane (C₂H₄Cl₂, 50 electrons) in the second void (30.2 Å³/atom). It was not possible to assign any physically meaningful parameters to the electron densities found in the difference fourier map. Therefore the SQUEEZE procedure was applied to account for these electron densities. 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-157414. 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).
- [7] O_β and C_β (O2 and C2) are positioned above and below the O1-M-C1 plane: the displacement of O2 from this plane is +0.51 Å in **2bA**⁺ and -0.46 Å in **2bB**⁺, compared to +0.49 Å in the 3-platina-1,2-dioxolane. The displacement of C2 is -0.21 Å in **2bA**⁺ and +0.27 Å in **2bB**⁺, compared to -0.29 in the 3-platinadioxolane.
- [8] This range is based on O-O bonds in 48 crystal structures containing a M-O-O-C fragment (M = any metal); 4 outliers were not taken into account.

- [9] This range is based on O-C bonds in 48 crystal structures containing a M-O-O-C fragment (M = any metal); 9 outliers were not taken into account.
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A Striking, Multifaceted, Decalithium Aggregate with Carbanion, Organoamide, and Alkoxide Functionalities**

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Mixed-anion alkali metal complexes are of significant interest because of their ability to act as superbases.^[1] Normally superbase aggregates are composed of two anions and two differing metals, [R'M·M'OR]_n (R' = alkyl, aryl, amide; R = alkyl; M = Li; M' = Na, K), and it is these complexes that display greatest reactivity and have the widest application in synthetic processes.^[1d,e] Solid-state structural information on mixed-anion systems is of vital importance to provide a more complete understanding of the reasons behind their differing reactivity. However, such complexes have historically proved extremely difficult to crystallize,^[1a,2] hence solid-state structures are scarce despite the emergence of some data for each class of mixed-anion alkali metal complexes.^[3]

Unimetallic mixed-anion aggregates (M = M'), though usually less effective, are also of significant synthetic importance since, with suitable anions and metal, they can also show increased reactivity over that of the two separate starting reagents, for example [nBuLi·LiO(CH₂)₂NMe₂].^[4]

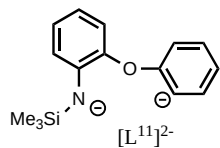
Herein, we report the crystallization and structure determination of the remarkable multifaceted unimetallic complex [(N(SiMe₃)(2-(2'-C₆H₄O)C₆H₄))₂Li₄·LiOEt·(Et₂O)]₂·hexane, **1**·hexane, which contains *three* different superbase anionic components, amide, carbanion, and alkoxide. The presence of *ethoxide* is particularly striking since Lochmann has indicated that the most stable mixed-anion aggregates are

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formed with bulky alkoxides, as exemplified by the presence of $t\text{BuO}^-$ in many known alkoxo solid-state structures.^[1a]

Deprotonation of N -(2-phenoxyphenyl)- N -(trimethylsilyl)-amine generates a highly useful lithium organoamide $\text{Li}(\text{L}^1)$ ($\text{L}^1 = \text{N}(\text{SiMe}_3)(2\text{-PhOC}_6\text{H}_4)$)^[5] which reacts further with $n\text{BuLi}$ to form $\text{Li}_2(\text{L}^{11})$ ($\text{L}^{11} = \text{N}(\text{SiMe}_3)(2\text{-(2'-C}_6\text{H}_4\text{O)C}_6\text{H}_4)$), containing a Li-carbanion derived from abstraction of the proton from the *ortho* position of the phenyl substituent.^[5b] Remarkably, on attempted reaction of $\text{Li}_2(\text{L}^{11})$ with LaCl_3 in diethyl ether, a decalithium



assembly, $1 \cdot \text{hexane}$, comprising four $\text{Li}_2(\text{L}^{11})$ units and two LiOEt groups (Figure 1) was serendipitously crystallized. The lithium ethoxide is presumably derived from ether cleavage, and is dependent upon the presence of the lanthanoid halide. In the absence of LaCl_3 , the formation of a product that incorporated a lithium alkoxide unit was not observed.^[5b] We have previously observed aryl ether cleavage with formation of $[\text{Yb}(\text{L}^1)_2\text{OPh}(\text{thf})]$ on decomposition of $[\text{Yb}(\text{L}^1)_2(\text{thf})_2]$, hence an intermediate unstable La complex is implicated in the present system.

Determination of the structure of $1 \cdot \text{hexane}$ by X-ray crystallography^[6] revealed a centrosymmetric decalithium aggregate (Figure 1) located at each of the eight unit cell

vertices, with a molecule of hexane positioned in a channel parallel to the a axis in the center of the unit cell. The asymmetric unit encompasses five unique Li atoms, two L^{11} ligands and an ethoxide group. Each of the chelating L^{11} ligands binds through bridging amide and aryl ether moieties. One ligand is coordinated by both to Li1 and Li3, whilst the other has the amide nitrogen (N2) bridging Li2 and Li4 and the aryl ether oxygen (O2) bridging Li4 and Li5A. The Li–N(amide) distances (av 2.05 Å) are typical of these structural features, whilst the less common bridging aryl ether oxygen atoms have one long (av 2.42 Å) and one shorter (av 2.08 Å) Li–O(ether) bond length.^[7a] Characteristic of lithium amides,^[7] Li1 is also coordinated by a molecule of diethyl ether which presumably inhibits further agglomeration of the aggregate. The ethoxide group is bound to three lithium atoms, Li1, Li2, and Li3 with one shorter (Li2–O3 1.839(5) Å) and two longer (Li1–O3 1.918(5), Li3–O3 1.890(5) Å) Li–O distances, though all are in the reported RO–Li range.^[8b] A μ_3 -alkoxide– Li_3 arrangement is characteristic of lithium clusters with bulky alkoxides, $[\text{Li}(\text{OR})]_n$ ($n = 4, 6$)^[3b, 7a] and presumably the rare incorporation of the much smaller OEt anion in the current structure is facilitated by the steric protection provided by the two nearby bulky SiMe_3 groups (Figure 1). The third anionic component is derived from the phenyl carbanion that bridges three lithium atoms in different modes. One phenyl group binds to Li2, Li4, and Li5 through a single

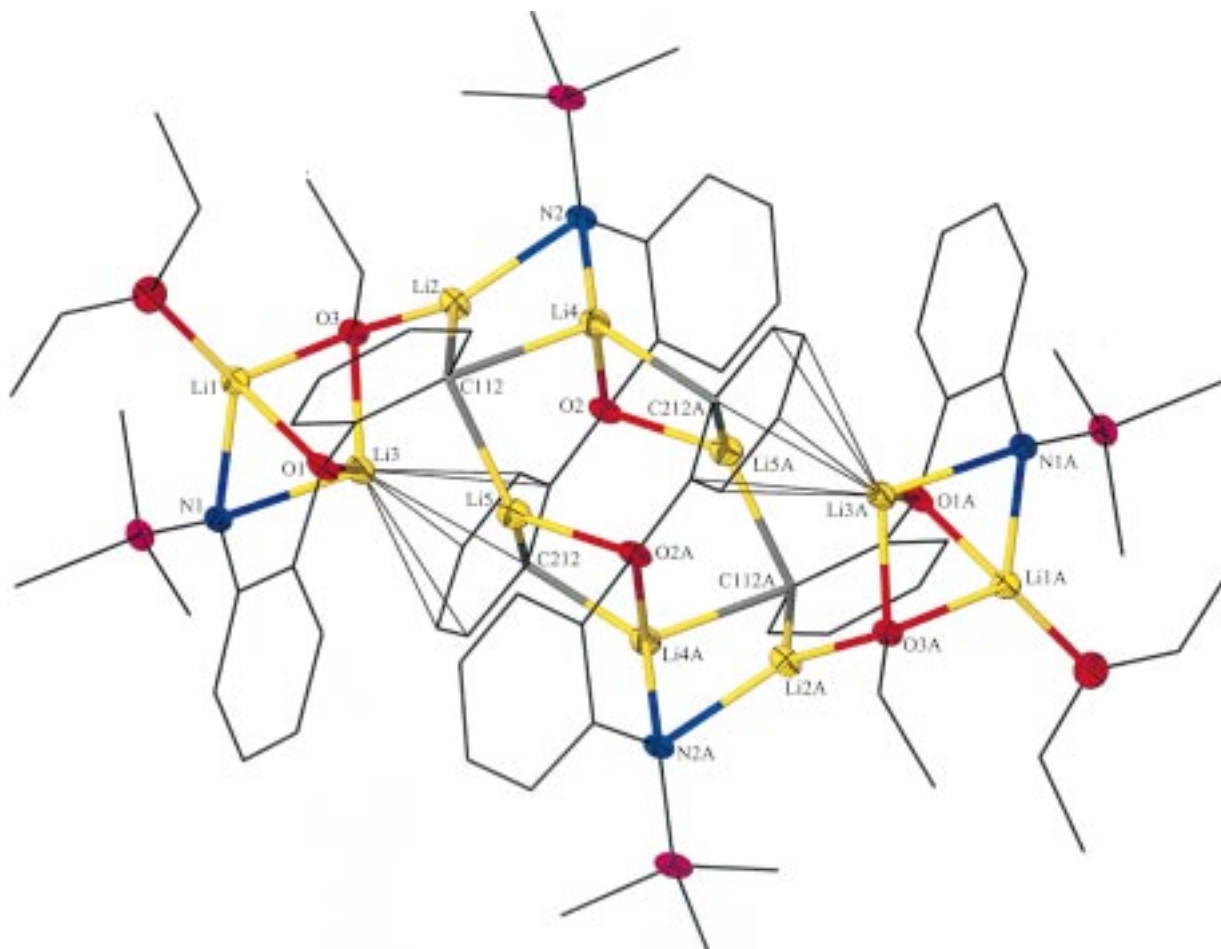


Figure 1. Molecular structure of $1 \cdot \text{hexane}$ with the thermal ellipsoids shown at 30% probability level for the non-carbon atoms. For clarity, the molecule of hexane and the hydrogen atoms have been omitted and the carbon atoms are represented by lines.

carbon atom (C112), whilst the other has a μ_2 -C (C212) interaction to Li5 and Li4A but also coordinates more weakly with Li3 by means of an η^6 - π -Ph interaction. The range of the shorter carbon–lithium bond lengths (2.128(5)–2.367(5) Å) has some longer than those observed in aryllithium clusters which similarly contain a μ_3 -aryl-Li₃ arrangement (e.g. [Li(3,5-*t*Bu₂C₆H₃)]₆: Li–C 2.119(7)–2.247(7) Å^[9]). The relative positions of the lithium atoms Li2, Li4, and Li5 (Figure 2a) and Li4A and Li5 (Figure 2b) and of the

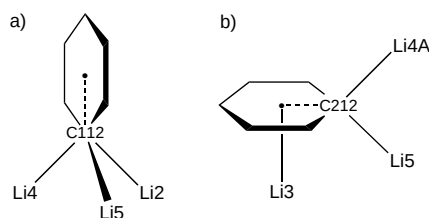


Figure 2. Schematic representation of Li–aryl bonding in **1**·hexane. a) Relative positions of Li2, Li4, and Li5 (a) and Li4A and Li5 (b) to the associated phenyl rings.

associated phenyl rings in **1** (Li–C to C₆ ring plane angles 0.4–59.2°) suggest predominantly σ -Li–C bonding. The π -Ph coordination to Li3 (Li–C₆ centroid to C₆ ring plane angle 84.3°) occupies a vacant tetrahedral coordination site on this lithium atom. The average Li–C separation (av Li–C 2.62 Å) is at the longer extreme of the range (2.28–2.77 Å)^[10a–c] previously observed for Li complexation by a neutral arene. Presumably a closer approach to Li3 is prevented by the bonding of the phenyl ring to Li2A and Li5 as well as being fixed to the L¹¹ backbone through the aryl ether oxygen O2. All Li–C(π -phenyl) distances are much less than the sum (3.30 Å) of the metallic radius for Li^[10d] and the van der Waals radius of an arene ring.^[10e]

The above bonding arrangements give five distinct lithium environments: Li1 four-coordinate (distorted tetrahedral), Li2 three-coordinate (trigonal planar Σ (°) 359.9), Li3 three-coordinate (pyramidal) augmented by the η^6 - π -Ph interaction to become pseudo-tetrahedral, Li4 four-coordinate (the donor atoms at the vertices of a triangular pyramid), and Li5 three-coordinate (near trigonal-planar Σ (°) 351.0). The Li2 environment is unique in lithium coordination chemistry being ligated by three “superbase” anions, amide, alkoxide, and carbanion with three different donor atoms (see also a Li/Na bimetallic complex with Li coordinated by hydroxide, alkoxide, and amide^[11]). The ⁷Li NMR spectrum of a [D₈]toluene solution of **1**·hexane showed only four separate broad peaks at room temperature, but on cooling, these resolved into the expected five sharp resonance signals. Similarly, variable-temperature ¹H NMR spectroscopy indicated some fluxional behavior that could be frozen at low temperature (see Experimental Section). However, two distinct L¹¹ environments were detected (even at room temperature) which suggests that the gross structure may remain largely intact in solution as was also observed in the unimetallic mixed-anion complex [(*i*Pr)₂NLi·{(Me₂NCH₂)₂-CHOLi}]₂.^[3e] The unexpected stability may be attributed to the integrity of [Li₂(L¹¹)]₂ units, which under appropriate

conditions can sequester small LiX entities in solution, and appears to support the observations of Schleyer et al. on the conformational stability of mixed aggregates in “superbase” mixtures.^[12] Indeed we have also isolated a *n*BuLi adduct from these systems.^[5b] Although it is premature to speculate on the possible behavior of triple anion aggregates as superbases, the successful isolation of **1**·hexane should encourage their more deliberate synthesis and hence investigation of their superbase role. The presence of chelation in **1** may be, but is not necessarily, a deterrent to superbase behavior (see ref. [4a]), especially since coordination fluxionality has been detected at room temperature.

Experimental Section

1: *n*BuLi (3.1 mL, 4.9 mmol) was slowly added to a stirring solution of *N*-(2-phenoxyphenyl)-*N*-(trimethylsilyl)amine (0.63 g, 2.45 mmol) in Et₂O (40 mL), and the mixture was stirred until it had warmed to room temperature (ca. 1 h). LaCl₃ (0.60 g, 2.45 mmol) was added and the reaction mixture was then stirred overnight. After the solvent had been removed under vacuum, hexane (25 mL) was added which gave a white precipitate. The reaction mixture was filtered at –78 °C and the filtrate was reduced under vacuum (ca. 15 mL) whereupon colorless crystals of **1**·hexane deposited (0.15 g, 18%). M.p. 180–184 °C (decomp); IR (Nujol): $\tilde{\nu}$ = 1589 s, 1561 w, 1544 w, 1408 vs, 1281 brs, 1244 s, 1147 vs, 1105 vs, 1162 m, 1044 s, 999 w, 945 s, 929 s, 886 w, 864 w, 828 s, 786 w, 768 s, 749 vs, 727 w, 668 w, 617 w cm^{–1}; ¹H NMR (400 MHz, [D₈]toluene, 303 K): δ = 0.02 (vbrs, 18H; Si(CH₃)₃), 0.24 (s, 18H; Si(CH₃)₃), 0.78 (t, ³*J* = 7.0 Hz, 12H; CH₃(OEt₂)), 0.81–0.98 (m, 12H; CH₃(hexane) CH₃(OEt₂)), 1.23 (brm, 8H; CH₂(hexane)), 3.03 (q, ³*J* = 7.0 Hz, 8H; CH₂(OEt₂)), 3.39 (brq, 4H; CH₂(OEt₂)), 5.70 (brs, 2H; Ar), 6.08 (brs, 4H; Ar), 6.29 (brs, 2H; Ar), 6.45 (brt, 4H; Ar), 6.66 (brs, 2H; Ar), 6.80–7.10 (brm, 12H; Ar), 7.29 (brs, 2H; Ar), 7.82 (brdd, 4H; Ar); ¹H NMR (400 MHz, [D₈]toluene, 213 K): δ = 0.35 (s, 18H; Si(CH₃)₃), 0.37 (s, 18H; Si(CH₃)₃), 0.86–0.99 (m, 18H; CH₃(OEt₂) CH₃(hexane)), 1.00–1.15 (brm, 6H; CH₃(OEt₂)), 1.17–1.38 (brm, 8H; CH₂(hexane)), 2.65 (brm, 4H; CH₂(OEt₂)), 2.82 (brm, 4H; CH₂(OEt₂)), 3.32 (brm, 2H; CH₂(OEt₂)), 3.47 (brm, 2H; CH₂(OEt₂)), 5.71 (d, ³*J* = 7.3 Hz, 2H; Ar), 6.05 (d, ³*J* = 7.7 Hz, 2H; Ar), 6.22 (t, ³*J* = 7.0 Hz, 2H; Ar), 6.38–6.57 (m, 4H; Ar), 6.64 (d, ³*J* = 8.2 Hz, 2H; Ar), 6.70–6.88 (m, 4H; Ar), 6.93–7.17 (m, 12H; Ar), 7.20 (brd, 2H; Ar), 7.37 (d, ³*J* = 7.5 Hz, 2H; Ar); ⁷Li NMR (155.51 MHz, [D₈]toluene, 303 K): δ = –2.57, 0.68, 1.16, 2.27; (183 K) –3.11, 0.67, 1.72, 1.95, 3.14: A satisfactory C analysis could not be obtained presumably owing to decomposition.^[13]

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- [6] Crystal data for **1**·hexane: colorless crystal, $0.18 \times 0.23 \times 0.38$ mm, triclinic, PI , $a = 10.7828(3)$, $b = 13.1998(5)$, $c = 16.1826(7)$ Å, $\alpha = 105.724(2)$, $\beta = 103.774(2)$, $\gamma = 92.199(3)^\circ$, $V = 2140.2(7)$ Å³, $Z = 1$, $\rho_{\text{calcd}} = 1.098$ g cm⁻³, $\mu = 0.120$ mm⁻¹, $2\theta_{\text{max}} = 56.5^\circ$. A total of 10232 ($R_{\text{int}} = 0.053$) unique reflections were collected (Enraf Nonius CCD, MoK α radiation ($\lambda_0 = 0.71073$ Å), $T = 123$ K) and used in least-squares refinement on F^2 , 469 refined parameters, GOF = 1.030 (based on F^2), $R1 = 0.073$, $\omega R2 = 0.169$ ($I > 2\sigma(I)$), $R1 = 0.134$, $\omega R2 = 0.198$ (all data), residual electron density $-0.366/0.525$ e Å⁻³. The hydrogen atoms were placed in calculated positions using a riding model. 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-157276. 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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- [13] Typical elemental analyses calcd for **1** C₇₂H₉₈Li₁₀N₄O₈Si₄ (%): C 65.06, H 7.43, N 4.21 (**1**·hexane C₇₈H₁₁₂Li₁₀N₄O₈Si₄: C 66.19, H 7.98, N 3.96); found: C 62.98, H 7.74, N 4.44.

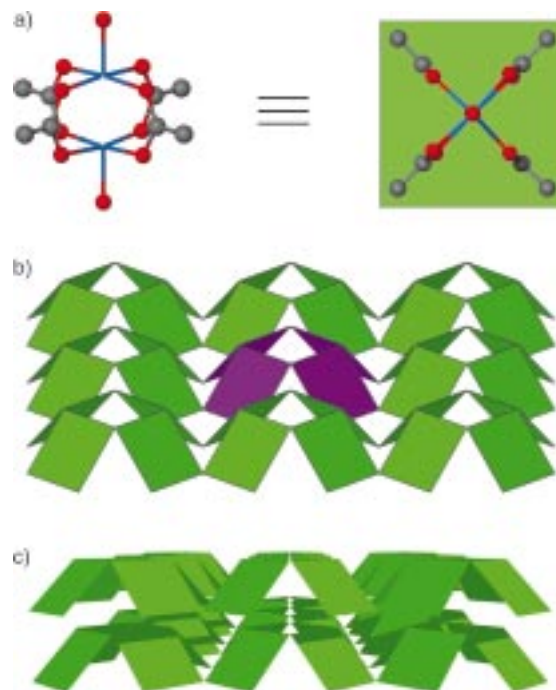
Self-Assembly of Nanometer-Scale Secondary Building Units into an Undulating Two-Dimensional Network with Two Types of Hydrophobic Cavity**

Susan A. Bourne, Jianjiang Lu, Arunendu Mondal, Brian Moulton, and Michael J. Zaworotko*

By using some of the recently enunciated principles of crystal engineering^[1–3] and self-assembly it has become possible to design and construct new classes of crystalline compounds from molecular components that possess useful

physical properties including bulk magnetism,^[4] nonlinear optical properties,^[5] and porosity.^[6–9] Open-framework structures can be assembled by using metals or metal clusters as nodes and multifunctional organic ligands to link these nodes. This approach has afforded structures that exhibit high surface areas, affinity for a wide range of organic guest molecules,^[10] and some show potential for catalysis.^[9] Herein we illustrate how the use of metal-organic secondary building units (SBUs) that are linked by angular ligands can generate nanoscale SBUs (nSBUs) with curvature.

The use of carboxylate-bridged metal clusters as metal-organic SBUs to build extended self-assembled structures has been delineated by Yaghi et al.^[8] Scheme 1 illustrates such a



Scheme 1. Schematic illustrations of a) the square SBU (green) based on metal ions bridged by carboxylate anions, b) how the square SBUs can self-assemble at their vertices to generate nanosized bowls (purple) which in turn form curved sheets, and c) how the curved sheets pack because of shape considerations.

cluster—in this case two metal ions are bridged by four carboxylate anions and each metal is bonded to one axial pyridine ligand. When viewed along the axial direction the extension of the carboxylate ligands forms a “square SBU”. Such clusters are ubiquitous in the Cambridge Structural Database,^[11] but most contain monofunctional carboxylates and, therefore, they will not generate extended structures. However, the use of bifunctional carboxylate ligands such as 1,4-benzenedicarboxylate allows the formation of self-assembled infinite structures that contain channels capable of incorporating a variety of guest molecules.^[12–15] 1,3-Benzenedicarboxylate is suitable for the linking of square SBUs at 120° and Scheme 1b shows one of the ways in which square SBUs can pack when there is a 120° angle at their vertices: a two-dimensional (2D) infinite metal-organic framework resembling a layer of upended bowls. In such a structure one bowl

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may be regarded as a “nanometer-scale SBU” (nSBU) which consists of four metal cluster SBUs.

The compounds $\{[M_2(1,3\text{-bdc})_2(\text{py})_2]_4\}_n$ (**1**) (1,3-bdc = 1,3-benzenedicarboxylate, py = pyridine, M = Zn, **1a**, Cu, **1b**) demonstrate that four square SBUs can indeed combine to form one bowl-shaped nSBU ($[M_2(1,3\text{-bdc})_2(\text{py})_2]_4$), which in turn self-assembles with other nSBUs to form the undulating sheet structure depicted in Scheme 1b. Each bowl has an outer diameter of 0.94 nm; a depth (as measured by the perpendicular distance from the center of the base to midpoint of a line joining the top hydrogen atoms on opposite bdc moieties) of 0.84 nm and a solvent-accessible volume of 0.518 nm^3 .^[16] The bowls are occupied by disordered benzene or pyridine guests and by the bottom of a bowl from the adjacent sheet. The layers therefore pack as illustrated in Scheme 1c, giving rise to a channel between adjacent bowls. The channels are hour-glass-shaped with a cavity of maximum dimensions of about $0.90 \times 0.90 \times 0.65 \text{ nm}$ and are occupied by benzene or pyridine guest molecules (in one unit cell the solvent-accessible volume is 0.28 nm^3 ^[16]). Between these cavities the channel narrows to an opening of about $0.15 \times 0.15 \text{ nm}$ which restricts the movement of the guest molecules through the channel. The distance between guest molecules is 0.81 nm. Figure 1a presents the coordination networks, and Figure 1b illustrates the networks in stick representation and the guest molecules in the channel in space-filling mode (the guests in the bowls have been omitted for clarity). The profile of the hour-glass channel is shown in Figure 1c. The total volume of both types of cavity represents about 23 % of the volume of the unit cell.^[17] Single crystals maintained at room temperature under vacuum overnight gave identical thermogravimetry MS curves to those obtained directly from solution, indicating that **1** is stable at ambient temperatures. However, thermogravimetry data also indicates that crystals of **1** are not stable to loss of guest because the pyridine ligands must be removed from the metal cluster to facilitate free release of guest molecules.

In summary, **1a** and **1b** exhibit an infinite 2D structure formed by the self-assembly of nSBUs that are formed by four square carboxylate-bridged di-metal(II) SBUs. Compounds **1a** and **1b** are curved as a result of the 120° angle subtended by the bdc ligands and that they may be considered to be supramolecular isomers^[18] of discrete polyhedra based upon molecular squares. The shape and chemical nature of the bowls in **1** resembles calixarenes and we are investigating the ability to incorporate guest molecules that are known to form complexes with calixarenes.^[19]

Experimental Section

$\{[Zn_2(1,3\text{-bdc})_2(\text{py})_2]_4\}_n$ (**1a**): A methanolic solution (20 mL) of $Zn(NO_3)_2 \cdot 6H_2O$ (1 mmol, 0.297 g) and benzene-1,3-dicarboxylic acid (1 mmol, 0.166 g) in the presence of pyridine (0.5 mL) and benzene (1 mL) was refluxed for about 30 mins. Slow cooling at room temperature afforded colorless crystalline plates of **1a**.

$\{[Cu_2(1,3\text{-bdc})_2(\text{py})_2]_4\}_n$ (**1b**): An ethanolic (10 mL) solution containing lutidine (0.90 mmol, 0.1 mL) was layered onto $Cu(NO_3)_2 \cdot 2.5H_2O$ (0.231 g, 1.0 mmol) and benzene-1,3-dicarboxylic acid (0.360 g, 2.2 mmol) in DMF (10 mL). Slow diffusion over several days yielded blue platelike crystals of **1b**. Single crystals of **1a** and **1b** were subjected to thermogravimetry–mass spectrometry (TG-MS) analysis on a TA Instruments 2950 TGA with N_2 as

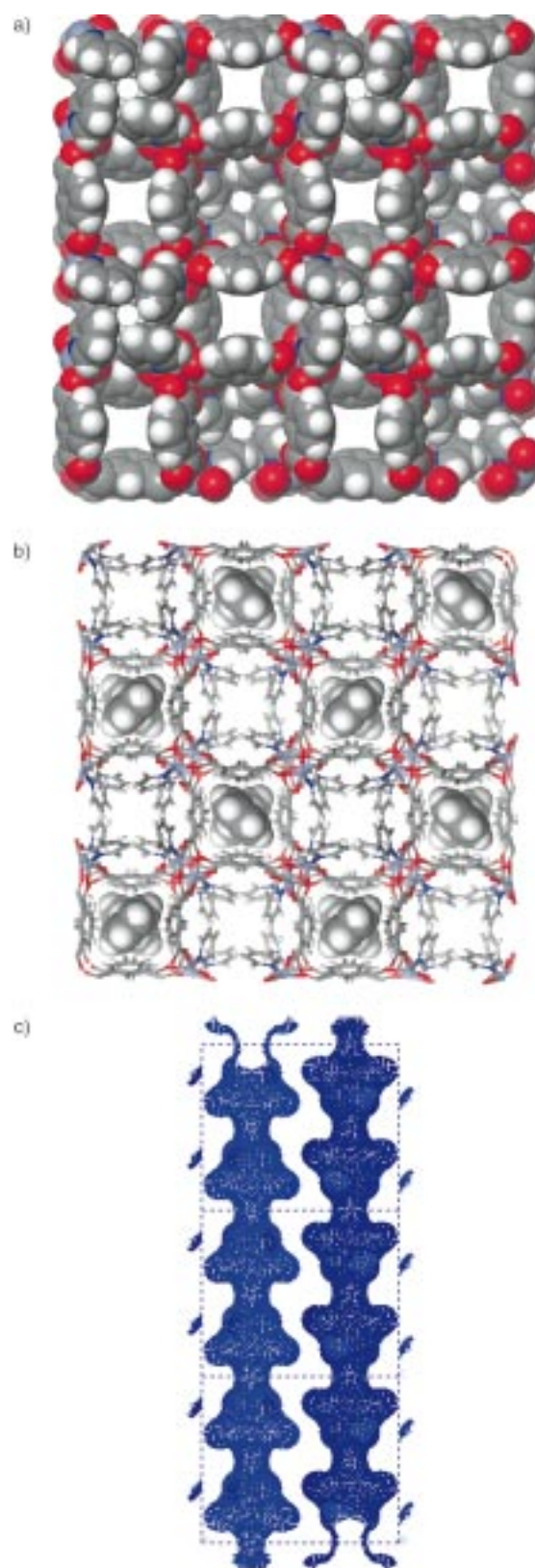


Figure 1. a) Space-filling diagram of the crystal structure of $\{[M_2(1,3\text{-bdc})_2(\text{py})_2]_4\}_n$. Guest molecules have been omitted for clarity. b) Structure of $\{[M_2(1,3\text{-bdc})_2(\text{py})_2]_4\}_n$ viewed along [001]. The guest molecules occupying the hour-glass channels are shown with van der Waals radii. Each bowl is also occupied by a benzene or pyridine guest, which has been omitted for clarity. c) Profile of the hour-glass shaped channels between adjacent bowls. The shaded area is the empty volume; guest molecules are located in the widest areas of the channels.

purge gas. The crystals are thermally stable to above 150 °C after which the TG curve shows a mass loss of about 33 % between 180 and 300 °C, which is consistent with and corresponds to the loss of benzene ($M^+ = 78$) and pyridine ($M^+ = 79$). Further heating leads to decomposition above 400 °C. The IR spectrum shows two strong peaks at 1635 cm^{-1} and 1446 cm^{-1} ; the difference between these peaks is 189 cm^{-1} as would be expected for bridging bidentate carboxylates.^[20]

Crystal data for **1a**: Tetragonal, $P4/ncc$, $a = 19.0356(9)$, $c = 16.253(1)$ Å, $V = 5889.3(6)$ Å³, $Z = 8$ (for $[\text{Zn}_2(1,3\text{-bdc})_2(\text{py})_2]$), $\rho_{\text{calc}} = 1.744$ g cm^{-3} , $\mu = 1.69$ mm⁻¹, $F(000) = 3168$, $2\theta_{\text{max}} = 50.1^\circ$. Crystal data for **1b**: Tetragonal, $P4/ncc$, $a = 18.7912(8)$, $c = 16.8886(10)$ Å, $V = 5963.5(8)$ Å³, $Z = 8$ (for $[\text{Cu}_2(1,3\text{-bdc})_2(\text{py})_2]$), $\rho_{\text{calc}} = 1.507$ g cm^{-3} , $\mu = 1.48$ mm⁻¹, $F(000) = 2750$, $2\theta_{\text{max}} = 56.54^\circ$. The data for **1a** and **1b** were collected at -100 °C on a Bruker SMART APEX diffractometer using $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å) and were corrected for Lorentz and polarization effects. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 .^[21] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms on the pyridine and bdc ligands were placed in geometrically calculated positions and refined with temperature factors 1.2 times those of their parent atoms. The guest molecules inside the bowl-shaped cavity were disordered in such a manner that they could not be readily resolved. Guest molecules in the hour-glass-shaped channels were better resolved, but it is not possible to differentiate between benzene and pyridine molecules in these channels. Guest atoms were therefore treated as carbon atoms and refined with fixed isotropic thermal parameters and variable site occupancy. Final residuals for **1a** were $R1 = 0.0372$ and $wR2 = 0.0958$ for 1782 reflections with $I > 2\sigma(I)$, and $R1 = 0.0591$, $wR2 = 0.1028$ for all 2625 data (181 parameters). Values for **1b** were $R1 = 0.0407$ and $wR2 = 0.1063$ for 2289 reflections with $I > 2\sigma(I)$, and $R1 = 0.0680$, $wR2 = 0.1139$ for all 3632 data. Residual electron density was 0.82 and -0.58 e Å⁻³ for **1a** and 0.96 and -0.87 e Å⁻³ for **1b**. 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-152547 and CCDC-162957. 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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Polygons and Faceted Polyhedra and Nanoporous Networks**

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Design principles that are based upon the concepts of crystal engineering and self-assembly have recently afforded new classes of crystalline solids that possess important physical properties such as bulk magnetism^[1, 2] or porosity.^[3–5] Furthermore, given that these structures are designed from first principles, they offer chemists an inherent ability to control the chemical nature of the molecular components and therefore influence the bulk physical properties of the material. Similar principles of self-assembly have been applied toward the design and isolation of nanosized spheroid architectures that are based upon regular (Platonic) and semiregular (Archimedean) polyhedral solids.^[6–13] However, there exist other well-documented examples of uniform polyhedra^[14, 15] that to our knowledge remain unexplored at the molecular level. In particular, there are nine polyhedra that are closely related to Platonic and Archimedean solids but differ in that they can be designed and built through linking of the vertices of polygons rather than the edges of polygons. Such structures are termed *faceted polyhedra*^[16] (Figure 1a) since they necessarily contain both open and closed faces. Of particular interest in the context of this study are those polyhedra that are sustained by triangles, squares, or combinations thereof.

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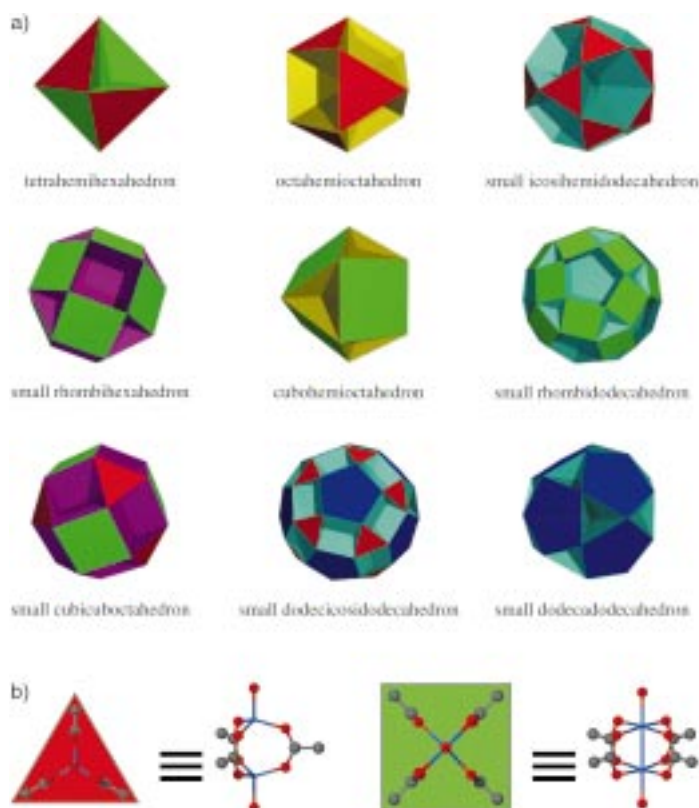


Figure 1. a) Schematic illustrations of the nine possible faceted polyhedra; throughout this contribution squares are color-coded green and triangles red. b) The secondary building units (SBUs) employed for the construction of faceted polyhedra in this study.

The molecular triangles and squares that we have targeted for study are the previously reported metal-organic secondary building units^[17] (SBUs) $M_2(RCO_2)_3$ (**A**) and $M_2(RCO_2)_4$ (**B**) (Figure 1b). It has already been demonstrated that use of polycarboxylate ligands in $M_2(RCO_2)_4$ (e.g. benzene-1,4-dicarboxylate) affords self-assembled infinite structures with predictable topology and relatively high thermal stability.^[18] It therefore occurred to us that complexation of the angular trifunctional ligand benzene-1,3,5-tricarboxylate (btc) with **A** and **B** should also afford predictable infinite networks. Indeed, complexation of btc with Zn^{II} affords two remarkable new structures that represent prototypes for porous structures that are based upon faceted uniform polyhedra.

Small cubicuboctahedra (1): The crystal structure of **1** (Figure 2) can be described as being composed of molecular squares (green) and triangles (red) that self-assemble into small cubicuboctahedra because two of the btc carboxylate moieties impose a 120° angle at the linkage between the polygons. There are eight triangular faces and six square faces and each square face is fused (i.e. shared) with the square face of an adjacent small cubicuboctahedron. The framework portion of **1** should therefore be formulated $\{[Zn_2(btc)]_8[Zn_2(btc)_{1.333}]_3\}_n$ or $(A_8B_3)_n$. The connectivity of the small cubicuboctahedra generates one of the other faceted polyhedra, an octahemiocuboctahedron (see Figure 1a). The framework exhibited is low density because the faceted polyhedra are inherently open (white squares and channels in schematic portion of Figure 2).

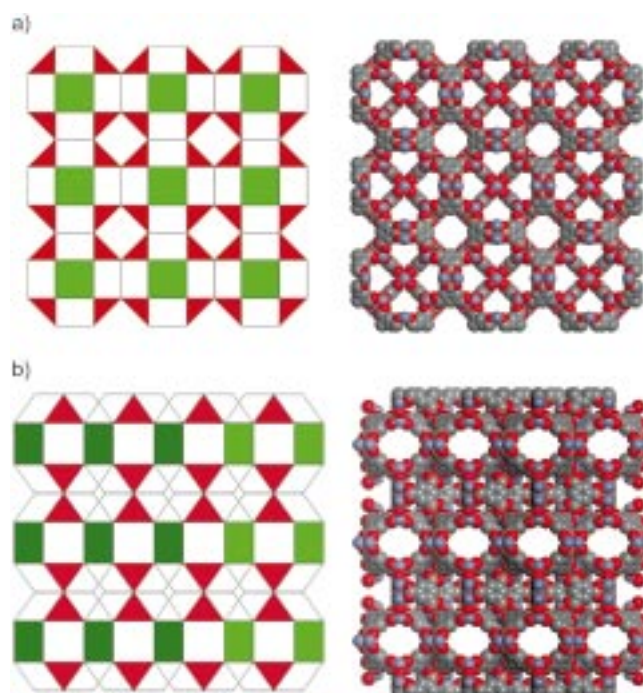


Figure 2. Crystal structure and schematic illustration of $\{[L_2Zn_2(btc)_1]_8[L_2XZn_2(btc)_{1.333}]_3\}_n$ (**1**; L = pyridine or water, X = NO_3^-). a) View along the [100] crystallographic plane and b) view along the [110] crystallographic plane. The schematics illustrate how these structures are generated by close packing and predict the openness of the observed crystal structure of **1**.

An aspect of uniform polyhedra that makes them desirable as nanoscale building blocks is that there is inherently a great deal of control concerning the framework geometries that they must adapt if they close-pack (tessellate). For example, for combinations of Platonic and Archimedean polyhedra, there exist only eleven possible space-filling infinite frameworks. However, there are even greater restrictions for faceted polyhedra since they must pack such that each polygon is connected only by its vertices and does not share its edges. Indeed, the possible close-packing modes for faceted polyhedra are restricted to only three related space-filling architectures (Figure 3a; see also Figure 1a): rhombicuboctahedra/cuboctahedra/cubes (1:1:3); rhombicuboctahedra/cubes/tetrahedra (1:1:2); cuboctahedra/octahedra (1:1). These structures have long-been documented^[19, 20] and correspond to self-assembly of triangles and squares or squares only. Indeed, Andreini^[21] and Wells^[22] have already discussed these networks in terms of the space group symmetry of the network edge-skeletons.

Since the small cubicuboctahedron in **1** has a congruent edge-skeleton with a rhombicuboctahedron (Figure 3b), it must adapt one of only two possible frameworks. Furthermore, only one of these frameworks can sustain vertex-only connected triangles and squares. It therefore follows that self-assembly of small cubicuboctahedra can result in only one framework, 3a. The structure of **1** therefore appears to be preordained and, furthermore, is clearly prototypal for other frameworks that might be formed from other molecular triangles and squares. The dimensions of the small cubicuboctahedron in **1** are the same as the unit cell dimensions, as

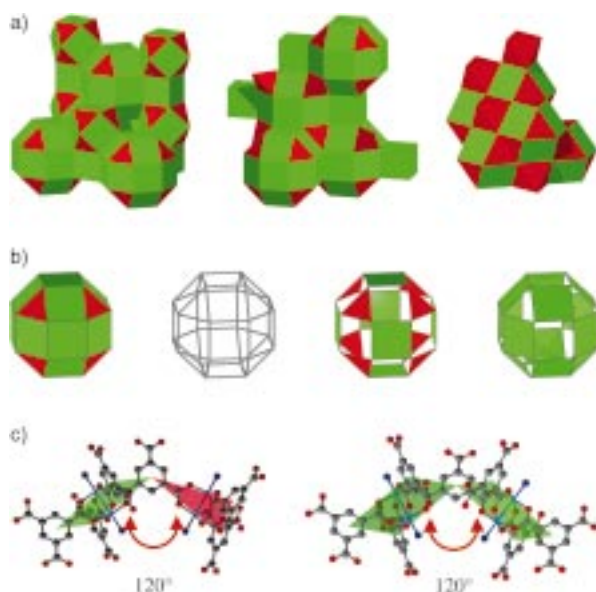


Figure 3. a) Schematic illustrations of the three uniform space fillings based upon Platonic and Archimedean polyhedra that are possible for faceted polyhedra. b) A schematic illustration of how the small cubicuboctahedron and the small rhombihexahedron have a congruent edge-skeleton with the rhombicuboctahedron. c) An illustration of how the vertices of the molecular squares and triangles are connected by the btc moieties.

there is only one small cubicuboctahedron per unit cell. The separation between opposite square faces is therefore 2.05 nm and the dimensions of the windows are about 0.9 nm. The overall structure contains channels and cavities that are entirely predictable based upon the dimensions of **A**, **B**, and btc. Notably, the dihedral angle imposed by the btc ligands (120°) is close to the ideal angle of $125^\circ 16'$ that would exist in a perfect small cubicuboctahedron (Figure 3c).

Small rhombihexahedra (2): The crystal structure of **2** (Figure 4) consists of small rhombihexahedra, which also have congruent edge-skeletons with the rhombicuboctahedron (Figure 3b) that are fused at the square faces. Once again, there is only one possible space-filling arrangement that generates a close-packed framework for these polyhedra, a structure that must be based upon squares alone, dihedral angles of 120° (Figure 3c), and the rhombicuboctahedron edge-skeleton: rhombicuboctahedra/cubes/tetrahedra (1:1:2), 4b. The small rhombihexahedron in **2** is slightly larger than the polyhedron seen in **1**. It has a diameter of 2.30 nm and the triangular windows have dimensions of about 0.9 nm. An isostructural analogue of **2** was recently reported by Williams et al., $[\text{L}_3\text{Cu}_3(\text{btc})_2]_n$, $\text{L} = \text{pyridine}$.^[23]

Single crystals of **1** and **2** are stable indefinitely when in contact with mother liquor. Weight losses of 7.2 and 8.2%, respectively, consistent with loss of methanol occur under ambient conditions (isothermal room-temperature thermogravimetric analysis (TGA)), and the samples remain crystalline as confirmed by single-crystal diffraction patterns that are consistent with the frameworks of **1** and **2**. Greater weight losses and irreversible decomposition occur upon heating and correspond to further loss of methanol and then loss of coordinated pyridine molecules (confirmed by TG-MS). The interconnectivity of the cavities in **1** and **2** is quite different

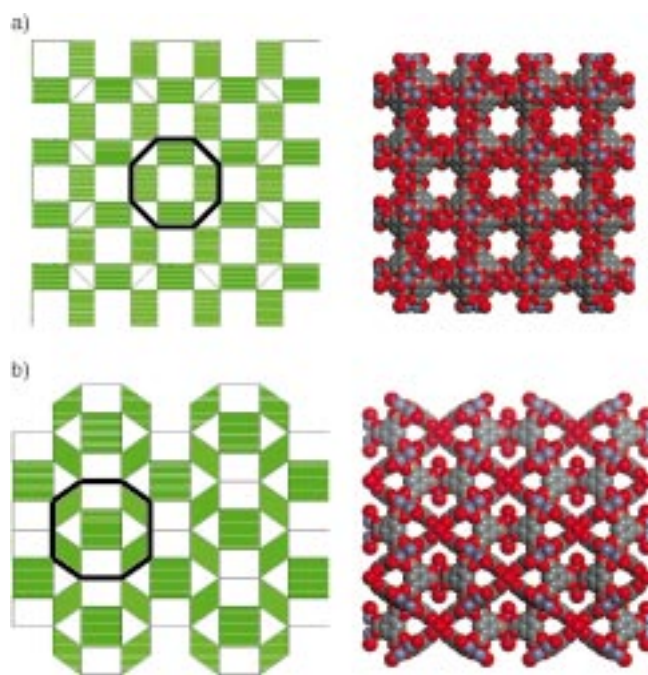


Figure 4. Crystal structure and schematic illustration of $[\text{L}_2\text{Zn}_2(\text{btc})_{1.333}]_{12n}$ (**2**; $\text{L} = \text{pyridine}$ or water). a) View along the [100] crystallographic plane and b) view along the [110] crystallographic plane. Note how the schematics predict the porosity observed in the crystal structure of **2**.

but the windows (0.9 nm) and free volume of the desolvated structures (calculated using Cerius² to be about 75.6 and 70.3% for **1** and **2**, respectively) are similar.

In summary, we have demonstrated that molecular polygons can self-assemble at their vertices to produce molecular architectures and crystal structures that are consistent with long-established geometric constraints. These structures therefore differ in terms of design and function from structures that are generated from Platonic and/or Archimedean building blocks. The strategy represents a potentially broad-ranging approach to the design of nanoporous structures from a wide range of chemical components that are based upon molecular shape rather than chemical formula. In effect, we present another example of the “Molecular Meccano”^[24] approach to self-assembled structures.

Experimental Section

1: A solution of $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (220 mg, 0.741 mmol) and 1,3,5-benzenetricarboxylic acid (220 mg, 1.05 mmol) in methanol (10 mL) was layered onto a solution of nitrobenzene (10 mL) containing pyridine (0.23 mL, 2.8 mmol). Large single crystals ($0.30 \times 0.30 \times 0.15$ mm) formed within hours under ambient conditions. Crystal data of **1**: $[\text{L}_2\text{Zn}_2(\text{btc})]_8[\text{XL}_2\text{Zn}_2(\text{btc})_{1.333}]_3$ ($\text{L} = \text{C}_5\text{H}_5\text{N}$ or H_2O , $\text{X} = \text{NO}_3^-$), $M_r = 5018.1$, cubic, $Pm\bar{3}m$, $a = b = c = 20.4582(13)$ Å, $V = 8562.5(9)$ Å³, $Z = 1$, $\rho_{\text{calcd}} = 0.973$ g cm⁻³, $2\theta_{\text{max}} = 37.7^\circ$ ($-18 \leq h \leq 15$, $-6 \leq k \leq 18$, $-18 \leq l \leq 18$), $T = 173$ K, 14454 measured reflections, $R_I = 0.1278$ for 510 reflections ($I > 2\sigma(I)$), $wR2 = 0.3648$ for 740 independent reflections (all data) and 104 parameters, $GOF = 1.559$.

2: A solution of $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (202 mg, 0.679 mmol) and 1,3,5-benzenetricarboxylic acid (126 mg, 0.600 mmol) in methanol (10 mL) was layered onto a solution of benzene (10 mL) containing pyridine (0.10 mL; 1.24 mmol). Large single crystals ($0.30 \times 0.25 \times 0.20$ mm) formed within hours under ambient conditions. Crystal data of **2**: $[\text{L}_2\text{Zn}_2(\text{btc})_{1.333}]_{12n}$ ($\text{L} =$

C₃H₅N or H₂O), $M_r = 7084.54$, cubic, $Fm\bar{3}m$, $a = b = c = 26.5200(13)$ Å, $V = 18651.8(16)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.261$ g cm⁻³, $2\theta_{\text{max}} = 50.0^\circ$ ($-31 \leq h \leq 31$, $-31 \leq k \leq 18$, $-28 \leq l \leq 31$), $T = 173$ K, 22842 measured reflections, $RI = 0.0602$ for 670 reflections ($I > 2\sigma(I)$), $wR2 = 0.1840$ for 891 independent reflections (all data) and 63 parameters, $GOF = 0.990$.

Data were collected on a Bruker SMART-APEX CCD diffractometer using MoK α radiation ($\lambda = 0.71073$ Å), operating in the Ω and φ scan mode. All crystal data were corrected for Lorentz and polarization effects, and the SADABS^[25] program was used for absorption correction. The structures were solved by direct methods and the structure solutions and refinements were based on $|F^2|$. All non-hydrogen atoms were refined with anisotropic displacement parameters, whereas hydrogen atoms were placed in calculated positions and given isotropic U values 20% higher than the atom to which they are bonded. All crystallographic calculations were conducted with the SHELXTL^[26] software suite. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-156776 (1) and CCDC-156777 (2). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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A Rationally Designed NH₄⁺ Receptor Based on Cation– π Interaction and Hydrogen Bonding**

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Design and synthesis of ammonium ion receptors have received much attention, not only because ammonium binding is one of the fundamental problems of molecular recognition, but also because such receptors serve as an essential component of sensors used in clinical^[1] and environmental analyses.^[2] Most of the NH₄⁺ receptors known to date harness hydrogen bonding in binding an ammonium ion.^[3] For example, nonactin (see Scheme 1), a natural antibiotic agent and one of the most effective NH₄⁺ receptors, utilizes four ethereal and four carbonyl oxygen atoms to bind NH₄⁺ through hydrogen bonding.^[4] While hydrogen bonding is most commonly involved in molecular recognition, cation– π interaction has drawn much attention in recent years.^[5] In fact, cation– π interaction has been successfully employed in designing synthetic receptors for alkylammonium ions and alkali metal ions.^[5, 6] Despite extensive theoretical studies on NH₄⁺– π interaction, however, no synthetic NH₄⁺ receptor exploiting cation– π interaction had been reported until recently. We recently reported a novel NH₄⁺ receptor based on tris(pyrazol-1-ylmethyl)benzene that is highly selective for binding NH₄⁺ over alkali metal ions.^[7] Subsequent theoretical studies on this receptor by us^[8] and others^[9] suggest that the cation– π interaction between the substrate and the central benzene ring of the receptor plays a significant role in the binding affinity and selectivity of the tripodal receptor toward NH₄⁺. Despite the high selectivity, however, the ion-selective electrode (ISE) based on this receptor shows low sensitivity and strong pH dependence of its performance in comparison to a nonactin-based ISE, and this hampers practical applications as a sensor. Here we present a rationally designed cage-type NH₄⁺ receptor that binds the cation by both cation– π interaction and hydrogen bonding, with high sensitivity and selectivity comparable or superior to those of nonactin over a wide range of pH.

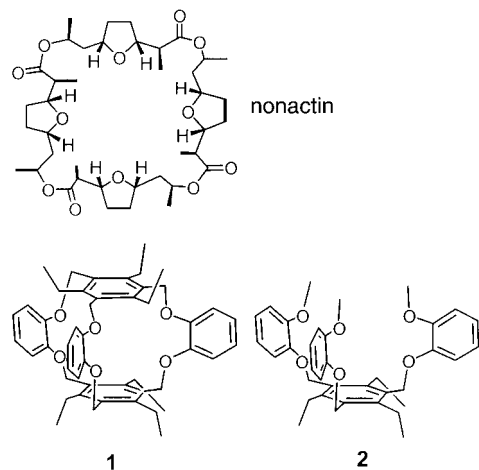
In designing the receptor, we considered the following stereoelectronic features: 1) spatial distribution of lone-pair

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electrons for effective hydrogen bonding with the tetrahedral NH_4^+ ion, 2) benzene rings ideally positioned for strong cation- π interaction, and 3) a rigid framework with a cavity of correct size for binding NH_4^+ . With this in mind, we designed receptor **1** in which two benzene rings are rigidly held together by three dialkoxybenzene units (Scheme 1). We chose phenolic oxygen atoms as



Scheme 1. Chemical structures of the ammonium receptors discussed here.

hydrogen bonding acceptors because their $\text{p}K_{\text{a}}$ values are larger than those of nitrogen atoms, and thus we can lower the pH dependence of the receptor performance. Molecular mechanics calculations^[10] on **1** and its NH_4^+ complex showed that each dialkoxybenzene unit is almost ideally positioned to “bite” NH_4^+ through hydrogen bonding, while the two benzene rings are properly positioned at the top and bottom of the cage for cation- π interaction with NH_4^+ , with an $\text{N} \cdots$ benzene centroid distance of about 3.0 Å. In addition, the cavity size of **1** is perfect for NH_4^+ but too large for smaller ions such as Li^+ and Na^+ .

Receptor **1** is easily synthesized from the reaction of catechol with 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene^[11] in two steps in good yield. The X-ray crystal structures^[12] of **1** (see Supporting Information) and its NH_4^+ complex $[\mathbf{1}\text{-NH}_4]\text{PF}_6$ (Figure 1) are in good agreement with those calculated by molecular modeling. These structures reveal that the only significant structural change in the receptor associated with NH_4^+ binding is that the mean distance between the two benzene rings increases from 5.588 to 5.966 Å. In $[\mathbf{1}\text{-NH}_4]\text{PF}_6$, as expected, the NH_4^+ ion is located at the center of the receptor and forms hydrogen bonds with six oxygen atoms. A set of oxygen atoms (O2, O2A, and O2B) interacts with the NH_4^+ ion with $\text{O} \cdots \text{N}$ distances of 3.224(5) Å and $\text{N-H} \cdots \text{O}$ angles of 168(12)°, whereas the other set (O1, O1A, and O1B) has $\text{O} \cdots \text{N}$ distances of 3.226(5) Å and $\text{N-H} \cdots \text{O}$ angles of 122(7)°.^[13] The average distance between the nitrogen atom of NH_4^+ and the center of the top or bottom benzene ring is 2.985 Å, which is in good agreement with the optimal distance for cation- π interaction between NH_4^+ and benzene suggested by theoretical studies.^[5, 14] The PF_6^- counterion is located outside the cage with no apparent interactions.

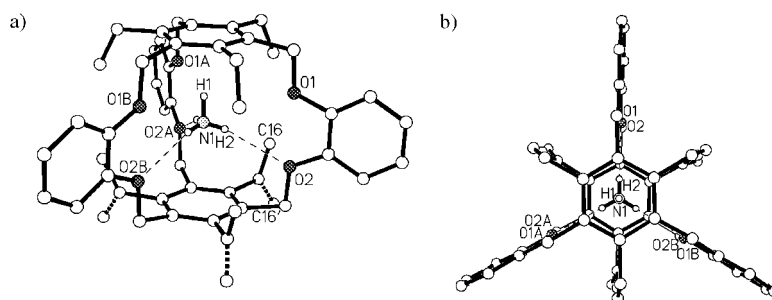


Figure 1. a) Side and b) top views of $[\mathbf{1}\text{-NH}_4]\text{PF}_6$ in the solid state. Hydrogen atoms (except for those of NH_4^+) and the PF_6^- counterion are omitted for clarity. The ethyl groups of the “bottom” benzene ring are disordered over two sites (occupancy: C16 0.64, C16' 0.36). Selected interatomic distances [Å] and angles [°]: $\text{O1} \cdots \text{N1}$ 3.226(5), $\text{N1-H2} \cdots \text{O1}$ 122(7), $\text{O2} \cdots \text{N1}$ 3.224(5), $\text{N1-H2} \cdots \text{O2}$ 168(12), centroid of “top” benzene $\cdots \text{N1}$ 2.991, centroid of “bottom” benzene $\cdots \text{N1}$ 2.980.

The performance of an ISE based on **1**^[15] is comparable or even superior to that of a nonactin-based ISE in terms of sensitivity and selectivity (Figure 2): detection limit $3.2 \times 10^{-6} \text{ M}$ (**1**) versus $1.5 \times 10^{-6} \text{ M}$ (nonactin); selectivity coefficients $\lg K_{\text{NH}_4^+/\text{K}^+} = -0.97$ (**1**) versus -0.88 (nonactin), and $\lg K_{\text{NH}_4^+/\text{Na}^+} = -3.00$ (**1**) versus -2.85 (nonactin). Furthermore, it displays only a small pH dependence (see Supporting Information) which is also comparable to that of the nonactin-based ISE.

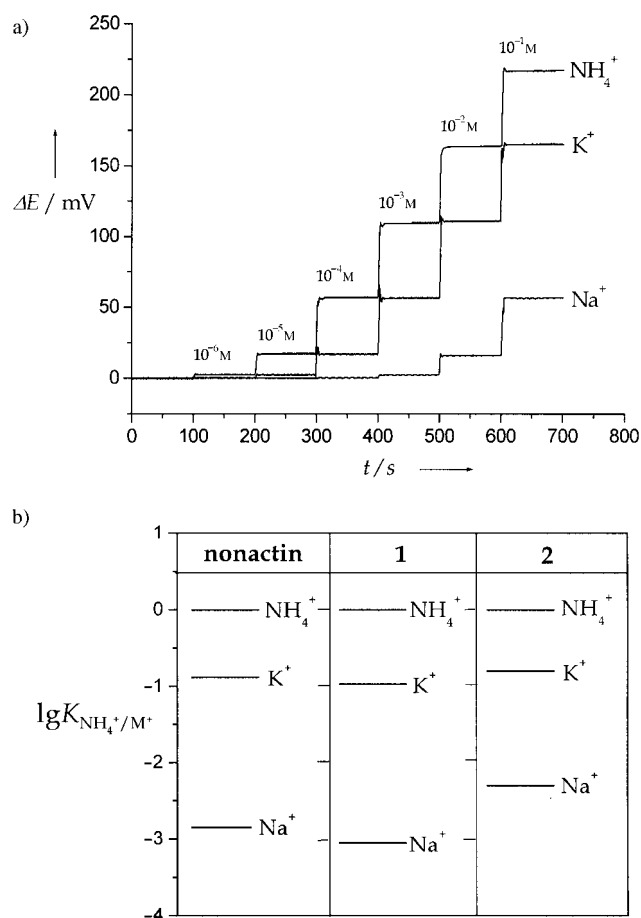


Figure 2. Responses of ISEs to NH_4^+ , K^+ , and Na^+ (background electrolyte: 0.05 M Tris-HCl, pH 7.2). a) Responses of an ISE based on **1**. b) Selectivity coefficients of ISEs based on nonactin, **1**, and **2**.

To understand the role of cation– π interaction in **1** in binding NH_4^+ , we synthesized the modified receptor **2**, which does not have the “top” benzene ring (see Scheme 1). As expected, the binding affinity of **1** toward NH_4^+ is at least ten times higher than that of **2**: the association constants for binding of NH_4^+ to **1** and **2**, determined by the extraction method,^[16] are 3.3×10^7 and $1.9 \times 10^6 \text{ M}^{-1}$, respectively.^[17] This difference in binding affinity was also confirmed by a theoretical study. A gas-phase calculation^[18] showed that the binding energies $-E_{\text{BSSE}}$ of **1** and **2** for NH_4^+ are 62.3 and 58.2 kcal mol⁻¹, respectively. The difference in binding energy between the two receptors (4.1 kcal mol⁻¹) is in reasonable agreement with the experimental value (ca. 1.7 kcal mol⁻¹)^[19] calculated from the association constants if we consider solvation effects.^[5, 20] These experimental and theoretical studies support a prominent role of cation– π interaction in the recognition of NH_4^+ by **1**.

In conclusion, we have presented a rationally designed cage-type receptor that binds NH_4^+ by cation– π interaction and hydrogen bonding, with high sensitivity and selectivity comparable or even superior to those of nonactin over a wide range of pH. In particular, this work demonstrates that an appropriate combination of hydrogen bonding and cation– π interaction can produce a large synergic effect in recognizing NH_4^+ . The high performance, low cost, and easy synthesis may warrant practical applications of this receptor as an ammonium ion sensor.

Experimental Section

1: A solution of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (58 mg, 0.13 mmol) and 1,3,5-tris[(2-methoxyphenoxy)methyl]-2,4,6-triethylbenzene (69 mg, 0.13 mmol) in DMF (26 mL) was added to a suspension of K_2CO_3 (109 mg, 0.79 mmol) and [18]crown-6 (7 mg, 0.026 mmol) in DMF (6 mL) at 85 °C over 12 h. The resulting mixture was stirred for an additional 4 h and then cooled to room temperature. After addition of water and chloroform to the mixture, the aqueous layer was separated and extracted twice with chloroform. The combined organic layers were concentrated and purified by chromatography on silica to afford **1** (43 mg, 46 %). ¹H NMR (CDCl_3): δ = 6.92 (s, 2H), 4.96 (s, 2H), 2.60 (q, 2H), 1.03 (t, 3H); ¹³C NMR (CDCl_3): δ = 149.6, 145.6, 131.8, 120.2, 111.1, 63.9, 23.1, 16.6; MS (FAB): m/z : 727.3 [M^+]; satisfactory elemental analysis (C, H).

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Macrocycles within Macrocycles: Cyclen, Cyclam, and Their Transition Metal Complexes Encapsulated in Cucurbit[8]uril**

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Dedicated to Professor Eiichi Kimura on the occasion of his retirement

Inclusion of a macrocycle in a macrocycle, reminiscent of Russian Matryoshka dolls, is a rare phenomenon, although inclusion of crown ethers, cryptands, and their alkali metal complexes inside the cavity of γ -cyclodextrin has been known for many years.^[1] Recently, the encapsulation of cryptands, crown ethers, and their alkali metal complexes in supramolecular capsules and cages held together by hydrogen bonds and coordination bonds, respectively, has also been reported.^[2, 3] However, few examples of the inclusion of transition metal macrocyclic complexes in synthetic molecular or supramolecular host systems are available in the literature^[4] even though such systems are potentially useful as catalysts with high specificity as a result of the unique microenvironment around the transition metal ion which is reminiscent of metalloenzymes.

Cucurbituril (CB[6]), a macrocycle comprising six glycoluril units, forms stable host–guest complexes with small

molecules, such as aliphatic and aromatic amines.^[5] Our recent discovery^[6] of new cucurbituril homologues, cucurbit-[*n*]uril (CB[*n*]; *n* = 5, 7, and 8), containing five, seven, and eight glycoluril units has opened up new opportunities to expand the host–guest chemistry of cucurbituril. For example, the largest member of the cucurbituril family, CB[8], has a cavity comparable to that of γ -cyclodextrin and can accommodate two aromatic guest molecules to form 1:2 host–guest complexes,^[6] or 1:1:1 ternary complexes.^[7] The large cavity prompted us to explore the inclusion of macrocycles and their transition metal complexes in CB[8]. Of the many potential candidates for the guest macrocycles we chose tetraazamacrocycles, not only because they are effective hosts for transition metal ions^[8] but also because their transition metal complexes exhibit catalytic activities in many reactions, such as epoxidation and DNA hydrolysis.^[9] Here we present novel macrocycles within macrocycles, in which cyclen (1,4,7,10-tetraazacyclododecane), cyclam (1,4,8,11-tetraazacyclotetradecane), and their transition metal complexes are encapsulated in CB[8].^[10]

Heating an aqueous solution of CB[8] and cyclen tetrahydrochloride at 100 °C for 2 h, followed by slow cooling to room temperature produces colorless crystals of complex **1a**. The ¹H NMR spectrum of **1a** in D₂O reveals a shift of the cyclen signal to higher field relative to that of free cyclen, which is consistent with the formation of a 1:1 host–guest complex of CB[8], and cyclen.^[11] The X-ray crystal structure of **1a** (Figure 1) confirms the encapsulation of a fully protonated cyclen macrocycle in the cavity of CB[8] with four Cl[−] counterions residing outside CB[8]. The inner macrocycle is significantly tilted with respect to the outer macrocycle: the angle between the average planes of the inner

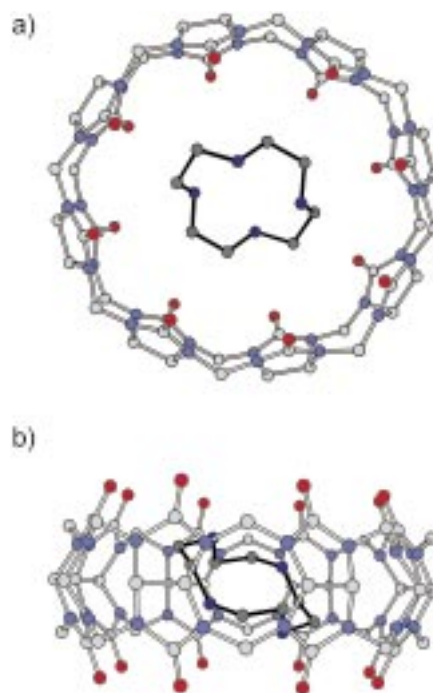


Figure 1. X-ray crystal structure of **1a**: a) top view and b) side view. Color code: oxygen: red, nitrogen: blue, carbon: gray. Hydrogen atoms, counterions (Cl[−]), and solvent (H₂O) molecules are omitted for clarity.

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and outer ones is about 38° . The crystal structure indicates that the van der Waals interactions between the inner macrocycle and the inside wall of the outer macrocycles are mostly responsible for the stability of complex **1a**. A 1:1 inclusion complex of cyclam in CB[8] (**1b**) was also obtained by the same procedure and fully characterized. The X-ray crystal structure of **1b** (see Supporting Information) reveals that the encapsulated cyclam is even more tilted with respect to CB[8] with an angle between the average planes of the inner and outer macrocycles of approximately 59° . Presumably, the larger ring size of cyclam forces it to adopt the more tilted orientation in the cavity of CB[8] in complex **1b**.

The inner macrocycles in **1a** and **1b** can be metalated. For example, heating an aqueous solution of **1a** (or **1b**) with an excess of $\text{Cu}(\text{NO}_3)_2$ at 100°C for 2 h, followed by slow cooling to room temperature produces deep blue crystals of complex **2a** (or purple crystals of complex **2b**) in which a Cu^{II} ion is coordinated by cyclen (or cyclam) encapsulated in CB[8]. Similarly, a Zn^{II} ion can be introduced into the inner macrocycles. The structure of **2a** was determined by X-ray crystallography (Figure 2) and confirms the presence of

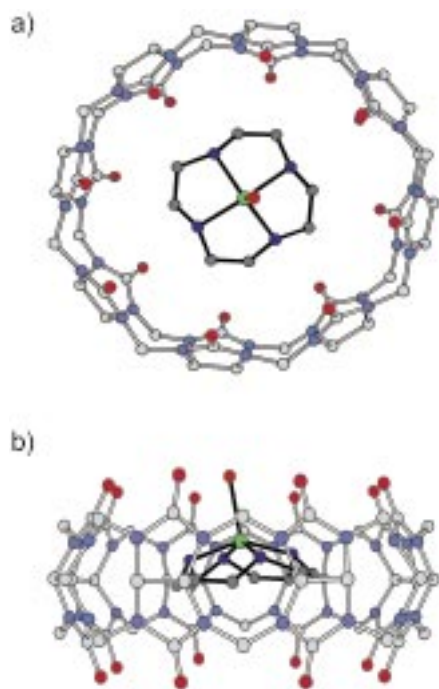


Figure 2. X-ray crystal structure of **2a**: a) top view and b) side view. Color code: copper: green, oxygen: red, nitrogen: blue, carbon: gray. Hydrogen atoms, counterions (NO_3^-), and solvent (H_2O) molecules are omitted for clarity. The $[\text{Cu}(\text{cyclen})(\text{H}_2\text{O})]$ unit is disordered over two sites as a result of a crystallographic inversion center at the middle of the CB[8] host. Only one orientation is depicted.

$[\text{Cu}(\text{cyclen})(\text{H}_2\text{O})]^{2+}$ in the cavity of CB[8]. The crystallographic inversion center at the middle of the CB[8] host results in the encapsulated metal complex being disordered over two sites. The complex contains a five-coordinate Cu^{II} ion in a square-pyramidal environment, with the Cu ion being $0.652(10)$ Å above the average plane of the four N atoms of cyclen, and with the Cu–N bond lengths ranging from $2.040(2)$ to $2.220(2)$ Å. A water molecule is bound to the axial position

of the copper ion (Cu–O bond length: $2.010(8)$ Å) while slightly tilted toward one side of the portal of CB[8]. In contrast to **1a**, the inner macrocycle in **2a** is almost parallel to the outer macrocycle, with an angle between their average planes of about 4° . It is interesting to note that attempts to introduce $[\text{M}(\text{cyclen})]$ ($\text{M} = \text{Cu}^{\text{II}}$ or Zn^{II}) into CB[8] have failed even under forcing conditions. Presumably, the increased conformational rigidity of the macrocycle upon metalation hinders its inclusion in the cavity of CB[8].

Cyclic voltammetry was performed on free $[\text{Cu}(\text{cyclen})(\text{NO}_3)_2]$ and **2a** in order to understand the effect of encapsulation in CB[8] on the redox properties of metal macrocyclic complexes. Free $[\text{Cu}(\text{cyclen})(\text{NO}_3)_2]$ undergoes a reversible, one-electron reduction at -0.85 V (versus SCE), which corresponds to the reduction of Cu^{II} to Cu^{I} . For **2a**, however, the same redox couple is observed at -0.72 V (versus SCE) with a large separation (ca. 0.24 V) between the cathodic and anodic peaks. This result suggests that the encapsulation of $[\text{Cu}(\text{cyclen})]$ in CB[8] increases the stability of the Cu^{I} state, but considerably slows down the electron transfer between the electrode and the redox center. Similar behaviors have been observed in the direct electrochemistry of metalloproteins in which redox centers are embedded in protein coats.^[12]

The aqua ligand in **2a** can be replaced by other ligands, such as ammonia and imidazole. For example, treatment of a solution containing **2a** with ammonia gas results in an instant color change of the solution: the absorption band corresponding to the d–d transition shifts from 600 to 650 nm. A similar change in the visible spectrum is observed when the solution is treated with excess imidazole. The spectral change is caused by the replacement of the aqua ligand with ammonia or imidazole; this has been confirmed by a preliminary X-ray diffraction study.^[13] Further studies on the ligand exchange are in progress.

In summary, we have synthesized and fully characterized novel macrocycles within macrocycles. The host–guest chemistry presented here involves multiple complexation events: a macrocycle is first encapsulated by the CB[8] host, and a transition metal ion is subsequently introduced into the inner macrocycle. These transition metal macrocyclic complexes with the exchangeable axial ligand within CB[8] may serve as biomimetic systems for the binding, activation, and catalytic transformation of specific substrates.

Experimental Section

1a: CB[8] (100.0 mg, 59.4 μmol) and cyclen·4HCl (120.0 mg, 6.3 equiv) were dissolved in distilled water (10.0 mL) and heated at 100°C for 2 h. Slow cooling of the solution to room temperature produced colorless crystals of **1a** (82.0 mg, 73 %). ^1H NMR (500 MHz, D_2O): $\delta = 2.55$ (s, 16H), 4.31 (d, 16H), 5.62 (s, 16H), 5.82 (d, 16H); ^{13}C NMR (125 MHz, D_2O): $\delta = 43.92$, 54.20, 72.45, 157.20; ESI-MS: m/z : 751.31 $[\text{M}+2\text{H}]^{2+}$, 1501.42 $[\text{M}+\text{H}]^+$. Elemental analysis calcd for $[(\text{C}_{48}\text{H}_{48}\text{N}_{32}\text{O}_{16})(\text{C}_8\text{H}_{20}\text{N}_4)] \cdot 4\text{HCl} \cdot 13\text{H}_2\text{O}$: C 35.75, H 5.25, N 26.80; found: C 35.89, H 5.51, N 26.81.

2a: An aqueous solution of **1a** (30.0 mg, 15.9 μmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (30.0 mg, 6.3 equiv) was heated at 100°C for 2 h. Slow cooling of the mixture to room temperature produced deep blue crystals of **2a** (26.8 mg, 83 %). ESI-MS: m/z : 782.77 $[\text{M} - \text{H}_2\text{O}]^{2+}$. Elemental analysis calcd for $[(\text{C}_{48}\text{H}_{48}\text{N}_{32}\text{O}_{16})(\text{CuC}_8\text{H}_{20}\text{N}_4)(\text{H}_2\text{O})] \cdot 2\text{NO}_3 \cdot 19\text{H}_2\text{O}$: C 33.11, H 5.26, N 26.20; found: C 32.98, H 5.00, N 25.99.

Crystal data for **1a**: $[(C_{48}H_{48}N_{32}O_{16})(C_8H_{20}N_4)] \cdot 4HCl \cdot 19.67H_2O$, $M_r = 2001.50$, rhombohedral, space group $R\bar{3}$ (No. 148), $a = b = 29.1533(10)$, $c = 26.7471(13)$ Å, $V = 19687.1(14)$ Å³, $Z = 9$, $\rho_{\text{calc}} = 1.519$ g cm⁻³, $T = 188$ K, Siemens SMART CCD diffractometer, MoK_{α} ($\lambda = 0.71073$), $\mu = 2.42$ cm⁻¹. The structure was solved by the Patterson method (SHELXS-86). All non-hydrogen atoms were refined anisotropically (SHELXL-93). Final block-diagonal matrix least-squares refinement on F^2 with all 6967 reflections and 628 variables converged to $R1$ ($I > 2\sigma(I)$) = 0.0923, $wR2$ (all data) = 0.2737, and GOF = 1.068. Crystal data for **1b**: $[(C_{48}H_{48}N_{32}O_{16})(C_{10}H_{24}N_4)] \cdot 4HCl \cdot 18H_2O$, $M_r = 1999.64$, rhombohedral, space group $R\bar{3}$ (No. 148), $a = b = 29.3372(7)$, $c = 26.6945(10)$ Å, $V = 19897.1(10)$ Å³, $Z = 9$, $\rho_{\text{calc}} = 1.502$ g cm⁻³, $T = 213$ K, $\mu = 2.38$ cm⁻¹. $R1$ ($I > 2\sigma(I)$) = 0.1005, $wR2$ (all data) = 0.2957, and GOF = 1.088. Crystal data of **2a**: $[(C_{48}H_{48}N_{32}O_{16})(Cu_8H_{20}N_4)(H_2O)] \cdot 2NO_3 \cdot 16H_2O$, $M_r = 1995.30$, rhombohedral, space group $R\bar{3}$ (No. 148), $a = b = 29.8575(3)$, $c = 24.8758(4)$ Å, $V = 19205.0(4)$ Å³, $Z = 9$, $\rho_{\text{calc}} = 1.553$ g cm⁻³, $T = 188$ K, $\mu = 3.70$ cm⁻¹. $R1$ ($I > 2\sigma(I)$) = 0.1015, $wR2$ (all data) = 0.3134, and GOF = 1.063. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-156566 (**1a**), -156567 (**1b**), and -156568 (**2a**). 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 Perfluorinated Nanosphere: Synthesis and Structure of Perfluoro-deca-*B*-methyl-*para*-carborane**

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In the early stages of the chemistry of polyhedral boranes the direct, exhaustive halogenation of *closo*-boranes and carboranes was one of the first reactions studied in detail.^[1] The most challenging endeavor in this context, their perfluorination, led to the synthesis of B₁₂F₁₂²⁻,^[2] 1,2-(H)₂-1,2-C₂B₁₀F₁₀,^[3] 1,7-C₂B₁₀F₁₂,^[3,4] and 1,12-(H)₂-1,12-C₂B₁₀F₁₀.^[3] While the existence of B₁₂F₁₂²⁻ was never confirmed,^[5] all three carborane fluorides can be isolated and 1,12-(H)₂-1,12-C₂B₁₀F₁₀ can even be handled in the presence of moist air. In aqueous media however, they hydrolyze to form boric acid as the final product.^[3] The recently reported anion 1-HCB₁₁F₁₁⁻ has been shown to undergo the nucleophilic substitution at the B-F moieties by OH⁻ as well, but under basic aqueous conditions.^[6]

History repeated itself with the discovery of C₆₀.^[7] Shortly thereafter its exhaustive fluorination was intensively investigated^[8] and it is now widely accepted that C₆₀F₄₈ is the most fluorine-rich fullerene which can be isolated.^[9] However, C₆₀F₄₈ is metastable in solution, decomposing according to the reaction C₆₀F₄₈ → C₆₀F₃₆ + 6F₂,^[10] and hydrolyzing rapidly in aqueous media.^[11] The idea of a chemically resistant "fluorinated ball" based on C₆₀ was further pursued through its perfluoroalkylation.^[12] Up to 14 perfluoroalkyl addends (R_f) (R_f = CF₃, C₂F₅, C₃F₇, C₆F₁₅) can be added to C₆₀, about half the number needed to achieve a perfluorinated surface. Solutions of the mixtures of C₆₀(R_f)_nH_m have been shown to be resistant to acids and bases.^[12]

The generation of a neutral perfluorinated nanosphere by replacement of all H atoms of per-*B*-methylated carboranes by fluorine appeared to us to be a feasible goal. Previously, the radical chlorination of 1,12-(H)₂-1,12-C₂B₁₀Me₁₀ (**1**), yielding 1,12-(H)₂-1,12-C₂B₁₀(CHCl₂)₁₀,^[13] as well as the synthesis of the 1-hydroxymethyl-2-hydroxyimino derivative of **1**^[14] demonstrated the viability of radical reactions to transform the methyl substituents of camouflaged species such as **1**, leaving

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the underlying B–B framework intact. In fact, the explosive “inert” anion $1\text{-CB}_{11}(\text{CF}_3)_{12}^-$ was synthesized starting from the permethylated anion $1\text{-CB}_{11}(\text{CH}_3)_{12}^-$ by using F_2 and K_2NiF_6 as fluorination reagents.^[15] This report cited our preliminary results on the fluorination of **1**^[16] and its 1,12-dimethyl derivative 1,12- $\text{C}_2\text{B}_{10}\text{Me}_{12}$ (**2**).^[16a]

Initially, the fluorination of **2** was studied, and it was found that at 25 °C using various F_2/N_2 (10–100 % F_2) concentrations only partial fluorination occurred to yield 1,12- $\text{C}_2\text{B}_{10}\text{C}_{12}\text{H}_n\text{F}_{36-n}$ ($n=3-6$). At a reaction temperature of 60 °C the formation of the desired 1,12- $\text{C}_2\text{B}_{10}(\text{CF}_3)_{12}$ (**3**) was observed. However, under these conditions partial disruption of the C–C bonds of **2** also led to the formation of 1- CF_3 -12-F-1,12- $\text{C}_2\text{B}_{10}(\text{CF}_3)_{10}$ (**4**) and 1,12-(F) $_2$ -1,12- $\text{C}_2\text{B}_{10}(\text{CF}_3)_{10}$ (**5**). Under no conditions examined did compound **3** form without the concomitant formation of **4** and **5**. All attempts to separate compounds **3–5** were unsuccessful.

Fluorination of **1** was initially conducted at low temperature (<35 °C) using various F_2/N_2 concentrations with the goal of 1,12 C–H retention. However, under the varied reaction conditions employed only mixtures of **5**, 1,12-(H) $_2$ -1,12- $\text{C}_2\text{B}_{10}(\text{CF}_3)_{10}$ (**6**), and 1-H-12-F-1,12- $\text{C}_2\text{B}_{10}(\text{CF}_3)_{10}$ (**7**) were obtained in ratios which depended on the reaction temperature and time. Attempts to separate compounds **5–7** from each other by gradient sublimation^[17] or column chromatography were unsuccessful. Single crystals of 1-H-12-X-1,12- $\text{C}_2\text{B}_{10}(\text{CF}_3)_{10}$ (X = 92 % H, 8 % F) (**8**), obtained from sublimation, were suitable for an X-ray diffraction study.^[18] The refined structure revealed that all methyl groups were converted into CF_3 groups.

Fluorination of **1** at elevated temperatures (>35 °C) using a high F_2 to N_2 ratio (1:3) for 14 days provided **5** in quantitative yield. Product formation was monitored by both mass spectrometry and ^{11}B NMR analysis. Compound **5** is a colorless solid that sublimates at 65 °C/0.01 mmHg to give colorless crystals. It has a melting point of 186 °C (sealed tube) and the molten compound remains colorless and inert up to 300 °C. In contrast to $1\text{-CB}_{11}(\text{CF}_3)_{12}^-$, **5** does not detonate on percussion.^[17] It is sparingly soluble in all common organic solvents, does neither hydrolyze in the presence of H_2O and nor oxidize on air. In acidic medium ($\text{CH}_2\text{Cl}_2/\text{CF}_3\text{COOH}$) **5** remains unchanged, whereas under basic conditions ($\text{CH}_2\text{Cl}_2/\text{NEt}_3$) it slowly decomposes. The ^{11}B NMR spectrum reveals that deboronation occurs initially to produce *nido* species which finally decompose to borates. The nature of the decomposition products has not yet been determined. The ^{19}F NMR spectrum of **5** shows a signal for the F atoms of its C–F vertices at $\delta = -157.5$ comparable with the shifts of the ^{19}F NMR resonance signals observed for $\text{BF}_3 \cdot \text{THF}$ ^[19] ($\delta = -155.7$) or the *para*-F atom in *trans*- $\text{C}_6\text{F}_5\text{CH}=\text{CHCl}$ ($\delta = -155.3$).^[20] Single crystals of **5** were obtained by the slow evaporation of a solution of **5** in toluene and Freon 113. The structure of **5** determined by X-ray analysis^[21] is shown in Figure 1. It represents the first structurally characterized perfluorinated icosahedral borane derivative.

Compound **5** crystallizes in the triclinic space group $P\bar{1}$ with one carborane per unit cell. Each molecule of **5** occupies a crystallographic inversion center. There are no unusually short intermolecular contacts. The C_2B_{10} core is indistinguish-

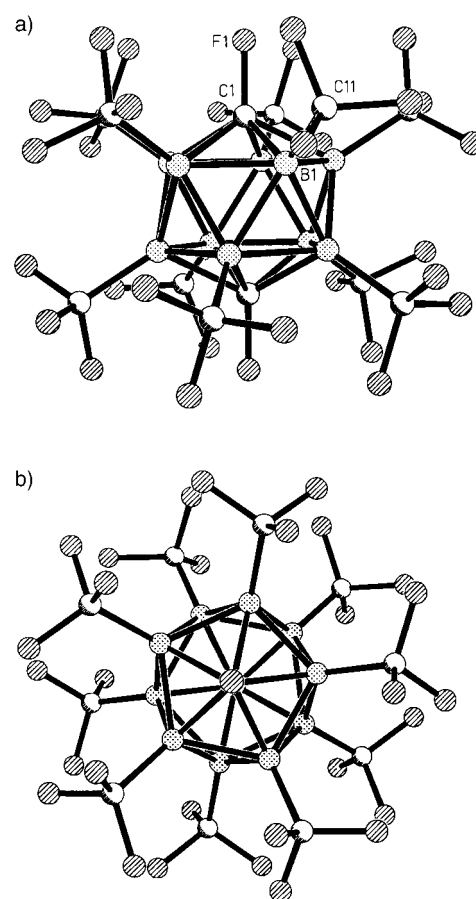


Figure 1. Molecular structure of **5**. a) View roughly perpendicular to the apical axis, showing the C–F bonds, b) view approximately along the apical axis. Selected bond lengths [Å]: C1–F1 1.326(11), B–C_{apical}(av) 1.741(15), B–C_{F3}(av) 1.627(15), C–F(av) 1.337(13).

able from those reported for analogous carboranes such as **1**^[16a] and 1,12-(H) $_2$ -1,12- $\text{C}_2\text{B}_{10}(\text{CHCl}_2)_{10}$.^[13] As predicted by Michl and King for the anion $1\text{-CB}_{11}(\text{CF}_3)_{12}^-$,^[15] the average diameter (as calculated by F...F distances) of the fluorinated sphere is approximately 8.04 Å. All other metrical parameters are typical and do not warrant further comment. Aside from the difference in the crystal packing, these findings account as well for **8**.^[18]

We are currently exploring the feasibility of performing reactions at the C–H vertices of mixtures such as **8**.^[22] Their 1- and 1,12-functionalization would allow their separation by column chromatography and open an avenue for further chemistry. At the same time we are probing the fluorination of other camouflaged carborane compounds^[16b] including the possibility of generating fluorinated sticks and ropes from rigid rods consisting of tethered species derived from **1**.^[23]

Experimental Section^[24]

Caution! Fluorine is a powerful oxidizer and should not be handled except in carefully controlled environments.^[25, 26]

Caution! Compounds such as **5** are potentially explosive.^[15] In spite of having not experienced explosions when preparing or handling **5**, we advise extreme caution in doing so.

Analytical instruments used: VG analytical ZAB2-E mass spectrometer (HR-MS); Varian Unity plus-300 (^{19}F NMR); Bruker ARX 400 (^{13}C NMR);

Bruker ARX 500 (^{11}B NMR); Nicolet Nexus 470 (FT-IR); Spex 1402 double monochromator, RCA C31034 photomultiplier tube, Stanford research systems SR400 photon counter (Raman).

5: The fluorination of **1** with the goal of 1,12 C–H conversion to 1,12 C–F was carried out in a solution-phase fluorination reactor which has been described in previous articles.^[24,25] The reactor was filled with perfluorononane (Exfluor Research Corp.) (300 mL, b.p. 125 °C) and NaF (25 g, 0.59 mol). The reactor was then purged with N_2 (100 $\text{cm}^3\text{min}^{-1}$, 1 h). Compound **1** (500 mg, 1.75 mmol), dissolved in perfluorononane (150 mL), was pumped into the reactor (25 mL h^{-1}). During the addition of **1** a mixture of F_2 and N_2 was bubbled through the reactor at a rate of 100 and 400 $\text{cm}^3\text{min}^{-1}$, respectively. After the addition of the solution containing **1** was completed, the F_2/N_2 flow rate was reduced to 25 and 25 $\text{cm}^3\text{min}^{-1}$, respectively, and the temperature was gradually raised to 110 °C (240 h). The reaction was held at 110 °C for an additional 4 days. The F_2 was turned off and the reactor was allowed to purge (4 h). The contents of the reactor were filtered and excess solvent was removed under reduced pressure. Sublimation of product (65 °C/0.01 mm, 181 °C/760 mm) furnished **5** as a colorless solid (1.39 g, 94%). M.p. 186 °C (sealed tube); ^{11}B NMR (160.5 MHz, Freon 113, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ external): $\delta = -15.8$ (s); ^{19}F NMR (376.5 MHz, Freon 113, 5% CDCl_3): $\delta = -49.1$ (d, 30F, $^2J(\text{B,F}) = 60$ Hz; CF_3), -157.5 (s, 2F; CF); ^{13}C NMR (100.6 MHz, Freon 113, 5% CDCl_3): $\delta = 111$ (CF_3), 109 (d, $^3J(\text{B,F}) = 60$ MHz; CF); IR (neat): $1/\lambda = 1258$, 1160, 1149, 1133, 1029, 980 cm^{-1} ; Raman^[27] (neat) $1/\lambda = 194$ (s), 219 (s), 266, 441, 539 (w), 641.5 (w), 715, 1166 (w), 1190 (w), 1258 (w) cm^{-1} ; HR-MS (CI-): m/z : calcd 860.0496; found 860.0483.

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crystals containing compound **6**, with small amounts of **5** and **7**. Compound **6**: ^{11}B NMR (160.5 MHz, Freon 113, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ external): $\delta = -17.7$ (s); ^{19}F NMR (499.3 MHz, Freon 113, 5% CDCl_3): $\delta = -51.7$ (d, 30F, $^2J(\text{B},\text{F}) = 55$ Hz, CF_3); ^1H NMR (499.8 MHz, Freon 113, 5% CDCl_3): $\delta = 5.1$ (s); HR-MS (CI): m/z : calcd 826.0608, found 826.0586; compound **7**: ^{11}B NMR (160.5 MHz, Freon 113, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ external) $\delta = -15.8$ (s), -17.7 (s); ^{19}F NMR (499.3 MHz, Freon 113, 5% CDCl_3): $\delta = -49.1$ (d, 30F, $^2J(\text{B},\text{F}) = 60$ Hz, CF_3), -51.7 (d, 30F, $^2J(\text{B},\text{F}) = 55$ Hz, CF_3), -157.5 (s, 1F, CF); ^1H NMR (499.8 MHz, Freon 113, 5% CDCl_3): $\delta = 5.1$ (s); HR-MS (CI): m/z : calcd 844.0514, found 844.0538.

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Modular Self-Assembly of a Microporous Solid Based upon Mercuracarborand-4 and a New Bonding Motif**

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M. Frederick Hawthorne*

Mercuracarborands^[1] comprise a class of novel macrocyclic multidentate Lewis acids^[2] and possess useful properties in molecular recognition,^[1, 3] optical sensors,^[4] and catalysis.^[5] Macrocyclic mercuracarborands are composed of alternating *ortho*-carborane icosahedra and mercury atoms linked by C–Hg–C moieties. The electron-withdrawing character of the *o*-carborane cage strengthens the Lewis acidity of the mercury centers, thereby enhancing the ability of the mercuracycle to function as a host for electron-rich guests.^[2] An added benefit derived from the carborane cage is the fact that the boron vertices can be selectively functionalized to manipulate solubility^[6, 7] and/or structural features required for supramolecular self-assembly.^[8] The majority of carborane self-assembly chemistry is directed by the acidic C–H vertices of the carborane^[9] and examples in which nonacidic B–H vertices direct self-assembly are limited.^[10] As part of our ongoing investigation of mercuracarborand chemistry, we now report the synthesis and solid-state structure of $\text{Li}_2[(\text{HgC}_2\text{B}_{10}\text{H}_8\text{I}_2)_4 \cdot \text{I}_2]$ ($\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$), an example of self-assembly directed by novel B–I $\cdots$ Li $\cdots$ I–B linkages which form microporous channels subsequently occupied by solvent molecules.

Electrophilic iodination at the electron-rich 9,12-vertices of *ortho*-carborane^[6] followed by lithiation of the C–H vertices^[11] provided the corresponding dilithium reagent, $\text{Li}_2\text{C}_2\text{B}_{10}$ –

H_8I_2 . The reaction of $\text{Li}_2\text{C}_2\text{B}_{10}\text{H}_8\text{I}_2$ with one molar equivalent of HgI_2 in dry diethyl ether at room temperature afforded the diiodide ion complex, $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$, of the *bis*-iodo-tetrameric cycle, **1**, in 78% yield. The resulting $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$ species is an air- and moisture-stable crystalline solid that is soluble in a variety of organic solvents such as acetone, acetonitrile, diethyl ether, and dichloromethane. The ^1H , ^{13}C , and ^{11}B NMR spectra of $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$ revealed a highly symmetrical structure in solution. The ^{199}Hg NMR spectrum of $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$ in acetone exhibits a sharp singlet at $\delta = -622$ which is essentially independent of concentration at room temperature. The negative-ion fast atom bombardment mass spectrum exhibits a peak centered at m/z 2640, with the isotopic pattern expected for $\text{Li}[\mathbf{1} \cdot \text{I}_2]^-$, and an anion envelope at m/z 2505, which corresponds to $[\mathbf{1} \cdot \text{I}]^-$. The species at m/z 2505 is presumed to arise through the elimination of LiI from $\text{Li}[\mathbf{1} \cdot \text{I}_2]^-$, since a second resonance signal was not observed in the ^{199}Hg NMR spectrum of the latter.

A single crystal of $[\text{Li}_2\{(\text{CH}_3)_2\text{CO}\}_6][\mathbf{1} \cdot \text{I}_2] \cdot 4\text{H}_2\text{O}$, grown from an acetone/dichloromethane solution, was selected for an X-ray diffraction study.^[12] It crystallized in the monoclinic space group *C2/m*. The $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$ structure consists of four divalent 9,12- I_2 -1,2- $\text{C}_2\text{B}_{10}\text{H}_8$ cages linked at carbon by four Hg atoms in a cyclic tetramer with an iodide ion located above and below the tetramer cavity (Figure 1). The four Hg atoms

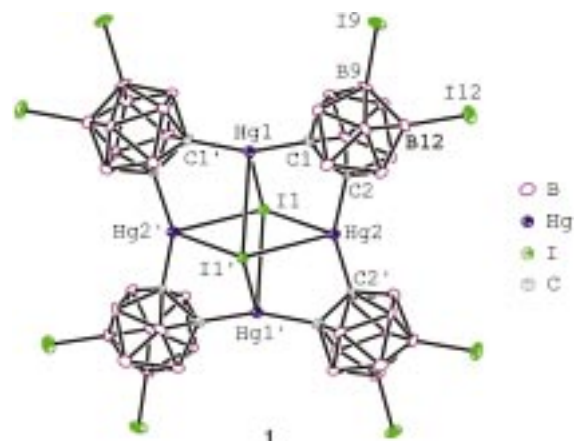


Figure 1. Structure of the building block $[\mathbf{1} \cdot \text{I}_2]^{2-}$ (ORTEP diagram; solvent molecules and hydrogen atoms omitted for clarity). Selected interatomic distances [Å] and bond angles [°]: Hg1–I1 3.213(2), Hg2–I1 3.313(1), Hg1–I1' 3.607(2), Hg1–C1 2.07(1), Hg2–C2 2.134(9), Hg1 $\cdots$ Hg2 3.901(1), B9–I9 2.20(1), B12–I12 2.19(1); C1–Hg1–C1' 157.4(6), C2–Hg2–C2' 151.9(5), Hg1–C1–C2–Hg2 1(1).

are coplanar and lie in a parallelogram with sides of Hg1 $\cdots$ Hg2 3.901(1) Å and internal angles of Hg2–Hg1–Hg2' 87.40(4)° and Hg1–Hg2–Hg1' 92.60(4)°. Iodide ions are located 1.912(1) Å above and below the plane of the four Hg atoms. Each iodide ion is bonded to all four Hg atoms; the Hg $\cdots$ I distances range from 3.213(2) to 3.607(2) Å, that is less than the sum of the van der Waals radii of 3.88 Å (Hg = 1.73^[13] and I = 2.15 Å^[14]). The Hg $\cdots$ I distances are comparable to those in previously reported mercuracyclic Hg $\cdots$ I complexes (3.249–3.487 Å).^[3, 7, 15, 16] The Hg $\cdots$ I coordination in $[\mathbf{1} \cdot \text{I}_2]^{2-}$ arises from the interaction of filled iodide ion p orbitals with empty mercury p orbitals that have the proper orientation to form three-center, two-electron bonds.^[1]

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A crystal packing diagram of $[\text{Li}_2\{(\text{CH}_3)_2\text{CO}\}_6][\mathbf{1} \cdot \text{I}_2] \cdot 4\text{H}_2\text{O}$ shows infinite one-dimensional chains composed of $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$ units linked by intermolecular $\text{B} \cdots \text{I} \cdots \text{Li} \cdots \text{I} \cdots \text{B}$ bonds (Figure 2). The $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$ units of the polymeric chains are arranged in layers. The polymeric chains assemble to produce linear channels perpendicular to the polymer chains. The $\text{Li1} \cdots \text{I12}$ distance (3.753(7) Å) is shorter than the van der Waals separation of 3.97 Å ($\text{Li} = 1.82^{[17]}$ and $\text{I} = 2.15$ Å) and the I12-Li1-I12' angle is $162(1)^\circ$. The other I substituent, I9, participates in intermolecular $\text{I} \cdots \text{I}$ contacts ($\text{B9-I9} \cdots \text{I9'-B9'}$ 3.870 Å) between the polymeric chains, and the distance is within known $\text{I} \cdots \text{I}$ contacts.^[18] The remaining ligands of the Li coordination sphere are three acetone molecules with distances of Li1-O1S 3.11(5) and two of Li1-O2S 3.20(4) Å.

The cross-section of the channels adopts the approximate shape of a rectangle whose sides are effectively 8.6 and 11.5 Å (Figure 3).^[19] These distances are comparable with the dimensions of channels present in other metal-organic porous solids.^[20] In the present case, the channels contain water molecules (eight per unit cell) which are separated by a distance of $\text{O1W} \cdots \text{O1W'}$ 4.72(5) Å, along the channel. The water molecules are not coordinated to the Li or Hg atoms; nearest distances: $\text{O1W} \cdots \text{Li1}$ 5.58(5), $\text{O1W} \cdots \text{Hg2}$ 5.52(2), $\text{Hg1} \cdots \text{O1W}$ 8.57(2) Å. Between the layers, the interlayer

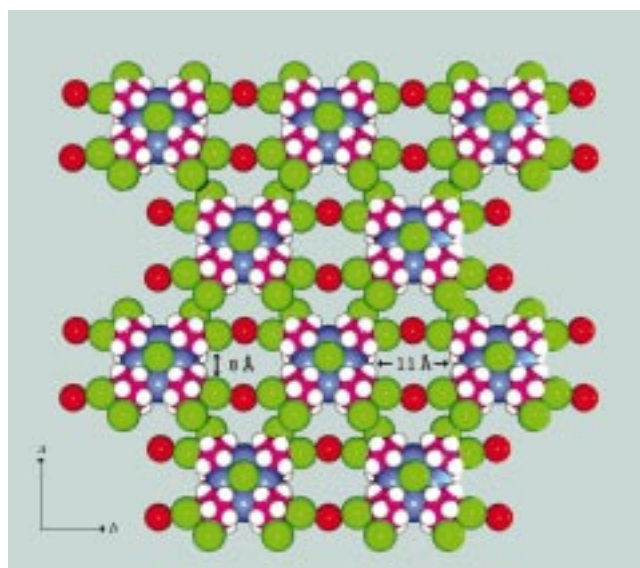


Figure 3. Space-filling model of the packing lattice of $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$. The acetone and water molecules are omitted for clarity. Color code: B: purple; C: gray; H: white; Hg: blue; I: green; Li: red.

$\text{Hg} \cdots \text{I}$ distance is 4.396(2) Å between Hg1 and I1'. The shortest $\text{I} \cdots \text{I}$ distance between two mirror-related anions is 7.416(4) Å.

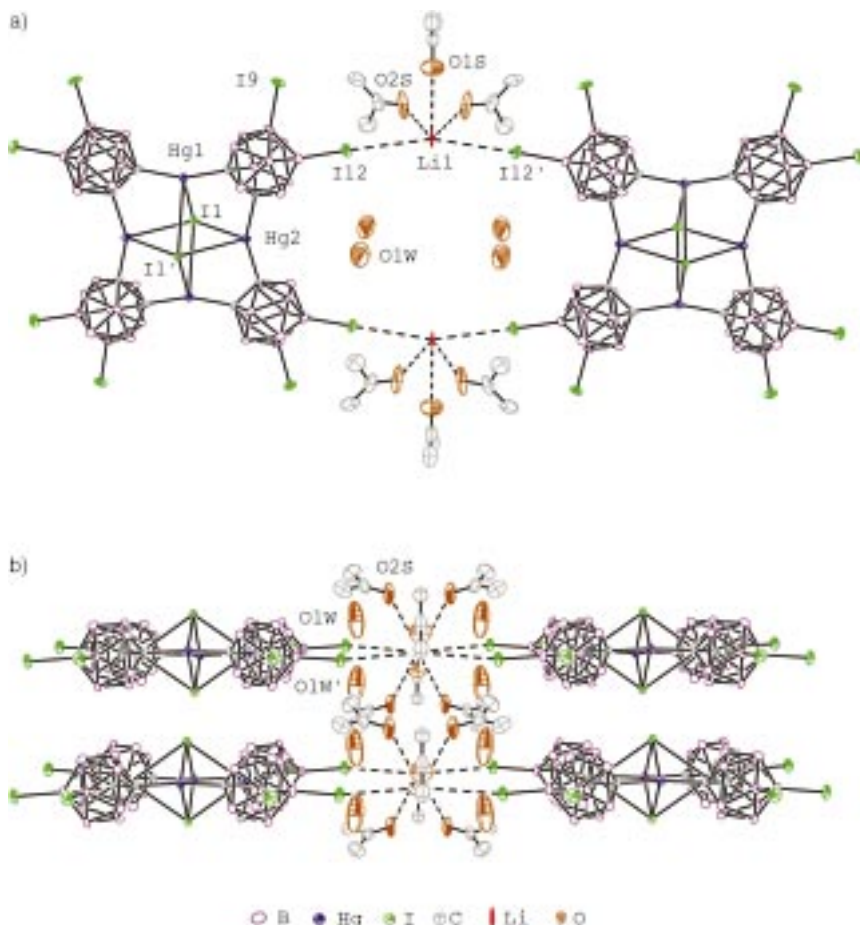


Figure 2. Crystal packing representation of $[\text{Li}_2\{(\text{CH}_3)_2\text{CO}\}_6][\mathbf{1} \cdot \text{I}_2] \cdot 4\text{H}_2\text{O}$ (ORTEP diagram; hydrogen atoms omitted for clarity). a) Projection perpendicular to the Hg_4 plane. b) Projection parallel to the Hg_4 plane. Selected interatomic distances [Å] and bond angles $^\circ$: $\text{I12} \cdots \text{Li1}$ 3.753, $\text{Li1} \cdots \text{O1S}$ 3.114, $\text{Li1} \cdots \text{O2S}$ 3.20(4), $\text{O1W} \cdots \text{O1W'}$ 4.72(5); $\text{I12} \cdots \text{Li1} \cdots \text{I12'}$ $162(1)^\circ$.

Previously reported crystal structures of $\text{Li}_2[\text{HgC}_2\text{B}_{10}\text{H}_8\text{R}_2)_4 \cdot \text{I}_2]$ ($\text{R} = \text{H}, \text{CH}_3, \text{CH}_2\text{CH}_3$) species do not demonstrate the formation of self-assembled porous material in the solid state.^[1, 3] Presumably, the heretofore unobserved $\text{B} \cdots \text{I} \cdots \text{Li}$ and $\text{B} \cdots \text{I} \cdots \text{I} \cdots \text{B}$ interactions of $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$ direct crystal lattice organization. This intermolecular interaction provides a new bonding motif for supramolecular self-assembly which involves nucleophilic halogen centers attached to electron-rich boron vertices of carborane cages. Recently, microporous materials have been utilized in enantioselective separation and catalysis.^[21] Currently, the molecular inclusion properties of $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$ are under investigation.

Experimental Section

$\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$: To a dry ethereal solution (20 mL) of *closo*-9,12- I_2 -1,2- $\text{C}_2\text{B}_{10}\text{H}_{10}\text{I}_2$ ^[6] (0.210 g, 0.530 mmol) at 0°C was added *n*-butyllithium (1.1 mmol, 0.44 mL, 2.4 M solution in hexanes), and the resulting mixture was stirred at room temperature under nitrogen. After 4 h, the mixture was cooled back to 0°C and treated with HgI_2 (0.241 g, 0.530 mmol). The reaction was stirred at room temperature for 8 h, then quenched with water, and the organic phase was separated. The water layer was extracted with diethyl ether (3×10 mL). The combined organic phase was dried over anhydrous magnesium sulfate and filtered. The solvent was removed under vacuum and triturated with pentane to give $\text{Li}_2[\mathbf{1} \cdot \text{I}_2]$ as a white solid in 78% yield. $[\text{Li}_2 \cdot \{(\text{CH}_3)_2\text{CO}\}_6][\mathbf{1} \cdot \text{I}_2] \cdot 4\text{H}_2\text{O}$ forms on crystallization from acetone. ^1H NMR (400 MHz, $[\text{D}_6]$ acetone, 25°C): $\delta = 3.5\text{--}2.0$ (B–H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $[\text{D}_6]$ acetone, 25°C): $\delta = 89.5$ (carborane-C); $^{11}\text{B}\{^1\text{H}\}$ NMR (160 MHz, acetone, 25°C , $\text{BF}_3 \cdot \text{Et}_2\text{O}$

external): $\delta = -5.8, -10.5, -16.0$ (2:6:2); $^{199}\text{Hg}\{^1\text{H}\}$ NMR (89.6 MHz, acetone, 25 °C, external 0.5 M PhHgCl in $[\text{D}_6]\text{DMSO}$: chemical shift $\delta = -1187^{[22]}$ upfield from neat Me_2Hg): $\delta = -622$; negative-ion FAB-MS: m/z (%): 2505 (100) $[\text{I} \cdot \text{I}]^-$, 2640 (45) $[\text{Li} \cdot \text{I} \cdot \text{I}]^-$.

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- [12] Crystallographic data collection for $[\text{Li}_2((\text{CH}_3)_2\text{CO})_6][\text{I}_2 \cdot \text{I}] \cdot 4\text{H}_2\text{O}$: $\text{C}_{15}\text{H}_{34}\text{B}_{20}\text{Hg}_2\text{I}_3\text{LiO}_8$, $M_r = 1529.22$, crystal dimensions $= 0.15 \times 0.15 \times 0.25 \text{ mm}^3$, monoclinic, space group $C2/m$, $a = 31.26(1)$, $b = 22.14(1)$, $c = 7.068(3) \text{ \AA}$, $\beta = 94.463(9)^\circ$, $V = 4876(4) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 2.083 \text{ mg cm}^{-3}$, $T = 100(2) \text{ K}$, absorption coefficient $\mu = 9.476 \text{ mm}^{-1}$. Data were collected on a Bruker SMART CCD diffractometer, using $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). Unit cell parameters were determined from a least-squares fit of 916 accurately centered reflections ($4.33^\circ < 2\theta < 55.80^\circ$). A total of 6001 unique reflections were measured, of which 3832 reflections were considered observed with $I > 2\sigma(I)$. All reflections were used for structure analysis. The intensity data were corrected for Lorentz and polarization effects, absorption, and secondary extinction. Atoms were located by use of heavy atom methods. With the exception of Li, all non-hydrogen atoms were refined with anisotropic parameters. With the exception of H of water (not located), all H were included in structure factor calculations but parameters were not refined. The H atoms were assigned isotropic displacement values based approximately on the value for the attached atom. The final discrepancy index was $R = 0.055$, $R_w = 0.133$ ($w = 1/\sigma^2(|F_o|)$) for 3832 independent reflections with $I > 2\sigma(I)$. The largest peak maximum and minimum on a final difference electron density map were 2.724 and $-3.020 \text{ e \AA}^{-3}$, both near Hg. Data were processed by using the Bruker SMART 1000 software package. 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-158870. 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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Optically Tuning the Rate of Stoichiometry Changes: Surface-Controlled Oxygen Incorporation into Oxides under UV Irradiation

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Stoichiometry changes are fundamental to all solid-state chemical reactions and thus one of the most central processes in solid-state chemistry. Moreover, the relevant stoichiometry determines whether an ionic material is ionically or electronically conducting, whether it is an n- or p-type electronic conductor, and may even determine whether or not it is superconducting. The kinetics of in- and exorporation reactions are also directly involved in the functioning of electroceramic devices, such as permeation membranes, electrodes in fuel cells, and chemical sensors.^[1–4] The stoichiometry change process consists of surface reaction steps in series with a bulk diffusion step, of which the former become increasingly important at lower temperatures.

In this Communication, we present results on the use of UV light to tune the rate of oxygen incorporation into the bulk of a model mixed conductor, iron-doped SrTiO_3 , by altering the rate of the surface reaction under conditions where the surface reaction determines the overall kinetics of the stoichiometry change. While the effects of illumination on the surface composition (see, for example, refs. [5, 6]) and on the catalytic activity of wide-bandgap semiconductors have drawn much attention, for example with regard to the photolysis of water, the selective oxidation of hydrocarbons, and the removal of organic pollutants from air or water,^[7–10] the effect of irradiation on the kinetics of bulk stoichiometry changes (in the surface-controlled regime) has, to the best of our knowledge, not yet been reported.

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The stoichiometry relaxation experiments were performed on single crystalline iron-doped SrTiO_3 , a material for which the defect chemical parameters and transport properties of the bulk are well known.^[11–14] In SrTiO_3 , Fe substitutes onto the Ti site and is present as both Fe^{3+} and Fe^{4+} ; the ratio of the valence states depends on temperature and oxygen partial pressure. Fe^{3+} ions on Ti^{4+} sites are negatively charged defects and are mainly compensated by oxygen vacancies, whose concentration is large compared with the concentration of electron holes, the majority electronic carrier. The concentrations of all relevant defects, which were calculated for an oxygen partial pressure $P_{\text{O}_2} = 0.1$ bar from parameters given in ref. [11], are shown in Figure 1.

Oxygen incorporation into SrTiO_3 occurs by oxygen molecules annihilating oxygen vacancies to produce electron holes. Under a local electronic equilibrium, the increased concentration of holes gives rise to an increase in the concentration of Fe^{4+} (at the expense of Fe^{3+}). Thus, Fe^{4+} ions provide a sensitive measure of the oxygen stoichiometry of the sample. Oxygen in- or exorporation due to changes in P_{O_2} can consequently be followed in situ by spectroscopically monitoring the visible absorption band of Fe^{4+} centered at 590 nm (absorption of Fe^{3+} coincides with SrTiO_3 bandgap absorption). For the irradiation experiments, we examined the effect of photon energies above and below the bandgap energy.

Generally, surface and diffusion kinetics are both important with regard to the stoichiometry relaxation of a SrTiO_3 sample after a sudden P_{O_2} change. Within the range of conditions of this study, defined by the sample dimensions, bare polished surfaces, temperatures, and oxygen partial pressures, the oxygen transport was essentially controlled by the surface kinetics,^[15, 16] that is the chemical diffusion of oxygen in the bulk is much faster than the surface reaction rate and hence the vacancy concentration is almost constant across the sample. The oxygen vacancy concentration, $[\square]$, which is linearly related to the absorbance A of the Fe^{4+} band,^[8] then follows an exponential rate law, which depends only on an effective rate constant, $\bar{k}^\delta$, and the sample thickness, $2L$.

Data obtained under UV irradiation could also be described by Equation (1), even though the two sides of the

sample were not identical. We have to replace $\bar{k}^\delta$ therefore with an effective quantity $\langle \bar{k}_{\text{UV}}^\delta \rangle$. It was found from finite difference calculations that $\langle \bar{k}_{\text{UV}}^\delta \rangle$ was, to a good approximation, the arithmetic mean of $\bar{k}_{\text{UV}}^\delta$ of the irradiated surface and of $\bar{k}^\delta$ of the unirradiated back surface (that is, the error introduced was negligible for all experiments performed).

$$\frac{[\square]_t - [\square]_{t=\infty}}{[\square]_{t=0} - [\square]_{t=\infty}} = \frac{A_t - A_{t=\infty}}{A_{t=0} - A_{t=\infty}} = 1 - \exp\left(-\frac{\bar{k}^\delta t}{L}\right) \quad (1)$$

First, let us briefly consider the stoichiometric relaxation kinetics without irradiation. These $\bar{k}^\delta$ values are plotted versus the final oxygen partial pressure in Figure 2a. It is seen that

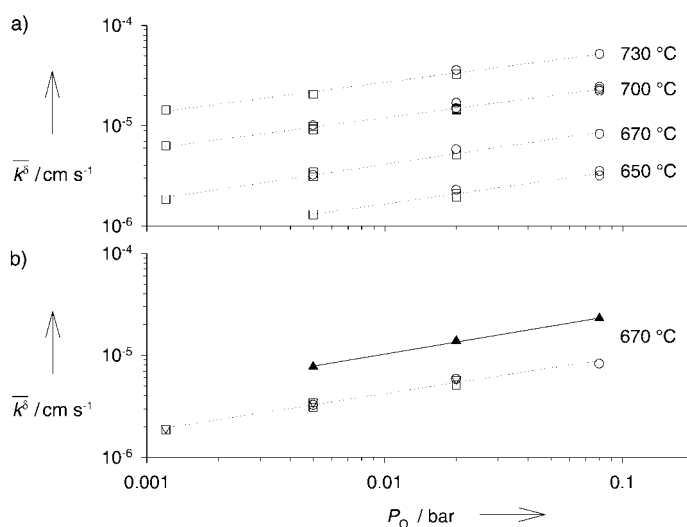


Figure 2. Effective rate constants as a function of final P_{O_2} : a) $\bar{k}^\delta$, for oxygen in- (circles) and exorporation (squares); b) $\bar{k}^\delta$ for oxygen in- (circles) and exorporation (squares), and $\bar{k}_{\text{UV}}^\delta$ for oxygen in- (solid triangles) and exorporation (open triangles).

the $\bar{k}^\delta$ values obtained for partial pressure jumps to the same final P_{O_2} , either from lower or higher P_{O_2} values, are identical within experimental error. The P_{O_2} dependence of $\bar{k}^\delta$, determined from linear regression analysis, is $\bar{k}^\delta \propto P_{\text{O}_2}^{0.33 \pm 0.02}$ at all the temperatures examined. The fact that the exponent is the same for all (fairly high) temperatures examined is evidence that the fraction of surface sites occupied by adsorbed species is very small. The Arrhenius plots of $\bar{k}^\delta$ (Figure 3) yield an effective activation energy of $274 \pm 2 \text{ kJ mol}^{-1}$, which is independent of P_{O_2} .

We first examined the effect of UV irradiation on an equilibrated sample (no P_{O_2} jump). After an irradiation period of 1 h, the absorbance had increased slightly, although the change was small compared to the absorbance changes due to the P_{O_2} jumps. For conditions other than those considered here, the effect can be significant. A detailed analysis of this will be given elsewhere. The relaxation after the irradiation period took place on the same time scale as the stoichiometry relaxation after a jump in P_{O_2} .

For UV irradiation during stoichiometry change experiments, irradiation had no measurable effect for jumps from higher to lower P_{O_2} .

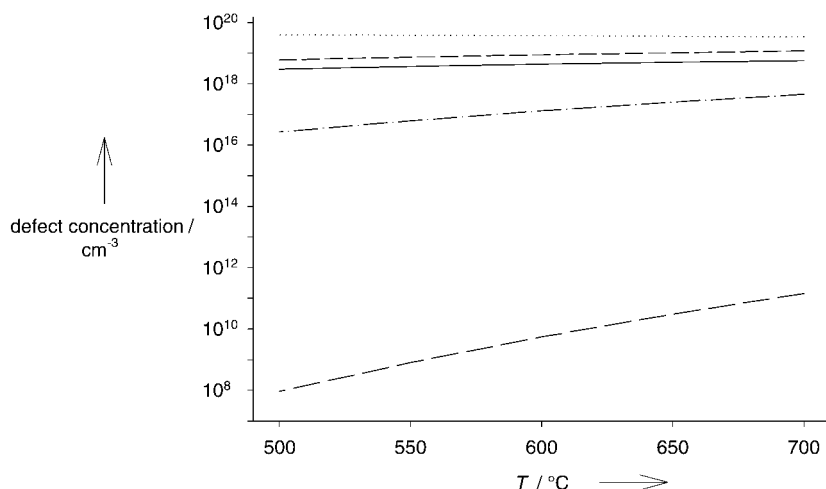


Figure 1. Defect concentrations in Fe-doped SrTiO_3 (Fe content = $4.6 \times 10^{19} \text{ cm}^{-3}$) at $P_{\text{O}_2} = 0.1$ bar calculated from known defect chemical parameters.^[11] Dotted: Fe^{4+} , short dash: Fe^{3+} , solid: oxygen vacancies, dot-dash: electron holes, long dash: conduction electrons.

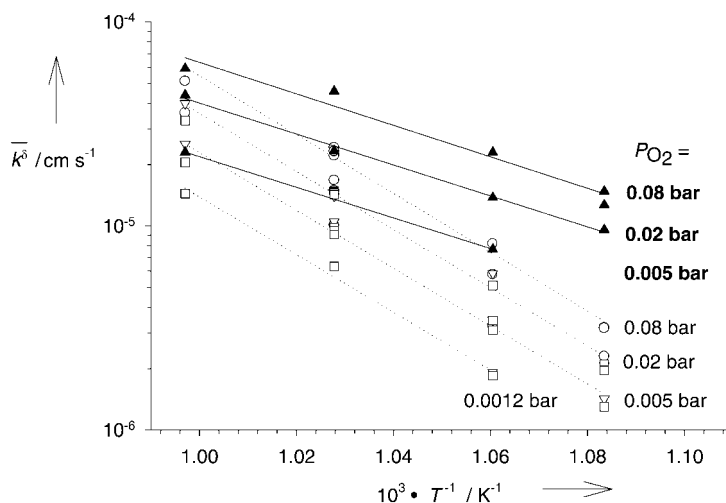


Figure 3. Arrhenius plots of the effective rate constants $\bar{k}^{\delta}$ for oxygen in- (circles) and ex-corporation (squares) without UV irradiation, and oxygen in- (solid triangles) and ex-corporation (open triangles) with UV irradiation.

values, while it substantially increased the effective surface rate for jumps to higher P_{O_2} values. The increase in $\bar{k}_{\text{UV}}^{\delta}$ was a factor of two at 700 °C and almost a factor of five at 650 °C, and hence leads to a strongly decreased effective activation energy of $145 \pm 2 \text{ kJ mol}^{-1}$ (Figure 3). Extrapolating to temperatures below 600 °C, we therefore expect more than an order of magnitude difference between $\bar{k}_{\text{UV}}^{\delta}$ and $\bar{k}^{\delta}$. The P_{O_2} dependence of $\bar{k}_{\text{UV}}^{\delta}$ appears to exhibit no significant difference compared to that for $\bar{k}^{\delta}$ at all the temperatures examined ($\bar{k}_{\text{UV}}^{\delta} \propto P_{\text{O}_2}^{0.37 \pm 0.10}$); the data at 670 °C is shown in Figure 2b. In Figure 4 it is shown that for jumps to higher oxygen partial pressures, $\bar{k}_{\text{UV}}^{\delta}$ displayed an almost linear increase with increasing UV irradiation intensity for two different, final P_{O_2} values at 670 °C. We note that sub-bandgap irradiation at 515–700 nm had no effect on the oxygen exchange kinetics.

The possibility that the increase in the relaxation rate is caused by a local temperature increase upon irradiation can be discounted for three reasons: Only the incorporation (and

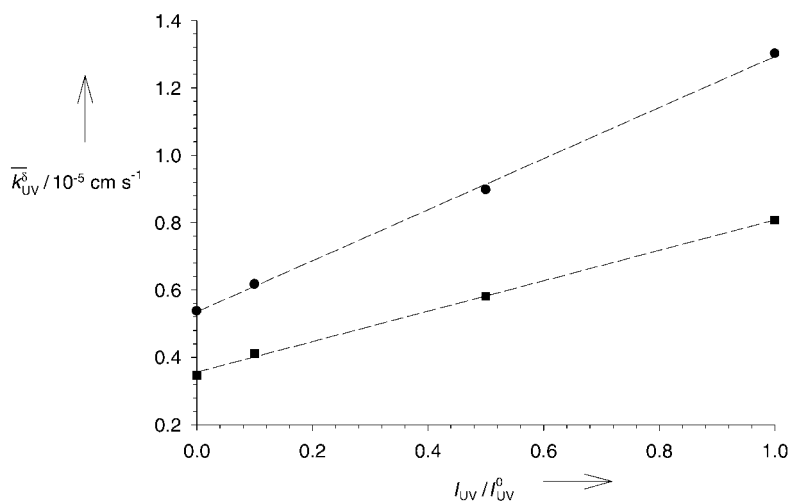


Figure 4. Dependence of $\bar{k}_{\text{UV}}^{\delta}$ on UV irradiation intensity at 670 °C for final P_{O_2} values of 0.08 (circles) and 0.02 bar (squares). I_{UV}^0 is the full UV intensity; I_{UV} is the intensity attenuated by neutral density filters.

not the ex-corporation) kinetics were accelerated; sub-bandgap irradiation of similar intensity did not produce an effect; and, in any case, the intensity of the UV radiation is small compared to radiation from the furnace.

The absorption coefficient α of SrTiO₃ for UV radiation is $\sim 10^5 \text{ cm}^{-1}$,^[17] from which the photon penetration depth is calculated to be about 100 nm. Unfortunately, there are no literature data on the lifetime of the photogenerated electron–hole pairs in SrTiO₃. Values exist for TiO₂ at room temperature and are in the range of 3×10^{-11} to $1 \times 10^{-9} \text{ s}$.^[18, 19] Assuming that the values for SrTiO₃ are of the same order of magnitude, we estimate the concentration of photogenerated electrons and holes in the irradiated surface layer to be about $3 \times 10^{13} - 1 \times 10^{15} \text{ cm}^{-3}$. This is a significant enhancement with respect to the concentration of thermally generated electrons, which is $\sim 2 \times 10^{11} \text{ cm}^{-3}$, but negligible compared to the hole concentration of $3 \times 10^{17} \text{ cm}^{-3}$ (compare with Figure 1).

The fact that oxygen incorporation is accelerated under UV irradiation, while ex-corporation remains unchanged, indicates that the sample is far from equilibrium and the UV-accelerated forward reaction rate becomes dominant. Detailed analysis, based on a recent theoretical treatment,^[20, 21] of $\bar{k}^{\delta}$ and $\bar{k}_{\text{UV}}^{\delta}$ therefore requires knowledge of the exact mechanistic reaction scheme for oxygen incorporation, which is not yet known. Some conclusions can nevertheless be drawn from the experimental data. Since UV irradiation increases, relatively speaking, the electron concentration but not the hole concentration at the surface, this suggests that, for oxygen incorporation, conduction band electrons participate in one or more of the elementary reaction steps up to and including the rate-determining step; quantitative analysis of the relationship between $\bar{k}_{\text{UV}}^{\delta}$ and the UV intensity may be expected to provide further mechanistic information in this regard. Since oxygen ex-corporation is not affected by UV irradiation, this suggests that if any electronic species are involved in surface reaction steps following the rate-determining step, they must be holes.

In short, we have measured the effect of UV irradiation on oxygen incorporation into a model, wide-bandgap electro-ceramic oxide. The advantage of UV irradiation, in contrast to the other possibilities (changing the temperature, the dopant concentration, or adding catalytic coatings) is that it enables us under isothermal conditions to turn on and off the surface reaction in situ. We will be exploring this effect in the near future with regard to locally structuring electro-ceramic oxides, and novel optoelectrochemical devices, such as a chemical valve.

Experimental Section

A SrTiO₃ single crystal (Frank & Schulte GmbH, Essen, Germany) with an iron content of $4.6 \times 10^{19} \text{ cm}^{-3}$ was cut and polished to give a sample with the dimensions $6 \times 6 \times 1 \text{ mm}$. The large faces exhibited (110) orientation, which upon thermal pretreatment at 900 °C in O₂ became faceted into the more stable (100) and (010) surfaces (indicated by atomic force microscopy).

Oxygen stoichiometry changes were performed between 650 and 730 °C by switching P_{O_2} between 0.0012 $\leftrightarrow$ 0.005 $\leftrightarrow$ 0.02 $\leftrightarrow$ 0.08 bar (achieved with O_2 /Ar mixtures; flow rate 100 mL min⁻¹). The set-up for the in situ optical spectroscopy is described in detail in ref. [15]. The integral Fe⁴⁺ concentration was monitored continuously by measuring the absorption at 595 nm with a UV/Vis spectrometer (Perkin–Elmer Lambda 2). A narrow bandpass filter was placed between the sample and the detector to block thermal radiation.

For the irradiation experiments, a 200 W Hg high pressure arc lamp (LOT Oriel) was used, whose spectral output was restricted to 280–420 nm by means of UG5 and WG280 filters (Schott). The bandgap of SrTiO₃ at 700 °C is 2.7 eV,^[15] which corresponds to the absorption of light of 460 nm. The total irradiation intensity was 250 mW cm⁻² in front of the quartz rod, that acted as light guide to irradiate one of the large faces of the sample, and was attenuated for some experiments by neutral density filters. The UV irradiation was interrupted for $\approx$ 30 s at appropriate intervals to permit the 595 nm extinction measurements to be made. The effect of sub-bandgap irradiation of 515–700 nm with a total intensity of 190 mW cm⁻² was also investigated.

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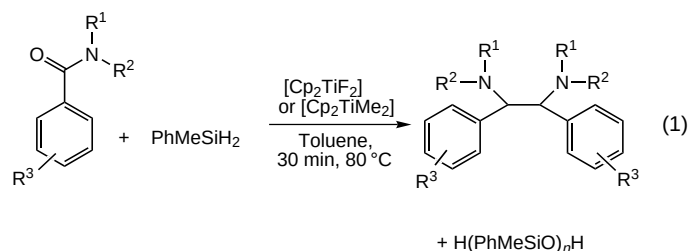
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Titanocene-Catalyzed Coupling of Amides in the Presence of Organosilanes To Form Vicinal Diamines**

Kumaravel Selvakumar and John F. Harrod*

Vicinal diamines occur widely in natural products and have many applications in medicinal chemistry and organic synthesis.^[1] Despite the existence of many synthetic approaches, there is still a pressing need for better and more general methods based on simple and inexpensive starting materials. We report herein a novel reduction–deoxygenation coupling of amides catalyzed by [Cp₂TiX₂] (Cp = η^5 -cyclopentadienyl; X = Me or F) in the presence of a stoichiometric amount of an organosilane. To the best of our knowledge, such a reaction has not been reported previously, although the literature extensively covers the titanium-mediated coupling of carbonyl^[1,2] and imine^[1,3] compounds in the presence of strong reducing agents.^[2] The intramolecular coupling of 1,2-acylamido compounds to form indoles and pyrroles has also been extensively studied.^[4]

Both dimethyltitanocene and difluorotitanocene have been used as catalysts for a variety of hydrosilylation reactions.^[5–7] We attempted to use these catalysts to effect the hydrosilylation of some amides with PhMeSiH₂ and found that the main reaction product in the case of *N,N*-dimethylbenzamide was the vicinal diamine, 1,2-dimethylamino-1,2-diphenylethane [Eq. (1)].



The effects of a number of chemical and physical variables on the outcome of the reaction are summarized in Tables 1–3. At 80 °C, the reactions of *N,N*-dialkylbenzamides and some other related aromatic amides proceed smoothly to give good to excellent yields of the substituted ethylenediamine products (Table 1). Different substituents can be tolerated, as shown in the reactions of 4-chloro-, 4-methoxy-, and 4-trifluoromethylbenzamide. There is no significant difference in the results obtained with the difluoro- and dimethyltitanocene precatalysts. None of the reactions shows significant stereoselectivity.

Reactions at room temperature show an interesting decline in chemoselectivity relative to those carried out at higher temperature (Table 2). Certain substitution patterns also

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Table 1. Results for the titanocene-catalyzed reductive coupling of amides at 80 °C.

R ¹	R ²	R ³	Method ^[a]	meso:rac ^[b]	Yield ^[c]
Me	Me	H	A	52:48	84
			B	52:48	80
Et	Et	H	A	52:48	92
			B	53:47	88
Et	Et	4-Cl	A	53:47	93
			B	53:47	90
Et	Et	4-OMe	B	56:44	94
Me	Ph	H	A	50:50 ^[e]	77 ^[d]
Et	Et	4-CF ₃	A	53:47	96
Et	Et	4-Me	A	62:38	91
		<i>N,N</i> -diethyl-2-naphthamide	A	54:46	83 ^[f]
		<i>N,N</i> -diethylnicotinamide	A	57:43	27 ^[g]

[a] See Experimental Section: A = Cp₂TiF₂, B = Cp₂TiMe₂. [b] Ratios of isomers are calculated after isolation, or by ¹H NMR spectroscopic analysis. [c] Yields are given for isolated compounds. [d] *N*-Methyl-*N*-benzylaniline is one of the products (8%). [e] Isomers were not separated. [f] *N,N*-Diethyl-2-naphthylamine is formed as a side product (9%). [g] 3-(*N,N*-Diethylaminomethyl)pyridine is also formed as a side product (25%).

favor the formation of a tertiary benzylamine (carbonyl reduction) and a benzaldehyde (N–C bond hydrogenolysis) product as well as the ethylenediamine coupling product ([Eq. (2)], Table 2). The formation of the tertiary benzylamine product is analogous to the reactions of amides with

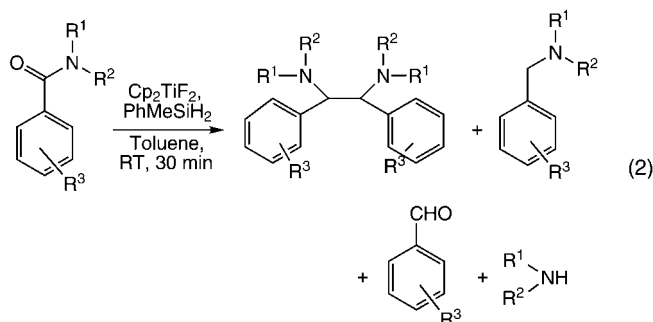


Table 2. Results for the [Cp₂TiF₂]-catalyzed reductive coupling of amides at 20 °C.

R ¹	R ²	R ³	Ratio of products [%]		
			diamines (meso:rac)	amine	aldehyde
Me	Me	H	81.3 (54:46)	2.0	16.7
Et	Et	H	97.7 (60:40)	–	2.3
Et	Et	4-Cl	44.8 (53:47)	29.9	25.3
Et	Et	4-OMe	100 (53:47)	–	–
Me	Ph	H	14.7 (55:45)	44.2	41.1
Et	Et	4-CF ₃	55.9 (53:47)	20.6	23.5
Et	Et	4-Me	100 (50:50)	–	–
		<i>N,N</i> -diethyl-2-naphthamide	51.2 (48:52)	39.6	9.2
		<i>N,N</i> -diethylnicotinamide	43.5 (56:44)	34.1	22.4

silanes catalyzed by rhodium complexes in which the tertiary amine is the only reported product.^[8] We have also shown that [Cp₂TiX₂] complexes catalyze silane reduction of *N,N*-dialkylacetamides to the tertiary amine, with no coupling product, and the results will be reported elsewhere.

In the cases in which the benzaldehyde product is observed, an equivalent amount of the secondary amine is also produced

(Table 2). The stoichiometric reaction of Ti(OiPr)₄ and Ph₂SiH₂ with acetamides has been reported previously as a method for the transformation of acetamides into aldehydes.^[9]

Several hydrosilanes were studied as reducing agents (Table 3). In general there is no significant difference in the stereoselectivity, but some variation in chemoselectivity is apparent. In particular, the use of *n*-hexylsilane results in

Table 3. Results for the reductive coupling reactions of *N,N*-dimethylbenzamide using various silanes.

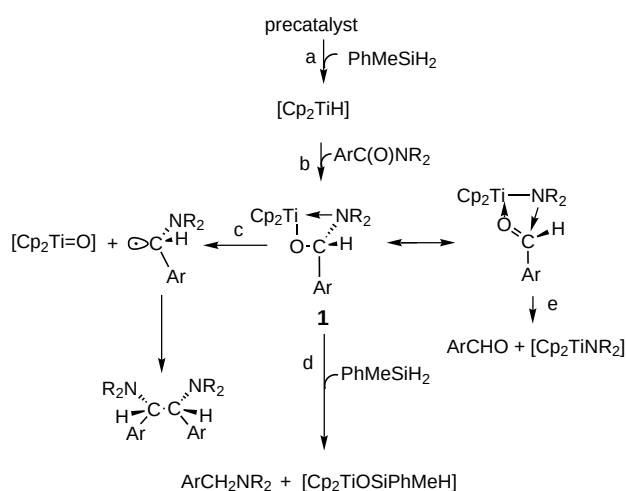
T [°C]	Silane ^[a]	Ratio of products [%] ^[b]			Yield [%] ^[c]
		diamines (meso:rac)	benzylamine	aldehyde	
20	PhSiH ₃	92(54:46)	8	–	86
80	PhSiH ₃	100(57:43)	–	–	83
20	<i>n</i> -HexSiH ₃	51(55:45)	30	19	66
80	<i>n</i> -HexSiH ₃	85(56:44)	15	–	90
20	D ₄ ^[d]	43(52:48)	9	48	40
80	D ₄ ^[d]	92(55:45)	8	–	81 ^[e]
20	PMHS ^[f]	59(56:44)	1	40	37
80	PMHS ^[f]	no reaction			

[a] D₄^H = 2,4,6,8-Tetramethylcyclotetrasiloxane. PMHS = Polymethylhydrosiloxane. [b] By integration of ¹H NMR peaks. [c] Yields are for isolated amine products separated by HCl extraction. [d] One equivalent of D₄^H was used. [e] The solution gels at the end of the reaction. [f] 300 mg of PMHS was used.

more carbonyl reduction (benzylamine) and more C–N bond cleavage than PhMeSiH₂ or PhSiH₃. On the other hand, the hydrosiloxanes D₄^H and PMHS show greatly increased C–N bond cleavage at room temperature. In contrast to other titanocene-catalyzed hydrosilylations, in which the polymerization of PhSiH₃ to polyphenylsilane by dehydrocoupling competes with the hydrosilylation reaction, and results in the inefficient use of the Si–H, no concomitant polymerization of PhSiH₃ was detected in the amide reactions. The behavior of PhSiH₃ and PhMeSiH₂ is essentially identical.

So far, the simple titanocene catalysts have only shown high activity and specificity for the deoxygenative coupling of tertiary aromatic amides. We continue to seek similar catalysts of broader and greater activity, as well as greater stereoselectivity.

On the basis of presently available evidence it is difficult to assign mechanisms to these reactions with any degree of confidence. Scheme 1 shows a cycle which provides a reasonable explanation for many of their features. In this scheme, it is assumed that the primary catalyst is [Cp₂TiH], a species frequently cited in the mechanisms of titanocene-catalyzed reactions of silanes.^[7] The amide carbonyl group is expected to undergo insertion into the Ti–H bond, with the oxygen atom attacking the oxophilic Ti, as proposed for other hydrosilylations of carbonyl compounds.^[10–12] The resulting α-aminoalkoxy product **1** could undergo several different reactions. First, in pathway c it is presumed to undergo homolysis of the C–O bond, followed by subsequent coupling of two benzylamine radicals to form the 1,2-diaminoethane product. We are unaware of any precedent for this homolysis reaction, but it is expected to be a high activation-energy process that would be favored under the high temperatures of the experimental conditions. A consequence of the radical



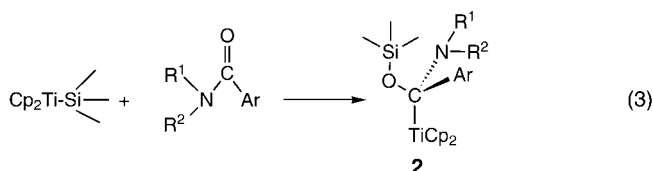
Scheme 1. A $[\text{Cp}_2\text{TiH}]$ -mediated reaction sequence for the reduction, deoxygenation, and coupling of amides in the presence of PhMeSiH_2 . See text for details.

coupling mechanism in this reaction is that the structure of the catalyst complex has no influence over its stereochemical outcome.

In pathway d a σ -bond metathesis between the C–O bond and Si–H cleaves off the benzylamine product, with the concomitant formation of a siloxytitanium complex. Another possible mechanism for the formation of the benzylamine is the abstraction of an H atom from Si–H by the aminotolyl radical. In this case, the ratio of ethylenediamine to benzylamine products is simply a reflection of the competitive rates of the recombination and hydrogen-abstraction rates of the aminotolyl radicals. Some of the variations in chemoselectivity evident in Table 3 may be a result of the different rates of H-atom abstraction from the different silanes.

Finally, in step e an intramolecular metathesis, which is initiated by attack of the basic amine nitrogen, leads to the formation of a covalent Ti–N bond and the displacement of the aryl aldehyde. In these reactions, the aldehyde appears directly in the reaction and does not seem to be derived from an enamine intermediate (see ref. [8]). The titanium complexes produced as coproducts in pathways c, d, and e are all expected to regenerate the titanocene hydride catalyst by reaction with PhMeSiH_2 .

A plausible set of alternative reactions could involve the addition of a silyl titanocene catalyst to the carbonyl group [Eq. (3)]. It is well established that both Ti–H and Ti–Si



species are formed by the reactions of hydrosilanes with $[\text{Cp}_2\text{TiX}_2]$ complexes,^[7] and that hydrosilylation can be initiated either by the addition of M–H or M–Si to a multiple bond.^[13] The direction of insertion shown in Equation 3 is chosen on the basis of the known greater oxophilicity of Si than that of Cp_2Ti . The presence of a Ti–C bond would

facilitate the production of a C-based radical because of the relatively weak Ti–C bond. Further speculation concerning the possible reactions of **2** will be deferred until more is known about the chemistry of such species.

Experimental Section

The reactions with $[\text{Cp}_2\text{TiF}_2]$ were carried out at both 20 °C and 80 °C (Method A, Table 1). The reactions with $[\text{Cp}_2\text{TiMe}_2]$ were carried out only at 80 °C (Method B, Table 1), by using the same procedure as with the fluoride. Typical procedures are as follows:

80 °C: *N,N*-Dimethylbenzamide (149 mg, 1 mmol), $[\text{Cp}_2\text{TiF}_2]$ (21 mg, 0.1 mmol), and MePhSiH_2 (0.28 mL, 2 mmol) were mixed in toluene (1 mL) at room temperature and then stirred on a preheated 80 °C oil bath for 1 h. On cooling the green solution to room temperature, *meso*-*N,N,N',N'*-tetramethyl-1,2-diphenylethylenediamine precipitated as a crystalline solid. Diethyl ether (5 mL) was added to the mother liquor, and the solution was extracted with aqueous HCl (1 M, 3 × 2 mL). The aqueous extract was neutralized with KOH (3 M) and extracted with diethyl ether. *rac*-*N,N,N',N'*-Tetramethyl-1,2-diphenylethylenediamine was separated from the residual *meso* isomer by column chromatography.

20 °C: $[\text{Cp}_2\text{TiF}_2]$ (21 mg, 0.1 mmol) and MePhSiH_2 (40 μL , 3 mmol) in toluene (0.5 mL) were heated at 70 °C for 10 min to effect activation (reduction) of the precatalyst. The green solution was cooled to room temperature, and further aliquots of MePhSiH_2 (0.28 mL, 2 mmol) and *N,N*-dimethylbenzamide (149 mg, 1 mmol) dissolved in toluene (0.5 mL) were added. The reaction was monitored by thin-layer chromatography, and the ratios of the products were calculated from their ¹H NMR spectra. The identities of the products were confirmed by comparing their properties to those in the literature.^[14]

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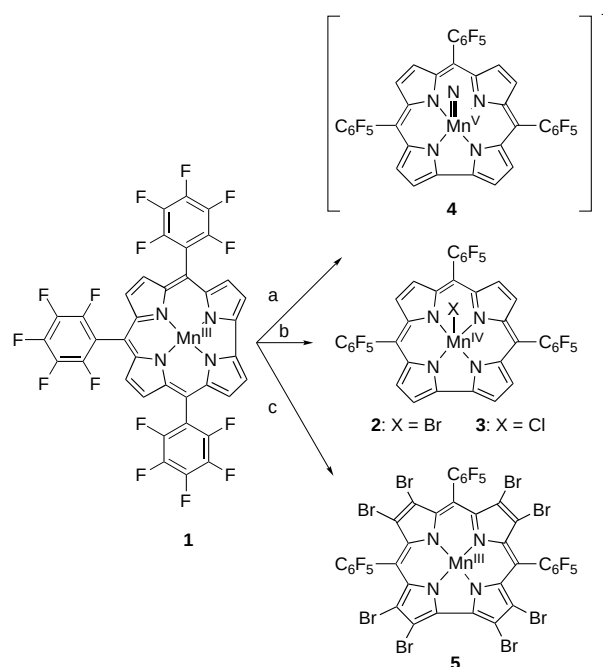
High-Valent Manganese Corroles and the First Perhalogenated Metalloporphyrin**

Galina Golubkov, Jesper Bendix, Harry B. Gray,*
Atif Mahammed, Israel Goldberg,* Angel J. DiBilio,
and Zeev Gross*

Two major goals of research on the manganese(III) porphyrin catalyzed oxygenation of hydrocarbons are improved activity/lifetime profiles and the identification of reaction intermediates.^[1] Increasingly more active catalysts have been obtained by replacing tetraphenylporphyrin with halo-phenyl analogues, and then with derivatives in which the β -pyrrole carbons are halogenated as well.^[2] Interestingly, this effect is more pronounced for manganese than for iron porphyrins.^[1a, 2b] Spectroscopic identification—particularly by NMR—of proposed manganese(V) intermediates should be relatively straightforward, since d^2 metalloporphyrins with strong π -donor ligands are expected to be diamagnetic. The first ^1H NMR spectroscopic characterization of a (nitrido)manganese(V) complex indeed dates from 1983,^[3] but the spectrum of an (oxo)manganese(V) porphyrin was obtained only very recently.^[4] Manganese(IV) porphyrins are more stable: X-ray structures have been reported for several $[\text{Mn}(\text{por})(\text{OR})_2]$ complexes (e.g., $\text{R} = \text{CH}_3$, C_6H_5 , $\text{por} = \text{porphyrin}$);^[5] but so far the characterization of high-valent manganese porphyrins with oxo or halo ligands is limited to spectroscopic methods.^[6]

Corroles are known to be superior to porphyrins in stabilizing high oxidation states of various transition metals,^[7] but until recently only trivalent complexes were reported for manganese.^[8, 9] Furthermore, the oxidation state assignment of the *formally* manganese(III) and manganese(IV) complexes of octaalkylcorroles remained ambiguous because of some indications that the corrole is oxidized.^[8, 9] In addition, octaalkylcorrole metal complexes have never been examined in oxidation catalysis, probably because *meso* aryl substitution is almost always required in the related porphyrin-based catalysts. However, this situation is changing dramatically as a

result of the introduction of the electron-poor 5,10,15-tris(pentafluorophenyl)corrole ($\text{H}_3(\text{tpfc})$),^[10] tpfc = the trianion). The iron, manganese, and rhodium complexes of $\text{H}_3(\text{tpfc})$ have been shown to be potent catalysts for the oxygen and carbene transfer to olefins and alkanes,^[11] with a readily observed (oxo)manganese(V) intermediate in epoxidation catalyzed by $[\text{Mn}(\text{tpfc})]$ (**1**).^[11b] In addition, the $\text{Fe}^{\text{IV}}(\text{Cl})$, $\text{Rh}^{\text{III}}(\text{PPh}_3)$, $\text{Cr}^{\text{V}}(\text{O})$, and $\text{Mn}^{\text{III}}(\text{OPPh}_3)$ complexes have been fully characterized by a combination of spectroscopic methods and X-ray crystallography.^[12] In all these complexes there were no indications for oxidation of the corrole, as opposed to the ambiguity in the case of the iron and manganese octaalkylcorroles.^[8, 9, 13] We now show that **1** can be functionalized at both the metal and the corrole centers, which leads to the isolation and full characterization of two manganese(IV) corroles, a stable (nitrido)manganese(V) corrole, and a perhalogenated manganese(III) corrole (Scheme 1). Preliminary results for the perhalogenated manganese(III) corrole demonstrate its superior activity as an oxidation catalyst.



Scheme 1. a) NaN_3 , $h\nu$, b) $1/2\text{X}_2$ ($\text{X} = \text{Cl}, \text{Br}$), c) excess Br_2/MeOH .

Cyclic voltammetry of **1** reveals a redox potential of 0.71 V (vs. standard calomel electrode (SCE)), suggesting that mild oxidants could be used for the isolation of novel high-valent manganese corroles. Indeed, treating a green hexane solution of the highly soluble **1** with bromine or tris(4-bromophenyl)-aminium hexachloroantimonate results in the immediate and quantitative precipitation of $[\text{Mn}(\text{tpfc})(\text{Br})]$ (**2**) and $[\text{Mn}(\text{tpfc})\text{Cl}]$ (**3**), respectively.^[14, 15] The electronic spectra of these complexes (each exhibits a single Soret band) are very similar to those of manganese(IV) porphyrins,^[4–6] suggesting that the oxidations are metal rather than corrole centered. Reduction of **2** (Figure 1) produces a UV/Vis spectrum that is identical to that obtained by adding $n\text{-Bu}_4\text{N}^+\text{Br}^-$ to **1**, corresponding to the metal-centered couple $[\text{Mn}^{\text{IV}}\text{–Br}]/$

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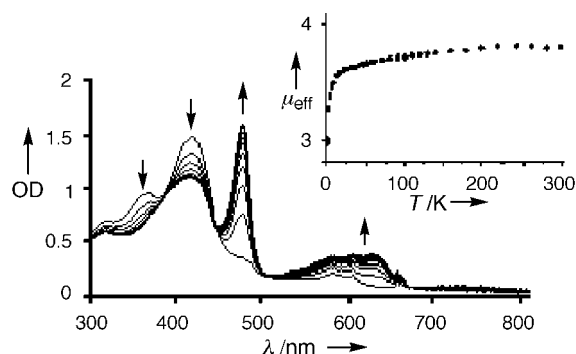


Figure 1. Spectroelectrochemical reduction of **2** at 0.4 V and a plot of the magnetic moment versus T for **2**.

$[\text{Mn}^{\text{III}}-\text{Br}]^-$. Also consistent with the reduction of the metal center is the large dependence of the reduction potential on axial ligation; $E_{1/2} = 0.69$ and 0.41 V for **2** and **3**, respectively. This proposal was further supported by magnetic susceptibility measurements (SQUID, Figure 1, inset) on **2** and its EPR spectra (not shown, frozen CH_2Cl_2 at 130 K; solid at room temperature). The magnetic moment of $3.80 \mu_{\text{B}}$ and the EPR data (broad $g = 4.3$ signal and a $g = 1.99$ signal with resolved Mn hyperfine structure, $a_{\text{Mn}} = 85$ G) confirm an isolated $S = 3/2$ system, in line with the electronic structure of other manganese(IV) complexes.^[16] The alternative formulation of **2** and **3** as manganese(III) corrole radical complexes is expected to result in much more complex magnetic data and EPR spectra.^[6b]

X-ray crystallographic analysis of **2** and **3** (Figure 2) reveals a pronounced doming of the corrole framework in both structures, with all four pyrrole nitrogens lying significantly

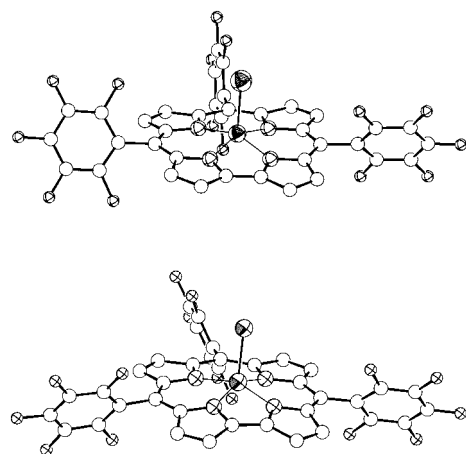


Figure 2. ORTEP views of $[\text{Mn}(\text{tpfc})(\text{Br})]$ (**2**; top) and $[\text{Mn}(\text{tpfc})(\text{Cl})]$ (**3**; bottom).

above the 19-membered carbon ring (average out of plane distance of $0.065 \text{ \AA}$ in **2** and $0.21 \text{ \AA}$ in **3**). As expected, the manganese(IV)–halide bond lengths of 2.428 and $2.312 \text{ \AA}$ in **2** and **3**, respectively, are shorter (by approximately $0.05 \text{ \AA}$) than those found in analogous manganese(III) porphyrin complexes.^[17, 18] The average Mn–N bond lengths in **2** ($1.925 \text{ \AA}$) and **3** ($1.932 \text{ \AA}$) are longer than those in $[\text{Mn}^{\text{III}}(\text{tpfc})(\text{OPPh}_3)]$ ($1.916 \text{ \AA}$),^[12c] but this is because of very large differences in the out of plane displacements of the manga-

nese atom. Corresponding deviations from the N4 and corrole planes are 0.42 and $0.47 \text{ \AA}$ in **2**, 0.43 and $0.58 \text{ \AA}$ in **3**, but only 0.29 and $0.29 \text{ \AA}$ in $[\text{Mn}^{\text{III}}(\text{tpfc})(\text{OPPh}_3)]$.^[12c] Interestingly, the Mn–Cl and Mn–N bond lengths in **3** and $[\text{Mn}(\text{oec})(\text{Cl})]$ are very similar,^[9] despite the large structural and electronic differences between the corroles.

In the course of these studies, we noted two other unique features of **1**, both of which could be exploited for preparation of novel manganese corroles. First, the aforementioned high affinity of **1** for Br^- was also applied to N_3^- , which led to a one-pot version of the known protocol for preparation of (nitrido)metal complexes:^[19] irradiation of a mixture of **1** and NaN_3 in CH_3CN resulted in very clean conversion into $[\text{Mn}^{\text{V}}(\text{tpfc})(\text{N})]^- \text{Na}^+$ (**4**). This complex, which is stable at room temperature in solution or as a solid, was identified by a combination of spectroscopic methods (Figure 3). Both the sodium ion and the nitrido ligand are apparent in the mass spectrum (MS); sharp resonance signals in the NMR spectrum are consistent with a diamagnetic manganese(V) center; and the UV spectrum of **4** is very similar to that of analogous neutral (nitrido)manganese(V) porphyrins.^[3]

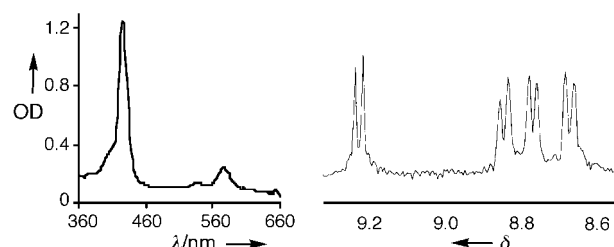


Figure 3. ^1H NMR and UV/Vis spectra of **4** in CD_3CN at room temperature.

Second, we noticed remarkably facile pyrrole-substitution during the aforementioned metal-based oxidation of **1**. In fact, the first two crystal structures of **2** and **3** were obtained with partially halogenated (Br, Cl) corroles. This phenomenon was exploited by treating **1** with an excess of Br_2 in MeOH, which allowed isolation of the fully brominated complex,^[20] $[\text{Mn}(\text{Br}_8\text{tpfc})]$ (**5**), in high yield. In contrast, the preparation of analogous porphyrins requires four synthetic steps: metallation of the porphyrin by zinc, bromination of the zinc complex with NBS (1-bromo 2,5-pyrroledione), not Br_2 as with the corrole, removal of the zinc, and metallation by manganese.^[2] The transformation of **1** to **5** causes a 0.37 V shift of the $\text{Mn}^{\text{III}}/\text{Mn}^{\text{IV}}$ couple in the cyclic voltammogram (Figure 4), which is the reason that **5** is isolated in the manganese(III) oxidation state, despite the fact that the first equivalent of bromine oxidizes **1** to **2**. To assess differences in reactivity between the “second and third generation” manganese(III) corroles,^[2a] **1** and **5** were compared as catalysts for oxygenation of three representative substrates (Scheme 2). Both complexes catalyze the oxidation of styrene by iodosylbenzene in very high yield, but with a very large difference in reaction time: 10 h with **1** compared to 15 min with **5**. These differences were amplified with the less reactive substrates: yields of 100% versus 40% for *trans*-stilbene and 100% versus only 11% for cyclohexene catalyzed by **5** (15 min) and

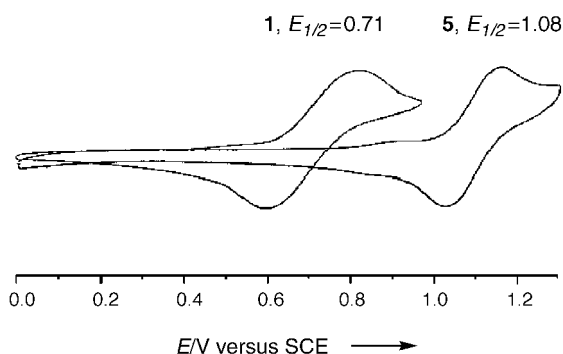
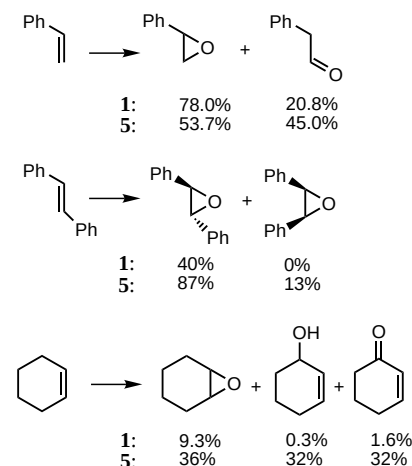


Figure 4. Cyclic voltammetry of [Mn(tpfc)] (**1**) and [Mn(Br₈tpfc)] (**5**), in CH₂Cl₂ with 0.1 M TBAP.



Scheme 2. **1** and **5** as oxygenation catalysts, reaction conditions: substrate (1.2 mmol), iodosylbenzene (0.12 mmol), catalyst (1.2 μmol), benzene (1 mL) at room temperature under Ar, for 15 min with **5** and 10–12 h with **1**.

1 (12 h), respectively. Most significantly, **5** was not bleached at the end of all reactions, while this is only true for **1** in the reaction with styrene.

In conclusion, we have demonstrated that functionalization of the manganese(III) complex of H₃(tpfc) provides a facile route to various high-valent manganese corroles and to the first perhalogenated corrole-based catalyst, all in very simple one-pot syntheses. The very large increase in catalytic activity upon β-pyrrole bromination of **1** to **5** will be fully investigated.

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- [14] **2**: A hexane solution of **1** (10 mg, 11.8 μmol) was treated with a hexane solution of Br₂ (5.9 μmol), which resulted in quantitative precipitation of **2** as a red-brown solid. MS[−]: *m/z* (%): 927 (40) [*M*[−]], 848 (100) [*M*[−] − Br], UV/Vis (CH₂Cl₂) λ_{max} [nm] (lg ε) 368 (4.63), 416 (4.72), 582 (3.74); elemental analysis (%) calcd for C₃₇H₈BrF₁₅MnN₄·2H₂O: C 46.08, H 1.25, N 5.81; found: C 45.76, H 1.38, N 6.20. Recrystallization from benzene/heptane resulted in X-ray quality crystals. [Mn(tpfc)(Br)], crystallized as benzene hemi-solvate (C₃₇H₈BrF₁₅MnN₄)·½(C₆H₆): formula weight 967.38, monoclinic, space group *P*2₁/*c*, *a* = 13.425(1), *b* = 23.629(1), *c* = 11.208(1) Å, β = 98.38(1)°, *V* = 3517.5(2) Å³, *Z* = 4, *T* = 110 K, ρ_{calcd} = 1.827 g cm^{−3}, μ(MoKα) = 1.63 mm^{−1}, 6636 unique reflections, *R*₁ = 0.053 for 4854 observations with *F*_o > 4σ(*F*_o), *R*₁ = 0.082 (*wR*₂ = 0.148) for all unique data, |Δρ| = 1.31 e Å^{−3}.
- [15] **3**: A hexane solution of **1** (2.5 mg, 3 μmol) was treated with a dichloromethane solution of tris(4-bromophenyl)ammonium hexachloroantimonate (2.5 mg, 3 μmol), which resulted in quantitative precipitation of **3** as a red-brown solid. MS[−]: *m/z* (%): 883 (25) [*M*[−]], 848 (100) [*M*[−] − Cl]; UV/Vis (CH₂Cl₂) λ_{max} [nm] (lg ε) 362, 414 (Soret), 582 (Q band). Recrystallization from benzene/heptane resulted in X-ray quality crystals. [Mn(tpfc)(Cl)], crystallized as dibenzene solvate (C₃₇H₈ClF₁₅MnN₄)·2(C₆H₆): formula weight 1040.08, triclinic, space group *P*1̄, *a* = 8.547(1), *b* = 13.488(1), *c* = 19.675(1) Å, α = 71.08(1), β = 85.59(1), γ = 73.88(1)°, *V* = 2061.1(2) Å³, *Z* = 2, *T* = 110 K, ρ_{calcd} = 1.676 g cm^{−3}, μ(MoKα) = 0.50 mm^{−1}, 7056 unique reflections, *R*₁ = 0.062 for 4274 observations with *F*_o > 4σ(*F*_o), *R*₁ = 0.128 (*wR*₂ = 0.147) for all unique data, |Δρ| = 0.55 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-147467 (**2**) and CCDC-147468 (**3**). 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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- [20] [Mn(Br₈tpfc)] **5**: A solution of bromine (5 mL, 0.2 g, 1.2 mmol) and **1** (10 mg, 12 μmol) in methanol was stirred overnight, after which the methanol and excess bromine were removed under vacuum. Recrystallization from ethanol/water afforded 14.8 mg (85% yield) of **5**. MS[−]: *m/z* (%): 1479 (100) [*M*[−]], 1399 (10) [*M*[−] − Br]; UV/Vis (CH₂Cl₂) λ_{max} [nm] 402 (4.73), 422 (4.70), 490 (4.38), 612 (4.24); ¹⁹F NMR (CDCl₃): δ = −138 (two overlapping brs, 6F), −152.3 (brs, 1F), −153.2 (brs, 2F), −160.5 (brs, 2F), −161.4 (brs, 4F).

Self-Assembly of Uniform Spherical Aggregates of Magnetic Nanoparticles through $\pi-\pi$ Interactions**

Jian Jin, Tomokazu Iyoda, Changsheng Cao, Yanlin Song, Lei Jiang,* Tie Jin Li,* and Dao Ben Zhu

The assembly of nanostructured materials into organized and designed structures is an important goal in materials chemistry for application in electronic devices.^[1] The building and patterning of inorganic nanoparticles into two- and three-dimensional organized structures by manipulation of individual units is a potential route to chemical, optical, magnetic, and electronic devices with useful properties.^[2] Among these, the synthesis of magnetic nanoparticles which endow superparamagnetic properties is an issue of current interest, both from a fundamental point of view and for applications in materials science.^[3–5] For example, the composite formed from magnetic nanoclusters and conducting oligomers may possess unique applications in such areas as electromagnetic interference shielding and electrochromic devices, as well as sensing and actuating technologies.^[6, 7]

Self-assembly based on the spontaneous control of materials through noncovalent interactions (hydrogen bonding,^[8, 9] van der Waals forces,^[10, 11] and electrostatic forces^[12, 13]) with no external intervention provides a powerful method for employing pre-programmed materials with the potential for multi-dimensional ordering for the creation of well-defined structure at a molecular level. Monolayer-functionalized nanoparticles that act as building blocks have been fabricated into ordered architectures for such approaches. Recently, Rotello and co-workers^[14] reported that polymeric monolayer-protected gold particles self-assembled into spherical aggregates through hydrogen-bonding interactions. In their strategy, the polymers acted as the mortar to hold the colloidal particles together to form spherical aggregates. However, these aggregates were not very uniform, since the uniformity of the aggregates is governed by the uniformity of the polymer chain and the self-assembly process. Herein, we report the surprising finding that individual monolayer-coated magnetic nanoparticles self-assemble into uniform spherical aggregates through $\pi-\pi$ interactions. The monolayer used was 2-carboxy-

terthiophene (TTP-COOH). Thiophene oligomers have been used as active organic semiconductor materials because of their attractive nature as conjugators and electrical conductors. Thiophene oligomers undergo self-assembly by holding together individual molecules (elemental bricks) in an orderly manner through weak van der Waals forces to build up materials.^[15]

The formation of a magnetite crystal phase in a TTP-COOH-coated Fe_3O_4 aggregate powder was identified from the X-ray diffraction pattern (Figure 1). The pattern obtained confirms that the nanoparticles prepared in this study are the magnetite nanocrystals. The Bragg reflection peaks are all relatively broad because of the extremely small dimensions of the Fe_3O_4 nanocrystals.

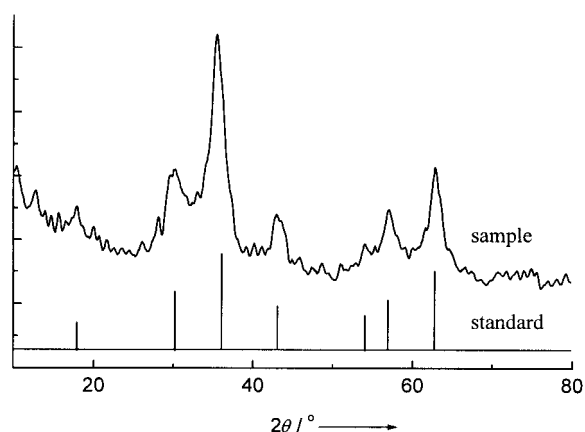


Figure 1. X-ray diffraction pattern of TTP-COOH-coated Fe_3O_4 aggregate powder. The vertical lines at the bottom are the reference data for the Fe_3O_4 standard taken from powder diffraction file 19-0629 from the Database of the International Center for Diffraction Data (ICDD).

The formation of self-assembled spherical aggregates can be directly visualized by transmission electron microscopy (TEM; Figure 2a, b). It can be seen that highly ordered and uniform spherical aggregates with a mean diameter of 148 ± 5 nm are obtained. These spherical aggregates are composed of 2000–4000 intensely dark spots per microsphere. These dark spots are individual TTP-COOH-coated Fe_3O_4 nanoparticles. Every nanoparticle, with a size of 6.0 ± 1.3 nm, appears as a discrete entity in the microsphere. The microspheres are transparent and the intersection between two clusters can be clearly seen. However, the interaction between individual particles is relatively weak and the spherical aggregates can be destroyed by sonication. As shown in Figure 2c, the self-assembled microspheres disappear after sonication treatment and the individual nanoparticles are monodispersed. The mean diameter of the individual nanoparticles is about 6–8 nm, which is consistent with the size of the dark spots in the microsphere.

A model for the self-assembly observed in the aggregated structure is shown in Figure 3. The driving force for the formation of aggregates is considered to be $\pi-\pi$ interactions between individual nanoparticles. This can be confirmed by examination of the absorption spectra (Figure 4). Pure TTP-COOH in toluene shows one strong absorption band at 378 nm, while in TTP-COOH-coated Fe_3O_4 aggregates in

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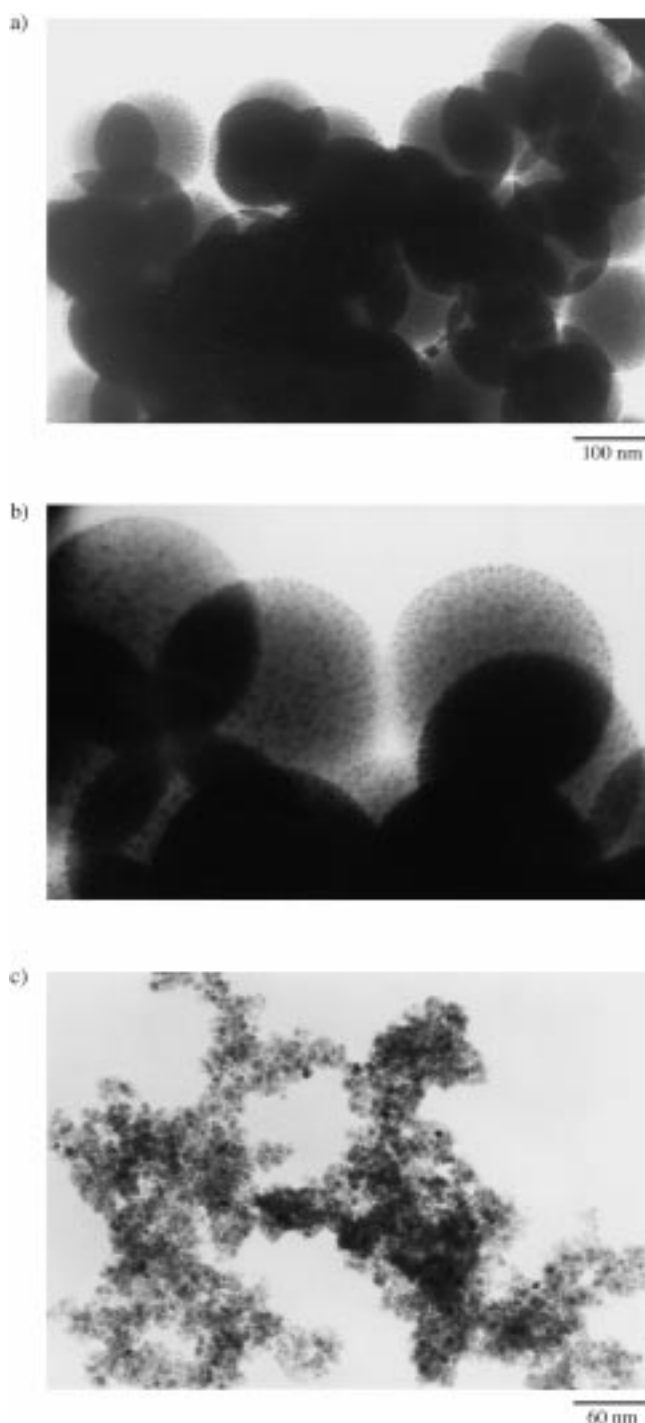


Figure 2. TEM images of a) self-assembled microspheres prepared by dropping the as-prepared TTP-COOH-coated Fe_3O_4 solution on a carbon-coated copper grid, b) enlarged image, c) parent solution treated by sonication (at a working frequency of 40 kHz for 20 min) dropped on a carbon-coated copper grid.

ethanol the TTP-COOH absorption band is red-shifted to 400 nm. After sonicating the solution used to generate curve b, the red-shifted absorption band returns to 378 nm, which corresponds to the pure TTP-COOH absorption band. These results confirm the existence of π - π interactions between individual nanoparticles in the microsphere. The anti-parallel dipole interaction between the conjugated back-

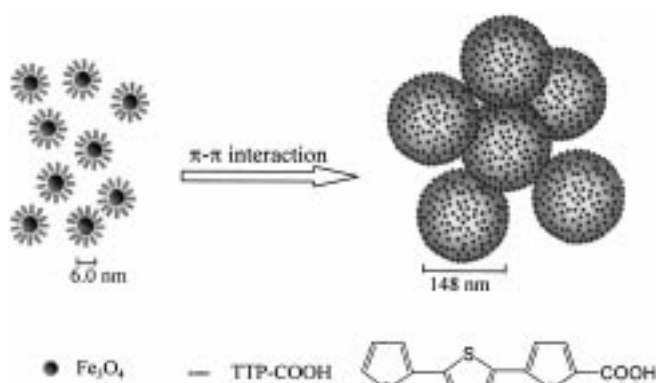


Figure 3. Structure model proposed for the self-assembly process of individual nanoparticles to form microspheres through π - π interactions. The sizes of individual nanoparticles and microspheres can be determined directly by TEM.

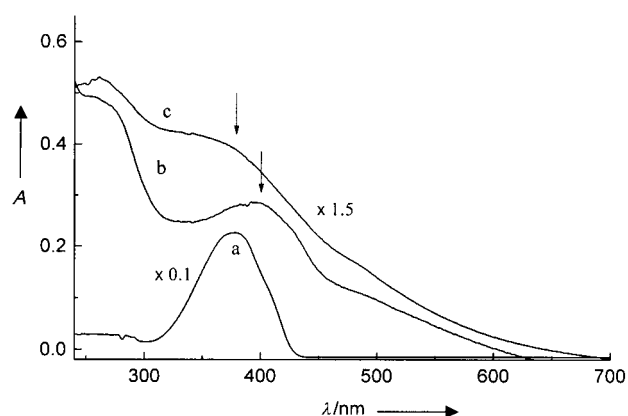


Figure 4. UV/Vis absorption spectra of a) pure TTP-COOH in toluene at a concentration of $5 \times 10^{-6} \text{ mol L}^{-1}$, b) as-prepared TTP-COOH-coated Fe_3O_4 solution in ethanol after dilution, and c) diluted TTP-COOH-coated Fe_3O_4 solution in ethanol after sonication (working frequency: 40 kHz).

bone of terthiophene molecules in adjacent nanoparticles leads to the red-shift of the absorption band.^[16] In general, there is an indirect dipole-dipole interaction between adjacent core/shell magnetic nanoparticles as a result of the existence of the shell.^[17] The indirect magnetic interaction will cause the nanoparticles to form an isometric shape with a fractal structure.^[18, 19] The formation of spherical aggregates in the present system indicates that the magnetic interaction contributes little to the structure compared with the effect of the π - π interaction.

The formation of spherical aggregates from individual magnetic nanoparticles is considered to be a cooperative effect between the π - π interaction and the particle growth in the given reaction environment. The formation of spherical aggregates is divided into two stages. The first stage is the formation of individual TTP-COOH-coated Fe_3O_4 nanoparticles. This is a rapid process and can be completed by vigorous stirring. The magnetite nanoparticles were synthesized by a typical chemical coprecipitation of Fe^{II} and Fe^{III} salts in ammonium hydroxide solution. The size of the nanoparticles is controlled by the reaction conditions, such as temperature, stirring rate, and concentration. In our experimental conditions, the size of the nanoparticles is

limited to 6–8 nm, which is in agreement with the results obtained by other researchers who used the same coprecipitation method.^[20, 21] In the second stage, the individual nanoparticles coagulate into aggregates (called secondary particles) through intermolecular interactions (π – π interactions), and is controlled by diffusion-controlled growth. According to the theory of diffusion-controlled growth, every nuclei gathers the neighboring primary particles within its individual field of attraction, which extends as a circular arc around a spherical particle to a defined distance from the center of the particle. It is not therefore surprising that the secondary particles obtained are spherical when the formation process is considered.^[22] The growth of the microspheres in the water/oil (toluene) mixture solution is also influenced strongly by the variation of the surface energy with size. The particles tend to grow into a spherical shape in order to minimize their surface energy.^[23] The critical size distribution of the spherical aggregates is also in accordance with the principle of diffusion-controlled growth, which states that the size distribution becomes narrower with particle growth.^[24]

The magnetic characteristics of the aggregates were examined on a superconducting quantum interference device (SQUID) magnetometer. The field- and temperature-dependent magnetization data for the aggregates is shown in Figure 5. The curves obtained at 300 K are perfectly superimposable as the field is cycled between –5 and 5 kOe. The

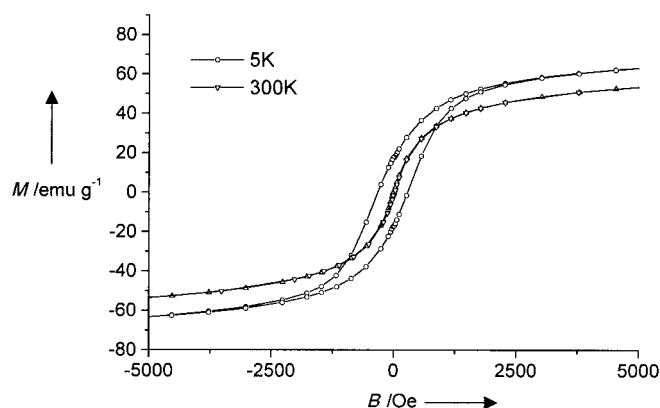


Figure 5. Magnetization versus applied field plots at 300 and 5 K for TTP-COOH-coated Fe_3O_4 aggregates.

curves are consistent with superparamagnetic behavior and the nanoscale dimensions of the particles.^[25, 26] As the temperature is lowered to 5 K, the magnetization of the aggregates increases and exhibits a symmetric hysteresis loop, which indicates the transition from superparamagnetic to ferrimagnetic behavior.

In this work, a new method to build nanostructured spherical aggregates from individual magnetic nanoparticles has been developed. The results demonstrate a strategy directed by π – π interactions for the self-assembly of individual magnetic nanoparticles into structured ensembles. Discrete microspheres formed using this method are highly ordered and uniform on the nanometer scale. This work represents a powerful and general strategy for the creation of highly structured multifunctional materials.

Experimental Section

Synthesis of 2-carboxyterthiophene: Terthiophene (2.480 g, 0.01 mol)^[27] was added to dried THF (30 mL), and then a solution of lithium diisopropylamide ($\text{LiN}(\text{iPr})_2$, 0.54 g, 5.0 mmol) in *n*-hexane (20 mL) added dropwise within 10 min. The reaction was maintained at -87°C for 1 h before purging with dried CO_2 gas for 30 min. The mixture was then stirred for 2 h at -78°C . The temperature was then raised slowly to room temperature and stirred for 24 h. The resulting mixture was neutralized carefully by the addition of an aqueous solution of HCl (3%) and then filtered. Diethyl ether (100 mL) was added to the filtrate and the organic layer was washed sequentially with 3% aqueous HCl (3×10 mL) and water (3×25 mL). After drying with MgSO_4 , the solvent was removed by rotary distillation. The resulting product was separated by column chromatography on SiO_2 (4.0×20 cm, acetone/*n*-hexane 1/9). The product yield was 34.2%. M.p. 239 – 240°C ; FT-IR (KBr, cm^{-1}): $\bar{\nu}$ = 3066.26, 1625.70, 1427.07, 696.18 (thiophene), 1625.70 ($-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$), 1427.07 ($-\text{CH}=\text{S}-$), 1691.27 ($-\text{COOH}$); UV/Vis (DMF): 265, 378 nm. Elemental analysis calcd (%) for $\text{C}_{13}\text{H}_8\text{O}_2\text{S}_3$: C 54.87, H 3.28, S 31.39; found: C 54.83, H 3.19, S 31.07.

Synthesis of TTP-COOH-coated Fe_3O_4 nanoparticles and spherical aggregates: $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (0.15 g) and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (0.416 g) were dissolved under N_2 in deaerated Milli-Q water (20 mL) with vigorous stirring. As the solution was heated to 60°C , $\text{NH}_3 \cdot \text{H}_2\text{O}$ (28% (w/w), 1 mL) was added, quickly followed by a solution of TTP-COOH (3 mg) in DMF (17 mL; a small quantity of toluene was added to enhance the solubility). The reaction was allowed to proceed for 1 h at 80°C with constant and vigorous stirring to produce a stable, water-based suspension. The reaction mixture was then cooled slowly to room temperature. The suspension was washed sequentially with DMF, ethanol, and acetone (each $\times 3$).

The X-ray diffraction pattern was recorded on a Rigaku D/max-2400 diffractometer using the monochromatized X-ray beam from nickel-filtered $\text{Cu}_{\text{K}\alpha}$ radiation. TEM was performed on a JEM 100CX electron microscope operating at 200 kV by placing a drop of the suspension solution onto a carbon-coated copper grid and letting the water evaporate slowly in air. The UV/Vis absorption spectra were recorded on a Shimadzu UV-3101 spectrophotometer. Magnetic data were obtained on a SQUID magnetometer (Quantum Design MPMS-5S).

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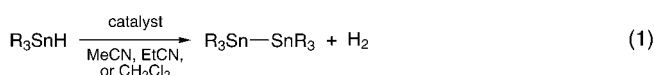
Dehydrogenative Dimerization of Tin Hydrides Catalyzed by Ruthenium–Allenylidene Complexes**

Susan M. Maddock and M. G. Finn*

The cycloaromatization rearrangement of *ortho* alkyl-substituted aromatic transition metal vinylidene complexes provides a means for a terminal alkyne to act as a synthon for a benzylic radical.^[1] In an effort to engender the

production of a higher-energy sp^2 radical, we have prepared several metal–allenylidene species with the requisite alkynyl substituents. In the course of screening H-atom donors with which to study the as yet undetermined decomposition pathways of these species, we observed a rapid dehydrogenative dimerization of tributyltin hydride, this dimerization requires the presence of a pendant unsaturated substituent. Here we describe this process and report the results of experiments designed to probe the catalytic mechanism.

The generation of $R_3Sn-SnR_3$ dimers from the corresponding monohydrides [Eq. (1)] is known to be catalyzed by a



diverse set of transition metal complexes, including simple Pd^{II} precursors,^[2–4] $[Cp_2YH]$ (Cp = cyclopentadiene),^[5] and $[(PPh_3)_3AuCl]$.^[6] By far the most active catalysts are several diphosphane-bridged Fe/Pd heterobimetallic complexes in which the reaction is thought to occur at the Pd center, while the Fe center is proposed to play an important supporting role.^[4, 7] Similar dehydrogenative pathways are presumably employed in the synthesis of oligomeric and polymeric diorganostannanes from tin dihydrides,^[4] including reactions catalyzed by low-valent metallocene or Group VI hexacarbonyl complexes.^[8]

Allenylidene complexes of the $[CpRu(PMe_3)_2]^+$ ion were prepared by the method of Selegue (details in Supporting Information).^[9] A total of 13 derivatives were assembled (for the structures of complexes **1–13** see Table 1), in all cases, ^{13}C NMR signals were observed at $\delta = 293–299$, $213–228$, and $149–154$, for the C_α , C_β , and C_γ centers, respectively, with no attached protons, and a sharp band was found in the infrared spectrum at $1913–1925\text{ cm}^{-1}$. These data serve to substantiate the allenylidene structure and rule out the cyclic isomer recently identified for analogous complexes of the $[Cl_2(PR_3)_2Ru]$ fragment.^[10] An X-ray crystal structure obtained for the *para*-nitro derivative **12** (Supporting Information)^[11] is similar to the parent complex **2**.^[12]

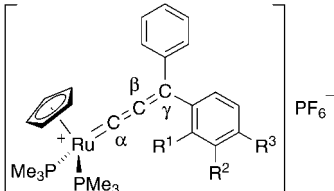
Complex **1** (see Table 1), prepared for the study of diradical cycloaromatization, induces rapid gas evolution and clean production of $(Bu_3Sn)_2$ when added to a large excess of Bu_3SnH in acetonitrile or dichloromethane. With 3 mol % **1** relative to tin hydride, 96% conversion is obtained within 10 mins at room temperature under nitrogen atmosphere. The structural elements necessary for catalysis were probed with complexes **2–12** (Table 1).^[13] Comparisons of activity were made by determining the extent of conversion of Bu_3SnH after exactly 5 mins under a standard set of conditions (1.4 mol % ruthenium catalyst relative to Bu_3SnH); such results do not allow separate analysis of the initial rate and lifetime. Of those species bearing substituents in the *ortho* position, allenylidenes **3** and **4** are of comparable activity to **1** (Table 1), demonstrating that the olefinic moiety of **1** (intended as an intramolecular radical trap in the event of cycloaromatization) is not involved in the catalytic process. Vinylidene complexes **14** and **15**, analogous to **4**, and the

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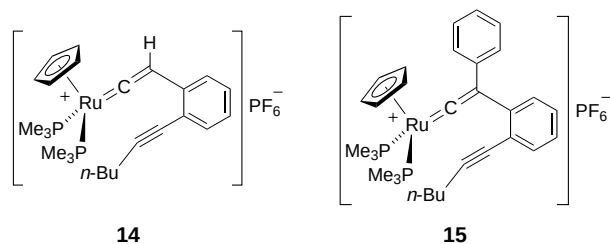
Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

Table 1. Catalytic activity of ruthenium allenylidene complexes.

					
Compound	R ¹	R ²	R ³	Activity (N ₂) ^[a]	Activity (air) ^[b]
1		H	H	68.3 ± 6	n.d.
2	H	H	H	0	trace
3		H	H	67.8 ± 9	100.0 ^[c] , 68.3 ± 8 ^[d]
4		H	H	82.5 ± 9	95.9 ± 5
5		H	H	trace	n.d.
6	<i>n</i> -C ₆ H ₁₃	H	H	trace	0
7	I	H	H	0	n.d.
8	H	H		33.8 ± 11	84.6 ± 7
9	H	H		63.5 ± 7	97.4 ± 1
10	H	H		6.8 ± 0.4	10
11	H		H	52.7 ± 9	n.d.
12	H	H	NO ₂	0	0
13	H	H		13.5 ± 1	46.7 ± 1

[a] Conversion [%] after 5 mins under nitrogen atmosphere (see Experimental Section). [b] Conversion [%] after 5 mins in air (see Experimental Section). [c] Reaction was complete for two independent runs. [d] In the presence of hydroquinone (n.d. = not determined).

Grubbs carbenoid complex **16**, are ineffective, suggesting that the allenylidene unit is required. Complexes **2**, **6**, and **7**,



bearing H, *n*-hexyl, and iodo substituents, respectively, all show little or no activity. Furthermore, the introduction of a methylene spacer between the alkyne and aryl groups (complex **5**) also eliminates catalysis. Thus, direct conjugation of the alkyne with the aryl unit is important for catalytic activity.

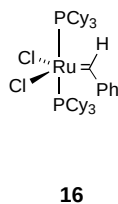
Active catalysts are also obtained when the pendant alkyne fragment is moved to the *para* (complexes **8–10**) and *meta* (complex **11**) positions, allowing our attention to be directed to the electronic properties of the alkyne as opposed to a coordinative or structural role, and ruling out cycloaromatization as a part of the catalytic cycle. The importance of electronic factors is further highlighted by the observation that activity is enhanced by an electron-withdrawing substituent (**9** versus **8**) and nearly abolished by an electron-

donating group (**10** versus **8**). However, the installation of a *para* nitro group in place of a *para* nitro-substituted phenyl-acetylene unit eliminates catalysis (**12** versus **9**), showing that it is the alkyne fragment that is crucial. An (*E*)-1-hexenyl group at the *para* position (**13**) provides modest catalytic activity, indicating that an olefin is more activating than an alkyl group (**5** and **6**), but not as activating as an alkyne.

The electronic nature of complexes **8–10** was probed by cyclic voltammetry in CH₂Cl₂ solution. Reversible reduction waves, presumably arising from the Ru^{III/I} redox couple, were observed at the

following potentials (relative to ferrocene/ferrocenium ion (Fc/Fc⁺)): **10** –1.030 V, **8** –1.023 V, **9** –0.987 V, representing a trend toward slightly easier reduction with increasing electron-withdrawing power of the *para* substituent. In each case, irreversible one-electron oxidation (ca. +0.8 V versus Fc/Fc⁺) and reduction (ca. –1.8 V versus Fc/Fc⁺) waves were also observed. No correlation between catalytic activity and ¹³C NMR spectroscopic chemical shifts, or between catalytic activity and the positions and intensities of UV/Vis bands, or infrared spectral features of the allenylidene complexes are apparent.

Catalytic reactions involving **3** and **4** were examined further. Under a nitrogen atmosphere, the extent of conversion at 5 min is not affected by the presence of 50 equiv-



alents (with respect to Ru) of hydroquinone, suggesting that the process is not radical in nature.^[14] However, it appears that competitive with the catalytic reaction is a decomposition process that is slowed or reversed by the presence of oxygen. For example, reducing the loading of complex **4** to 0.11 mol % gives 98 % conversion of Bu₃SnH in 6 h in air (ca. 900 turnovers), but only 79 % conversion under a nitrogen atmosphere. In this case, the reactions proceed to the same extent after the first hour (54 %), but the reaction in air is longer-lived. For a variety of allenylidene complexes, additional catalytic activity was sometimes observed after a flask that contained a reaction that had slowed or stopped under nitrogen was opened to the air. Thus, dehydrodimerization reactions performed entirely in air using complexes **3**, **4**, **8**, **9**, and **13** show increased activities in the standard assay (Table 1) than those in nitrogen. Note, however, that for complex **3** the beneficial effect of air is eliminated by the presence of hydroquinone.

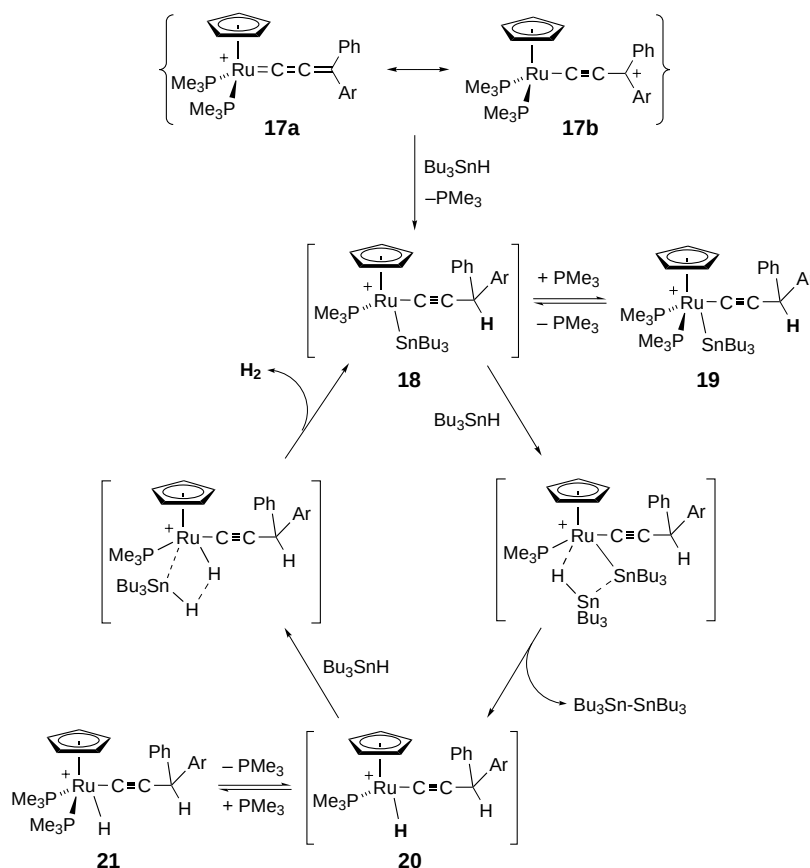
Even in air, catalyst decomposition masks what is a relatively fast process. Thus, a modest kinetic isotope effect (k_H/k_D) of 1.22 ± 0.1 was measured by competition reactions between Bu₃SnH and Bu₃SnD using complex **3** in air. During these studies, the rapid loss of catalytic function was again noted, with reactions being 50 % complete after 30 seconds, 74 % complete after 2 mins, 84 % complete after 8 mins, and 96 % complete after 15 mins. Initial turnover rates are therefore at least 1 s⁻¹, substantially greater than are indicated by the activity values shown in Table 1. These allenylidene systems are slower and shorter-lived than the Fe–Pd bimetallic catalysts of Braunstein et al. (maximum turnover frequency of ca. 8000 s⁻¹ and turnover number of 1×10^6)^[4, 7] but more potent than simple Pd (300–2000 turnovers)^[3, 4] or Au^[6] catalysts.

Loss of catalytic activity is accompanied by a change in color from brown to yellow. This same color change occurs for the catalytically inactive complex **2** over 5–10 mins in the presence of excess Bu₃SnH, suggesting that the process that deactivates the catalysts may not require an allenylidene unit. Unfortunately, no conclusions could be drawn from NMR spectroscopic investigation of the Ru species remaining after catalysis is complete. No evidence of Ru–H bonds was obtained, and the presence of more than one species was suggested by the presence of multiple resonance signals in ³¹P NMR spectra.

In analogy with previous mechanistic hypotheses for other catalysts,^[4] distannane and dihydrogen may be produced from σ -bond metathesis reactions of M–SnR₃ and M–H intermediates, respectively, with R₃Sn–H.^[15] The observed kinetic isotope effect, while substantially smaller than that observed for related reactions of Group IV organometallics with silanes ($k_H/k_D = 2.7–3.6$),^[16] is close to the value found for a σ -

bond metathesis process involving interaction of H centers with [Cp(PR₃)₂Ru]⁺ and boron ($k_H/k_D = 1.62 \pm 0.13$).^[17]

If one accepts the above assumption, then the crucial mechanistic issues are the generation of the required coordinatively unsaturated species containing a Ru–Sn or Ru–H bond, and the roles of the diarylallenylidene fragment and its alkyne or alkene substituents in facilitating that process. The outline of a working hypothesis is shown in Scheme 1. Although not a major contributor (as indicated by X-ray crystal structures and ¹³C NMR spectroscopic data), resonance form **17b** can be involved in the distribution of charge in allenylidene complexes, and provides a way to connect reactivity at the metal center with substituents on the remote aromatic groups. Oxidative addition of tin hydride across the allenylidene unit would make available 16 electron or 18 electron Ru^{IV} intermediates **18** and/or **19** as the true catalyst(s) of sequential σ -bond metathesis steps to create Sn–Sn and H–H bonds as shown.^[18] While the Hammett constants of *para* and *meta* substituents are substantially different for strongly donating groups such as NH₂ ($\sigma_{para} = -0.66$, $\sigma_{meta} = -0.16$), they are quite similar for other π -conjugated units such as CN (0.66, 0.56), Ph (–0.01, 0.06), and even NO₂ (0.78, 0.71). Thus, it is reasonable to expect both *meta* and *para* alkyne substituents to play a similar role if their electron-delocalizing abilities are important, as is indeed observed (complexes **4** and **11**, Table 1). However, the role played by such delocalization (explaining, for example, why **9** is active and **12** is not) and the exact nature of the active catalytic species remain to



Scheme 1. Possible catalytic cycle for the ruthenium-catalyzed dehydrogenative dimerization process.

be established. Although persistent radical species do not appear to be present,^[14] paramagnetic ruthenium intermediates may be involved in the ability of dioxygen to slow or reverse catalyst decomposition.

The use of the 16 electron $[(\eta^6\text{-arene})(\text{PR}_3)(\text{Cl})\text{-Ru}=\text{C}=\text{C}=\text{CR}_2]^+$ species in ring-closing metathesis^[19, 20] represents the only other known example of catalytic reactivity involving metal–allenylidene complexes. The influence of remote aryl substituents on catalytic activity in the present case, along with similar observations for the metathesis process,^[19] suggest that metal-centered reactivity in allenylidene systems may be tuned by purely electronic factors.

Experimental Section

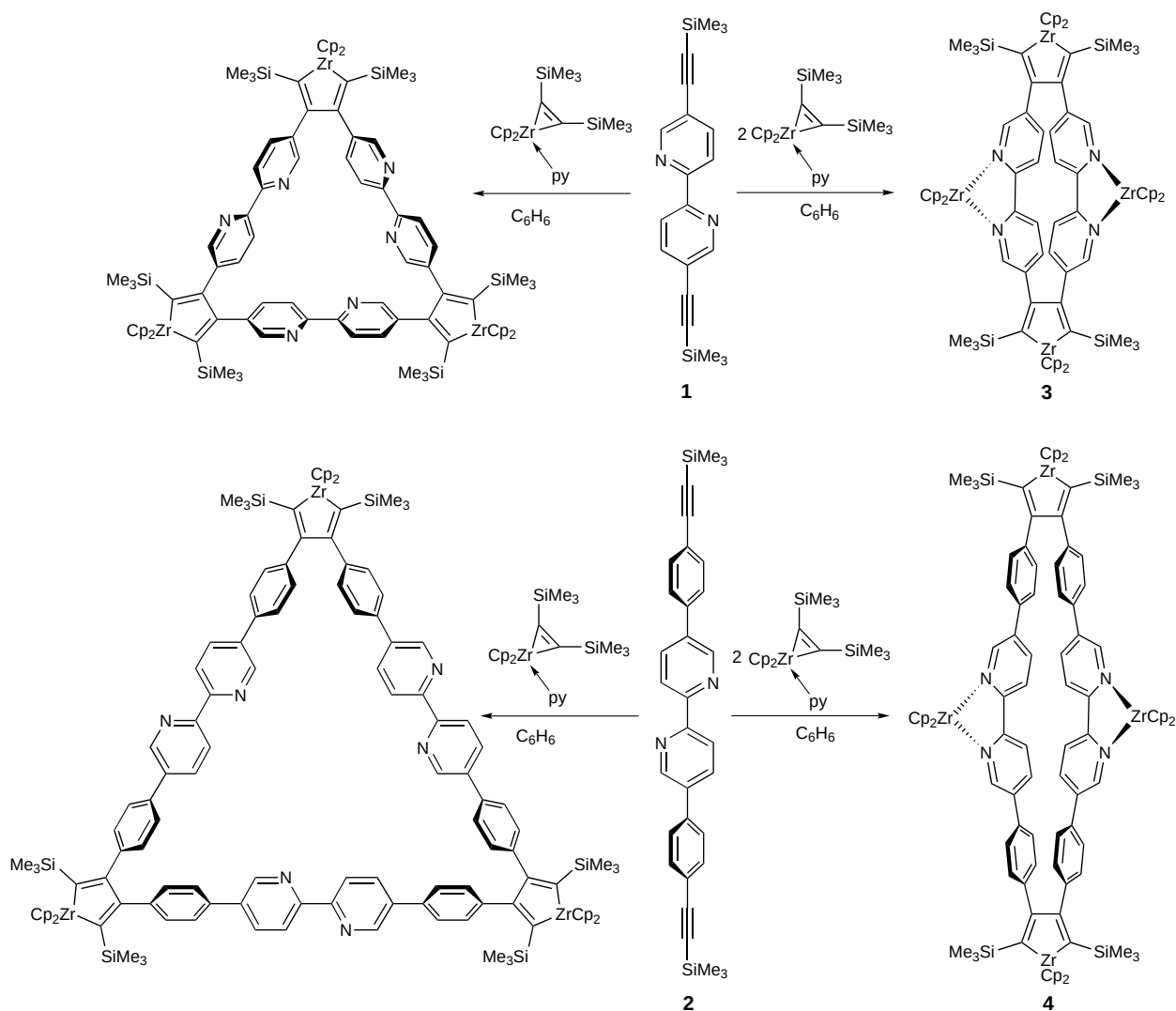
Catalytic reactions: Bu_3SnH (0.10 mL, 0.37 mmol) was added rapidly in a single portion to a solution of the ruthenium complex (0.0053 mmol) in CH_2Cl_2 (15 mL), either in the open air or an inert-atmosphere drybox. Immediate gas evolution was observed, along with a gradual color change from dark brown to light yellow. An internal standard (SnBu_4 , 0.034 mL, 0.104 mmol) was added; after exactly five minutes reaction time, a 2 μL aliquot was removed into 1 mL of solvent, thereby stopping the reaction for analysis by gas chromatography mass spectrometry (GC-MS; DB-5 column). Conversion into $\text{Bu}_3\text{SnSnBu}_3$ was determined by comparisons of the peak areas of both starting tin hydride and distannane to the internal standard, using independent calibration curves that were periodically updated and found to be highly reproducible. Only peaks for starting material and product were observed; the clean nature of the catalytic reactions was confirmed by NMR spectroscopy of unpurified reaction mixtures. Values reported in Table 1 are the average of 2–5 independent runs. Similar catalytic activities are observed in toluene and acetone solvents. See the Supporting Information for details of the syntheses of ruthenium–allenylidene complexes, determination of the deuterium isotope effect, electrochemistry, and X-ray crystallography.

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- [12] Steric factors play a large role in the chemistry of these species. For example, complexes derived from benzaldehydes (thus lacking the

unsubstituted phenyl group at C_γ in the allenylidene structure) are sensitive to attack of ethanol at C_γ under standard conditions for the reaction of terminal alkyne with the ruthenium precursor. This reaction, essentially the reverse of the dehydration step that converts vinylidene into allenylidene, is blocked for diarylallenylidenes. In addition, when a phenylacetylene group is placed at the *ortho* position, the corresponding allenylidene moiety could not be generated from the derived vinylidene, even upon treatment with strong acid. Attempted installation of an *ortho*-(*E*)-hexenyl group was rewarded with some of the desired allenylidene complex, as an unpurifiable mixture with contaminating by-products.

- [13] The addition of 2-hexyne to reactions involving **1**, **3**, or **4** does not substantially inhibit the dehydrogenative dimerization process (kinetic measurements were not performed), nor does 2-hexyne stimulate the parent complex **2** to become an active catalyst. Catalysis using **4** is also unaffected by the presence of a large excess of 1-octene, and added trimethylphosphane irreversibly attacks the allenylidene complex (presumably at C_γ), eliminating catalytic activity. Ph_3SnH undergoes dehydrogenative dimerization slowly with our catalysts, while Et_3SiH is unreactive.
- [14] Species with unpaired electrons were not detected when an active reaction mixture was quickly frozen in liquid nitrogen and examined by EPR spectrometry. Thawing of the frozen solution afterwards resulted in a resumption of catalytic activity.
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Scheme 1. The reported syntheses of trimeric macrocycles from bpy-containing diynes^[4a,b] and the syntheses of **3** and **4** from the same starting materials.

reaction of $[\text{Cp}_2\text{Zr}(\text{py})(\text{Me}_3\text{SiC}\equiv\text{CSiMe}_3)]$ and diyne **1** (2:1 ratio) in benzene. This reaction is complete after seven days at 40 °C, giving **3** in 96 % yield as black crystals, some of which were of X-ray quality. Crystalline **4** was obtained under identical conditions in 95 % yield. The use of zirconocene as both templating and macrocyclization reagent thus allows a high level of control over the macrocyclization stoichiometry, based simply on the ratio of reagents employed.

The ready formation of trimeric macrocycles in the absence of a second equivalent of $[\text{Cp}_2\text{Zr}(\text{py})(\text{Me}_3\text{SiC}\equiv\text{CSiMe}_3)]$ suggests that the alkyne groups are the first site of zirconocene complexation. Numerous species are likely to be present in the reaction mixtures which yield **3** and **4**, but the equilibrating nature of the zirconocene-coupling reaction results in the eventual formation of a single product.

An ORTEP diagram of **3** is given in Figure 2. The bpy units in this molecule are bent to an even greater degree than in $[\text{Cp}_2\text{Zr}(\text{bpy})]$ (angle between the planes of 125°), suggesting that this macrocycle may be strained. Macrocycle **4** (Figure 3) has an analogous angle across bpy of 135°, intermediate between those of **3** and $[\text{Cp}_2\text{Zr}(\text{bpy})]$. The range of angles observed for bpy in complexes $[\text{Cp}_2\text{Zr}(\text{bpy})]$, **3**, and **4**

indicates that the energy required to bend the bpy unit is greatly reduced by its coordination to the Cp_2Zr fragment. Both **3** and **4** exhibit bond alternations in the bpy rings that are similar in magnitude to those observed in $[\text{Cp}_2\text{Zr}(\text{bpy})]$.

The diamond-shaped central cavity of the larger macrocycle **4** contains a benzene guest molecule. Based on examination of the crystal structures, the largest sphere that could be accommodated in the cavity of **3** would have a van der Waals radius of 1.15 Å, while a sphere of radius 2.83 Å would fit into the cavity of **4**. However, larger, more elongated objects could fit readily into these cavities.

The ^1H and ^{13}C NMR spectra of **3** exhibit resonance signals for three distinct Cp groups in a

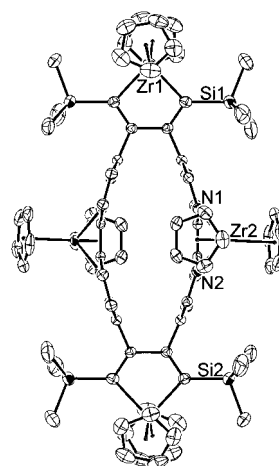


Figure 2. ORTEP diagram of **3**. Thermal ellipsoids are set at the 50 % probability level and the heteroatoms of the asymmetric unit are labeled.

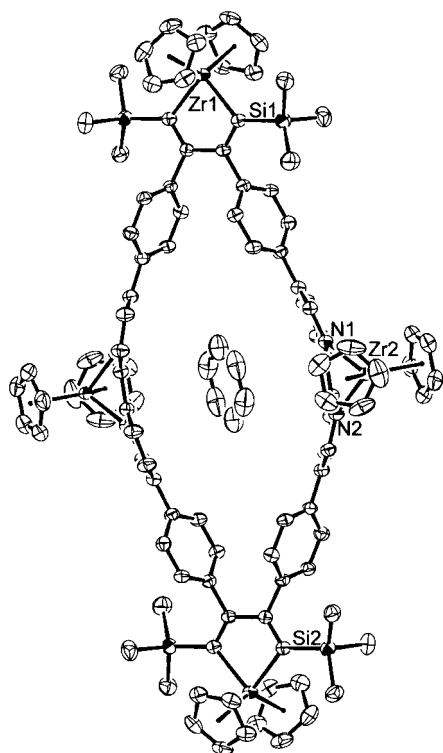


Figure 3. ORTEP diagram of **4** showing the benzene guest molecule. Thermal ellipsoids are set at the 50% probability level and the heteroatoms of the asymmetric unit are labeled.

2:1:1 ratio. This indicates that in toluene and THF solution as well as in the solid state the two Cp rings of the $[\text{Cp}_2\text{Zr}(\text{bpy})]$ fragment are distinct (chemically inequivalent). This situation appears to result from the compact and constrained geometry of **3**. The bpy rings of this molecule may not readily rotate past one another, as would be required to interconvert the Cp rings. Heating a solution of **3** in $[\text{D}_8]$ toluene results in decomposition to multiple products within minutes at 110°C , before any coalescence of the Cp resonances. Decomposition of **3** occurs more rapidly in $[\text{D}_8]$ THF, with the resonances assigned to **3** disappearing within one minute at 60°C as resonance signals from multiple unidentified products appear.

In contrast, the ^1H NMR spectrum of **4** at 25°C in $[\text{D}_8]$ THF exhibits only two resonance signals for the Cp rings, indicating that the $[\text{Cp}_2\text{Zr}(\text{bpy})]$ fragments are freely rotating in the more open structure of **4**. Cooling a $[\text{D}_8]$ THF solution of **4** at -20°C results in decoalescence of one of the Cp resonance signals ($\delta = 5.69$ at room temperature). At -40°C these Cp groups give two resonance signals at $\delta = 5.29$ and 6.15 , which sharpen further as the temperature is lowered. This corresponds to a barrier to Cp ring exchange of $11.5\text{ kcal mol}^{-1}$.^[8]

This work demonstrates a new means for precisely controlling the stoichiometry of macrocyclization through the use of a single zirconocene reagent as both templating and macrocyclization reagent. We are currently investigating methods for selectively derivatizing the two distinct zirconocene sites in these macrocycles and exploring the potential of this templating approach in controlling macrocycle size and shape.

Experimental Section

$[\text{Cp}_2\text{Zr}(\text{bpy})]$ was synthesized as previously described.^[4a] X-ray quality crystals were obtained through vapor diffusion of pentane into a benzene solution.

Macrocycle **3**. Diyne **1**^[4b] (0.370 g, 1.06 mmol) and $[\text{Cp}_2\text{Zr}(\text{py})(\text{Me}_3\text{SiC}\equiv\text{C-SiMe}_3)]$ ^[6] (1.00 g, 2.12 mmol) were loaded into a 100 mL Schlenk flask, which was then charged with dry benzene (50 mL). The flask was sealed, and the reaction mixture was sonicated at room temperature for 10 min. The reaction mixture was then heated to 40°C for 7 days. Black crystals of the product, some of which were of X-ray quality, precipitated from solution over this time. The solvent was removed by cannula filtration, and the product was dried under vacuum. The isolated yield was 0.806 g, 96%; ^1H NMR (500 MHz, $[\text{D}_6]$ benzene, 298 K): $\delta = 0.20$ (s, 18H, $\text{Si}(\text{CH}_3)_3$), 5.40 (s, 5H, Cp), 5.82 (d, $J = 9\text{ Hz}$, 2H, bpy), 5.86 (s, 5H, Cp), 6.10 (s, 10H, Cp), 6.50 (d, $J = 9\text{ Hz}$, 2H, bpy), 6.89 (s, bpy); (300 MHz, $[\text{D}_8]$ toluene, 298 K): $\delta = 0.18$ (s, 18H, $\text{Si}(\text{CH}_3)_3$), 5.33 (s, 5H, Cp), 5.78 (d, $J = 9\text{ Hz}$, 2H, bpy), 5.85 (s, 5H, Cp), 6.08 (s, 10H, Cp), 6.47 (d, $J = 9\text{ Hz}$, 2H, bpy), 6.84 (s, bpy); (300 MHz, $[\text{D}_8]$ THF, 298 K): $\delta = 0.06$ (s, 18H, $\text{Si}(\text{CH}_3)_3$), 5.18 (s, 5H, Cp), 5.82 (d, $J = 9\text{ Hz}$, 2H, bpy), 5.92 (s, 5H, Cp), 6.33 (s, 10H, Cp), 6.64 (d, $J = 9\text{ Hz}$, 2H, bpy), 6.77 (s, bpy); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $[\text{D}_6]$ benzene, 298 K): $\delta = 3.6$ ($\text{Si}(\text{CH}_3)_3$), 102.5 (Cp), 106.4 (Cp), 111.4 (Cp), 116.2, 122.6, 127.5, 135.5, 145.3, 149.5, 206.8 (C-Zr); elemental analysis (%) calcd for $\text{C}_{80}\text{H}_{88}\text{N}_4\text{Si}_4\text{Zr}_4$: C 60.71, H 5.60, N 3.54; found: C 60.57, H 5.32, N 3.39.

Macrocycle **4**. Diyne **2**^[4a] (0.500 g, 0.998 mmol) and $[\text{Cp}_2\text{Zr}(\text{py})(\text{Me}_3\text{SiC}\equiv\text{C-SiMe}_3)]$ ^[6] (0.945 g, 2.01 mmol) were loaded into a 100 mL Schlenk flask, which was then charged with dry benzene (90 mL). The flask was sealed, and the reaction mixture was sonicated at room temperature for 10 min. The reaction mixture was then heated to 40°C for 7 days. Black crystals of the product, some of which were of X-ray quality, precipitated from solution over this time. The solvent was removed by cannula filtration, and the product was dried under vacuum, yield was 0.895 g, 95%. The product is extremely air-sensitive, and has very low solubility in hydrocarbon solvents and diethyl ether. Decomposition was observed in THF solution at room temperature over several hours, but proton NMR spectra could be obtained if the sample was frozen for transit to the spectrometer. ^1H NMR (300 MHz, $[\text{D}_8]$ THF, 298 K): $\delta = -0.18$ (s, 18H, $\text{Si}(\text{CH}_3)_3$), 5.69 (s, 10H, Cp), 6.44 (s, 10H, Cp), 6.58 (d, $J = 9\text{ Hz}$, 4H, phenylene), 6.74 (d, $J = 8\text{ Hz}$, 2H, bpy), 6.99 (d, $J = 9\text{ Hz}$, 4H, phenylene), 7.11 (d, $J = 8\text{ Hz}$, 2H, bpy), 7.86 (s, bpy); (300 MHz, $[\text{D}_8]$ THF, 203 K): $\delta = -0.21$ (s, 18H, $\text{Si}(\text{CH}_3)_3$), 5.29 (s, 5H, Cp), 6.18 (s, 5H, Cp), 6.49 (s, 10H, Cp), 6.56 (brd, 4H, phenylene), 6.96 (br, 6H, phenylene and bpy), 6.23 (brd, 2H, bpy), 8.02 (s, 2H, bpy); elemental analysis (%) calcd for $\text{C}_{104}\text{H}_{104}\text{N}_4\text{Si}_4\text{Zr}_4$: C 66.19, H 5.55, N 2.97; found: C 65.96, H 5.32, N 2.93.

Crystal data for $[\text{Cp}_2\text{Zr}(\text{bpy})] \cdot (\text{C}_{20}\text{H}_{18}\text{N}_2\text{Zr})$: crystal dimensions $0.21 \times 0.20 \times 0.14\text{ mm}$, orthorhombic, space group $P2_12_12_1$, $a = 8.9433(8)$, $b = 9.6960(9)$, $c = 18.728(2)\text{ \AA}$, $V = 2176.94(2)\text{ \AA}^3$, $\rho_{\text{calcd}} = 1.54\text{ g cm}^{-3}$, $2\theta_{\text{max}} = 51.1^\circ$, $\text{MoK}\alpha$ radiation ($\lambda = 0.71069\text{ \AA}$), ω scans, $T = -113^\circ\text{C}$, of 7331 measured reflections, 1664 were unique, and 1189 were observed (with $I > 3.00\sigma(I)$), data corrected for Lorentz and polarization effects, analyzed for agreement and absorption using XPRED with an empirical absorption correction using SADABS ($T_{\text{max}} = 0.86$, $T_{\text{min}} = 0.63$). The structure was solved by direct methods (SIR92) and developed by least-squares refinement against $|F|$. No. of parameters, 204; H atoms were calculated but not refined; $R = 0.039$, $R_w = 0.044$, GOF = 1.30.

Crystal data for **3** ($\text{C}_{46}\text{H}_{50}\text{N}_2\text{Si}_2\text{Zr}_2$): crystal dimensions $0.40 \times 0.30 \times 0.32\text{ mm}$, monoclinic, space group $P1$, $a = 13.8846(1)$, $b = 14.0501(1)$, $c = 14.2032(1)\text{ \AA}$, $\alpha = 61.385(1)^\circ$, $\beta = 87.029(1)^\circ$, $\gamma = 65.559(1)^\circ$, $V = 2176.94(2)\text{ \AA}^3$, $\rho_{\text{calcd}} = 1.33\text{ g cm}^{-3}$, $2\theta_{\text{max}} = 52.1^\circ$, $\text{MoK}\alpha$ radiation ($\lambda = 0.71069\text{ \AA}$), ω scans, $T = -109^\circ\text{C}$, of 10481 measured reflections, 7292 were unique, and 6416 were observed (with $I > 3.00\sigma(I)$), data corrected for Lorentz and polarization effects, analyzed for agreement and absorption using XPRED with an empirical absorption correction using SADABS ($T_{\text{max}} = 0.90$, $T_{\text{min}} = 0.80$). The structure was solved by direct methods (SIR92) and developed by least-squares refinement against $|F|$. No. of parameters, 469; H atoms were calculated but not refined; $R = 0.028$, $R_w = 0.042$, GOF = 1.80.

Crystal data for **4** ($\text{C}_{76}\text{H}_{76}\text{N}_2\text{Si}_2\text{Zr}_2$): crystal dimensions $0.20 \times 0.18 \times 0.15\text{ mm}$, monoclinic, space group $P1$, $a = 14.6211(2)$, $b = 15.0342(2)$, $c = 17.7675(1)\text{ \AA}$, $\alpha = 65.455(1)^\circ$, $\beta = 66.895(1)^\circ$, $\gamma = 88.621(1)^\circ$, $V =$

3222.32(8) Å³, $\rho_{\text{calcd}} = 1.29 \text{ g cm}^{-3}$, $2\theta_{\text{max}} = 52.3^\circ$, MoK α radiation ($\lambda = 0.71069 \text{ Å}$), ω scans, $T = -115^\circ\text{C}$, of 15 644 measured reflections, 10 891 were unique, and 8247 were observed (with $I > 3.00\sigma(I)$), data corrected for Lorentz and polarization effects, analyzed for agreement and absorption using XPREP with an empirical absorption correction using SADABS ($T_{\text{max}} = 0.78$, $T_{\text{min}} = 0.71$). The structure was solved by direct methods (SIR92) and developed by least-squares refinement against $|F|$. No. of parameters, 739; H atoms were calculated but not refined; $R = 0.032$, $R_w = 0.039$, GOF = 1.61.

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-153030 (3), CCDC-153031 (4), and CCDC-153749 ([Cp₂Zr(bpy)]). 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).

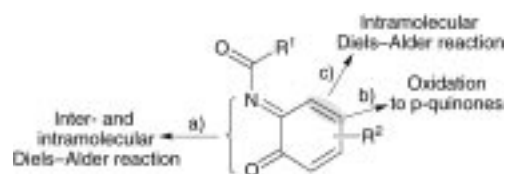
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Rapid Access to Complex Molecular Architectures via *o*-Azaquinones**

K. C. Nicolaou,* Yong-Li Zhong, Phil S. Baran, and Kazyuki Sugita

We have recently reported a number of new synthetic technologies^[1] based on the use of the hypervalent iodine reagent DMP and its precursor IBX (for abbreviations of reagents, see legends to schemes). Despite their similar structures and ability to oxidize alcohols to carbonyl compounds, IBX and DMP exhibit distinctly different reactivity profiles towards a multitude of organic substrates. The facile generation of *o*-azaquinone-type structures from anilides and DMP, and their demonstrated ability to undergo inter- and intramolecular Diels–Alder reactions as heterodienes (Scheme 1, path a)^[1a,f] or to undergo further oxidation to *p*-quinones^[1f] (Scheme 1, path b) prompted us to investigate

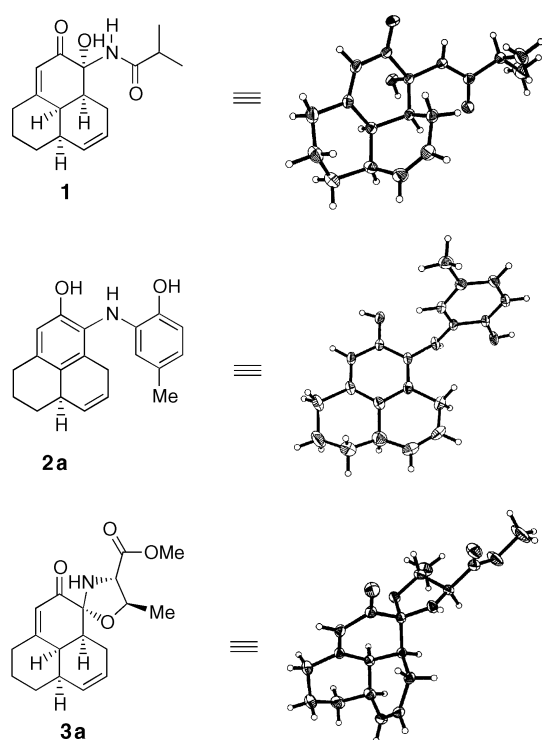


Scheme 1. Reactivity of *o*-azaquinones as versatile chemical entities. a) Participation in inter- and intramolecular Diels–Alder reactions (ref. [1a,f]), b) oxidation to *p*-quinones (ref. [1f]), and c) proposed intramolecular Diels–Alder reactions.

them further. Close inspection revealed the potential of utilizing these quinones to construct rapidly complex mimics of known natural products and potential protein ligands. Herein we report a new mode of reactivity of these underexplored molecular entities in which the double bond adjacent to the imide moiety (Scheme 1, path c) is richly exploited by means of cascade reactions. Initiated by DMP, this pathway proceeds through an intramolecular Diels–Alder reaction of the generated *o*-azaquinone–diene constructs and leads, via ketohydroxyamides, to a multitude of molecules (e.g. **1**, **2a**, and **3a**, Scheme 2), which resemble the pseudopterosin natural products.^[2] Alternatively, further

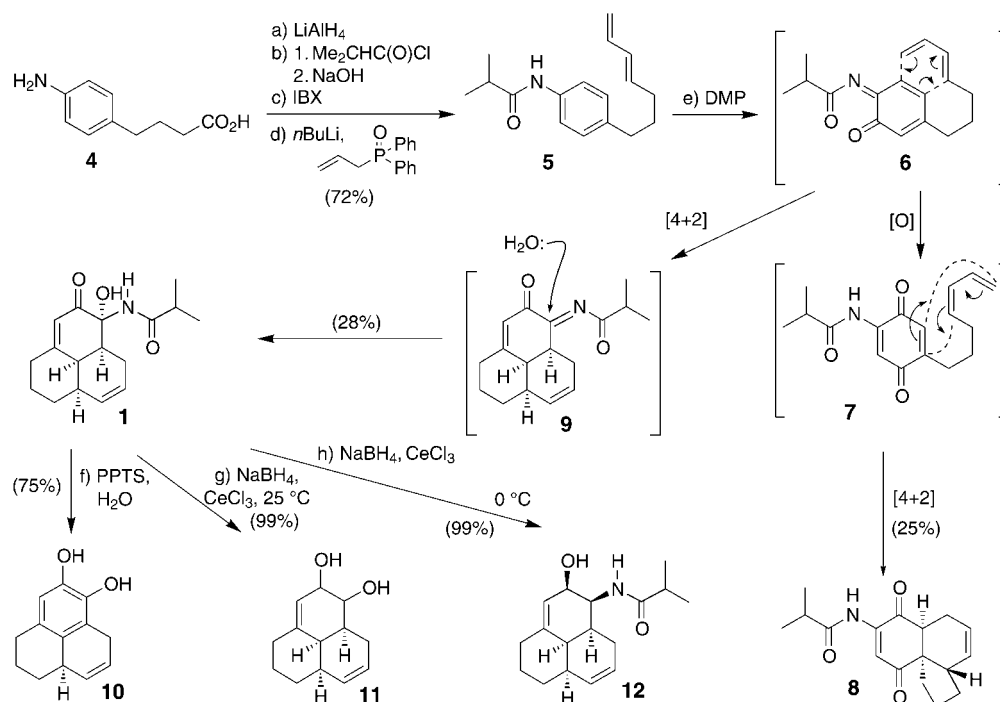
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Scheme 2. ORTEP diagrams of complex, natural product like compounds obtained from chemical synthesis.^[7]

oxidation to *p*-quinones and intramolecular Diels–Alder fusion leads to the full carbon skeleton of the elisabethin type of natural products.^[3]



Scheme 3. Rapid entry into complex pseudopterisins and elisabethin analogues from anilides and DMP. Reagents and conditions: a) LiAlH_4 (5.0 equiv), THF, $0 \rightarrow 25^\circ\text{C}$, 2 h, 96%; b) 1. $\text{Me}_2\text{CHC}(\text{O})\text{Cl}$ (3.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 1 h, 2. NaOH (1N, 3.0 equiv), MeOH , 50°C , 2 h, 95% for two steps; c) IBX (2.0 equiv), DMSO, 25°C , 6 h, 95%; d) $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{CH}=\text{CH}_2$ (3.0 equiv), $n\text{BuLi}$ (2.5 equiv), HMPA (6.0 equiv), THF, -78°C , 20 min; then add aldehyde, $-78 \rightarrow 25^\circ\text{C}$, 14 h, 83%; e) DMP (4.0 equiv), H_2O (2.0 equiv), CH_2Cl_2 , 25°C , 3 h, 28% (**1**), 25% (**8**); f) PPTS (0.2 equiv), H_2O , 50°C , 30 min, 75%; g) NaBH_4 (5.0 equiv), CeCl_3 (10.0 equiv), THF, 25°C , 99%; h) NaBH_4 (5.0 equiv), CeCl_3 (1.1 equiv), THF, 0°C , 99%. IBX = *o*-iodoxybenzoic acid, DMP = Dess–Martin periodinane, HMPA = hexamethyl phosphoramide, PPTS = pyridinium 4-toluenesulfonate.

To investigate the reactivity of the olefin adjacent to the imide group in *o*-azaquinones (Scheme 1, path c), the diene **5** (Scheme 3) was designed and targeted for synthesis. Anilide **5** was prepared efficiently from the commercially available amino acid **4** in 72% overall yield by means of the sequence summarized in Scheme 3. Exposure of **5** to DMP (4.0 equiv)/ H_2O (2.0 equiv) led to ketohydroxyamide **1** (Scheme 2, Table 5) and quinone **8** (Scheme 3, Table 5). The former presumably arises from the hydration of the initially formed intramolecular Diels–Alder product **9**. To the best of our knowledge, the intramolecular Diels–Alder reaction of *o*-azaquinones (acting as a dienophile) has not been explored. More importantly, ketohydroxyamide **1** closely resembles the pseudoserin natural products. The quinone **8**, which embodies the full carbon skeleton of the naturally occurring elisabethin A,^[3] was undoubtedly formed by means of an intramolecular Diels–Alder fusion of the intermediate *p*-quinone **7**, which was generated from **6** by the oxidative action of DMP.^[1f]

The easy access to ketohydroxyamides such as **1** coupled with their scarcely investigated chemistry^[4] offered us the opportunity to explore their reactivity and synthetic potential (Scheme 3). We were able to access compounds **11** (99% yield) and **12** (99% yield) under reductive conditions (NaBH_4) simply by altering the temperature of the reaction. On the other hand, compound **1** was cleanly converted into diphenol **10** by the catalytic action of PPTS (75% yield).

We reasoned that a dicarbonyl compound was a fleeting intermediate in the conversion of ketohydroxyamide **1** into diphenol **10** (Scheme 3) and sought to trap this reactive

species with an array of nucleophiles as a means of expanding the accessible molecular complexity. Thus, in the presence of catalytic amounts of PPTS, anilines were treated with compound **1** at 90 °C to afford polycyclic amines (**2a–d**, [Eq. (1)]),

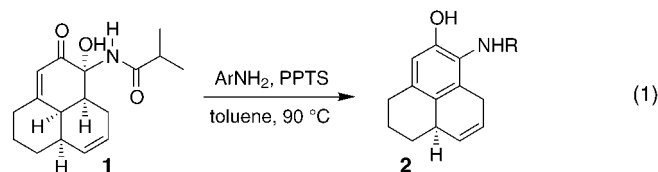
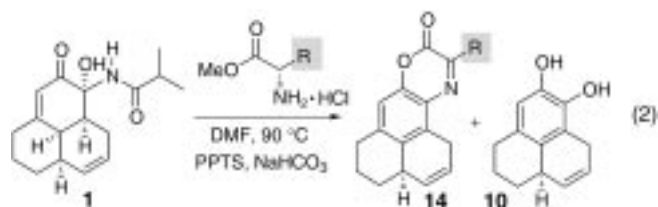


Table 1. Synthesis of polycyclic anilines from ketohydroxyamide **1**.^[a]

RNH ₂	Product	Yield [%]
		84
		71
		45 ^[b]
		89

[a] Reagents and conditions: ArNH₂ (5.0 equiv), PPTS (0.2 equiv), toluene, 90 °C, 3–24 h. [b] Accompanied with 20% of **10**.

Table 1, Table 5). As this reaction was highly efficient, we treated **1** with C-protected amino acids and discovered an interesting cascade heterocyclic annulation. Under similar conditions as those used for the amines, ketohydroxyamide **1** was easily converted into the complex polycyclic scaffolds **14a–g** ([Eq. (2)], Table 2). A postulated mechanism for this



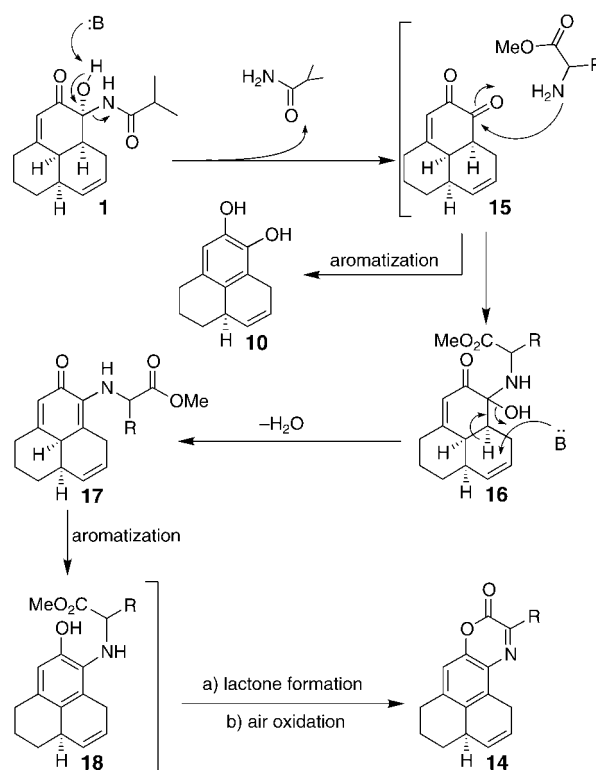
cascade reaction begins with the conversion of **1** into the corresponding diketone **15** after the expulsion of isobutyramide. This is followed either by the formation of diphenol **10** (after aromatization), or by addition of the amino group of the amino acid derivative to form intermediate **16**. Dehydration

Table 2. Synthesis of complex polycyclic systems from ketohydroxyamide **1** and C-protected amino acid derivatives.^[a]

Protected amino acid	Product (yield [%])	Bis-phenol 10 (yield [%])
	14a (51)	23
	14b (49)	20
	14c (80)	5
	14d (53)	15
	14e (72)	10
	14f (66)	10
	14g (39)	31

[a] Reagents and conditions: C-protected amino acid (3.0 equiv), PPTS (0.2 equiv), NaHCO₃ (3.0 equiv), DMF, 90 °C, 6–24 h.

of **16** followed by aromatization may then furnish, via **17**, intermediate **18**, which rapidly cyclizes and undergoes oxidation by air to give the observed product **14** (Scheme 4).



Scheme 4. Postulated mechanism for the cascade reactions that lead to polycyclic systems **14** from ketohydroxyamide **1** and amino acid derivatives.

Given the importance of N-heterocycles in medicinal chemistry,^[5] we then turned our attention to the synthesis of pyrazines. The combination of ketohydroxyamide **1** with a number of 1,2-diamines led smoothly to complex polycyclic pyrazines ([Eq. (3)], Table 3, **19a–e**) in a highly efficient

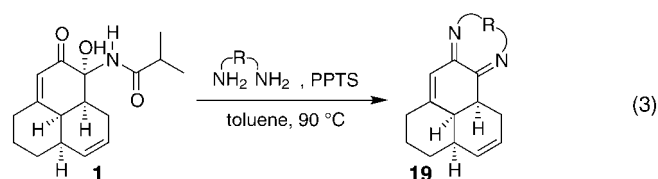


Table 3. Synthesis of polycyclic pyrazines from ketohydroxyamide **1**.^[a]

Diamine	Product	Yield [%]
		85
		73
		94
		90
		88

[a] Reagents and conditions: diamine (5–10 equiv), PPTS (0.2 equiv), toluene, 90 °C, 3–8 h.

manner (73–94 % yield). Additionally, by enlisting 1,2-amino alcohols in this reaction we were able to effect a unique heterocyclic spiroannulation reaction and obtain yet another series of novel heterocycles ([Eq. (4)]; Table 4, **3a–d**, **20a–d**; Table 5).

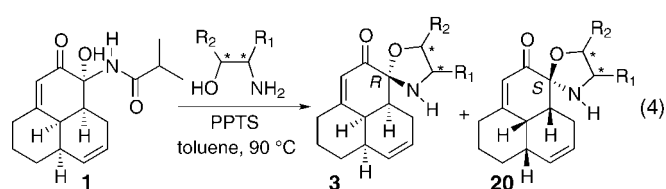


Table 4. Synthesis of complex spiroheterocycles from ketohydroxyamide **1** and 1,2-hydroxyamines.^[a]

Amino alcohol	Products (Yield)	

[a] Reagents and conditions: Amino alcohol (3.0 equiv), PPTS (0.2 equiv), toluene, 90 °C, 6–24 h.

Finally, amino acid- and diamine-derived polycycles ([Eq. (2)], Table 2 and [Eq. (3)], Table 3, respectively) could easily be dehydrogenated by heating in air at 100 °C in *N,N*-dimethylformamide or toluene (48 h), to furnish unusual polyaromatic systems such as **14d'** (95 % yield) and **19c'**.

In conclusion, we have demonstrated a new and highly productive mode of reaction of *o*-azaquinones, which can be derived from anilides and DMP, and explored its scope and generality. Through a series of cascade reactions that involve two previously unexplored chemical species (*o*-azaquinones and ketohydroxyamides), a number of complex natural

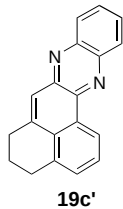
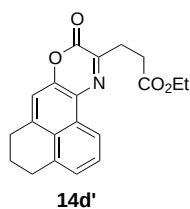
Table 5. Data for selected compounds: **1**, **2a**, **3a**, and **8**.

1: Colorless needles; m.p. 112–113 °C (hexane/Et₂O 2/1); R_f = 0.35 (silica gel, hexane/EtOAc 1:1); IR (film): $\tilde{\nu}_{\max}$ = 3378, 2967, 2931, 2867, 1664, 1506, 1463, 1427, 1399, 1239, 1180, 1081, 1055, 754 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.20 (br s, D₂O exchangeable, 1H), 5.85 (t, J = 2.2 Hz, 1H), 5.66–5.61 (m, 1H), 5.46 (ddd, J_1 = 9.9 Hz, J_2 = 4.1 Hz, J_3 = 1.2 Hz, 1H), 4.82 (br s, D₂O exchangeable, 1H), 3.26 (ddd, J_1 = 11.0 Hz, J_2 = 7.0 Hz, J_3 = 4.0 Hz, 1H), 3.23–3.18 (m, 1H), 2.73–2.66 (m, 1H), 2.50–2.30 (m, 1H), 2.45 (sep, J = 7.0 Hz, 1H), 2.35–2.36 (m, 1H), 1.95–1.82 (m, 2H), 1.75–1.61 (m, 2H), 1.57–1.48 (m, 1H), 1.44–1.31 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 191.8, 179.5, 167.9, 131.2, 126.3, 121.1, 84.0, 40.4, 36.7, 35.9, 34.7 (2 C), 30.5, 23.2, 20.4, 19.7, 19.0; HR-MS (MALDI-FTMS) calcd for C₁₇H₂₃NO₃Na [M +Na⁺]: 312.1570, found: 312.1573

2a: Colorless plates; m.p. 206–208 °C (hexane/CH₂Cl₂); R_f = 0.29 (silica gel, hexane/EtOAc 1/1); IR (film): $\tilde{\nu}_{\max}$ = 3347, 2919, 2847, 1655, 1592, 1519, 1477, 1452, 1384, 1332, 1241, 1159, 1123, 1093, 1027, 787 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 6.77 (s, 1H), 6.67 (bd, J = 7.9 Hz, 1H), 6.47 (bd, J = 7.9 Hz, 1H), 6.15 (br s, D₂O exchangeable, 1H), 5.82–5.75 (m, 2H), 5.24 (br s, D₂O exchangeable, 1H), 4.70 (br s, D₂O exchangeable, 1H), 3.21 (dt, J_1 = 20.2 Hz, J_2 = 4.4 Hz, 1H), 3.10–3.00 (m, 1H), 2.96 (dd, J_1 = 20.2 Hz, J_2 = 8.3 Hz, 1H), 2.87–2.75 (m, 2H), 2.19–2.11 (m, 1H), 2.10 (s, 3H), 2.00–1.82 (m, 2H), 1.51–1.40 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 152.7, 141.7, 137.1, 135.5, 133.9, 132.4, 132.2, 129.0, 124.6, 123.2, 120.2, 115.3, 114.9, 112.8, 35.2, 30.4, 29.5, 26.6, 22.9, 21.0; HR-MS (MALDI-FTMS) calcd for C₂₀H₂₁NO₂ 308.1645 [M +H⁺], found: 308.1646

3a: colorless cubes; m.p. 142–143 °C (hexanes/Et₂O); R_f = 0.49 (silica gel, hexane/EtOAc 1/1); [α]_D = +139.7° (0.35, CHCl₃); IR (film) $\tilde{\nu}_{\max}$ = 3283, 3017, 2929, 2862, 1740, 1678, 1437, 1374, 1239, 1202, 1147, 1086, 786 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 5.88 (t, J = 2.3 Hz, 1H), 5.71–5.63 (m, 1H), 5.46 (dq, J_1 = 10.0 Hz, J_2 = 2.0 Hz, 1H), 4.11 (br s, D₂O exchangeable, 1H), 3.77 (s, 3H), 3.58 (d, J = 8.6 Hz, 1H), 3.23 (br s, D₂O exchangeable, 1H), 3.80 (s, 3H), 3.74–3.63 (m, 1H), 3.46 (d, J = 9.0 Hz, 1H), 3.15–3.08 (m, 1H), 2.73–2.64 (m, 1H), 2.47 (bd, J = 15.5 Hz, 1H), 2.38–2.11 (m, 2H), 2.20–2.10 (m, 1H), 1.84 (dt, J = 13.2, 2.2 Hz, 1H), 1.75–1.53 (m, 5H), 1.46–1.36 (m, 1H), 1.35 (d, J = 5.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 194.2, 171.3, 167.8, 131.7, 127.6, 123.1, 96.8, 76.9, 66.5, 52.8, 42.6, 36.8, 34.9 (2 C), 30.7, 23.4, 20.5, 18.5; HR-MS (MALDI-FTMS) calcd for C₁₈H₂₃NO₄ [M +H⁺]: 318.1700, found: 318.1698

8: Yellow oil; R_f = 0.51 (silica gel, hexane/EtOAc 2/1); IR (film): $\tilde{\nu}_{\max}$ = 3330, 3028, 2969, 2932, 2873, 1688, 1668, 1613, 1504, 1467, 1385, 1318, 1157, 1099, 1026, 944, 884 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.89 (br s, D₂O exchangeable, 1H), 7.39 (s, 1H), 6.02 (dq, J_1 = 9.9 Hz, J_2 = 2.0 Hz, 1H), 5.47 (dq, J_1 = 9.9 Hz, J_2 = 3.2 Hz, 1H), 3.08 (dd, J_1 = 9.8 Hz, J_2 = 8.3 Hz, 1H), 2.60–2.49 (m, 2H), 2.25–2.13 (m, 3H), 2.00 (dd, J_1 = 12.9 Hz, J_2 = 8.5 Hz, 1H), 1.88–1.59 (m, 4H), 1.22 (d, J = 6.9 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 202.2, 198.3, 177.5, 138.3, 131.0, 124.0, 118.5, 59.7, 53.4, 45.7, 37.1, 35.8, 30.0, 26.0, 21.5, 19.4, 19.3; HR-MS (MALDI-FTMS) calcd. for C₁₇H₂₁NO₃ [M +H⁺]: 288.1594, found: 288.1589



product like compounds are now readily accessible. A solid-phase version that uses ketohydroxyamides in a “heterocycle release” strategy^[6] may expand the scope of the reported chemistry. Biological screening of the synthesized and projected compound libraries is expected to facilitate chemical biology studies and pharmaceutical research.

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Separation of Spliceosome Assembly from Catalysis with Caged pre-mRNA Substrates**

Steven G. Chaulk and Andrew M. MacMillan*

Pre-messenger RNAs (pre-mRNAs) in eukaryotes are characterized by a split-gene structure in which coding exon sequences are separated by noncoding intron sequences.^[1] The process by which the introns are excised from the pre-mRNA and the exons are joined together is known as pre-mRNA splicing and is catalyzed by the spliceosome—a biochemical machine that contains both protein and RNA components.^[2] The spliceosome includes the U1, U2, and U4/

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U5/U6 snRNPs (small nuclear ribonucleoprotein particles), each containing a unique RNA and associated proteins. In contrast to many biocatalysts, the functional spliceosome does not appear to exist independently of its substrate; instead, the active splicing catalyst assembles in an ATP-dependent, stepwise, ordered fashion on pre-mRNA substrates through the A, B, and C complexes, which may be visualized by native gel electrophoresis (Figure 1 a).^[3] It would clearly be useful to separate spliceosome assembly from the subsequent chemical steps of pre-mRNA splicing, such that the requirements for each could be studied independently.

The chemistry of pre-mRNA splicing involves two sequential transesterification reactions. During the course of spliceosome assembly, a specific adenosine residue in the branch region of the intron bulges out from an RNA duplex formed between the pre-mRNA and the U2 snRNA (Figure 1 b). The 2'-hydroxy group of this residue carries out a nucleophilic attack at the 5'-splice site to generate a free 5'-exon and a cyclic intermediate containing a 2'-5'-phosphodiester branch.^[4] Attack of the free 5'-exon at the 3'-splice site then yields ligated exons and a cyclic intron product. Removal of the nucleophilic hydroxy group from the branch adenosine by placement of a 2'-deoxy residue at this position prevents the branch formation from occurring at this position.^[5]

Here we describe an approach to the study of pre-mRNA splicing whereby reactivity of the branch adenosine in a pre-mRNA is transiently blocked with a photolabile caging group. Despite this modification to the pre-mRNA, the spliceosome is able to assemble on the caged substrate; subsequent photolysis frees the branch nucleophile to initiate the two transesterification reactions of splicing. Thus a caging approach effectively separates spliceosome assembly from catalysis.

We have previously demonstrated in the hammerhead ribozyme system that the reactivity of a unique 2'-hydroxy group within RNA can be transiently blocked by the presence of a photolabile nitrobenzyl ether at this position.^[6] In order

to prepare a caged pre-mRNA, we chemically synthesized a ten-base oligomer in which the branch adenosine was modified at the 2'-position as an *ortho*-nitrobenzyl ether^[6-8] and all other 2'-positions were protected with acid-labile 1-(2-fluorophenyl)-4-methoxypiperidin-1-yl (Fpmp) groups. Following standard workup, the purified caged oligomer was ligated to products of T7 RNA polymerase transcription, representing the 5'- and 3'-portions of the PIP85.B pre-mRNA substrate, in the presence of a bridging DNA oligonucleotide to yield a full length pre-mRNA with a caged branch nucleotide (Figure 2 a).^[9, 10] The resulting RNA contained a single ³²P-radiolabel situated two nucleotides in the 3'-direction of the caged nucleotide, which would facilitate analysis by denaturing polyacrylamide gel electrophoresis (PAGE).

We examined the reactivity of the caged RNA by carrying out photolysis experiments, with a xenon arc lamp as a light source, followed by RNase A and RNase T1 digestion and thin layer chromatography (TLC) analysis of the resulting RNA fragments. Although control RNAs were unaffected by photolysis, 90% of the caging groups were removed upon irradiation to yield free 2'-hydroxy groups (Figure 2 b, c).

We tested the behavior of the caged pre-mRNA under splicing conditions by incubating it in HeLa cell nuclear extract^[11] in the presence of adenosine 5'-triphosphate (ATP) and Mg²⁺—both of which are required cofactors for pre-mRNA splicing. Products associated with the first and second transesterification reactions of splicing are typically detected after an approximately 20 minute lag time required for the assembly of the spliceosome. However, in the case of the caged pre-mRNA, a negligible amount of splicing product was observed (approximately 3%, due to some uncaging during handling; Figure 3 b). The formation of spliceosomes on the caged pre-mRNA was confirmed by nondenaturing PAGE (Figure 3 a).^[4] Thus, while the caging group blocks the first chemical step of splicing, the caged

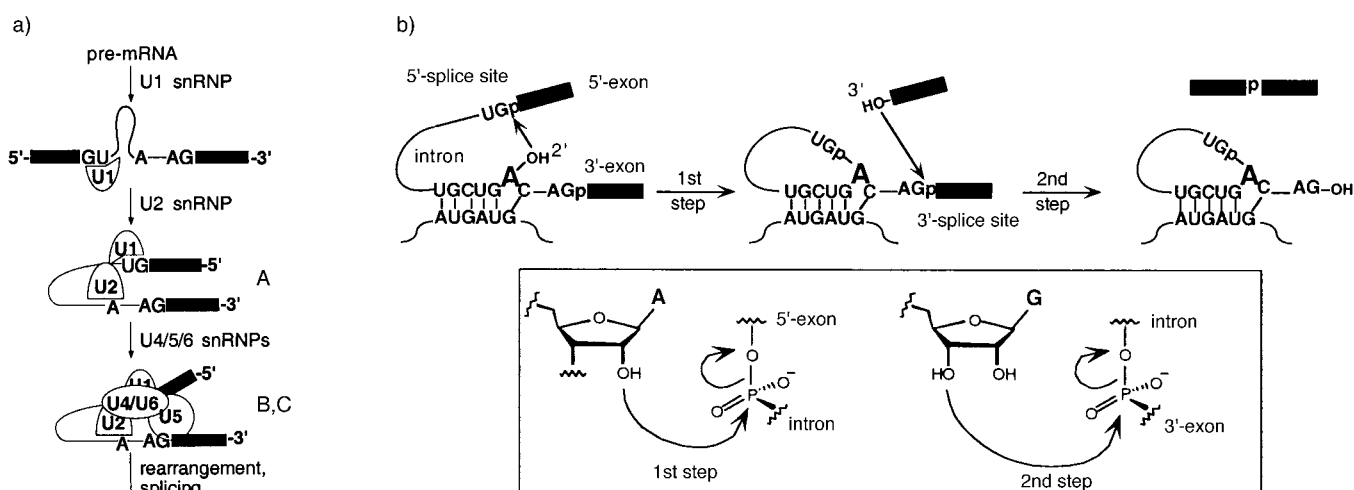


Figure 1. a) Assembly of individual snRNP particles on a pre-mRNA to form the active spliceosome. The conserved 5'-splice site (GU), branch site (A), and 3'-splice site (AG) sequences on the pre-mRNA are shown. The complexes formed as the spliceosome assembles are referred to as the A, B, and C complexes. b) Sequential transesterification reactions catalyzed by the spliceosome. In the first step, the 2'-hydroxy group of the branch adenosine (A) within the intron carries out a nucleophilic displacement at the 5'-splice site to generate a free 5'-exon and a cyclic intermediate. Attack of the free 5'-exon at the 3'-splice site then yields ligated exons and a cyclic intron product.

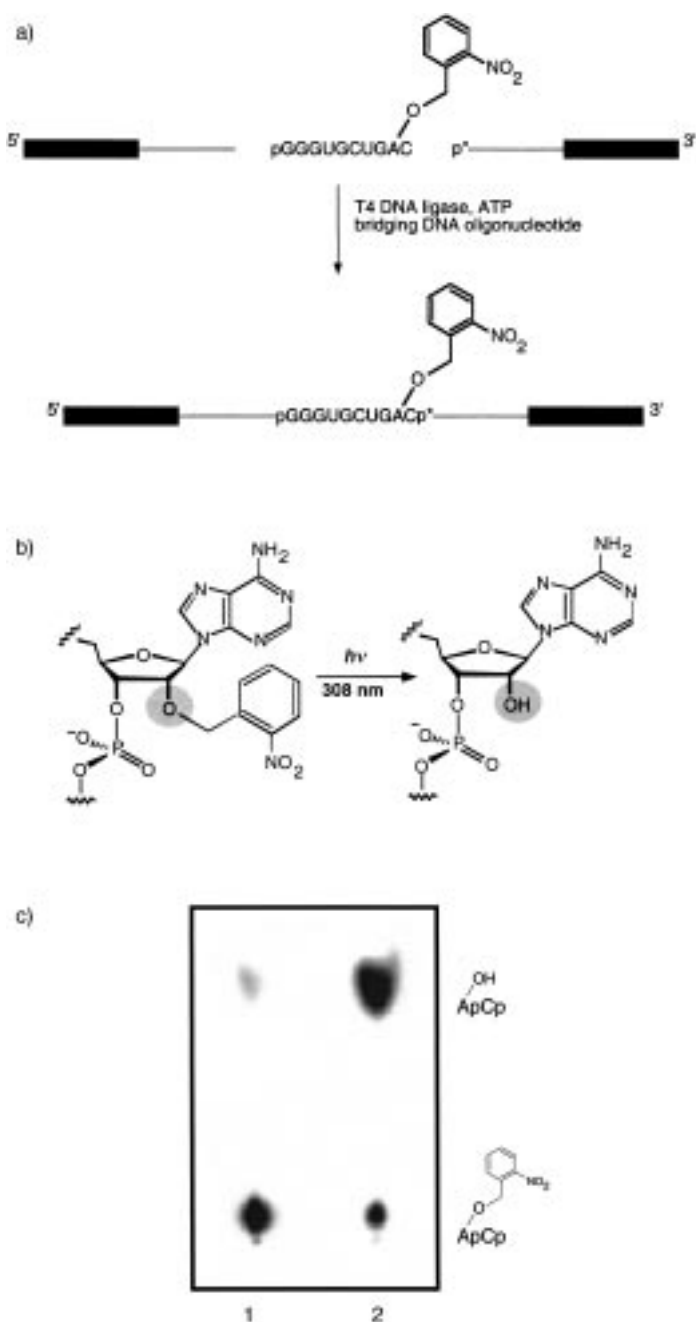


Figure 2. a) Synthesis of pre-mRNAs containing a caged 2'-hydroxy group at the branch position. A synthetic oligomer with a single modified adenosine residue was ligated to T7 RNA polymerase transcripts to yield full-length caged pre-mRNA with a single ^{32}P -radiolabel (shown as p*). b) Photolysis of caged adenosine to yield free adenosine. c) TLC analysis of photolysis of the caged pre-mRNA. Lane 1: unphotolyzed, caged pre-mRNA digested with RNase A and RNase T1; lane 2: photolyzed, uncaged pre-mRNA digested with RNase A and RNase T1.

pre-mRNA is still able to direct formation of the spliceosome.

In order to determine whether the spliceosomes formed on the caged substrates were catalytically competent, we incubated caged pre-mRNA in HeLa cell nuclear extract under splicing conditions, photolyzed the resulting complexes, removed aliquots over time, and analyzed the RNA by denaturing PAGE. These experiments showed that uncaging

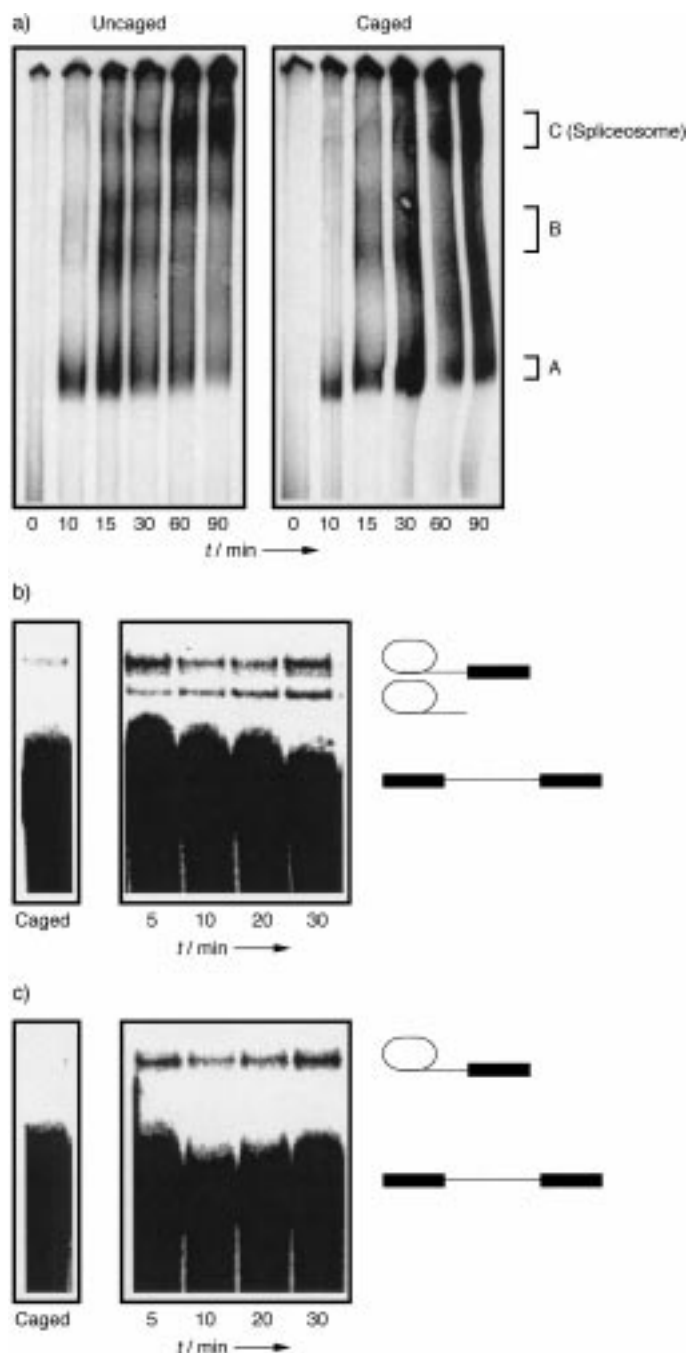


Figure 3. a) Spliceosome formation on uncaged and caged pre-mRNAs. Uncaged and caged ^{32}P -labeled pre-mRNAs were incubated under splicing conditions in HeLa cell nuclear extract for the indicated times, to allow formation of the A, B, and C (spliceosome) complexes, and analyzed by native gel electrophoresis (4%; 80:1; 50 mM trisglycine). b) Uncaging of pre-mRNA in HeLa cell nuclear extract; denaturing PAGE analysis of ^{32}P -labeled RNA. Left: caged pre-mRNA incubated for 60 minutes under splicing conditions; right: time course of splicing, after photolysis of pre-mRNA · spliceosome complexes, showing production of cyclic intermediate (first chemical step) and cyclic intron (second chemical step) products. c) Cofactor requirements after assembly of the spliceosome; denaturing PAGE analysis of ^{32}P -labeled RNA. Caged pre-mRNA was incubated in HeLa cell nuclear extract under splicing conditions to form pre-mRNA · spliceosome complexes after which ATP was depleted from the reaction by the addition of glucose and hexokinase. Left: caged pre-mRNA incubated for 60 minutes under splicing conditions; right: time course of splicing, after ATP depletion and photolysis of pre-mRNA · spliceosome complexes, showing production of cyclic intermediate (first chemical step) but no cyclic intron (second chemical step) products.

of the pre-mRNA occurred cleanly within the spliceosome and furthermore that the two chemical steps of splicing proceeded without a delay, which is consistent with the fact that the caged RNA is sequestered within a fully formed spliceosome (Figure 3b).

We examined the cofactor requirements of splicing by incubating caged pre-mRNA in HeLa cell nuclear extract in the presence of ATP to allow the ATP-dependent formation of the spliceosome. Following a 60 minute period, the reaction mixture was depleted of ATP by addition of glucose and the enzyme hexokinase.^[12] The reactions were irradiated to uncage the adenosine nucleophile and the products were analyzed by denaturing PAGE. Although the first step of splicing was observed under these conditions, depletion of ATP had the effect of blocking the second step (Figure 3c). Addition of excess ATP resulted in complete recovery of the second step of splicing in these reactions (data not shown).

Although ATP is required for spliceosome assembly, depletion of ATP from reactions containing fully formed spliceosomes did not prevent the first-step chemistry. This suggests that the caged pre-mRNA was poised to perform the first transesterification step and further indicates that ATP hydrolysis is in no way coupled to the nucleophilic attack at the 5'-splice site (the first step). ATP depletion did prevent the second step of splicing, which is in agreement with genetic studies in yeast^[13] and also with the ATP requirement for second-step chemistry in a trans-splicing system.^[14] This requirement most likely reflects the ATP requirement of RNA helicases involved in the rearrangement of RNA structure for the second step.^[2]

Our preliminary investigations show that spliceosome assembly can be uncoupled from the chemistry catalyzed by the spliceosome with caged pre-mRNAs. This approach should prove valuable in the elucidation of cofactor requirements, both during the assembly of the spliceosome and between the two chemical steps, and in the investigation of the possible role of kinase and phosphatase activities in pre-mRNA splicing.^[15] Finally the caging approach may be useful in transiently blocking reactivity in other RNA systems, including the Group II self-splicing intron.

Experimental Section

Preparation of caged pre-mRNA: A ten-base oligoribonucleotide containing a single caged adenosine was synthesized and purified as described elsewhere.^[6] The full-length caged pre-mRNA was synthesized by incubating a 5'-phosphorylated synthetic branch oligomer (300 pmol) with upstream (300 pmol) and 5'-³²P-labeled downstream (100 pmol) T7 RNA transcription products (representing the 5'- and 3'-portions of the PIP85.B pre-mRNA^[5]) in the presence of a bridging DNA oligonucleotide and 40 units of T4 DNA ligase (Conditions: 60 mM tris(hydroxymethyl)amino-methane (Tris) buffer (pH 7.8), 20 mM MgCl₂, 36 units of ribonuclease inhibitor, 1.2 mM ATP, 2.4% polyvinylpyrrolidone (PVP-40), 5 mM 1,4-dithiothreitol) at 30 °C for 3 hours. One unit is the quantity of enzyme required to transform one nmol of substrate in twenty minutes at 37 °C. Ligations were purified directly by PAGE (15%; 29:1). The products were visualized by autoradiography, extracted, dissolved in doubly distilled water, and stored at -20 °C.

TLC analysis of pre-mRNA: Caged pre-mRNAs containing a single ³²P-label situated two nucleotides in the 3'-direction of the modification were digested with 2 units each of RNase T1 and RNase A (20-μL reaction volume, 10 mM Tris buffer (pH 7)) both before and after photolysis

(irradiation at a distance of 1 cm with a 1000 W Oriel Xenon arc lamp for four seconds in 5 mm pyrex reaction vessels). Reaction mixtures were then concentrated, loaded onto a cellulose polyethyleneimine TLC plate (4 × 10 cm, J. T. Baker), and eluted for 1 hour in saturated (NH₄)₂SO₄/1M NH₄OAc/2-propanol (79:19:1). The air-dried TLC plate was exposed to a Molecular Dynamics phosphor screen and then scanned using a Molecular Dynamics Storm 860 Phosphorimager.

Splicing and photolysis of caged pre-mRNA: RNAs (50–100 × 10³ cpm) were incubated in 10-μL reaction mixtures containing 40% HeLa cell nuclear extract, 2 mM MgCl₂, 20 mM KCl, 1 mM ATP, 5 mM creatine phosphate, 4 units of ribonuclease inhibitor, and 4 μg of tRNA. Following a 60 minute incubation period at 30 °C, splicing complexes were photolyzed as described above. ATP depletions were effected by addition of glucose to a final concentration of 7 mM, then addition of 0.3 units of hexokinase, and incubation at 37 °C for 10 minutes. During the course of splicing, aliquots were removed at various times, the reactions in the aliquots were quenched by extraction with phenol/chloroform/isoamyl alcohol, the products were precipitated with ethanol, and then subjected to denaturing PAGE (15%; 29:1). Dried gels were exposed to a Molecular Dynamics phosphor screen which was then scanned using a Molecular Dynamics Storm 860 Phosphorimager.

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Polymerization of Ureidopyrimidinone-Functionalized Olefins by Using Late-Transition Metal Ziegler–Natta Catalysts: Synthesis of Thermoplastic Elastomeric Polyolefins**

Lee R. Rieth, Robert F. Eaton, and
Geoffrey W. Coates*

Many natural and synthetic polymers derive their unique functions and precise structures from hydrogen bonding. The double-helix conformation of DNA and the secondary structures of many proteins, both vital to the central mechanisms of living organisms, depend strongly upon the formation of specific hydrogen bonds. The amazing tensile strength and elasticity observed in spider silk results from strong intra- and intermolecular hydrogen bonds that stabilize the formation of helices and β -sheets.^[1] Hydrogen bonding between polymer chains also dictates the mechanical properties of many synthetic polymers: the high tensile strength of aromatic polyamides^[2] and the elastomeric properties of polyurethane block copolymers^[3] arise from intermolecular hydrogen bonding.

The introduction of hydrogen bonding arrays into polyolefins is particularly attractive.^[4] The nonpolar environment of the polyolefin matrix helps overcome the relative weakness of hydrogen bonds (compared to covalent bonds) and the entropic barrier to formation of hydrogen bond aggregates. Stadler et al. have shown that the hydrogen-bonding interactions of (4-carboxyphenyl)urazole moieties grafted onto polybutadiene significantly affect the properties of the bulk polymer due to the formation of a thermoreversible network.^[5] This system relies on highly ordered urazole junction zones which phase separate from the amorphous polymer; the hydrogen-bonding interactions between urazole groups are, individually, fairly weak ($K_{\text{dimer}} < 10^2 \text{ M}^{-1}$ in chloroform for typical donor–acceptor dimers).^[6]

Recent interest in the development of supramolecular polymers^[7] has led to synthesis of complementary hydrogen bonding arrays with extremely high dimerization constants in nonpolar environments. Meijer, Sijbesma, and co-workers^[8–10]

and Zimmerman and Corbin^[11] have developed heterocycles that dimerize strongly through an array of four hydrogen bonds arranged in a self-complementary donor-donor-acceptor-acceptor (DDAA) manner. For example, 2-ureido-4[1H]-pyrimidinones^[12] structurally similar to the one pictured in Figure 1 exhibit the dimerization constant K_{dimer} of $6 \times 10^7 \text{ M}^{-1}$ (in chloroform) and $6 \times 10^8 \text{ M}^{-1}$ (in toluene) at 298 K.^[9] Meijer, Sijbesma, and co-workers have demonstrated that telechelic oligomers with these 2-ureido-4[1H]-pyrimidinone endgroups self-assemble into supramolecular structures that behave like high molecular weight polymers;^[8, 13–15] further stabilization by phase separation is not observed.^[16]

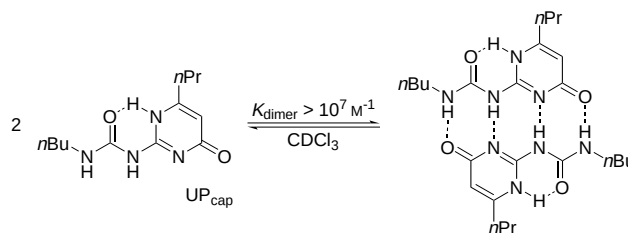


Figure 1. Quadruple hydrogen bonding of 2-ureido-4[1H]-pyrimidinones.

We are investigating the utility of 2-ureido-4[1H]-pyrimidinone derivatives as reversible crosslinks in polyolefin elastomers. Herein we report a simple method for randomly incorporating small percentages of olefinic 2-ureido-4[1H]-pyrimidinone (UP) derivatives within the main chain of amorphous polyolefins. The resulting pendant UP groups dimerize within the purified polymer matrix to form a reversible network,^[8, 16] with properties strikingly different from those of comparable polyolefin homopolymers.

To synthesize these novel materials, we employ a coordination polymerization route utilizing catalyst precursor **1** (Figure 2), recently developed by Brookhart et al. for polymerization of α -olefins.^[17–19] These catalysts undergo β -

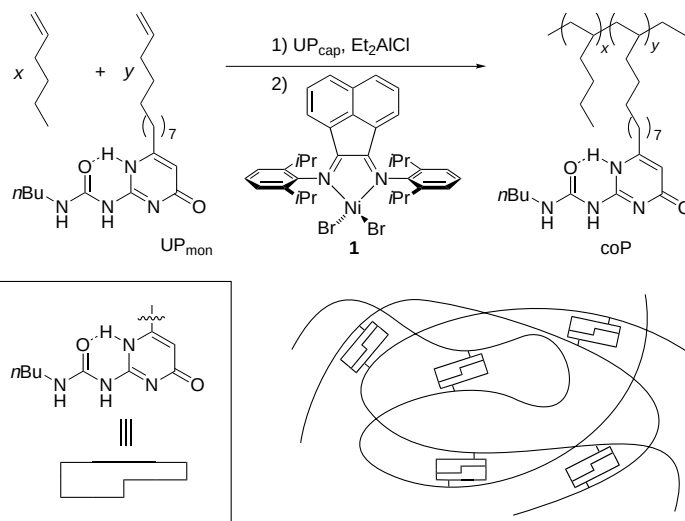


Figure 2. Synthesis and schematic drawing of 2-ureido-4[1H]-pyrimidinone-functionalized poly(1-hexene) (coP). The structure of the copolymer is more complicated than depicted due to chain-walking by the catalyst during polymerization, resulting in random branching in the main chain.

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hydride elimination followed by reinsertion (chain-walking) on a time scale faster than propagation, giving rise to unique, branched polyolefin architectures. Due to the low oxophilicity of nickel, they are also tolerant of functional Lewis basic groups, and are used here to copolymerize olefins with small amounts of UP_{mon} (typically 2%). Initial efforts have focused on 1-hexene as the primary comonomer. The relative rates of polymerization of 1-hexene and UP_{mon} are similar, ensuring that random copolymers are formed. Diethylaluminum chloride (Et₂AlCl) serves two purposes in this reaction. First, it activates the nickel catalyst precursor and serves as a weakly coordinating counteranion for the resultant cationic alkyl-nickel catalyst. Second, the aluminum reacts with UP derivatives, removing acidic hydrogens and protecting Lewis basic sites from reaction with the Ni center.^[20] Initial efforts to copolymerize 1-hexene and UP_{mon} led to precipitation of the growing polymer during the reaction. We attribute this phenomenon to the ability of aluminum to coordinate more than one UP molecule, leading to formation of Al/UP clusters and an insoluble network. The presence of three equivalents of non-olefinic UP (UP_{cap}) during the polymerization prevents formation of an insoluble network and leads to a homogeneous solution throughout the reaction. Subsequent precipitation of the copolymer with acidic methanol displaces aluminum and returns the UP derivatives to their original state. UP_{cap} and aluminum remain in solution and are eliminated from the polymer.

To investigate the nature of the reaction between UP and the aluminum cocatalyst, UP_{cap} was stirred with Et₂AlCl overnight; the reaction was then quenched with HCl/H₂O. The resulting organic-soluble product, recovered in 85% yield, proved to be UP_{cap} (by ¹H NMR spectroscopy), thereby verifying that comonomer UP_{mon} returns to its original state after the acidic quench. In a similar experiment, the reaction is instead quenched with DCl/D₂O; ¹H NMR spectroscopy reveals a considerable decrease in the intensities of shifts of protons attached to the urea and pyrimidine nitrogen atoms. These sites, which pose the biggest threat to the activity of the Ni catalyst,^[19] are apparently protected by aluminum during the polymerization.

NMR spectroscopy and gel permeation chromatography (GPC) studies provide evidence that UP is incorporated into the polymer and forms reversible crosslinks in solution. The proton NMR spectrum of the copolymer shows the same peaks above $\delta = 2.0$ found in the spectrum of UP_{mon} (in its H-bonded dimer form), except the olefin peaks have disappeared. This suggests that UP_{mon} has been incorporated into the polymer, and the incorporated UP groups are dimerizing (i.e. forming crosslinks). Furthermore, the GPC's UV detector (254 nm) generates a signal at the same elution volume as the RI-detected polymer, demonstrating that the chromophoric UP moiety must be covalently attached to the polymer backbone. Poly(1-hexene) homopolymer, made by homopolymerization of 1-hexene under the same conditions, shows no significant UV absorption. NMR and GPC studies also verify the complete elimination of UP_{cap} from the copolymer after precipitation.

Viscosity experiments support our assertion that pendant UP groups dimerize strongly in solution. As expected, the

viscosity of toluene solutions of homopolymer hP2 (Table 1) increases linearly with concentration (Figure 3). Solutions of coP2, however, show exponential increase in viscosity with increasing concentration. This phenomenon reveals the

Table 1. Homopolymers and UP-copolymers of 1-hexene prepared by using the Et₂AlCl-activated (α -diimino)NiBr₂ complex **1**.

Sample	% UP in polymer ^[a]	M_n ^[b]	M_w/M_n ^[b]
hP1	0	39000	1.6
hP2	0	104000	1.2
coP1	2.1	33000	1.4
coP2	1.9	74000	1.3
coP3	2.0	104000	1.2

[a] % mol of UP versus 1-hexene; determined by UV absorption.

[b] Determined by using GPC versus monodisperse polystyrene standards.

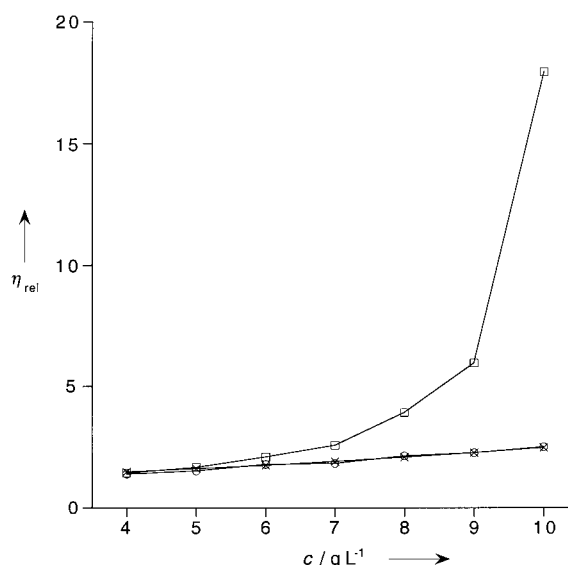


Figure 3. Relative viscosity (η_{rel} , versus pure toluene) of toluene solutions of homopolymer hP2 (x), copolymer coP2 (□), and coP2 with three molar equivalents of UP_{cap} (○) at various concentrations.

reversible nature of the UP crosslinks: at low copolymer concentrations, the equilibrium concentration of dimerized units is low, and the polymer behaves like the homopolymer. At higher copolymer concentration, the equilibrium concentration of dimerized units is high, and the effective molecular weight dramatically increases, leading to a large increase in viscosity. In fact, dissolving even higher concentrations of coP2 in toluene (> 20 g L⁻¹) leads to gelation.

Addition of three equivalents of UP_{cap} to solutions of the copolymer coP2 completely eliminates the crosslinking effect of the attached UP groups. This solution displays a viscosity profile very similar to the homopolymer hP2 (Figure 3). The viscosity of an 8.0 g L⁻¹ solution of coP2 in toluene rapidly decreases as UP_{cap} is added, approaching near constant viscosity at UP_{cap}/UP_{pol} = 1. These experiments suggest that individual sets of hydrogen-bonded dimers are the predominant source of network formation—stacks or clusters of UP moieties would not be completely broken down by the presence of UP_{cap}, and must therefore not be a significant

source of crosslinking.^[8, 14, 15] The clear, colorless appearance of the bulk copolymer further supports this assessment.

While the solution properties of the copolymer are intriguing, the primary motivation for this research was to demonstrate that the bulk copolymer forms an amorphous network with elastomeric properties. Consequently, tensile tests were performed on films of homopolymer and copolymer. Low molecular weight homopolymer hP1, a waxlike material, displayed tensile properties typical of a viscous liquid (Figure 4). After initial deformation associated with uncoiling the

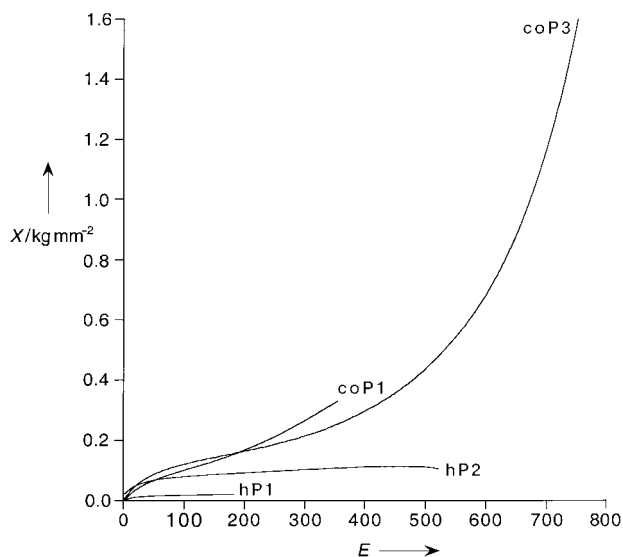


Figure 4. Stress–strain data for hP1, coP1, hP2, and coP3 (X = nominal stress; E = percent elongation).

amorphous polymer chains, the stress required to continue elongation increased minimally. The lack of strong intermolecular forces allows the chains to freely reptate under low stresses. In contrast, coP1 displayed an elastomeric tensile profile: initial elongation again occurs at low stresses because the amorphous polymer chains can easily uncoil. However, crosslinks inhibit the chains from moving past each other. As a result, stresses required to continue deformation increase dramatically once chains have uncoiled; bond stretching and bond angle deformation become the principle routes to further elongation.^[21] Thus, much higher stresses are observed at rupture. Higher molecular weight polymers hP2 and coP3 showed similar behavior under tension, except stresses and elongations were considerably higher at rupture, which we attribute to the increased intermolecular interactions of longer chains.

In conclusion, we report a convenient, one-pot synthesis of a new polyolefin elastomer. The polymer utilizes strongly dimerizing hydrogen-bonding arrays to form noncovalent crosslinks within the polymer matrix. The bulk polymer displays elastomeric properties at room temperature, verifying the formation of a network. Viscosity tests show, however, that the crosslinks are reversible: the copolymers are soluble in chloroform and toluene, and addition of small amounts of endcapper leads to dramatic decreases in viscosity. Studies of the thermomechanical properties of the polymer are underway.

Experimental Section

Synthesis: Catalyst **1**,^[17] monomer UP_{mon},^[15] and UP_{cap}^[10] were synthesized by using modifications of literature preparations. Diethylaluminum chloride (1.8M in toluene) was purchased from Aldrich. Toluene and 1-hexene were distilled from sodium benzophenone ketyl and 4 Å molecular sieves, respectively, and degassed by three freeze/pump/thaw cycles prior to use. All polymerizations were conducted under nitrogen using glovebox and Schlenk techniques. Reaction conditions: UP_{mon} (0.30 g, 0.80 mmol) and UP_{cap} (0.60 g, 2.4 mmol) were dissolved in toluene (75 mL). 1.8M Et₂AlCl (10.0 mL) was added, and the resulting solution was stirred for 15 min. 1-Hexene (5.0 mL, 40.0 mmol) was added, followed by Ni catalyst (20 mg) dissolved in toluene (25 mL). The reaction mixture was stirred at 0 °C (high molecular weight) or room temperature (lower molecular weight) for 20 h. The reaction was then quenched by slowly adding acidic methanol (100 mL; 1% HCl v/v), which caused the polymer to precipitate. The polymer was isolated (by decanting), washed with methanol, and dried in vacuo at 80 °C overnight. Residual aluminum was removed by redissolving the polymer in toluene (200 mL) and refluxing overnight with acidic methanol (20 mL; 5% HCl); then the polymer was reisolated by concentrating in vacuo and precipitating with excess methanol. Yields ranged between 75% and 80%.

Characterization of coP1–3: ¹H NMR (300 MHz, [D₈]toluene): δ = 13.4 (s, 1 H; NH), 12.3 (s, 1 H; NH), 10.9 (s, 1 H; NH), 5.7 (s, 1 H; =CH), 3.4 (t, 2 H; CH₂NHC(=O)), 0.8–1.8 (m; aliphatic CH, CH₂, CH₃). Molecular weights and molecular weight distributions were determined by gel permeation chromatography using THF solution versus polystyrene standards. Incorporation of UP monomer was determined by UV absorption at 245 nm in chloroform. Elemental analysis for residual aluminum (<0.02%) was performed by Desert Analytics. Viscosity measurements were performed by using a Canon 0B C202 Ubbelohde viscometer at 30.0 °C. Toluene solutions of the compounds were filtered through glass wool prior to testing. Relative viscosities are based on pure toluene. Tensile measurements were performed at an extension rate of 100 mm min⁻¹. Films were prepared by solvent evaporation from chloroform solutions, and samples were subsequently cut into strips (typical cross sections = 5.0 mm × 0.20 mm; clamp distance = 25.0 mm).

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Base-Assisted Formation of Organozirconium Oxides with the $[\text{Zr}_6(\mu_6\text{-O})(\mu_3\text{-O})_8]$ Core Structure**

Guangcai Bai, Herbert W. Roesky,* Peter Lobinger, Mathias Noltemeyer, and Hans-Georg Schmidt

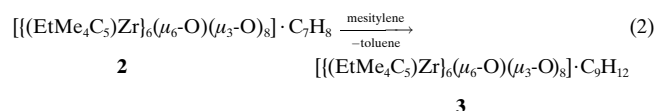
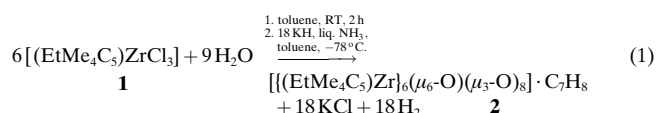
Dedicated to Professor Dieter Sellmann
on the occasion of his 60th birthday

Zirconium oxides have long-been used as catalysts for the hydrogenation of carbon monoxide^[1] and ethylene,^[2] the highly selective isomerization of 1-butene and the formation of 1-butene from 2-butanol or 2-butanamine,^[3] and the selective oxidation of hydroxy-containing organic compounds.^[4] In general, complete hydrolysis of zirconium chlorides leading to zirconium oxides without an appreciable amount of chloride and hydroxide is difficult to achieve and only possible at very high temperatures. ZrO_2 is prepared by treating $[\text{ZrOCl}_2 \cdot$

$8\text{H}_2\text{O}]$ at 1000°C ^[5] or by calcining zirconium hydroxide in O_2 at 500°C .^[1g, 3a] Base-assisted hydrolysis of organozirconium chlorides results in the formation of organozirconium oxide complexes containing chloride or hydroxide ligands, such as $[(\text{Cp}_2\text{ZrCl})_2(\mu\text{-O})]$,^[6] $[(\text{Cp}^*\text{ZrCl})(\mu\text{-OH})_3(\mu_3\text{-OH})(\mu_3\text{-O})] \cdot 2\text{THF}$,^[7] $[(\text{Cp}^*\text{ZrCl})(\mu\text{-OH})_3(\mu_3\text{-O})(\mu\text{-Cl})]$.^[8] To the best of our knowledge so far no larger aggregate of an organozirconium oxide has been isolated or detected.

We are interested in studying the products formed by the reaction of early transition metal compounds in the liquid ammonia/toluene two-phase system. Recently we reported on the reaction of $[\text{L}_2\text{TiCl}_2]$ ($\text{L} = p\text{-MeC}_6\text{H}_4\text{C}(\text{NSiMe}_3)_2$) with NaNH_2 in liquid ammonia and toluene^[9] to yield $[(\text{LTi})_6(\mu_3\text{-N})_2(\mu_3\text{-NH})_6] \cdot 6(\text{C}_7\text{H}_8)$, and on the formation of $[(\text{MeC}_5\text{H}_4)\text{Zr}]_5(\mu_5\text{-N})(\mu_3\text{-NH})_4(\mu\text{-NH}_2)_4$ from the reaction of $[(\text{MeC}_5\text{H}_4)_2\text{ZrCl}_2]$ with K in liquid ammonia and toluene.^[10] The imido-bridged dinuclear zirconium complex $[(\eta^3\text{-L}')\text{Zr}(\mu\text{-NH})_2]$ ($\text{L}' = (t\text{BuNP})_2(t\text{BuN})_2$) was obtained by treating $[\text{L}'\text{ZrCl}_2]$ with KH in liquid ammonia and toluene.^[11] These results prompted us to attempt the complete hydrolysis of metal chlorides, which is difficult to achieve under base-assisted conditions at low temperatures.

Herein we report on the reaction of $[(\text{EtMe}_4\text{C}_5)\text{ZrCl}_3]$ (**1**) with H_2O (1:1.5 molar ratio) in toluene at room temperature with successive treatment by KH (1:3 molar ratio) in liquid ammonia and toluene at -78°C . The strong basic reagent KH affords the complete removal of chloride and the formation of the organozirconium oxide **2** [Eq. (1)]. The influence of the solvent on the solid-state structure of **2** was demonstrated by recrystallization of **2** from mesitylene which gave cluster **3** [Eq. (2)].

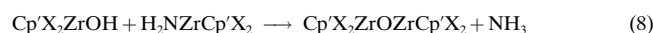
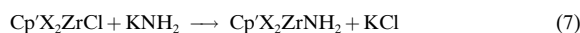
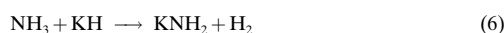
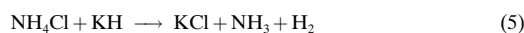
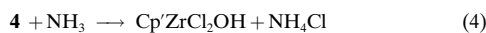
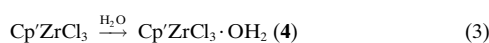


A proposed mechanism for the formation of **2** is given in Equations (3)–(8) ($\text{Cp}' = \text{EtMe}_4\text{C}_5$; $\text{X} = \text{Cl}$, NH_2 , or OH). The first step of the reaction involves the formation of the water adduct **4** [Eq. (3)]. The acidic nature of the hydrogen atoms of the coordinated H_2O results in hydrogen chloride elimination under formation of ammonium chloride in the presence of NH_3 [Eq. (4)]. We were unable to isolate **2** from the reaction of **1** with H_2O in liquid ammonia and toluene. Excess of ammonia does not result in a complete hydrolysis of **1**. Partial hydrolysis and ammonolysis have been also observed in the base-assisted hydrolysis of $[\text{Cp}^*\text{ZrCl}_3]$ ^[7, 8] and the ammonolysis of ZrX_4 ($\text{X} = \text{Cl}$, Br) in liquid NH_3 .^[12] In the presence of KH, NH_4Cl is converted to KCl and hydrogen [Eq. (5)]. On the other hand KH reacts with ammonia under formation of KNH_2 and hydrogen [Eq. (6)].^[13] Moreover, we have shown that KNH_2 reacts with a compound containing a $\text{Zr}\text{--}\text{Cl}$ bond to yield the amide [Eq. (7)].^[10] Due to the Lewis acidity of the Zr^{IV} center, the OH group functions as an acid

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and this favors the formation of a further Zr–O bond [Eq. (8)] rather than a Zr–N bond. Similar results were observed in the hydrolysis of $[\text{Cp}_2^*\text{HfH}(\text{NH}_2)]^{[14]}$ and $[(\text{Cp}^*\text{Ti})_4(\mu_3\text{-N})_4]^{[15]}$ which led to $[\text{Cp}_2^*\text{HfH}(\text{OH})]$ and $[(\text{Cp}^*\text{Ti})_4(\mu\text{-O})_6]$, respectively. Consequently, the addition of KH results in the complete hydrolysis of **1**. Certainly Equations (3)–(8) are



over simplified and other side reactions might occur. Evidently, the KH has two functions in this reaction, it completely converts the chloride to KCl and the resulting ZrOH and ZrNH₂ to ZrOZr species by an intermolecular ammonia elimination. It is well documented that the Zr–Cl, Zr–OH, and Zr–NH₂ compounds can be isolated when no KH is present in the reactions.^[7, 8, 10] Finally, the two-phase system (ammonia/toluene) increases the solubility of the organic and inorganic components, so that the reaction preferentially occurs at the interface. Therefore we assume that the presence of KH and the in situ formation of ZrNH₂ as well as the liquid ammonia/toluene two-phase system are important for the formation of **2**.

Compounds **2** and **3** are colorless crystalline solids with unusual thermal stability. The melting points of **2** and **3** exceed 410 °C. Compounds **2** and **3** are very stable to H₂O and O₂. No reaction was observed on exposing the solution of **2** (**3**) to H₂O or air. The most intense peak in the EI mass spectrum of **2** appears at m/z 1437 [$M^+ - \text{C}_7\text{H}_8 - \text{EtMe}_4\text{C}_5$], and the signal at 1586 (4%) is assigned to the [$M^+ - \text{C}_7\text{H}_8$] fragment. The corresponding peaks of **3** appear at m/z 1437 (100%) [$M^+ - \text{C}_9\text{H}_{12} - \text{EtMe}_4\text{C}_5$] and 1586 (12%) [$M^+ - \text{C}_9\text{H}_{12}$].

Single crystals of **2**^[16a] and **3**^[16b] suitable for X-ray structural analysis were obtained from toluene and mesitylene, respectively, by keeping the reaction mixtures at 0 °C for one week. The molecular structure of **2** is shown in Figure 1. Each molecule of **2** (**3**) contains one molecule of toluene (mesitylene). Compound **2** crystallizes in the triclinic space group $P\bar{1}$, and **3** in the monoclinic space group $C2/c$. The molecular structure of **2** in the crystal consists of a perfect octahedron with $(\text{EtMe}_4\text{C}_5)\text{Zr}$ fragments arranged around an interstitial oxygen atom. The angles between adjacent zirconium atoms are either 60° or 90°. Eight of the faces of the octahedron are topped each by oxygen resulting in twelve four-membered Zr₂O₂ rings. The average O–Zr–O and Zr–O–Zr angles in the Zr₂O₂ rings are 81.34° and 94.65°, respectively. The coordination sphere of each zirconium atom is completed by the ligand EtMe_4C_5 . The Zr–(μ_3 -O) bond lengths (2.136(2)–2.169(2) Å, av 2.156 Å) are similar to those in $[(\text{Cp}^*\text{ZrCl})(\mu\text{-OH})_3(\mu_3\text{-OH})(\mu_3\text{-O})] \cdot 2\text{THF}$ (Zr–(μ_3 -O) 2.134 Å)^[7] and in $[(\text{CpZr}(\mu\text{-OH}))_3(\mu_3\text{-O})(\mu\text{-C}_6\text{H}_5\text{COO})_3]^+$ (Zr–(μ_3 -O) 2.071(11) Å).^[17]

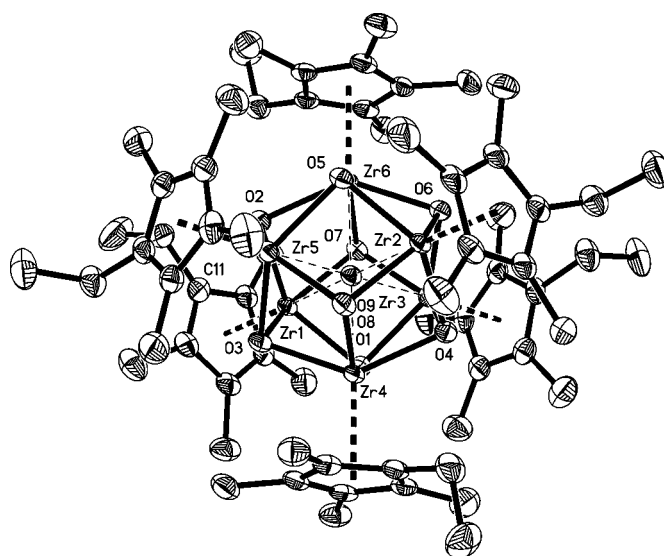


Figure 1. Molecular structure of **2** in the crystal. The hydrogen atoms and the toluene molecule are omitted for clarity. Selected bond lengths [Å] and angles [°]: Zr1–O1 2.136(2), Zr1–O2 2.169(2), Zr1–O3 2.142(2), Zr1–O7 2.165(2), Zr1–O9 2.241(2), Zr2–O9 2.245(2), Zr1–Zr4 3.1542(9), Zr1–Zr5 3.1657(11); O1–Zr1–O3 82.19(9), O1–Zr1–O7 81.42(9), O2–Zr1–O3 81.37(9), O2–Zr1–O7 80.53(9), Zr1–O1–Zr3 94.87(9), Zr1–O1–Zr4 94.48(9), Zr3–O1–Zr4 94.32(9), Zr4–Zr1–Zr5 60.25(2), Zr1–Zr4–Zr2 90.53(2), Zr1–O9–Zr4 89.70(8), Zr1–O9–Zr2 179.52(11).

Whereas the Zr–(μ_6 -O) bond lengths (2.231(2)–2.247(2) Å, av 2.241 Å) are distinctively longer. Moreover the Zr–(μ_3 -O) and Zr–(μ_6 -O) bond lengths are longer than the Zr–(μ -O) bond lengths in $[(\text{Cp}_2\text{ZrCl})_2(\mu\text{-O})]$ (1.945(3) Å),^[6] $[(\text{Cp}_2\text{ZrMe})_2(\mu\text{-O})]$ (1.948(1) Å),^[18] and $[(\text{Cp}_2\text{Zr}(\mu\text{-O}))_3]$ (1.959(3) Å).^[19] The Zr···Zr distances (3.1542(9)–3.1709(11) Å, av 3.1635 Å) are comparable to those in $[(\text{MeC}_5\text{H}_4)\text{Zr}]_5(\mu_5\text{-N})(\mu_3\text{-NH})_4(\mu\text{-NH}_2)_4]$ (Zr_a···Zr_b 3.1433(10) Å, Zr_b···Zr_b 3.1566(8) Å; Zr_a and Zr_b represent the apical and the four basal zirconium atoms of the square-pyramidal cluster, respectively).^[10] Furthermore the Zr···Zr distances are also similar to those exhibited by the zirconium halide clusters $[\text{KZr}_6\text{Cl}_{15}\text{C}]$ (3.225 Å),^[20] $[\text{CsZr}_6\text{I}_{14}\text{C}]$ (3.283 Å),^[21] $[\text{Zr}_6\text{Cl}_{12} \cdot \text{K}_2\text{ZrCl}_6]$ (3.201 Å),^[22] and $[\text{Zr}_6\text{Cl}_{14}\text{B}]$ (3.257 Å).^[23] The molecular structure of **3** in the crystal is more symmetric than that of **2** due to the more symmetric mesitylene in **3**. But the core structure of **3** is nearly the same as that of **2**. The bond lengths of Zr–(μ_3 -O) (2.145(2)–2.175(2) Å, av 2.163 Å) and Zr–(μ_6 -O) (2.2407(4)–2.2481(4) Å, av 2.2432 Å), and the Zr···Zr distances (3.1664(7)–3.1728(7) Å, av 3.1687 Å), as well as the average O–Zr–O (81.35°) and Zr–O–Zr (94.61°) angles in the four-membered Zr₂O₂ rings of **3** are almost the same as those found in **2**.

It is interesting to compare the coordination environment of Zr in **2** and **3** with that in monoclinic ZrO₂ (Figure 2).^[24] Compounds **2** and **3** can be regarded as deriva-

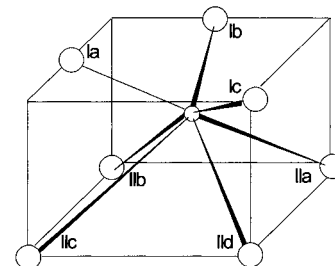


Figure 2. Monoclinic ZrO₂. Small circle = zirconium atom; large circles = oxygen atoms.

tives of ZrO_2 . One EtMe_4C_5 ligand is sterically equivalent to three O_I positions, while the interstitial O coordinates to zirconium from the center of the plane formed by the four O_{II} atoms by enlarging the $\text{O}_{II}\text{-Zr-O}_{II}$ angles (av 74.1° in ZrO_2). The $\text{Zr}-(\mu_3\text{-O})$ bond lengths in **2** and **3** are between the Zr-O_I ($2.07 \text{ \AA}$) and Zr-O_{II} ($2.21 \text{ \AA}$) bond lengths, while the $\text{Zr}-(\mu_6\text{-O})$ bond lengths are comparable to those of Zr-O_{II} .

In summary we describe a new method for the preparation of organozirconium oxides by hydrolysis of an organozirconium chloride at low temperatures. Using this method, we have obtained the organozirconium oxides **2** and **3**. In comparison to the traditional preparation of ZrO_2 from ZrCl_4 at 1000°C the new route yields crystalline products below room temperature. The core structures of **2** and **3** can be regarded as a dimer of the previously reported $[(\text{Cp}^*\text{ZrCl})(\mu\text{-OH})_3(\mu_3\text{-OH})(\mu_3\text{-O})] \cdot 2\text{THF}$ cluster^[7] (without containing six HCl, four THF, and one H_2O molecules). We assume that the formation of **2** proceeds via zirconium hydroxide and amide intermediates. KH and the two-phase system (NH_3 /toluene) are important for the formation of **2**. The more symmetric coordinated mesitylene leads to the more symmetric molecule of **3**, but has evidently no influence on the core structure. Further studies using this new method for the preparation of Ti-O, Hf-O, Al-O, and rare-earth systems are in progress.

Experimental Section

2: H_2O (0.08 g, 4.5 mmol) was added to the solution of **1** (1.04 g, 3.0 mmol) in toluene (80 mL) at room temperature. The solution turned light yellow and was stirred for 2 h at this temperature. KH (0.37 g, 9.2 mmol) was added to the solution, and then ammonia (50 mL) was condensed onto the resulting suspension at -78°C with stirring. The mixture was stirred for 1 h at this temperature. Then the excess of ammonia was allowed to evaporate from the reaction mixture over a period of 4 h. During this time the mixture slowly warmed to room temperature. The resulting solution was filtered and the remaining yellowish brown precipitate was extracted with warm toluene (50°C , $2 \times 20 \text{ mL}$). The combined light yellow solution was concentrated (to 15 mL) in vacuo and kept at 0°C for one week. Colorless crystals of **2** (0.10 g) were obtained. After concentration (to 5 mL) of the filtrate, the solution was kept at -20°C for one week. An additional crop of **2** (0.11 g) was obtained. Total yield 0.21 g (25 %); m.p. $> 410^\circ\text{C}$; IR (Nujol): $\bar{\nu} = 1580, 1309, 1261, 1097, 1050, 1023, 779, 727, 659, 562, 506, 454 \text{ cm}^{-1}$; ^1H NMR (200 MHz, C_6D_6 , 60°C): $\delta = 2.74$ (q, $^3J = 7.5 \text{ Hz}$, 12H; CH_2Me), 2.23, 2.17 (s, 72H; C_6Me_4), 1.08 (t, $^3J = 7.5 \text{ Hz}$, 18H; CH_2Me); EI-MS: m/z (%): 1586 (4) [$M^+ - \text{C}_7\text{H}_8$], 1437 (100) [$M^+ - \text{C}_7\text{H}_8 - \text{EtMe}_4\text{C}_5$]; elemental analysis (%) calcd for $\text{C}_{73}\text{H}_{110}\text{O}_9\text{Zr}_6$ (1679.0): C 52.2, H 6.6; found: C 52.7, H 6.7.

3: Crystals of **2** (0.05 g) were dissolved in warm mesitylene (80°C ; 8 mL). The resulting colorless solution was kept at 0°C for one week. A quantitative yield of colorless crystals of **3** was obtained; m.p. $> 410^\circ\text{C}$; EI-MS: m/z (%): 1586 (12) [$M^+ - \text{C}_9\text{H}_{12}$], 1437 (100) [$M^+ - \text{C}_9\text{H}_{12} - \text{EtMe}_4\text{C}_5$].

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- [16] a) Crystal data for **2**: $\text{C}_{73}\text{H}_{110}\text{O}_9\text{Zr}_6$ (including one toluene molecule), $M_r = 1678.93$, triclinic, space group $P\bar{1}$, $a = 12.959(3)$, $b = 14.341(4)$, $c = 19.189(5) \text{ \AA}$, $\alpha = 82.85(3)$, $\beta = 84.562(17)$, $\gamma = 83.767(13)^\circ$, $V = 3505.7(15) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.591 \text{ Mg m}^{-3}$, $F(000) = 1720$, $\lambda = 0.71073 \text{ \AA}$, $T = 200(2) \text{ K}$, $\mu(\text{MoK}\alpha) = 0.914 \text{ mm}^{-1}$. Data for the structure were collected on a Stoe-Siemens-AED2 four-circle diffractometer. Intensity measurement was performed at $200(2) \text{ K}$ on a rapidly cooled crystal with the dimensions $1.0 \times 0.6 \times 0.4 \text{ mm}^3$ in an oil drop^[25] in the range $7.04 \leq 2\theta \leq 50.10^\circ$. Of the 15669 measured reflections, 12318 were independent ($R_{\text{int}} = 0.0787$). The structure was solved by direct methods (SHELXS-90)^[26] and refined with all data by full-matrix least-squares on F^2 .^[27] The hydrogen atoms of C-H bonds were added in idealized positions. $R1 = 0.0408$ for $I > 2\sigma(I)$, $wR2 = 0.1187$ for all data. The final difference Fourier synthesis gave a min./max. residual electron density $-1.173/+0.891 \text{ e \AA}^{-3}$. b) Crystal data for **3**: $\text{C}_{75}\text{H}_{114}\text{O}_9\text{Zr}_6$ (including one mesitylene molecule), $M_r = 1706.98$, monoclinic, space group $C2/c$, $a = 22.641(5)$, $b = 13.0808(11)$, $c = 24.550(6) \text{ \AA}$, $\beta = 93.196(12)^\circ$, $V = 7259(2) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.562 \text{ Mg m}^{-3}$, $F(000) = 3504$, $\lambda = 0.71073 \text{ \AA}$, $T = 200(2) \text{ K}$, $\mu(\text{MoK}\alpha) = 0.884 \text{ mm}^{-1}$. Data for the structure were collected on a Stoe-Siemens-AED2 four-circle diffractometer. Intensity measurement was performed at $200(2) \text{ K}$ on a rapidly cooled crystal in an oil drop^[25] with the dimensions $0.6 \times 0.6 \times 0.4 \text{ mm}^3$ in the range $7.06 \leq 2\theta \leq 50.04^\circ$. Of the 7944 measured reflections, 6365 were independent ($R_{\text{int}} = 0.0330$). The structure was solved by direct methods (SHELXS-90)^[26] and refined with all data by full-matrix least-squares on F^2 .^[27] The hydrogen atoms of C-H bonds were added in idealized positions. $R1 = 0.0307$ for $I > 2\sigma(I)$, $wR2 = 0.0683$ for all data. The final difference Fourier synthesis gave a min./max. residual electron density $-0.476/+0.756 \text{ e \AA}^{-3}$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155721 (**2**) and CCDC-155720 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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A Luminescent Gold Ring That Flips Like Cyclohexane**

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Coordination-directed self-assembly of metal centers and multidentate ligands has successfully created many discrete inorganic molecules with intricate supramolecular architectures.^[1] Among these compounds are metallacycles^[2] which are not only aesthetically pleasing but potentially functional as catalysts, sensors, and in molecular electronics.^[3] The modular character of the compounds allows their physical properties to be tailored readily and previous studies of metallacycles focused mainly on their photoluminescence and electrochemistry.^[2b,c, 3, 4] On the other hand, our understanding of the fluxionality of metallacycles is still relatively limited. Given the rich fluxionality of organic rings and cyclophanes,^[5] it is surprising that analogous behavior is not widely observed in their inorganic counterparts. This paucity could be a result of the rigidity of many metallacycles. Outstanding examples of metallacycle fluxionality are the PtS₅ ring inversion in [NH₄]₂[Pt(S₅)₃] and the cyclooctane-like inversion of the eight-membered ring [Pt₂Me₄(μ-Me₂PCH₂Me₂)₂] reported by Riddell et al.^[6a] and Puddephatt and co-workers,^[6b] respectively. Herein we report the synthesis of 9,10-bis(diphenylphosphino)anthracene (PANP), a ligand designed to form emissive cyclophanes with low-valent metal centers. Subsequent treatment of PANP with Au^I ions produced a fluorescent trinuclear gold ring that has structure and fluxionality reminiscent of cyclohexane.

PANP (see Scheme 1) was synthesized from the reaction of dilithioanthracene and PPh₂Cl. A similar monodentate ligand 9-diphenylphosphinoanthracene was first synthesized by Mingos and co-workers.^[7] PANP shows a singlet at δ = −21.9 in the ³¹P{¹H} NMR spectrum and its structure was confirmed by X-ray crystallography (see Supporting Information). Prolonged reflux of PANP and Me₂SAuCl (1:1) in methanol

produced a yellow solution from which a trinuclear Au^I complex [Au₃(PANP)₃][ClO₄]₃ (**1**) was isolated. Single-crystal X-ray analysis shows that the cation of **1** is a ring comprising three bridging PANP ligands and three gold atoms (Figure 1).^[8] The three anthracenyl units are nearly perpendicular to the ring, the diameter of which, taken as the

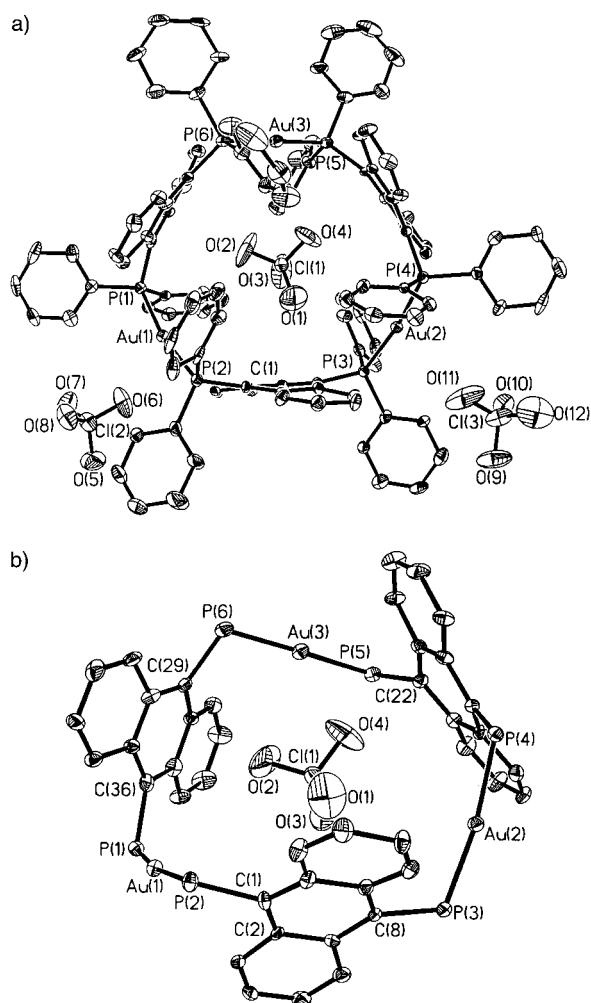


Figure 1. ORTEP drawing of **1** · 0.5 Et₂O; a) top and b) side view. H atoms, ClO₄ ions, Ph rings, and Et₂O are omitted for clarity (thermal ellipsoids are set at the 50% probability level). Selected bond lengths [Å] and angles [°]: Au(1)–P(1) 2.294(3), Au(2)–P(3) 2.312(3), Au(3)–P(5) 2.309(3), P(2)–C(1) 1.850(9), Au(1)···Au(2) 8.123(3), Au(1)···Au(3) 7.892(3), Au(2)···Au(3) 7.742(3); P(1)–Au(1)–P(2) 169.54(1), P(3)–Au(2)–P(4) 171.91(9), P(5)–Au(3)–P(6) 178.84(1), Au(1)–P(2)–C(1) 109.6(3).

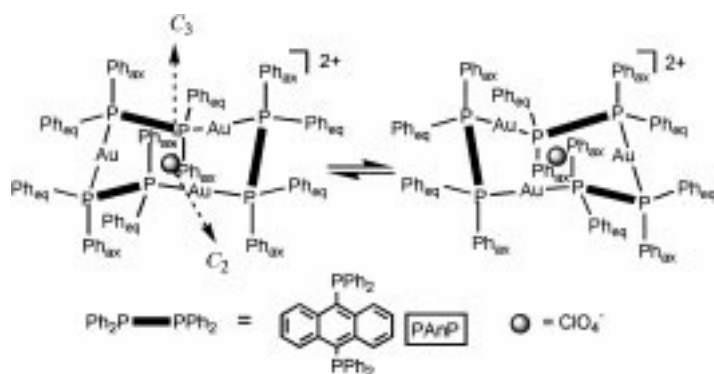
distance between P(1) and P(4), is 10.04 Å. One of the three ClO₄[−] ions is in the center of the ring and three of its oxygen atoms (O(1), O(2), and O(4)) are directed towards, and are almost equidistant from, the central rings of the three PANP anthracene units (3.083(3)–3.170(3) Å). Notably, the anthracenyl rings curve slightly from the center of the cavity, with a dihedral angle of 15.3° between the two lateral benzene rings. Similar ring distortion has been observed in 9,10-bis(trimethylsilyl)anthracene,^[9] and possibly occurs in **1** to alleviate steric congestion between the peripheral protons of anthracenyl and Ph rings. The coordination geometry of the Au atoms is close to linear (169.54(1)–178.84(1)°) and the

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average Au–P bond of 2.309 Å compares favorably with those observed in other Au^I–phosphane compounds.^[10] The long intra-annular Au...Au separations (7.742(3)–8.123(3) Å) preclude any aurophilic interaction between the gold atoms.^[10] The side view of the structure shows that the ring is puckered, displaying a chair conformation similar to that of cyclohexane (Figure 1b). While internal C–C–C angle of cyclohexane is 111.4°, the internal C(anthracenyl)–P–Au angles (108.4(3)–110.6(3)°) of the gold ring are very close to the ideal tetrahedral. Gold(II) metallacycles are known^[12] but **1** is the only one that shows a chair conformation. A similar conformation was reported by Che and co-workers for a luminescent Pt^{II} metallacycle.^[13] Like cyclohexane, which has axial and equatorial H atoms,^[5] **1** has two geometrically different sets of phenyl rings: six axial phenyl rings (Ph_{ax}) lying up and down along the central axis of the ring and six equatorial phenyl rings (Ph_{eq}) alternating about a plane at right angles to the central axis (Scheme 1). The Ph_{ax} and Ph_{eq} rings are diastereotopic.



Scheme 1.

Whereas the crystal structure of **1** slightly deviates from the maximum *D*₃ point group symmetry, the solution ³¹P{¹H} NMR spectrum shows a sharp singlet at δ = 34.9 (Figure 2b) which displays no significant change in line shape throughout temperature range of 302–213 K. This indicates that the gold ring reverts to *D*₃ symmetry in solution and its six P atoms, related by *C*₃- and *C*₂-rotations (Scheme 1), are equivalent. The gold ring is stable in solution and no NMR signals arising from free ligand or other species are observed even after

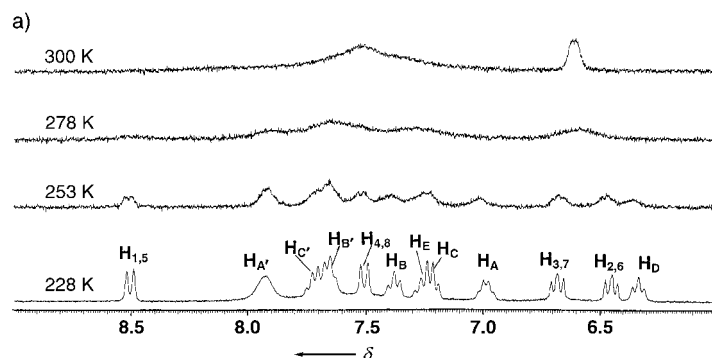


Figure 2. a) Variable temperature ¹H NMR spectra of **1** (300 MHz, CD₂Cl₂) and labeling scheme for the protons in the PAnP ligand in **1**; b) variable temperature ³¹P{¹H} NMR spectra of **1** (300 MHz, CD₂Cl₂).

several days. Surprisingly, the ¹H NMR spectrum of **1** is highly temperature dependent; the 300 K spectrum shows very broad signals (Figure 2a) which are better resolved as the temperature decreases. These seemingly contradictory ³¹P{¹H} and ¹H NMR results suggest that **1** exchanges between two conformations in which all the P atoms (but not the protons) have identical chemical environments. Given the structural resemblance between the gold ring and cyclohexane, we propose that the fluxional process is a ring inversion arising from the rotations of skeletal Au–P and P–C(anthracenyl) bonds (Scheme 1).

The proposed fluxional process was supported by low temperature NMR spectroscopy studies. The broad resonance signals in the ¹H NMR spectrum resolve into twelve multiplets as the fluxional process is slowed down at 228 K. Based on the ¹H–¹H COSY spectrum of **1** recorded at the same temperature (Figure 3), the multiplets can be assigned to the protons

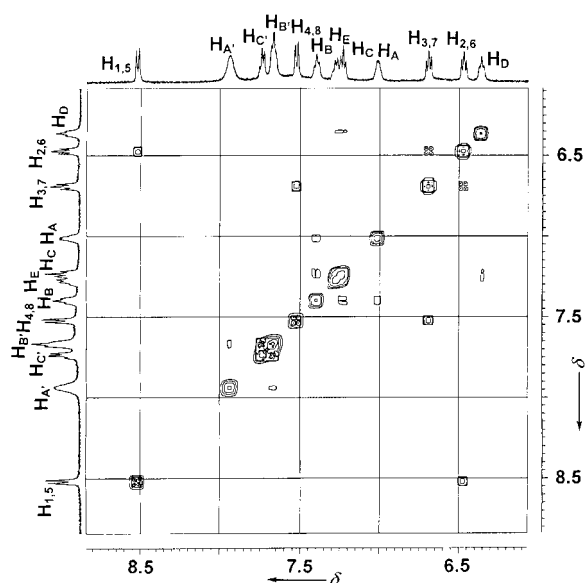
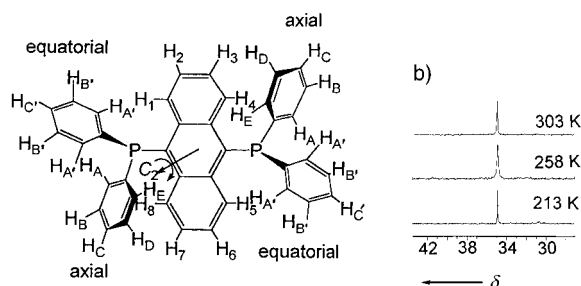


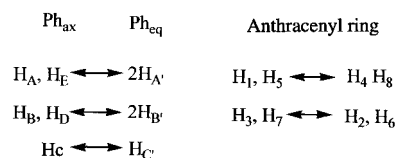
Figure 3. ¹H–¹H COSY spectrum of **1** recorded at 228 K (500 MHz, CD₂Cl₂).

in PAnP. (In the following discussion, the assignment is only made to one PAnP unit since the three ligands in **1** are equivalent). The diastereotopic Ph_{ax} and Ph_{eq} are expected to display different NMR signals. Indeed, COSY spectrum



shows that 8 of the 12 multiplets are attributable to the Ph_{ax} (in total 10 H, $\delta = 6.99$ (2 H, H_{A}), 7.38 (2 H, H_{B}), 7.21 (2 H, H_{C}), 6.34 (2 H, H_{D}), 7.24 (2 H, H_{E})), and Ph_{eq} (in total 10 H, $\delta = 7.92$ (4 H, H_{A}), 7.68 (4 H, H_{B}), 7.73 (2 H, H_{C})) rings.^[14] The observation of five distinct signals for Ph_{ax} protons implies a slow rotation of the ring around the P–C bond, probably hindered by the anthracenyl ring (the X-ray structure of **1** shows that the Ph_{ax} and anthracenyl rings are close to each other). On the other hand, the resonance signals arising from the $o\text{-H}_{\text{A'}}$ and $m\text{-H}_{\text{B'}}$ atoms of the Ph_{eq} ring remain broad and unresolved even at 228 K, indicating that the rotation of the ring, which is directed outward, is still fast on the NMR timescale. Because of the orientation of the diastereotopic Ph rings, the PAnP ligands show a local C_2 symmetry and the remaining four multiplets can be assigned to the four pairs of equivalent protons in the anthracenyl ring (in total 8 H, $\delta = 8.51$ (2 H, $\text{H}_{1,5}$), 7.51 (2 H, $\text{H}_{4,8}$), 6.70 (2 H, $\text{H}_{3,7}$), and 6.45 (2 H, $\text{H}_{2,6}$)).^[14]

It is well known that the axial and equatorial protons interchange their positions in the ring inversion of cyclohexane.^[5] Likewise, one would expect to see exchange of the Ph_{ax} and Ph_{eq} rings ($\text{Ph}_{\text{ax}} \leftrightarrow \text{Ph}_{\text{eq}}$) in the gold ring inversion. In addition, the flipping of Ph rings would also lead to a swapping of the anthracenyl proton positions (Scheme 2).



Scheme 2. Exchanges of position expected on ring inversion.

Cross-peaks corresponding to these exchanging pairs are clearly observed in the ^1H 2D-EXSY spectrum recorded at 228 K (Figure 4), confirming that the gold ring undergoes cyclohexane-like ring inversion in solution. The spectrum also

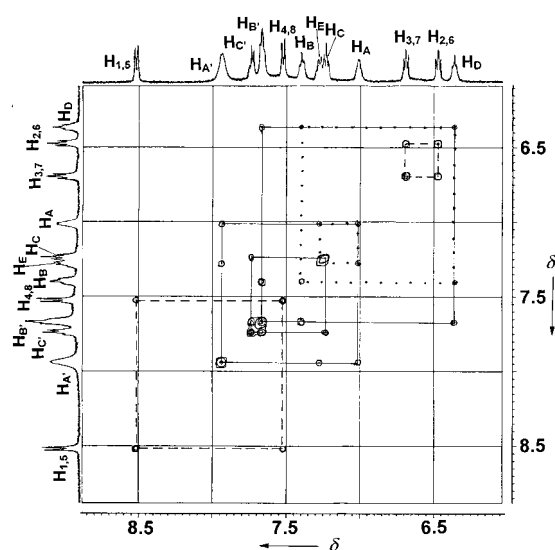


Figure 4. ^1H 2D-EXSY spectrum of **1** (500 MHz, CD_2Cl_2). Cross-peaks for the flipping of $\text{Ph}_{\text{eq}} \leftrightarrow \text{Ph}_{\text{ax}}$ (—), exchange of $\text{H}_{1,5} \leftrightarrow \text{H}_{4,8}$ and $\text{H}_{3,7} \leftrightarrow \text{H}_{2,6}$ in the anthracenyl ring (....) and rotation of the Ph_{ax} ring (●●●).

shows exchange cross-peaks for $\text{H}_{\text{A}} \leftrightarrow \text{H}_{\text{E}}$ and $\text{H}_{\text{B}} \leftrightarrow \text{H}_{\text{D}}$, supporting the idea that the Ph_{ax} ring is rotating, albeit slowly at 228 K. Since the signals of the exchanging pair $\text{H}_{3,7} \leftrightarrow \text{H}_{2,6}$ are well removed from the other signals, their coalescence temperature (278 K) is used to calculate the rate constant (k_{278}) and free enthalpy of activation ($\Delta G_{278}^\ddagger$) of the ring inversion which are 155 s^{-1} and 56 kJ mol^{-1} , respectively.^[15] The 2D-EXSY results clearly show that ring inversion is the *only* fluxional process displayed by **1**. Notably, all of the P atoms at the “corners” would remain equivalent throughout the process, which is consistent with the observation of a sharp singlet in the variable temperature ^{31}P NMR spectra (Figure 2b). Since the gold ring is chiral, the ring inversion can be regarded as enantiomerization. Although the hexanuclear cyclo- $[\{\text{ReH}(\text{CO})_4\}_6]$ complex is known as an inorganic structural analogue of cyclohexane,^[16] **1** shows both *structure* and *fluxionality* akin to that of the organic ring.

UV/Vis absorption spectra of PAnP and **1** show intense vibronic bands at 396 nm ($\epsilon_{\text{max}} 9285 \text{ M cm}^{-1}$) and 424 nm ($\epsilon_{\text{max}} 32857 \text{ M cm}^{-1}$) attributable to $^1\pi \rightarrow \pi^*$ transitions in the anthracenyl ring (see the Supporting Information). Excitation of an aerated or degassed CH_3CN solution of **1** at 400 nm gives an emission maximum at 475 nm with a quantum yield of 0.05 (Figure 5). On the contrary, PAnP is nonemissive.

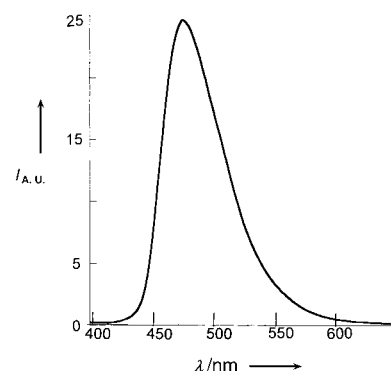


Figure 5. Emission spectrum of **1** in CH_3CN at 297 K. Excitation wavelength 400 nm. Excitation and emission slit widths 5 nm.

Probably the emitting state of PAnP is quenched by a rapid intramolecular electron transfer from the PPh_2 groups. Similar quenching has been observed in anthracenes containing electron-rich substituents.^[17] On the other hand, **1** is fluorescent because the lone-pairs of the PPh_2 groups, being donated to the Au^{I} ions, are not available for quenching. Unlike the highly vibronic fluorescence of anthracene and 9,10-disubstituted anthracenes,^[18] the emission of **1** shows no structure and is red shifted by $\sim 4000 \text{ cm}^{-1}$. As the absorption spectra of **1** and the free ligand are similar, the unique emission of **1** could not arise from a ground state interaction between anthracenyl rings; in fact, the red shift and the absence of vibronic structure suggest that the emission is excimeric in nature.^[19]

In conclusion a luminescent gold ring was shown to be an inorganic analogue of cyclohexane in terms of structure and solution dynamics. We are currently investigating the effect of the anion on the ring inversion of **1** and coordination chemistry of PAnP with other metals.

Experimental Section

All syntheses were carried out using standard Schlenk techniques. Solvents used for spectroscopic measurements were purified according to the literature methods.

Synthesis of 9,10-bis(diphenylphosphino)anthracene (PAnP): *n*BuLi (12 mmol) was added to a suspension of 9,10-dibromoanthracene (2.0 g, 6 mmol) in Et₂O (100 mL). The solution was stirred for 10 min before addition of PPh₂Cl (3.2 mL, 12 mmol). The suspension was stirred for 12 h, collected by filtration, and the yellow solid thus obtained washed with diethyl ether. Crystals were obtained from CH₂Cl₂/Et₂O by slow diffusion, yield 75%; elemental analysis calcd (%) for C₃₈H₂₈P₂: C 83.5, H 5.0; found: C 83.4, H 5.1, ¹H NMR (CD₂Cl₂, 300 MHz): δ = 7.23 (m, 4H, H_{2,3,6,7}, An), 7.25–7.43 (m, 20H, Ph), 8.85 (m, 4H, H_{1,4,5,8}, An). ³¹P{¹H} NMR (CDCl₃, 300 MHz): δ = –21.9; m.p. 260 °C (decomp).

1: A methanol suspension (50 mL) of PAnP (1.0 g, 1.8 mmol) and Me₃SAuCl (0.53 g, 1.8 mmol) was heated at reflux for 4 days, insoluble material was then removed by filtration. Excess LiClO₄ was added to the yellow filtrate and the resulting yellow solid was crystallized from CH₃CN/Et₂O at –20 °C, yield 40%, elemental analysis calcd (%) for C₁₁₄H₈₄Au₃Cl₃O₁₂P₆: C 54.1, H 3.4, P 7.4; found: C 54.3, H 3.5, P 7.3; m.p. 124 °C (decomp); for NMR data, see text.

Physical measurements: The UV/Vis absorption and emission spectra of the complexes were recorded on a Hewlett-Packard HP8452A diode array spectrophotometer and a Perkin-Elmer LS-50D fluorescence spectrophotometer, respectively. Anthracene was used as a standard in measuring the quantum yield of emission. ¹H and ³¹P{¹H} NMR spectra were recorded at 25 °C on either a Bruker ACF 300 spectrometer or a Bruker AMX500 spectrometer. All chemical shifts are quoted relative to SiMe₄ (¹H) or H₃PO₄ (³¹P). Variable temperature spectra were obtained by using a Bruker variable temperature unit B-VT2000 to control the probe temperature. The sample temperature is considered to be accurate to ±1 °C. ¹H 2D-EXSY and COSY spectra were obtained using standard NOESYPH.AU (mixing time of 0.5 s) and COSY-AU programs, respectively. Elemental analyses of the complexes were carried out in the microanalysis laboratory in the department of chemistry, the National University of Singapore.

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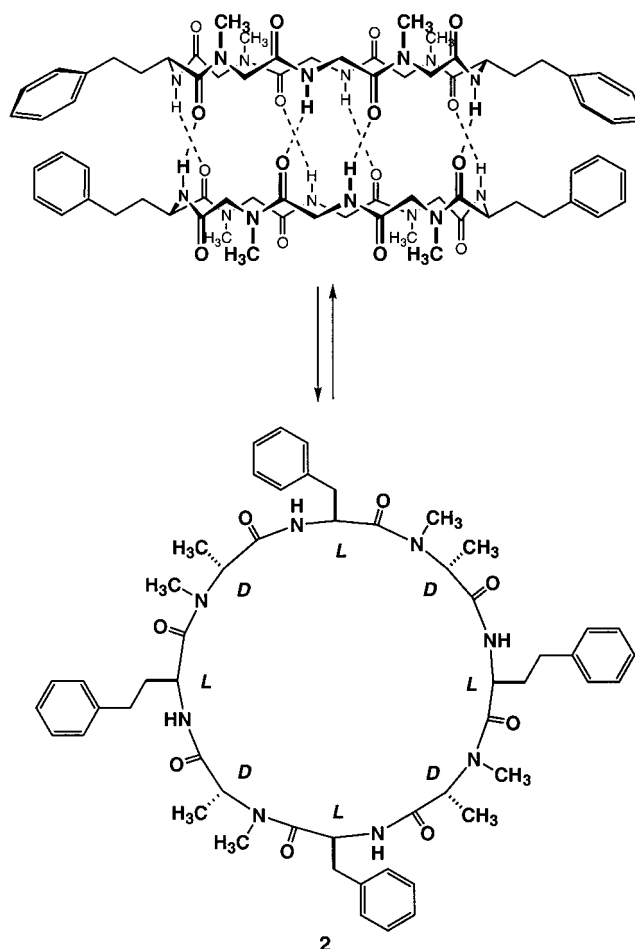
Self-Assembling Cyclic Peptide Cylinders as Nuclei for Crystal Engineering**

Dennis T. Bong and M. Reza Ghadiri*

Convergent assembly strategies for creating new information surfaces are well known in Nature, especially in the organization of structural proteins^[1] and gene transcription machinery.^[2] Such programmed molecular recognition captures the essence of supramolecular design.^[3–5] In noncovalent synthesis, achieving controlled, multidimensional self-assembly would allow the construction of ordered materials: in essence, crystal engineering.^[3, 6–8] We have previously reported the propensity of cyclic peptides of alternating D,L-amino acid configuration to adopt a flat-ring structure and stack by means of backbone hydrogen bonding in an antiparallel β -sheet fashion, yielding nanometer-scale, ordered, tubular peptide assemblies.^[9–11] In the present model study, we have coupled limited cylindrical assembly by means of backbone hydrogen bonding with the formation of a new, orthogonal recognition interface comprised of aromatic amino acid side chain functionality, which in turn induces higher order molecular organization in the solid state through aromatic edge-to-face interactions.

Aryl functionality recognition motifs, including weakly polar edge-to-face phenyl interactions,^[12–18] cation– π ,^[19–22] π – π ,^[16, 23–27] and quadrupole–quadrupole interactions,^[19, 20, 22] are excellent complements to hydrogen-bonding donor–acceptor interactions in supramolecular chemistry, as these recognition strategies can operate with minimal interference from each other. We have utilized cyclic peptide **2** (Scheme 1), with the sequence *cyclo*[(–L-Phe–D-MeN-Ala–L-hPhe–D-MeN-Ala)₂], to study aryl–aryl interactions templated by hydrogen bonding directed self-assembly. All four D-alanine residues are N-methylated, limiting the hydrogen-bonded assembly in organic solvents to D₂-symmetrical cyclic peptide dimers. The one-carbon homologation of the phenylalanine side chain to homophenylalanine (hPhe) was expected to provide the additional mobility necessary to allow the formation of cross-strand aromatic–aromatic interactions in the β -sheet dimer. Consistent with the high β -sheet propensity of Phe,^[28–30] replacement of Phe with hPhe results in a peptide with reduced dimerization capacity,^[31] but also more complex folding behavior.

X-ray crystallographic analysis of **2** proved extremely revealing.^[32] Aryl–aryl interactions apparently do not



Scheme 1. A two-dimensional representation of the chemical structure of peptide **2** (D and L refer to amino acid chirality). The assembly equilibrium between the monomer and one of two possible dimeric species in which cross-strand aromatic interactions are possible between hPhe residues. (For clarity, the Phe side chains are not shown in the dimer.)

strongly influence assembly in solution, as observed in the ¹H NMR spectrum in CDCl₃,^[33] but cumulative lattice energies drove the formation of a consensus hydrogen-bonded dimer of **2** in the solid state, in which like residues are paired cross-strand with like residues (Scheme 1). As intended, the solid-state structure revealed a canonical intradimer edge-to-face cross-strand phenyl–phenyl interaction between two hPhe residues. More strikingly though, the one-carbon homologation of phenylalanine completely altered the crystal packing of **2** relative to the parent peptide *cyclo*[(–L-Phe–D-MeN-Ala)₄] (**1**).^[31, 34] Unlike **1**, the homophenylalanine peptide **2** packs with a dimer as the asymmetric unit with two dimers in the unit cell (Figure 1). The dimers interact by means of a cluster of aromatic side-chain interactions, twisting their cylindrical axes nearly orthogonally to one another, at an angle of 74°. The crystal lattice of **1** (Figure 2a) is less complex: C₄ symmetry and use of the more conformationally constrained phenylalanine residues in all L positions results in a lattice in which the cylindrical axes of the cyclic peptide dimers are unidirectionally aligned.^[31, 34, 35] Peptide **3** (Figure 2b), *cyclo*[(–L-Phe–D-MeN-Ala–L-Leu–D-MeN-Ala)₂], another C₂-symmetrical cyclic peptide,^[35] similarly packs with

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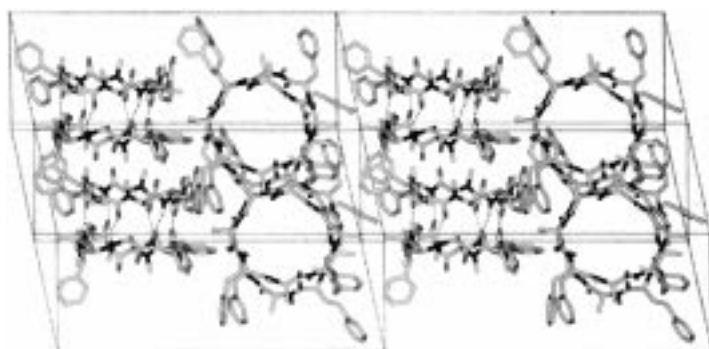


Figure 1. Stick representation of the crystal lattice of **2** viewed along one peptide cylindrical axis, with adjacent cylindrical peptide columns twisted at a 74° angle. Four unit cells are shown, with two dimers in each unit. Intradimer hydrogen bonds are shown with dotted lines.

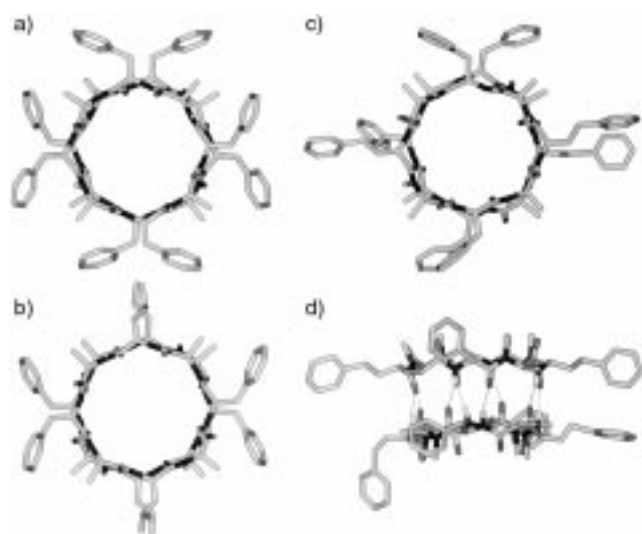


Figure 2. Crystal structures of dimeric β -sheet assemblies formed by a) *cyclo*[(-L-Phe-D-MeN-Ala)₄] (**1**); b) *cyclo*[(-L-Phe-D-MeN-Ala-L-Leu-D-MeN-Ala)₂] (**3**); c) *cyclo*[(-L-Phe-D-MeN-Ala-L-hPhe-D-MeN-Ala)₂] (**2**) viewed along the cylindrical axes, and d) across the dimeric interface of **2**.

the C_2 cylindrical axes aligned in the crystal,^[31] despite the reduced symmetry and the presence of a flexible γ -branched leucine side-chain. Presumably, the alignment is controlled by interdimer phe–phe contacts, and leu–leu contacts do not interfere with phe–phe packing. In contrast, the insertion of homophenylalanine residues in place of leucine in this C_2 -symmetrical framework has a dramatic effect on dimer interactions. The one additional methylene group in homophenylalanine provides enhanced conformational freedom in the χ angle as well as a longer backbone tether, allowing more options in the lattice packing of phenyl groups. Interestingly, the recognition of side-chain phenyl rings with themselves in all three structures is very similar to the packing of benzene^[36–38] with itself (Figure 3). Thus, it is as though each peptide dimer is coated with a layer of covalently bound benzene “solvent” that is assembled into interaction range by means of the noncovalent recognition of the peptide backbone (Table 1). This layer of phenyl rings from the hPhe side chains forms both intra- and interdimer contacts with both hPhe and Phe phenyl rings. These three peptide lattices display high sensitivity to side-chain functionality and perhaps

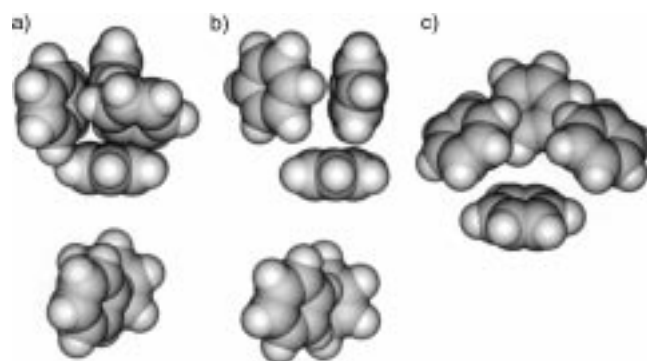


Figure 3. Space-filling representation of the principal phenyl–phenyl crystal contacts observed in a) benzene, b) peptide **2**, and c) peptides **1** and **3**.

Table 1. Comparison of benzene crystal contacts with cyclic peptide phenyl–phenyl contacts.

Crystal	Contact	Centroid–centroid distance [Å]	Interplanar angle
Benzene	Ph–Ph	5.986	86.1
		5.025	86.5
		5.812	29.4
1	F–F	5.77	45.87
		6.28	46.8
		5.77	46.26
2	hF–hF	5.12	87.2
		4.61	45.01
	F–hF	5.13	30.47
		5.83	60.04
		4.82	42.38
		6.6	76.67
		4.83	42.38
3	F–F	5.61	54.71
		5.34	31.3
	F–F	5.95	42.24
		5.97	43.69
		6.16	37.87

also the symmetry of substitution, despite the fact that the essential backbone-directed dimer remains identical. In fact, preferred β -conformations dictated by the backbone configuration are overridden by the lattice. Homophenylalanine side chains of peptide **2** are extended to maximize interdimer contacts (Figure 2c and d), and Phe side-chain conformational preferences are overridden to introduce additional contacts. Though one cross-strand pair of Phe residues in **2** adopts the preferred χ angles of $\approx 180^\circ$ observed in **1** and **3**, aromatic interactions with hPhe residues perturb the conformation of the other Phe cross-strand pair to yield a normally unfavorable cross-strand set of χ angles: -176° and -67° . This places the side-chain phenyl rings in an eclipsed conformation with one another, but allows interdimer contact (Figure 2). Remarkably, the functionality displayed on the exterior of the peptide cylinder nucleus is essentially unchanged between **1** and **2**, indicating that the extreme difference in lattice morphology is driven completely by the amplified effect of an additional methylene group in two out of four phenylalanine side chains.

The cyclic peptide scaffold also serves to template leucine–leucine van der Waals contacts,^[39] as observed in the crystal

structure of **3** (Figure 4). Indeed, the γ -carbon distances are similar to those seen in the tightly packed leucine zipper cores of the dimeric coiled coil region of GCN4 and the tetrameric

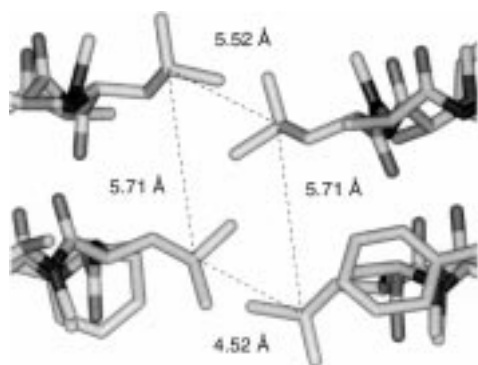


Figure 4. Stick representation of leucine-leucine interdimer lattice contacts in the crystal structure of **3**. Gamma-carbon distances are shown in Å.

variant of GCN4 (Table 2).^[40] No aliphatic-aromatic contacts were found in **3**, despite the favorable energetics of interaction observed between *tert*-butyl esters and phenyl groups,^[12, 13] suggesting that the construction of hydrocarbon contacts in the solid-state lattice may be more greatly influenced by shape selection rather than π -system interactions.

Table 2. Comparison of leucine-leucine contact distances in peptide **3** and leucine-core coiled coils.

Peptide (Leu-Leu contact)	γ -carbon distance [Å]
<i>cyclo</i> [Phe-MeN-D-Ala-Leu-MeN-D-Ala] ₂	4.52, 5.52, 5.71, 5.71
GCN4-p1	5.73, 5.42, 5.41, 5.67
GCN4-p4	4.69, 5.23, 5.41, 5.67

Certainly, the variability of lattice organization seen within this small set of crystal structures of similar peptides indicates the subtlety of crystal growth. Nevertheless, the cylindrical dimers studied here are useful models for crystallization nuclei that can present 16 functional groups in space by self-assembly, thus enhancing control over lattice contacts by preforming a multivalent cluster of functionality. Indeed, it has been demonstrated that it is possible to access multiple crystal forms with the identical peptide backbone fold by single atom determinants of structure in the case of the Phe→hPhe double mutant **2**. Further, the dimeric peptide system can be readily studied in solution, allowing rapid identification of interactions compatible with hydrogen bonding for inducing crystal growth orthogonal to the tubular axis, enabling further crystal engineering efforts. Current studies are directed towards manipulating these self-assembled functional surfaces to gain greater control over the molecular organization of the subsequent noncovalent tubular constructs, for use in biosensors and nanotechnological and biomedical applications.^[10]

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- [32] 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-157105 (**1**), -157092 (**2**) and -157104 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Briefly, **2** crystallized in the monoclinic system, *P*2₁ space group with unit cell dimensions of *a* = 13.689(3), *b* = 15.905(3), *c* = 29.521(6) Å, and β = 99.18°, a volume of 6345 Å³, and a calculated density of 1.021 Mg m⁻³ for an empirical formula of C₅₄H₆₈N₈O₈·H₂O, accounting for one water molecule per asymmetric unit. A full-matrix least-squares refinement was performed on $|F^2|$, converging to final *R* indices ($I > 2\sigma(I)$) of *R*₁ = 0.1010, *wR*₂ = 0.2671 and with all data, *R*₁ = 0.1875, *wR*₂ = 0.3353. (Two water molecules were found in the unit cell, disordered over seven positions likely accounting for the unusually high *R* factor.) 9280 reflections (9279 independent) were collected at 298 K, with a wavelength of 1.54178 Å with 0.89 Å dataset resolution on a Rigaku AFC6R diffractometer equipped with a rotating copper anode (Cu_{K α}) and a highly ordered graphite monochromator. Data were corrected for Lorentzian, polarization, and absorption effects using the psi-scan method. Hydrogen

atoms were included in the ideal positions with fixed isotropic values. Calculations were performed using the programs TEXSAN (data reduction) and SHELX-97 (refinement).

- [33] ^1H NMR spectroscopic analysis of **2** in chloroform solution at a 17-mM concentration indicated that **2** assembles to form the two expected dimeric assemblies as evidenced by two sets of hydrogen-bonded NH resonances, corresponding to two distinct sets of homophenylalanine and phenylalanine residues. Upon examination at low temperature, an additional set of hydrogen-bonded NH protons appeared possibly arising from a dimer desymmetrized by cross-strand aryl–aryl interaction, though subsequent two-dimensional ^1H NMR spectroscopic investigation was inconclusive (see Supplementary Information). T. D. Clark, J. M. Buriak, K. Kobayashi, M. P. Isler, D. E. McRee, M. R. Ghadiri, *J. Am. Chem. Soc.* **1998**, *120*, 8949–8962.
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A Large 24-Membered-Ring Germanate Zeolite-Type Open-Framework Structure with Three-Dimensional Intersecting Channels**

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The search for new topological microporous structures of extra-large-pore open frameworks with more than 12 tetrahedral atoms has been extremely intensive because of the widespread applications of these materials in catalysis and the separation of large molecules such as heavy oils or pharmaceuticals. Since the first molecular sieve containing 18-membered rings (18MR), aluminophosphate VPI-5, was discovered in 1988,^[1] many metal phosphates and aluminosilicates with extra-large-pore open frameworks such as $\text{AlPO}_4\text{-8}$ (14MR),^[2] Cloverite (20MR),^[3] JDF-20 (20MR),^[4] UTD-1 (14MR),^[5] CIT-5 (14MR),^[6] ND-1 (24MR)^[7] have been synthesized. Several useful synthetic approaches have been

studied to prepare such large-pore materials.^[8] Among these are, for example, the use of large templates, the selection of framework elements that can form three-membered rings, such as the zincosilicates and zincophosphates,^[9] or the use of tailored secondary building units (SBUs), for example, in the preparation of large-pore indium sulfide.^[10] However, most of the materials with extra-large-pore frameworks have only one-dimensional (1D) channels. Germanates are of particular interest because they can form extended structures with GeO_3 trigonal bipyramids or GeO_6 octahedra, as well as GeO_4 tetrahedra.^[11, 12] The high coordination numbers offer the possibility of synthesizing germanate frameworks with high charge densities, which may result in multidimensional channel systems and novel structures with large pores.^[13] Unfortunately, to date extra-large-pore germanate zeolite-type structures have not been successfully prepared. According to the host–guest charge-matching concept,^[14, 15] a highly charged inorganic framework should be templated by highly charged organic amines such as multiamines. Herein we report the synthesis and structure of the unique germanate zeolite analogue **1** (known as FDU-4) with a large 24-membered ring. Compound **1** was prepared by using an



organic multiamine, tris-(2-aminoethyl)-amine (TREN) as a structure-directing agent in a *N,N*-dimethylformamide (DMF)/water mixture. Interestingly, the novel germanate open-framework structure has a three-dimensional (3D) intersecting channel system, in which each 24MR channel is surrounded by six 12MR channels, and the 12MR and 24MR channels are connected by the alternating 8MR pore windows.

FDU-4 is the first germanate zeolite-type structure with the 24-member ring channels and it has a previously unknown framework topology with the space group $P6_3cm$ (No. 185, standard setting). A single-crystal X-ray diffraction analysis reveals the 3D open framework constructed from the SBU shown in Figure 1. The core of the SBU has C_{2v} symmetry and is composed of nine germanium centers, seventeen oxygen

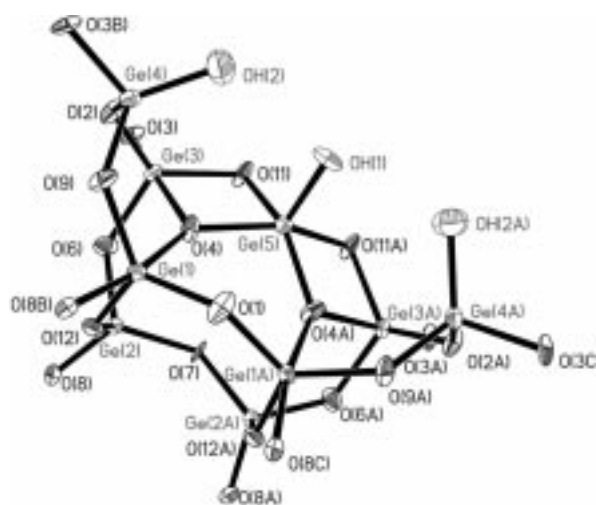


Figure 1. ORTEP view of the building block unit in crystalline FDU-4. Atoms labeled A, B, or C are symmetry generated.

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centers, and four OH units. A germanium center (Ge(5)) lies on the mirror plane, and is bound to five oxygen centers to yield a distorted square pyramid coordination geometry. Four germanium atoms (Ge(1), Ge(1A), Ge(3) and Ge(3A)) are each bonded to five oxygen atoms to give trigonal bipyramidal coordination, the remained four germanium atoms (Ge(2), Ge(2A), Ge(4), and Ge(4A)) have distorted tetrahedral coordination geometries. However, Ge(4), Ge(4A), and Ge(5) connect three terminal oxygen atoms belonging to hydroxide ligands, the presence of which is confirmed by the presence of a sharp FT-infrared (IR) band at 3730 cm^{-1} in the expected range for $\nu_{\text{O-H}}$ stretching frequencies. An intriguing feature of the FDU-4 structure is its relation to that of some previous germanates, such as ASU-12 and ASU-14^[12]. They all contain tricoordinate oxygen centers connected to three different five- or six- coordinate Ge centers. Three-coordinate oxygen centers favor not only trigonal bipyramidal or octahedral geometry but also three-membered rings,^[15] and such a structural feature is believed to be the key to frameworks with the lowest possible framework density.^[16] The framework density of FDU-4 measured by the number of polyhedra per $1000\text{ \AA}^3$ is 11.1, which is one of the lowest framework densities known.

All the Ge–O bonds for the tetrahedral Ge centers (mean $1.738(6)\text{ \AA}$) are very similar to those reported for the quartz modification of GeO_2 ($1.741(3)\text{ \AA}$).^[17] The Ge–O bonds of the five-coordinate Ge centers are in the range $1.753(5)$ – $2.163(5)\text{ \AA}$, in agreement with those observed for other germanates.^[11, 12, 18]

Neighboring SBUs are linked by bridging oxygen atoms to yield an open framework with an intersecting 3D channel system. There are two kinds of channels with 12 and 24 members, extending along the crystallographic c axis (Figure 2). Although the two kinds of channels have different

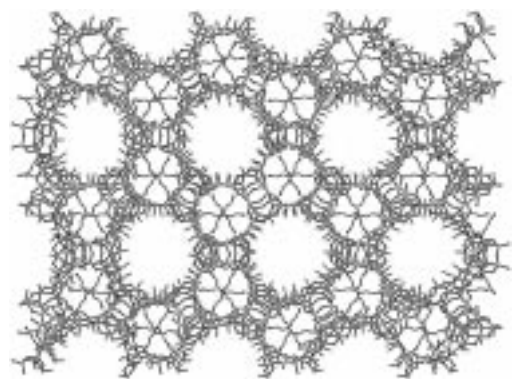


Figure 2. Projection of the 3D framework down the c axis in FDU-4. The DMF and water guests are omitted for clarity.

sizes, they can be arranged in close-packed hexagonal, honeycomb arrays, just as in the mesoporous materials MCM-41 or SBA-15.^[19] Each 24MR channel is surrounded by six 12MR channels and these are alternately surrounded by three 12MR channels and three 24MR channels. The approximate diameters of the narrowest cross section of the 24MR and 12MR channels are $12.65\text{ \AA}$ and $9.52\text{ \AA}$, respectively. The results imply that the formation of mesoporous materials with

two uniform, ordered, pore channels or/and microporous crystalline walls similar to the structure of FDU-4 is possible. The wall of the 12MR channels of FDU-4 is composed of a 4,8,8 net with alternating 4MR and 8MR (Figure 3a). The 8MR channels run in three directions perpendicular to the c axis, and cross at an angle of 120° . The wall of the 24MR channels includes 12MR windows (Figure 3b) resulting in an unprecedented 3D intersecting-channel germanate framework.

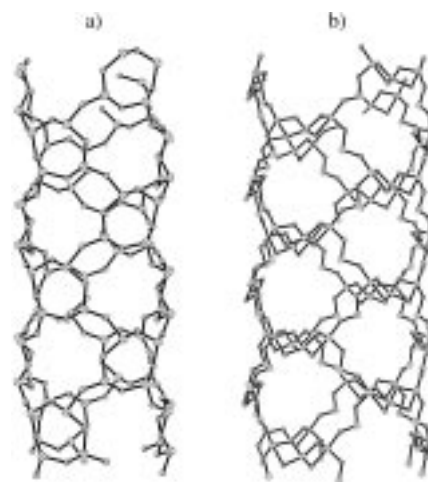


Figure 3. a) 12MR channel view normal to the $[001]$ direction; b) 24MR channel view normal to the $[001]$ direction.

The organic amine molecules in FDU-4 are located within the 12MR channels (Figure 2) and form hydrogen bonds with the framework oxygens. Some solvent species such as DMF (1/6 molecule per SBU) and water molecules ($11/3\text{ H}_2\text{O}$ per SBU) are disordered and located in the 24MR channels. The presence of DMF is also confirmed by the sharp FT-IR band at 1601 cm^{-1} correspond to $\tilde{\nu}_{\text{C=O}}$ stretching frequency. These results suggest that the large-pore channels do not need to be templated by large molecules, which is similar to the case in VPI-5.^[1] The structure requires that the framework has a 2 – charge per SBU, which should be balanced by 2/3 triprotonated TREN. This implies that there is one bridging hydroxide $[\text{Ge-O(H)-Ge}]$ per SBU in the framework. We believe that O(8) and O(8A) could be protonated with an occupancy of 0.5 because of their elongated Ge–O bonds (av $1.797\text{ \AA}$) and their low thermal parameter (0.016).

Preliminary thermogravimetric and differential thermal analyses for a crystalline sample of this material show three weight-loss steps accompanied by three endothermic peaks. One weight loss (7.5%) between 100°C and 240°C corresponds to the loss of H_2O and DMF (calculated 6.7%). Another weight loss of 8.2% between 280°C and 380°C is attributed to decomposition of H_3TREN (calculated 8.5%). After 380°C , a gradual weight loss of 4.5% until 700°C is observed and assigned to the loss of terminal OH groups from the framework (calculated 4.3%). Powder X-ray diffraction measurements show that the structure of FDU-4 collapses after heating at 400°C for 3 h, suggesting that the large-pore structure is unstable.

Experimental Section

Compound **1** was synthesized by using mixture of DMF and water as the solvent, and TREN as a structure-directing agent. A reaction mixture containing GeO₂ (0.413 g, 3.95 mmol), TREN (2.35 g, 16.1 mmol), water (5.01 g, 278 mmol), DMF (8.01 g, 110 mmol) was stirred at room temperature over night. The mixture was heated at 180 °C in a Teflon-lined steel autoclave for seven days. Colorless needlelike crystals were obtained in approximately 70% yield (based on GeO₂).

X-ray structure analysis: Needlelike single crystals of FDU-4 (0.20 × 0.03 × 0.04 mm) were analyzed at room temperature. Crystallographic data for FDU-4: hexagonal, space group *P6₃cm* (No. 185), *a* = 23.941(3), *b* = 23.941(3), *c* = 9.798(2) Å, *V* = 4863.2(14) Å³; *Z* = 6; ρ_{calc} = 2.399 g cm⁻³, *F*(000) = 3360, $\lambda(\text{MoK}\alpha) = 0.71073$ Å. A full hemisphere of diffracted intensities was measured with graphite-monochromated MoK α radiation on a Bruker/Siemens Smart1000-CCD. Of 22955 reflections collected, 4681 were independent (*R*_{int} = 0.1347). Cell constants were obtained from least-squares refinement in the range 0.98 < θ < 23.34°. The Siemens/Bruker program SHELXTL-PC software package was used to solve the structure by direct methods. Refinement was by full-matrix least-squares analysis with anisotropic thermal parameters for all non-hydrogen atoms. The final residuals were *R*₁(*F*) = 0.0606 with *I* > 2 σ and *wR*₂(*F*²) = 0.1551 with GOF(*F*) = 1.050. 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-151489. 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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Formation of Aryl- and Benzylboronate Esters by Rhodium-Catalyzed C–H Bond Functionalization with Pinacolborane**

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The catalytic functionalization of unreactive C–H bonds remains one of the major challenges in chemistry.^[1] Metal–boryl systems have been shown to promote stoichiometric^[2] and photocatalytic^[3] conversion of alkane and arene C–H bonds into C–B(OR)₂ groups by using B₂pin₂ (pin = OCMe₂CMe₂O). A [Cp*Ir] complex catalyzes^[4] the borylation of benzene with pinacolborane (HBpin), with about three turnovers obtained at 150 °C, and a related complex [Cp*Rh(η⁶-C₆Me₆)] is an excellent catalyst^[5] for aliphatic and aromatic C–H bond borylation at 150 °C, with B₂pin₂ being more effective than HBpin. As part of our studies of the reactivity of B–H bonds with Rh and Ir complexes,^[6] we report herein that [RhCl(PiPr₃)₂(N₂)] (**1**)^[7] is an efficient catalyst precursor for the borylation of aromatic and benzylic C–H bonds with HBpin, and that high selectivity for benzylic C–H functionalization was observed for the first time with toluene, *p*-xylene, and mesitylene. The boronate ester products represent an important class of synthetic intermediates.^[8]

The reaction of 0.2 M HBpin^[9] with benzene in the presence of 1.0 mol % of **1** at 140 °C gave PhBpin in 62% yield (62 turnovers) after 14 h and in 86% yield after 58 h (Scheme 1). When 0.3 mol % of **1** was used, 67% (222 turnovers) of PhBpin was obtained after 104 h. The yield improved at lower HBpin concentrations. Thus, with 1.0 M HBpin in benzene, PhBpin was obtained in 20% yield after 58 h, whereas dilution with hexane (fourfold) improved the yield to 35% in the same time. This effect can be attributed to degradation of HBpin, which is strongly concentration dependent.^[10] In addition to PhBpin, the dehydrodimerization product B₂pin₂ was formed, especially with higher concentrations of HBpin (ca. 7% for 1.0 M HBpin in benzene).

Toluene was less active than benzene, indicating that the methyl group deactivates the arene C–H bonds (Table 1, entry 1). Interestingly, the main product, PhCH₂Bpin, was not

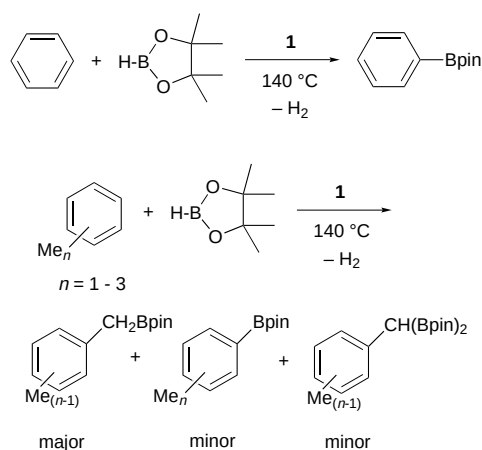
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 1. Reaction of HBpin with benzene and methylenes catalyzed by **1**.

derived from aromatic C–H activation but from benzylic C–H activation. In addition, one diborylated compound was formed which was confirmed to be PhCH(BPin)_2 by X-ray diffraction (Figure 1).^[11] Its yield of up to 7% is much higher than would be expected from the toluene/HBpin molar ratio of 47/1, indicating that the Bpin substituent activates the remaining benzylic C–H bonds.

We examined $[\text{Cp}^*\text{RhCl}_2]_2$ as a precursor for the “ Cp^*Rh ” system^[5] and found that it shows completely different selectivity from **1** for toluene borylation. After 36 h at 140 °C, using 0.2 M HBpin in toluene, 0.5 mol % of $[\text{Cp}^*\text{RhCl}_2]_2$ gave a 62% yield of monoborylated toluenes. The *m*-isomer, 3- $\text{MeC}_6\text{H}_4\text{Bpin}$, was the main product (*o*:*m*:*p* = 5:65:30). Only a trace ($\leq 0.5\%$) of PhCH_2Bpin was formed along with about 0.1% (based on GC–MS integration) of two isomeric disubstituted products, which have different GC retention times from that of PhCH(BPin)_2 .

As with toluene, *p*-xylene and mesitylene also reacted with HBpin in the presence of **1** to give benzylic substitution products (Table 1, entries 6 and 7). In contrast to “ Cp^*Rh ”,^[5]

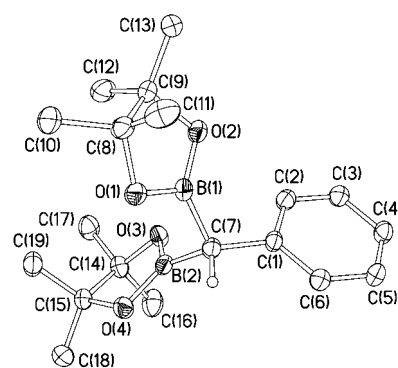


Figure 1. Molecular structure of PhCH(BPin)_2 with hydrogen atoms, other than the benzylic one on C(7), omitted for clarity. Selected bond lengths [Å]: C(7)–B(1) 1.577(2), C(7)–B(2) 1.592(2), B–O (av) 1.370(6), C–O (av) 1.472(3).

1 did not catalyze the borylation of benzene with B_2pin_2 , nor the reaction of simple alkanes with HBpin under our conditions.

As in some cases the formation of a black deposit was observed, we investigated whether the catalysis proceeds homogeneously or heterogeneously. Inhibition by dibenzo[*a,e*]cyclooctatetraene (DCT), a useful check for homogeneity of catalysis,^[12] proved unsuitable for the present reaction as the double bonds can be hydroborated by a noncatalytic reaction (Table 1, entry 2). Addition of Hg^[12, 13] did not alter selectivity (Table 1, entry 3); the decrease in yield is not nearly as significant as would be expected for a heterogeneous process, and can be attributed to an Hg-enhanced rate of HBpin degradation. This supports the homogeneity of the catalytic borylation. The strong preference for benzylic functionalization could indicate a radical mechanism; however, addition of the radical inhibitor 2,6-*t*Bu₂-4-Me-C₆H₂OH (BHT) did not affect significantly either activity or selectivity (Table 1, entry 4).

The oxidative addition of HBpin to **1** yielding *trans*- $[\text{Rh}(\text{Cl})(\text{H})(\text{BPin})(\text{P}i\text{Pr}_3)_2]$ (**2**) is very slow at room temper-

Table 1. Reaction of methylenes with HBpin catalyzed by **1**.^[a]

Entry	Arene	Time [h]	Additive (amount)	Total yield of borylated toluenes [%] ^[b]	Product ratio PhCH_2Bpin :2- $\text{MeC}_6\text{H}_4\text{Bpin}$: 3- $\text{MeC}_6\text{H}_4\text{Bpin}$:4- $\text{MeC}_6\text{H}_4\text{Bpin}$
1	toluene	14 58 80		40(3) 64(5) 69(7)	85:3:9:3 82:3:11:4 81:3:12:4
2	toluene	14	DCT ^[c] (2.4%)	36(2)	84:3:10:3
3	toluene	14	Hg (0.1 mL)	21(2)	87:3:7:3
4	toluene	14	BHT ^[d] (50%)	34(2)	86:2:9:3
5 ^[e]	toluene	14		48(4)	83:3:10:4
6	<i>p</i> -xylene	80		41 ^[f]	98:2 ^[g]
7	mesitylene	80		17 ^[h]	

[a] In an N₂ filled glove box, a 15-mL tube with a Young's tap was charged with **1** (2.0 mg, 0.0041 mmol, 1.0 mol %), HBpin (58 μL, 0.40 mmol), *n*-dodecane (standard for GC analysis, 0.065 mmol), and methylene (2.0 mL). The mixture was heated at 140 °C. Small samples were removed periodically for GC (FID) and GC–MS analysis. Yields and product ratios were determined by GC and are based on HBpin. The product can be isolated by bulb-to-bulb distillation or silica gel chromatography. [b] Includes PhCH(BPin)_2 for which the yield is also shown separately in parenthesis. [c] Dibenz[*a,e*]cyclooctatetraene (DCT), 2.4 mol % based on HBpin; see text. [d] 2,6-*t*Bu₂-4-Me-C₆H₂OH, 50 mol % based on HBpin; see text. [e] 1.0 mol % of **2** was used instead of **1**. [f] Yield of 4- $\text{MeC}_6\text{H}_4\text{CH}_2\text{Bpin}$. [g] Ratio of monoborylated products. The minor isomer (probably 2,5- $\text{Me}_2\text{C}_6\text{H}_3\text{Bpin}$) was only characterized by GC–MS. Two bisborylated compounds (4:1 by GC) were also observed. The GC ratio of mono:bisborylated compounds = 95:5. [h] Yield of 3,5- $\text{Me}_2\text{C}_6\text{H}_3\text{CH}_2\text{Bpin}$. No other isomer was detected. In addition, two bisborylated compounds and one trisborylated compound were detected by GC–MS. The ratio of borylated products = 85:6:8:1 in the order of their GC retention times.

ature, but almost instantaneous at 140 °C. The structure of **2** was determined by X-ray diffraction (Figure 2).^[11] The coordination of the Rh atom in **2** is intermediate between trigonal-bipyramidal (with the phosphane ligands in axial positions) and square-pyramidal with the apical site occupied

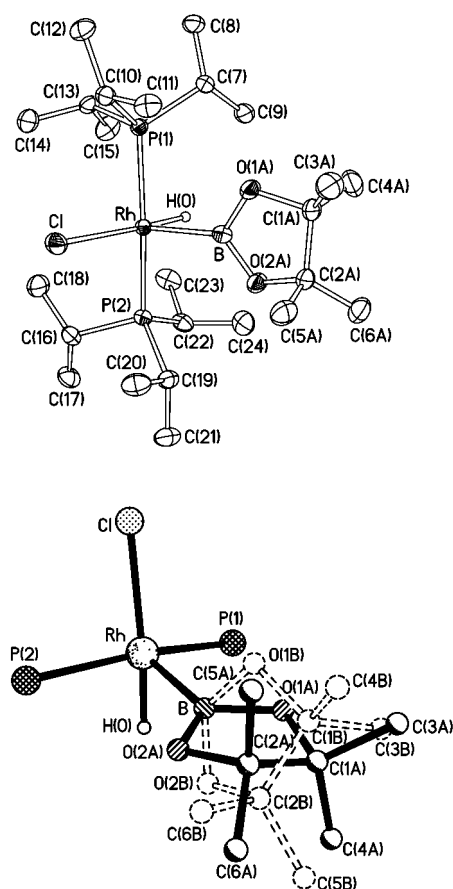


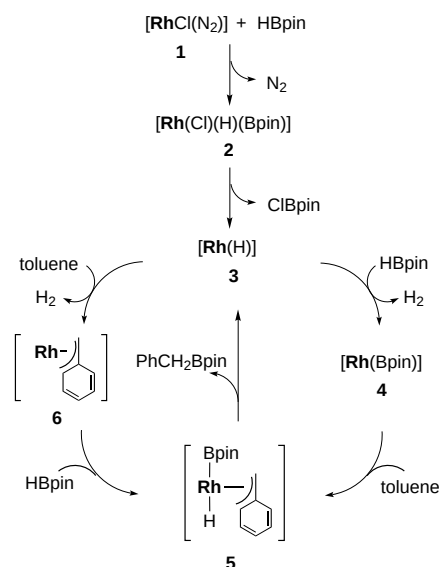
Figure 2. Top: Molecular structure of **2** with hydrogen atoms, other than the rhodium hydride H(0), omitted for clarity. Bottom: The boryl ligand is disordered between two positions with occupancies 85.3(2)% (solid) and 14.7(3)% (dashed). Selected bond lengths [Å] and angles [°]: Rh-P(1) 2.3476(4), Rh-P(2) 2.3442(4), Rh-Cl 2.4392(4), Rh-B 1.9812(15), Rh-H(1) 1.47(2), B-O(1) 1.391(2), B-O(2) 1.379(2); P(1)-Rh-P(2) 163.87(1), P(1)-Rh-Cl 93.25(1), P(2)-Rh-Cl 94.35(1), P(1)-Rh-B 94.32(4), P(2)-Rh-B 94.70(4), Cl-Rh-B 117.73(4), H(1)-Rh-P(1) 85.6(8), H(1)-Rh-P(2) 84.9(8), H(1)-Rh-Cl 172.2(8), H(1)-Rh-B 70.0(8).

by the boryl ligand which is disordered between two orientations by a 114° rotation around the Rh–B bond (Figure 2, bottom). The acute H–Rh–B angle of 70.0(8)° results in a short H⋯B distance of 2.02(3) Å, suggesting a small degree of residual H⋯B bonding.^[14] The boron atom has a trigonal-planar geometry. The observed Rh–H bond length of 1.47(2) Å is in agreement with neutron diffraction determinations^[15] of 1.54–1.58 Å, foreshortened as expected in the X-ray structure.

The isolated complex **2** also catalyzed the reaction of HBpin with toluene to give borylated products with the same ratio and slightly better yield than when using **1** (Table 1, entry 5). NMR analysis of a solution of HBpin in toluene containing 10 mol % of **1** which had been kept at 140 °C for 14 h, showed **2** to be the main Rh species present. However,

the reaction of isolated **2** with benzene or toluene in the absence of HBpin at 140 °C for 14 h gave only about 5 % of PhBpin or PhCH₂Bpin, respectively. In a separate experiment, reaction of **2** with benzene, monitored by NMR spectroscopy, yielded a large amount of Cl-Bpin (¹¹B NMR: δ = 28.1), an unidentified boron species (¹¹B NMR: δ = 34.4), free PiPr₃, and [Rh(Cl)(H)₂(PiPr₃)₂]^[16] (³¹P{¹H} NMR: δ = 63.5, d, *J*_{Rh,P} = 114 Hz; ¹H NMR: δ = –22.8, dt, 1H, *J*_{Rh,H} = 26, *J*_{P,H} = 14 Hz). The same reaction in the presence of one equivalent (to **2**) of HBpin gave a large amount (ca. 30 % by ¹¹B NMR) of PhBpin along with ClBpin, the unidentified boron species, and a small amount of B₂pin₃.

The reaction mechanism outlined in Scheme 2 is consistent with the above observations. Reductive elimination of ClBpin from **2** forms 14-electron [RhH(PiPr₃)₂] (**3**).^[17] Oxidative



Scheme 2. A possible reaction mechanism for the formation of PhCH₂Bpin. Rh = Rh(PiPr₃)₂.

addition of HBpin to **3** and reductive elimination of H₂ gives boryl complex **4**, which inserts into the benzylic C–H bond of toluene to form η³-benzyl complex **5**.^[18] Reductive elimination of PhCH₂Bpin from **5** regenerates **3**. Alternatively, **3** may react with toluene to form η³-benzyl complex **6**,^[18] which then reacts with HBpin to form **5**. The formation of B₂pin₂ as a by-product, especially at high HBpin concentrations, can be explained by the oxidative addition of HBpin to **4** to form [RhH(Bpin)₂(PiPr₃)₂], from which reductive elimination of B₂pin₂ regenerates **3**. The catalytic dehydrodimerization of HBpin to B₂pin₂ + H₂ represents a potentially useful new route to diboron(4) compounds.

In conclusion, **1** is an efficient homogeneous catalyst precursor for direct borylation of C–H bonds in benzene and methylarenes to form phenyl- and benzylboronate esters. The high degree of benzyl selectivity with toluene, *p*-xylene, and mesitylene is attributed to the formation of η³-benzyl intermediates which are well known in [Rh(PiPr₃)₂] and related systems. An examination of the scope and mechanism of the reaction, the potential for catalytic asymmetric borylations, and further studies regarding HBpin degradation are in progress.

Experimental Section

HBpin was prepared by the procedure of Knochel et al. from $\text{BH}_3 \cdot \text{SMe}_2$ and pinacol.^[9] After distillation, the product, which contained a small amount of unreacted $\text{BH}_3 \cdot \text{SMe}_2$, was treated with additional pinacol and redistilled to give pure HBpin. A commercial sample of HBpin (Aldrich) was also found to contain a small amount of $\text{BH}_3 \cdot \text{SMe}_2$. For a typical catalytic procedure, see Table 1.

2: A solution of **1** (230 mg, 0.47 mmol) and HBpin (132 mg, 1.0 mmol) in benzene (6 mL) was heated at 120 °C for 18 min under N_2 . After the solution had been cooled, the volatiles were removed in vacuo. The solid residue was dissolved in hexane (1.5 mL) and filtered through a membrane filter (0.20 μm), and the filter was washed with hexane (2×0.8 mL). The combined hexane solution was cooled at -40°C to give light brownish yellow crystals. The liquid portion was quickly removed by syringe, and the crystals were washed with cold hexane (ca. -40°C , 2×1 mL) and dried in vacuo to give **2** (218 mg; 79% yield). ^1H NMR (299.9 MHz, CDCl_3): $\delta = -16.81$ (dt, $J_{\text{Rh,H}} = 28$, $J_{\text{P,H}} = 14$ Hz, 1H), 1.14 (s, 12H), 1.28 (quasi quint, $J = 7$ Hz, 36H), 2.47–2.65 (m, 6H); $^{11}\text{B}\{^1\text{H}\}$ NMR (96.22 MHz, CDCl_3): $\delta = 31.8$; $^{31}\text{P}\{^1\text{H}\}$ NMR (80.96 MHz, CDCl_3): $\delta = 52.3$ ($J_{\text{Rh,P}} = 116$ Hz); elemental analysis (%) calcd for $\text{C}_{24}\text{H}_{55}\text{BClO}_2\text{P}_2\text{Rh}$: C 49.12, H 9.45; found: C 49.30, H 9.57.

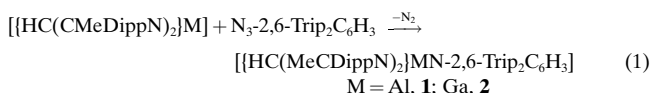
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Stable, Monomeric Imides of Aluminum and Gallium: Synthesis and Characterization of $[\{\text{HC}(\text{MeCDippN})_2\}\text{MN}-2,6\text{-Trip}_2\text{C}_6\text{H}_3]$ ($\text{M} = \text{Al}$ or Ga ; $\text{Dipp} = 2,6\text{-}i\text{Pr}_2\text{C}_6\text{H}_3$; $\text{Trip} = 2,4,6\text{-}i\text{Pr}_3\text{C}_6\text{H}_2$)*

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Imides of the Group 13 elements display a strong tendency to oligomerize, especially in the case of the heavier group members.^[1–3] This is attributable to the larger size of the heavier elements and the polar character of their metal–nitrogen bonding. Monomeric imides have been reported only for the lightest element boron,^[4] for which several examples have been spectroscopically and structurally characterized. The data show that boron and nitrogen have linear or almost linear coordination as well as B–N bond lengths in the range 1.23–1.26 Å. Furthermore, calculations^[5] on the hypothetical species HBNH indicate a B–N distance of 1.23 Å and a B–N bond strength of 88 kcal mol^{–1} (cf. a C–C bond length of 1.18 Å and a bond strength of ca. 94 kcal mol^{–1} for isoelectronic acetylene),^[6] which are consistent with B–N triple bonding. In contrast, the lowest degree of association known for congeneric aluminum or gallium imides occurs in the dimers of the general formula (RMNR')₂ ($\text{M} = \text{Al}^{[7–9]}$ or $\text{Ga}^{[10]}$) which have planar M₂N₂ ($\text{M} = \text{Al}$ or Ga) core structures. We now show that the reaction [Eq. (1)]



of the metal(II) β -ketiminate monomers $[\{\text{HC}(\text{CMeDippN})_2\}\text{M}]$ ($\text{Dipp} = 2,6\text{-}i\text{Pr}_2\text{C}_6\text{H}_3$; $\text{M} = \text{Al}^{[11]}$ or $\text{Ga}^{[12]}$) with the sterically encumbered azide $\text{N}_3\text{-}2,6\text{-Trip}_2\text{C}_6\text{H}_3$ ($\text{Trip} = 2,4,6\text{-}i\text{Pr}_3\text{C}_6\text{H}_2$)^[13] yields the compounds $[\{\text{HC}(\text{MeCDippN})_2\}\text{MN}-2,6\text{-Trip}_2\text{C}_6\text{H}_3]$ ($\text{M} = \text{Al}, \mathbf{1}$; $\text{Ga}, \mathbf{2}$), which are the first stable monomeric imides of the heavier Group 13 elements.

The reaction shown in Equation 1 occurs near room temperature in toluene, and it affords the products **1** and **2** as pale yellow (**1**) or red (**2**) crystals in moderate yield. The mildness of the reaction conditions and the large size of the ligands are notable features of the synthetic route. Previous approaches to the synthesis of Group 13 imides have usually involved the elimination of alkanes, alkenes, or hydrogen from metal amides which generally proceeds only at elevated

temperatures.^[1–3, 8, 9] This has frequently led to the activation of ligand C–H bonds rather than an imide product.^[10] Another disadvantage of this route is that the elimination of substituents from both the metal and nitrogen lowers their coordination number so that the imide is, in effect, less crowded than the amide precursor. This increases the likelihood of association. On the other hand, the reaction between a univalent metal species and an organoazide^[7, 11] (e.g., [Eq. (1)]) increases the metal coordination number, and leaves that of nitrogen unchanged, with the result that steric crowding becomes greater. Nonetheless, previous reactions of this type involving $[\text{Cp}^*\text{M}]$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$, $\text{M} = \text{Al}$ or Ga) with the azides RN_3 ($\text{R} = \text{Si}(i\text{Pr})_3$, $\text{Si}(t\text{Bu})_3$, SiPh_3 , or $2,6\text{-Me}_2\text{C}_6\text{H}_3$) have generally led to dimers $[(\text{Cp}^*\text{MNR})_2]$,^[7, 11] which suggested that the substituents were insufficiently large to prevent association. In contrast, the recently synthesized metal(II) species $[\{\text{HC}(\text{CMeDippN})_2\}\text{M}]$ ^[12, 13] and the bulky azide $\text{N}_3\text{-}2,6\text{-Trip}_2\text{C}_6\text{H}_3$ ^[14] provide the exceptional degree of crowding required to stabilize monomeric species, thereby enabling the isolation of the imides **1** and **2**.

Although crystals of **1** have not yet proved suitable for X-ray crystallographic studies, crystals of **2** yielded a good data set which, upon refinement, gave the structure presented in Figure 1.^[15] The gallium atom is bound to two β -ketiminate

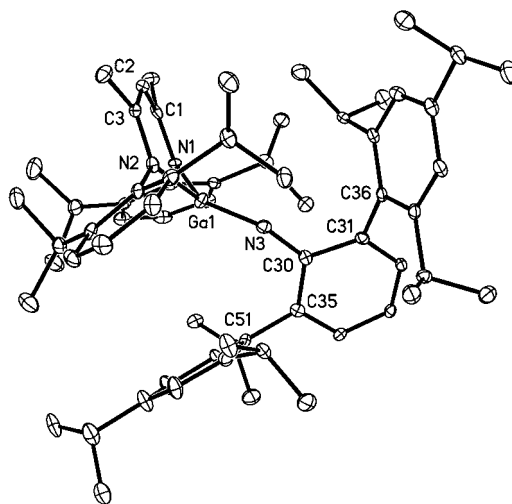


Figure 1. Structure of **2** (thermal ellipsoid (30 %)). Selected bond lengths [Å] and angles [°]: Ga1–N3 1.742(3), Ga1–N1 1.920(3), Ga1–N2 1.929(3); Ga1–N3–C30 134.6(3), N1–Ga1–N2 97.47(14), N1–Ga1–N3 140.22(15), N2–Ga1–N2 114.00(15).

nitrogens N1 and N2 (Ga1–N1, N2 1.920(3), 1.929(3) Å) and the imide nitrogen N3 (Ga1–N3 1.742(3) Å). The former pair of distances are slightly longer than what is normally observed for bonding between three-coordinate nitrogen and a three-coordinate gallium center substituted by three nitrogen ligands^[16] (cf. 1.868(1) Å in $[\text{Ga}\{\text{N}(\text{SiMe}_3)_2\}_3]$).^[17] However, this is consistent with the equal components of normal and dative character in these bonds.^[18] In contrast, the Ga–N3 imide distance is shorter than that of currently known Ga–N bonds in a stable compound,^[19] and represents a shortening of 6.75 % relative to the Ga–N bond in $[\text{Ga}\{\text{N}(\text{SiMe}_3)_2\}_3]$.^[17] Other aspects of the structure of **2** are in harmony with the

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multiple character of the Ga–N3 bond. For example, the imide nitrogen has a bent coordination geometry (Ga1–N3–C30 134.6(3)°), which is consistent with the presence of a stereochemically active lone pair of electrons. Thus, there is a total of two electron pairs available for the formation of the Ga1–N3 multiple bond. Although the classical model for such a bond would involve exact alignment of the Ga1 and N3 coordination planes to generate the highest overlap, the substituent sizes do not permit this configuration for steric reasons. The observed torsion angle of 26.4° thus represents a compromise between steric conflict and efficient orbital overlap. The high degree of crowding is also reflected in the N1–Ga1–N3 and N2–Ga1–N3 angles which differ by 26.22°, with the wider Ga1 angle being found in the *z* orientation with respect to the 2,6-Trip₂C₆H₃ group. Steric effects are probably also responsible for the slightly nonplanar coordination observed for gallium (Σ° Ga1 351.69°; Figure 2). As with

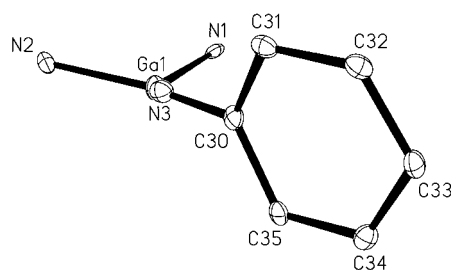
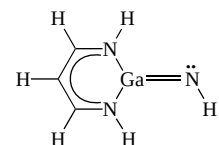


Figure 2. View of **2** along the Ga–N(imide) bond showing the slightly nonplanar geometry at gallium and the relatively low torsion angle between the gallium and nitrogen coordination planes.

most structures involving the HC(MeCDippN)₂[−] ligand, the C₃N₂M ring is folded along the N–N vector.^[20] This angle is 28.6° in **2**, and is comparable to the fold angles of 23.8, 26.3, and 33.2° observed in the gallium compounds [HC(MeCDippN)₂][GaX₂] (X = Cl, I, or Me, respectively).^[21] The existence of Ga1–N3 multiple bonding in **2** is also supported by ¹H and ¹³C NMR spectroscopic data. At 25 °C two sets of resonance signals are visible for the Dipp and methyl substituents of the β-diketiminato ring which is consistent with restricted rotation around the Ga–N bond and the presence of a Ga–N π bond involving overlap of gallium and nitrogen p orbitals.



To investigate the Ga–N bonding further, restricted Hartree–Fock calculations on the hypothetical molecule were performed with the Gaussian98 program^[22] using a 6-311G(d) basis set. A complete report of the calculations for **2**, and its aluminum congener **1**, will be discussed elsewhere, but some of the salient results are mentioned here. The fully planar geometry with the imido hydrogen atom coplanar with the GaN₂C₃ ring was found to be a minimum of the potential energy surface. The geometry, in which the imido hydrogen atom lies perpendicular to the plane of the remainder of the molecule, was optimized to a transition state for Ga–N rotation, and it showed one imaginary frequency. The energy difference between the

planar form and the transition state is 48.6 kJ mol^{−1}, which may be compared with 53.8 for H₂GaNH₂, 18.8 for H₂GaOH, or 35.3 kJ mol^{−1} for H₂GaSH, from similar calculations obtained previously.^[23, 24] The calculated optimum Ga–N bond lengths were 1.940 and 1.726 Å for the ring nitrogen atoms and the imido nitrogen atom, respectively. These compare very favorably with the corresponding, experimental distances of the substituted compound whose synthesis is reported here (1.920(3), 1.929(3) and 1.742(3) Å). The shortened Ga–N(imide) bond and the energy difference (48.6 kJ mol^{−1}) between the planar and perpendicular Ga–N–H orientations indicate that π-bond character is present, but relatively weak. The present calculations lend some support to the view that the Ga–N imide bond consists of strong σ donation by the gallium to nitrogen, with weaker π back donation from nitrogen to gallium. Other factors affecting the nature of this bonding (e.g. possible M–N(ring) delocalization) will be discussed in a full account of this work.

In summary, metal(II) species [HC(MeCDippN)₂][M:] (M = Al or Ga) are useful precursors for the synthesis of compounds with multiple M–N bonds. Experiments to extend this approach to compounds with multiple bonds between low-coordinate heavier Group 13 metals and other elements are in progress.

Experimental Section

All reactions were performed under anaerobic and anhydrous conditions.

1: Toluene (15 mL) was added to a mixture of [HC(MeCDippN)₂][Al:] (0.22 g, 0.5 mmol) and N₃-2,6-Trip₂C₆H₃ (0.265 g, 0.5 mmol) at −60 °C. The mixture was allowed to warm to room temperature and a slow color change from orange-red to yellow was observed in 1 h. The solution was stirred at room temperature for an additional 3 h, concentrated (ca. 5 mL) and stored at room temperature for 2 days to afford a yellow microcrystalline solid (0.26 g, 52 %) (attempts to grow single crystals of this compound in toluene, benzene, THF, CH₂Cl₂ were unsuccessful). M.p. 342 °C. EI-MS: *m/z* (%): 939 (10) [M⁺], 443 (90) [M⁺ − HN-2,6-Trip₂C₆H₃]. ¹H NMR (C₆D₆, 500 MHz): δ = 7.21 (m, 1 H; Ph), 7.13 (m, 1 H; Ph), 7.08 (m, 6 H; Ph), 6.97 (m, 3 H; Ph), 6.95 (m, 1 H; Ph), 6.61 (t, 1 H; Ph), 4.82 (s; γ-CH), 3.51, 3.41, 3.10 (sept, 3 H; CH(CH₃)₂), 2.96–2.83 (m, 3 H; CH(CH₃)₂), 2.46, 2.32 (sept, 2 H; CH(CH₃)₂), 1.51, 1.45 (s, 6 H; β-CH₃), 1.38–1.14 (m, 36 H; CH(CH₃)₂), 0.95 (q, 8 H; CHMe₂), 0.87 (d, 4 H; CHMe₂), 0.50 (d, 4 H; CH(CH₃)₂), 0.42 (q, 8 H; CH(CH₃)₂); ¹³C NMR (CDCl₃, 125.73 MHz): δ = 169.1 (CN), 168.9 (CN), 150.8, 149.9, 147.9, 147.6, 147.5, 146.7, 146.6, 146.1, 145.3, 143.7, 143.4, 142.3, 140.0, 138.4, 135.4, 133.4, 130.8, 127.5, 126.3, 125.9, 125.3, 125.2, 124.3, 122.9, 122.6, 122.1, 121.7, 120.7, 119.6, 113.7 (Ph), 98.8 (γ-C), 34.4, 33.9, 33.6, 31.4, 30.9, 29.6, 29.4, 28.3, 28.2, 27.4, (CHMe₂), 24.3, 24.2 (β-Me), 23.9, 23.7, 23.4, 23.3, 22.8, 22.7, 22.3, 22.0, 21.8, 21.1 (CHMe₂); ²⁷Al NMR (C₆D₆): no signal observed. Correct C,H,N analysis.

2: A toluene (25 mL) solution of [HC(MeCDippN)₂][Ga:] (0.487 g, 1 mmol) was added dropwise to a stirred solution of N₃-2,6-Trip₂C₆H₃ (0.524 g, 1 mmol) in toluene (10 mL) with cooling in an ice bath. The mixture gradually assumed a red color and nitrogen gas evolution was observed. Stirring was continued for 12 h and the solvent was reduced in volume to about 15 mL. Cooling in a refrigerator (ca. 4 °C) for 20 h afforded yellow crystals of **2**·PhMe. Yield: 0.73 g (74 %); m.p. 229–230 °C; UV/Vis: λ_{max} = 560 nm (sh); ¹H NMR (C₆D₆, 300 MHz): δ = 7.29–6.94 (m; ArH), 6.69 (t, ³J = 7.8 Hz, 1 H; *p*-C₆H₅), 4.71 (s, 1 H; γ-CH), 3.56 (sept, ³J = 6.9 Hz, 2 H; *p*-CH(CH₃)₂), 3.28–2.78 (overlapping septets, 8 H; *o*-CH(CH₃)₂), 1.51, 1.46 (s, 6 H; β-CH₃), 1.40–1.25 (m, 36 H; CH(CH₃)₂), 0.96 (q, 8 H; CH(CH₃)₂), 0.85 (d, 4 H; CH(CH₃)₂); ¹³C {¹H} NMR (75 MHz): δ = 170.38 (CN), 150.91, 150.55, 148.89, 148.13, 147.61, 147.35, 146.11, 144.49, 144.37, 142.32, 140.76, 137.99, 136.01, 134.34, 131.45, 131.19, 125.54, 124.98, 124.59, 124.33, 123.47, 122.70, 120.68, 119.85 (ArC), 97.15 (γ-C), 35.00, 34.79, 33.32, 31.22, 30.34, 30.18, 29.33, 28.84, 28.66, 27.90, 27.47, 26.95,

26.84, 25.86, 25.57, 25.39, 25.05, 24.84, 24.58, 23.97, 23.54, 21.79 (alkyl H). Correct C,H,N analysis.

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The Novel Open-Framework Vanadium Silicates $\text{K}_2(\text{VO})(\text{Si}_4\text{O}_{10}) \cdot \text{H}_2\text{O}$ (VSH-1) and $\text{Cs}_2(\text{VO})(\text{Si}_6\text{O}_{14}) \cdot 3\text{H}_2\text{O}$ (VSH-2)**

Xiqu Wang, Lumei Liu, and Allan J. Jacobson*

Porous silicates that contain transition metals in octahedral or distorted octahedral framework sites have attracted interest in part stimulated by the catalytic properties of the Ti-doped microporous silicate TS-1 for epoxidation reactions.^[1,2] A prominent example of a mixed octahedral/tetrahedral compound is the titanium silicate ETS-10 that has a 12-ring channel system. The framework of ETS-10 contains single chains of corner-shared TiO_6 octahedra isolated from each other by silicate tetrahedra and as a consequence has unusual optical properties in addition to its absorption and catalytic properties.^[3–8]

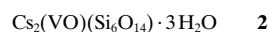
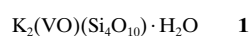
In contrast to octahedral/tetrahedral frameworks containing titanium and zirconium, analogous open-framework systems based on niobium and vanadium as the octahedral or distorted octahedral component are relatively rare. A vanadium silicate called AM-6 with the same structure as ETS-10 has been reported.^[9] The only other known open-framework silicates containing vanadium are cavansite and

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pentagonite, dimorphs of the mineral $\text{Ca}(\text{VO})(\text{Si}_4\text{O}_{10}) \cdot 4\text{H}_2\text{O}$.^[10,11] In both structures, silicate single layers are linked by $(\text{H}_2\text{O})\text{VO}_5$ distorted octahedra into a three-dimensional framework that contains channels. Cavansite and pentagonite, to the best of our knowledge have not been synthesized in the laboratory. In ETS-10 and AM-6 the transition metal centers are not accessible from the channels, whereas in the cavansite and pentagonite frameworks, the vanadium cations are directly exposed to ions or molecules inside the channels.

We are currently investigating the synthesis of vanadium silicates. Microporous vanadium silicates are expected to be of catalytic interest because of the presence of a redox-active transition metal center. The valence-state of vanadium can easily be manipulated and consequently we also can anticipate novel magnetic and electric properties. Herein, we report the synthesis of two new open-framework vanadium silicates **1** and **2**, the structures of which are closely related to those of cavansite and pentagonite.



Crystals of **1** and **2** were prepared by hydrothermal reactions and were grown as pale blue polyhedra with a maximum dimension of about 0.2 mm. The structures of both compounds were determined by single-crystal X-ray diffraction,^[12] and their compositions were measured by electron microprobe analysis.^[13]

The orthorhombic structure of compound **1** has space group symmetry *Pbca*. Figure 1 a shows the silicate single layer of **1** and Figure 1 b shows a view of the structure along [110]. The silicate layer is composed of single chains of SiO_4 tetrahedra running along [100]. Neighboring chains are linked to form a layer that consists of only 6-rings. The SiO_4 tetrahedra in each single chain have an alternating *UUDD* orientation, where *U* refers to a terminal oxygen corner pointing up and *D* down, while in the 6-rings they have the rare *UUDDUD* orientation. The silicate layers are cross-linked into a three-dimensional framework by interlayer VO_5 tetragonal pyramids. Each pyramid shares its basal plane corners with two *UU* tetrahedra from one silicate layer and two *DD* tetrahedra from an adjacent layer. The pyramid is disordered over two orientations that have the same basal plane and opposite apex corners. The oxygen atoms of two disordered water molecules complete the vanadium coordination at V–O distances of 2.68 and 3.14 Å. The framework has two intersecting 8-ring channel systems running along [110] and $[\bar{1}\bar{1}0]$ that are related by a symmetry glide plane. The free aperture of the channels is about 2.6×4.0 Å. The K^+ ions and water molecules are located within the channels and both are disordered. Thermogravimetric analysis (TGA) data for **1** measured in air indicated that dehydration of the compound starts at about 200 °C and is completed at about 460 °C.

Compound **2** crystallizes in the orthorhombic space group *Cmca*. As shown in Figure 2 a, the silicate single layer contains not only 6-rings similar to those of **1** but also 4-rings. The layer of **2** is composed of single tetrahedral chains running along [001] that are closely related to the [100] chains of **1**. In fact

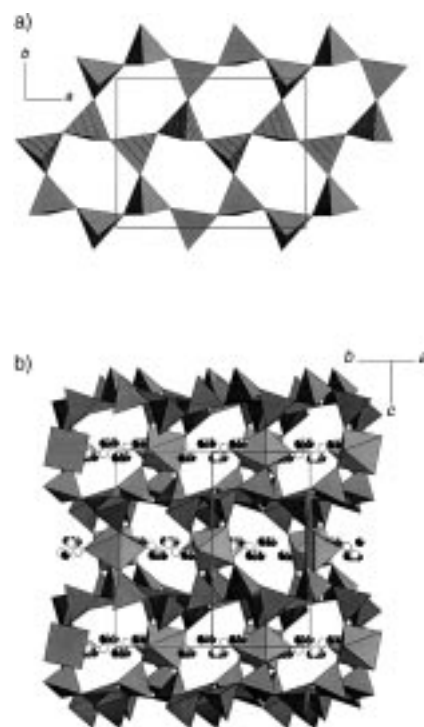


Figure 1. a) The silicate layer of **1**. A [100] chain is marked by hatching. b) A [110] view of the structure of **1**, showing the 8-ring channels. Open and solid circles represent water oxygen and potassium atoms, respectively.

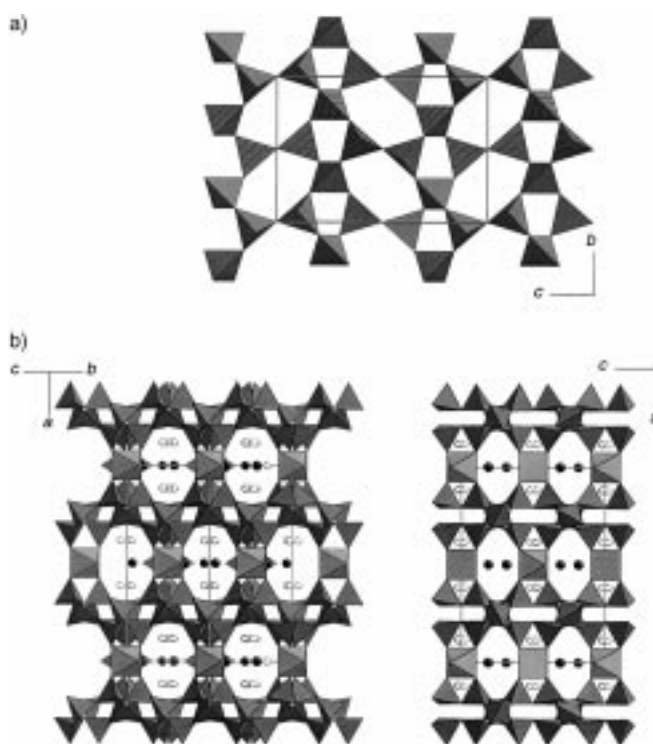


Figure 2. The silicate layer of **2**. A [001] chain is marked by hatching. b) Views of the structure of **2** along [011] (left) and [010] (right), showing the 8-ring channels. Open and solid circles represent water oxygen and cesium atoms, respectively.

the [001] chain of **2** can be derived by inserting an additional tetrahedron between the *UU* and *DD* pairs of the *UUDD* single chain of **1**. Therefore, the [001] chain in **2** has the

orientation of tetrahedra *UUQDD* where Q is a four-connected tetrahedron that has no terminal corner. The connection of adjacent silicate layers by VO_5 pyramids in **2** is very similar to that in **1**, that is, each pyramid shares its basal plane corners with two *UU* tetrahedra from one silicate layer and two *DD* tetrahedra from an adjacent layer. The orientational disorder of the VO_5 pyramids of **1** is also found in **2**. In **2**, the oxygen atom of the nearest water molecule is at 3.50 Å from the vanadium atom. The framework of **2** contains two intersecting channel systems running along [011] and $[0\bar{1}1]$ that are symmetry equivalent. These channels have a width defined by 8-rings and a free aperture of 3.0×3.6 Å. A third system of channels runs along [010] that also has a free width of 3.0×3.6 Å (Figure 2b). The Cs^+ ions and the water molecules occupy the space within the channels. TGA of **2** at a heating rate of 5 K min^{-1} shows loss of water molecules from the framework begins immediately on heating. By 350°C all of the water is removed. An X-ray powder pattern of the TGA sample after heating to a final temperature of 523°C was similar to that of the starting material. After dehydration at 500°C , the sample reabsorbs water on cooling in the presence of water vapor. The dehydration–rehydration behavior is reversible.

Bond valence sums^[14] calculated for the vanadium atoms are 4.1 and 3.8 v.u. for **1** and **2**, respectively, indicating their V^{4+} character similar to the vanadium atoms in cavansite and pentagonite. The silicate layers of both cavansite and pentagonite consist of alternating *UUDD* tetrahedral single chains similar to those of **1** (Figure 3). Different ways of linking such

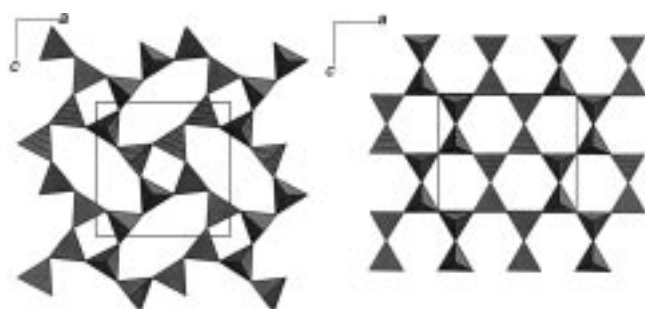


Figure 3. The silicate layers in cavansite (left) and pentagonite (right). The *UUDD* chains similar to that of **1** are marked by hatching.

chains lead to the different geometrical features of the layers in these compounds. The silicate layer of pentagonite comprises only 6-rings similar to that of **1**. However, the 6-rings in pentagonite have an *UUUDD* orientation of tetrahedra. The silicate layers of cavansite consist of both 4-rings and 8-rings. The ways of connecting adjacent silicate layers by the VO_5 pyramids in cavansite and pentagonite are the same to those in **1** and **2**. The *UU* and *DD* tetrahedra pairs apparently fit well to the pyramids and favor the formation of such structures. There are many hypothetical tetrahedral layers that can be built by interconnecting the single chains of **1** or its derivatives. Therefore, a series of open-framework structures similar to **1** and **2** are anticipated.

In conclusion, compounds **1** and **2** have small pore frameworks that can be considered as based on the same building principles as the mineral cavansite and pentagonite. The fact

that pentagonite has wider channels defined by 10-rings points to the possibility of synthesizing similar compounds with middle- and large-pore frameworks.^[15] Employing organic templates should be helpful in synthesizing such highly porous materials.

Experimental Section

1: A 0.5 M aqueous solution of $\text{VOSO}_4 \cdot 3\text{H}_2\text{O}$ (0.5 mL), 45% KOH (0.5 mL), H_2O (0.5 mL), and ethylene glycol (1 mL) was mixed together. The solution was sealed together with 0.64 g fumed silica and heated at 240°C for 3 days in a 23 mL Teflon-lined autoclave. Pale blue crystals of **1** were recovered by vacuum-filtering together with impurities of green powder.

2: A 0.5 M aqueous solution of $\text{VOSO}_4 \cdot 3\text{H}_2\text{O}$ (0.5 mL), 50% CsOH (0.5 mL), H_2O (0.5 mL), and ethylene glycol (1 mL) was mixed together. The solution was sealed together with 0.62 g fumed silica and heated at 240°C for 3 days in a 23 mL Teflon-lined autoclave. Pale blue crystals of **2** were recovered by vacuum-filtering together with impurities of brown powder.

Received: February 21, 2001 [Z16657]

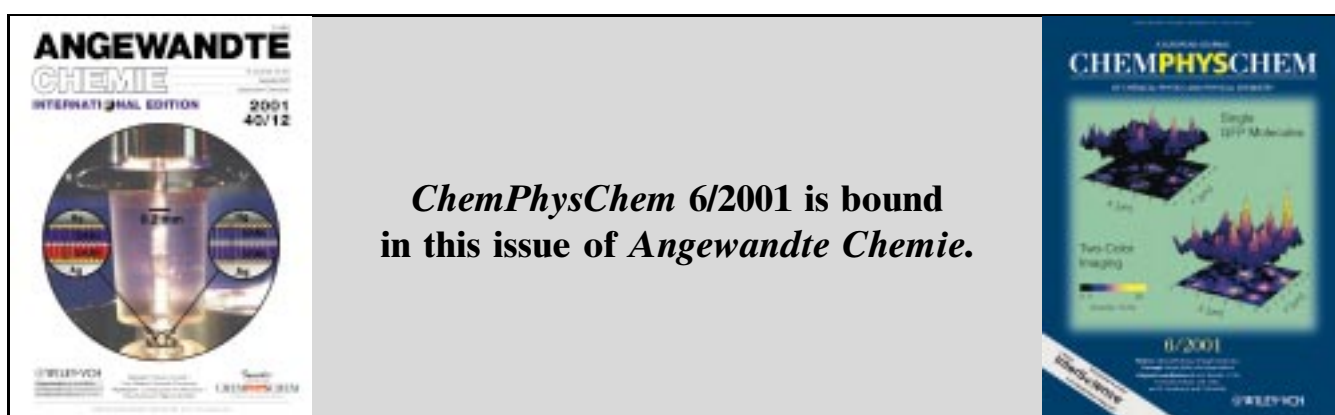
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- [12] X-ray crystal analysis for **1**: pale blue octahedra, $0.12 \times 0.09 \times 0.06$ mm, space group *Pbca*, $a = 10.258(2)$, $b = 8.2608(2)$, $c = 12.981(3)$ Å, $V = 1099.9(4)$ Å³, final *R* indices ($I > 2\sigma(I)$): $R1 = 0.0551$, $wR2 = 0.1321$, *R* indices (all data): $R1 = 0.0843$, $wR2 = 0.1443$. X-ray crystal analysis for **2**: pale blue plate, $0.11 \times 0.08 \times 0.03$ mm, space group *Cmca*, $a = 17.051(2)$, $b = 8.6630(9)$, $c = 12.384(1)$ Å, $V = 1829.3(3)$ Å³, final *R* indices ($I > 2\sigma(I)$): $R1 = 0.0457$, $wR2 = 0.1100$, *R* indices (all data): $R1 = 0.0707$, $wR2 = 0.1209$. Intensities were measured on a SMART platform diffractometer equipped with a 1K CCD area detector using graphite-monochromated $\text{MoK}\alpha$ radiation at 20°C . The structures was solved with direct methods and refined by using the SHELXTL program. All atom positions were refined anisotropically in the final refinements. The hydrogen atoms of the disordered water molecules were not located. Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-411750 and CSD-411751.
- [13] Electron microprobe analysis: JEOL JXA-8600 instrument operating at 15 KeV with a $10 \mu\text{m}$ beam diameter and a beam current of 30 nA. The measured atomic ratios are K:V:Si = 1.9:1.0:4.2 for **1** and Cs:V:Si = 1.9:1:6.5 for **2**.
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Cover Picture

R. Erik Holmlin, Rustem F. Ismagilov, Rainer Haag, Vladimiro Mujica, Mark A. Ratner, Maria Anita Rampi, and George M. Whitesides

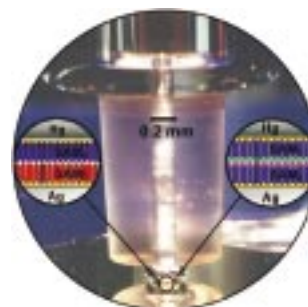
The cover picture shows a Hg-SAM₁//SAM₂-Ag nanojunction, which allows the rapid screening of various self-assembled monolayers (SAMs) for their electronic properties. The setup of this molecular junction, which consists of a mercury electrode with SAM₁ (top) and a silver-coated silicon wafer with SAM₂ (bottom), is simple and allows the rapid screening of various functionalized monolayers. In the picture an interfacial reflection (mirror image) of the mercury drop in the lower silver surface is observed. In this test-bed the electronic properties of various aromatic and terminally functionalized SAMs were determined and correlated with the molecular structure of the respective SAM. Further details on this nanojunction are reported by M. A. Rampi, G. M. Whitesides et al. on p. 2316 ff.



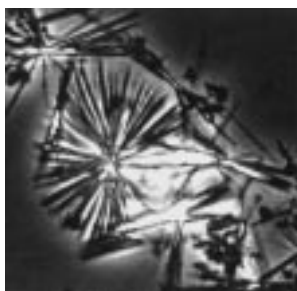


COVER PICTURE

The cover picture shows a Hg-SAM₁/SAM₂-Ag nanojunction, which allows the rapid screening of various self-assembled monolayers (SAMs) for their electronic properties. The setup of this molecular junction, which consists of a mercury electrode with SAM₁ (top) and a silver-coated silicon wafer with SAM₂ (bottom), is simple and allows the rapid screening of various functionalized monolayers. In the picture an interfacial reflection (mirror image) of the mercury drop in the lower silver surface is observed. In this test-bed the electronic properties of various aromatic and terminally functionalized SAMs were determined and correlated with the molecular structure of the respective SAM. Further details on this nanojunction are reported by M. A. Rampi, G. M. Whitesides et al. on p. 2316 ff.



Not just the tiresome first step towards an X-ray structure analysis: There is far more to the crystallization of proteins these days. Protein crystals (see picture) can be easily produced in a stable form and their chemical and physical properties make them interesting and useful for a whole range of disciplines. They are used as industrial catalysts and for enantioselective chromatography. Possible new areas of application are, for example, the purification and formulation of biopharmaceuticals.



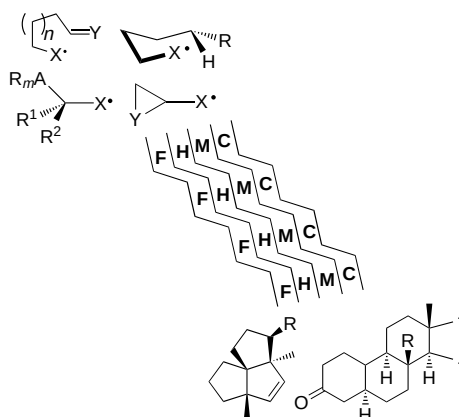
Angew. Chem. **2001**, *113*, 2262–2281

A. L. Margolin,*
M. A. Navia* 2204–2222

Protein Crystals as Novel Catalytic Materials

Keywords: biotransformations • drug research • enzyme catalysis • medicinal chemistry • protein crystals

Medium-ring cycles and polycycles (see scheme) are two of the most important target structures that can be formed with the aid of unimolecular cascades of radical rearrangements. In addition to a plethora of spectacular syntheses, a convenient system for classifying free-radical cascades is presented, which is based on the mechanisms of the individual reaction steps: **F** = fragmentation, **H** = H migration, **M** = 1,2-group migration, **C** = cyclization.



Angew. Chem. **2001**, *113*, 2282–2307

A. J. McCarroll,
J. C. Walton* 2224–2248

Programming Organic Molecules: Design and Management of Organic Syntheses through Free-Radical Cascade Processes

Keywords: cyclizations • domino reactions • radical reactions • rearrangements • synthetic methods

VIPs

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

The Reaction Mechanism of the Enzyme-Catalyzed Central Cleavage of β,β -Carotene to Retinal

M. G. Leuenberger,
C. Engeloch-Jarret,
W.-D. Woggon*

Activation, Tuning, and Immobilization of Homogeneous Catalysts in an Ionic Liquid/Compressed CO₂ Continuous-Flow System

A. Bösmann, G. Franció,
E. Janssen, M. Solinas,
W. Leitner,* P. Wasserscheid*

Synthetic seco Forms of (–)-Diazonamide A

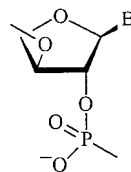
J. Li, X. Chen, A. W. G. Burgett,
P. G. Harran*

Targeting Molecular Recognition: Exploring the Dual Role of Functional Pseudo-Prolines in the Design of SH3 Ligands

G. Tuchscherer,* D. Grell,
Y. Tatsu, P. Durieux,
J. Fernandez-Carneado,
B. Hengst, C. Kardinal, S. Feller*

Tracing the origins of life: TNA (see picture) shows base pairing which is similar to that of pentose-based RNA in regard to specificity, strand orientation, and pairing strength. TNA hybridizes with the natural nucleic acids RNA and DNA and is able to form hairpin structures. The potential of TNA as a genetic precursor of RNA is discussed.

Angew. Chem. **2001**, *113*, 2309–2311

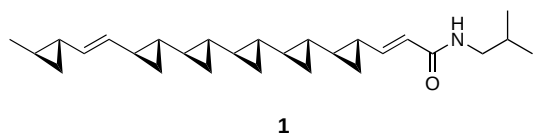


P. Herdewijn* 2249–2251

TNA as a Potential Alternative to Natural Nucleic Acids

Keywords: base pairing • DNA structures • nucleic acids • oligonucleotides • threose nucleic acids

It is amazing what three carbons can do! Nature, industry, and chemists working in academia continue to explore the cyclopropane moiety from various perspectives, among them biological activity, reactivity, and synthetic methodology. Breathing multiple cyclopropane ring structures such as **1** and **2** have recently been prepared and represent milestones in the field of small-ring chemistry.



Angew. Chem. **2001**, *113*, 2312–2314

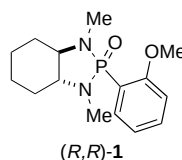
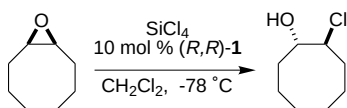
R. Faust* 2251–2253

Fascinating Natural and Artificial Cyclopropane Architectures

Keywords: carbocycles • cyclopropanations • natural products • small ring systems • strained molecules

CORRESPONDENCE

 **The reported ability of chiral phosphoramidate **1**** to effect the enantioselective opening of *meso* epoxides with silicon tetrachloride has not withstood experimental verification by Denmark's group. Having reexamined the ring-opening of cyclooctene oxide (see scheme), Denmark and co-workers found a serious discrepancy between their results (81–83% recovery of the epoxide and an essentially racemic product) and those reported by Buono et al. (77% yield and >99% *ee*).



Angew. Chem. **2001**, *113*, 2315–2316

S. E. Denmark,* T. Wynn,
B. G. Jellerichs 2255–2256

Beneficial Effect of *ortho*-Methoxy Groups in the Asymmetric Ring Opening of *meso* Epoxides with Silicon Tetrachloride Catalyzed by Chiral *ortho*-Methoxyphenyldiazaphosphoramidate Lewis Bases

Keywords: asymmetric catalysis • correspondence • epoxides • Lewis bases • ring opening

COMMUNICATIONS

Glycosphingolipid clustering and interactions at the cell membrane can be modeled by gold glyconanoparticles prepared with biologically significant oligosaccharides. Such water-soluble gold glyconanoparticles with highly polyvalent carbohydrate displays (see picture, gray hemisphere: gold nanoparticle) have been obtained by a simple and versatile strategy.



Angew. Chem. **2001**, *113*, 2318–2321

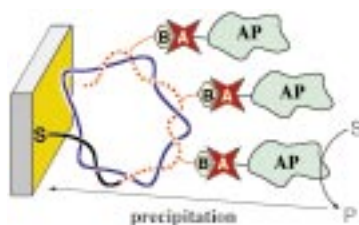
J. M. de la Fuente, A. G. Barrientos,
T. C. Rojas, J. Rojo, J. Cañada,
A. Fernández, S. Penadés* .. 2258–2261

Gold Glyconanoparticles as Water-Soluble Polyvalent Models To Study Carbohydrate Interactions

Keywords: carbohydrates • glycolipids • gold • nanoparticles • self-assembly

Replication, precipitation, and amplification:

Polymerase or reverse transcriptase induced replication of DNA/RNA on a transducer (electrode or piezoelectric crystal) leads to the ultrasensitive specific electronic transduction of viral genomes. Biotin tags (B) on the double-stranded assembly provide docking sites for a conjugate between avidin (A) and an alkaline phosphatase (AP). Enzyme biocatalysis of substrate (S) to the insoluble product (P), which precipitates onto the transducer (yellow surface), provides amplification in the analysis of the target DNA.



F. Patolsky, A. Lichtenstein, M. Kotler, I. Willner* 2261–2265

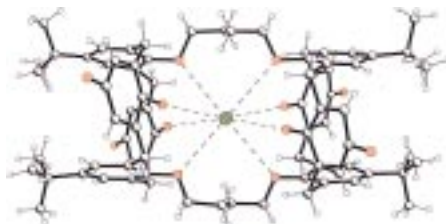
Electronic Transduction of Polymerase or Reverse Transcriptase Induced Replication Processes on Surfaces: Highly Sensitive and Specific Detection of Viral Genomes

Keywords: biosensors • DNA replication • impedance spectroscopy • quartz-crystal microbalance • RNA replication

Angew. Chem. **2001**, *113*, 2321–2325

**The length of the bridging alkylene chain**

between two calix[4]diquinone moieties determines the selectivity of the receptors for Group 1 metal ions. These redox-active receptors exhibit remarkable selectivity preferences and substantial electrochemical recognition effects towards Cs^+ and Rb^+ ions. The solid-state crystal structure of the Cs^+ complex of a bis(calix[4]diquinone) derivative is shown (green: Cs^+ , red: oxygen).



P. R. A. Webber, G. Z. Chen, M. G. B. Drew, P. D. Beer* .. 2265–2268

Cesium- and Rubidium-Selective Redox-Active Bis(calix[4]diquinone) Ionophores

Keywords: alkali metals • calixarenes • ionophores • quinones • redox chemistry

Angew. Chem. **2001**, *113*, 2325–2328

The stereoselective formation of a pseudo- S_6 hexamer resulted from the self-assembling reaction between $[\text{Rh}(\text{Cp}^*)(\text{H}_2\text{O})_3]^{2+}$ and 6-purinethione riboside (see left structure; $\text{Cp}^* = \text{C}_5\text{Me}_5$). The schematic representation (right) shows the direction of the coordination to the S^6 and $\text{N}(7)$ donor atoms. C (clockwise) and A (anticlockwise) indicate the chirality of each unit complex.



K. Yamanari,* S. Yamamoto, R. Ito, Y. Kushi, A. Fuyuhiko, N. Kubota, T. Fukuo, R. Arakawa 2268–2271

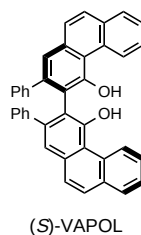
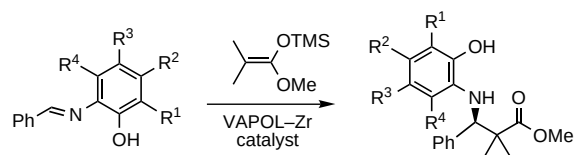
Cyclic Hexamer with a Cubic Cavity: Crystal Structure of $[\{\text{Rh}(\text{6-Purinethione Ribosido})(\text{Cp}^*)\}_6](\text{CF}_3\text{SO}_3)_6$

Keywords: chirality • nucleosides • rhodium • self-assembly • supramolecular chemistry

Angew. Chem. **2001**, *113*, 2328–2331



Unusually robust: A remarkably temperature-independent catalyst has been developed for the imino aldol reaction of imines derived from *ortho*-amino-phenols (see scheme). This catalyst is prepared from two equivalents of the VAPOL ligand and a zirconium tetraalkoxide. From a consideration of likely intermediates in the catalytic cycle it was deduced that a methyl substituent *ortho* to the phenol (R^1) should enhance induction. This resulted in asymmetric inductions in excess of 98% *ee* at room temperature as well as at 100°C. TMS = trimethylsilyl.



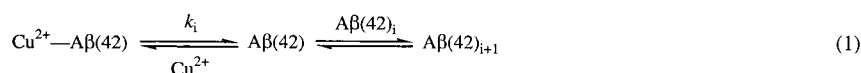
S. Xue, S. Yu, Y. Deng, W. D. Wulff* 2271–2274

Active Site Design in a Chemzyme: Development of a Highly Asymmetric and Remarkably Temperature-Independent Catalyst for the Imino Aldol Reaction

Keywords: asymmetric catalysis • imino aldol reaction • ligand effects • O ligands • zirconium

Angew. Chem. **2001**, *113*, 2331–2334

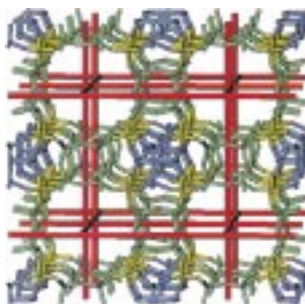
A distinct biochemical role of Cu^{2+} as an inhibitor in the aggregation of the peptide $\text{A}\beta(42)$ in vitro was revealed by thioflavin T fluorescence assay and atomic force microscopy. The Cu^{2+} – $\text{A}\beta(42)$ complex is responsible for the inhibition because it stabilizes the soluble form of $\text{A}\beta(42)$ and controls the conformational transition ($[\text{Eq. (1)}]; k_i = [\text{A}\beta(42)][\text{Cu}^{2+}]/[\text{Cu}^{2+} - \text{A}\beta(42)]$).



Angew. Chem. **2001**, *113*, 2334–2337

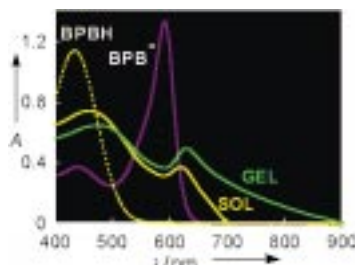


Substitution of germanium for silicon in the preparation of the zeolite Beta allows the synthesis and characterization of a third, heretofore predicted, polymorph “C”; a [001] view is shown in the picture. Germanium preferentially occupies positions in double four-membered ring cages, the secondary building units of polymorph C, and favors the formation of polymorph C regardless of which of the eight organic structure-directing agents were used.



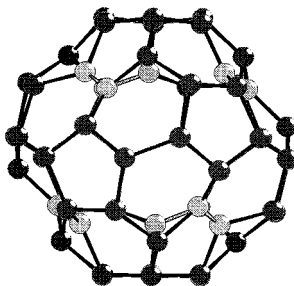
Angew. Chem. **2001**, *113*, 2337–2340

Efficient gelation of aqueous fluids by a novel tripodal trischolamide generates chiral hydrophobic pockets in the gel network. A yellow to green color change (see absorbance spectra) in the presence of bromophenol blue (BPH) indicates the formation of the gel. The bound (anionic) dye (BPB^-) shows induced circular dichroism, which is indicative of a chiral environment.



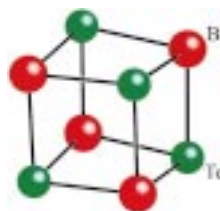
Angew. Chem. **2001**, *113*, 2341–2343

Deflated buckyballs: The single-crystal structure of $\text{C}_{60}\text{F}_{48} \cdot 2(\text{mesitylene})$ revealed the presence of both D_3 and S_6 isomers in the same crystal. $\text{C}(\text{sp}^2)$ – $\text{C}(\text{sp}^2)$ bonds (1.30 Å) are much shorter than $\text{C}(\text{sp}^3)$ – $\text{C}(\text{sp}^3)$ bonds (1.54–1.63 Å). The C_{60} cage is characterized by concave areas in the regions of six double bonds (see picture). Each double bond is effectively shielded by four F atoms, which accounts for the low reactivity of $\text{C}_{60}\text{F}_{48}$.



Angew. Chem. **2001**, *113*, 2345–2347

Two valence electrons more than in square-antiprismatic 38-electron clusters such as Bi_8^{2+} or Sn_8^{6-} : This is the reason for the unusual cube-shaped structure of the cation $\text{Bi}_4\text{Te}_4^{4+}$ (see picture), which is obtained as the chloroaluminate salt from acidic $\text{AlCl}_3/\text{Na}[\text{AlCl}_4]$ melts.



Angew. Chem. **2001**, *113*, 2347–2350

J. Zou, K. Kajita,
N. Sugimoto* 2274–2277

Cu^{2+} Inhibits the Aggregation of Amyloid β -Peptide(1–42) in vitro

Keywords: aggregation • copper • inhibitors • peptides

A. Corma,* M. T. Navarro, F. Rey, J. Rius,
S. Valencia 2277–2280

Pure Polymorph C of Zeolite Beta Synthesized by Using Framework Isomorphous Substitution as a Structure-Directing Mechanism

Keywords: germanium • polymorphism • zeolites

U. Maitra,* S. Mukhopadhyay, A. Sarkar,
P. Rao, S. S. Indi 2281–2283

Hydrophobic Pockets in a Nonpolymeric Aqueous Gel: Observation of such a Gelation Process by Color Change

Keywords: aggregation • gel • hydrophobic effect • materials science • steroids

S. I. Troyanov,* P. A. Troshin,
O. V. Boltalina,* I. N. Ioffe, L. N. Sidorov,
E. Kemnitz 2285–2287

Two Isomers of $\text{C}_{60}\text{F}_{48}$: An Indented Fullerene

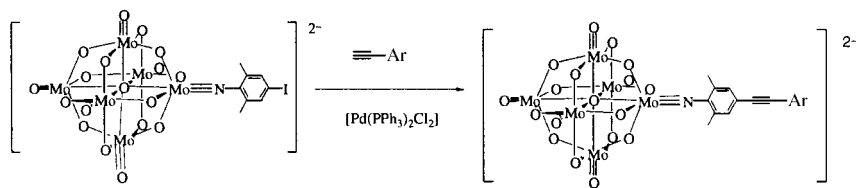
Keywords: fluorine • fullerenes • polyaddition • structure elucidation

J. Beck,* M. Dolg,
S. Schlüter 2287–2290

$\text{Bi}_4\text{Te}_4^{4+}$ —A Cube-Shaped, Polycationic Main Group Element Cluster

Keywords: ab initio calculations • bismuth • cluster compounds • polycations • tellurium

The Mo≡N bond is conjugated with the organic segment in the novel molecular organic–inorganic hybrid materials that have been obtained by Pd-catalyzed coupling of an iodo-functionalized hexamolybdate anion and an alkyne (see scheme; Ar = 4-methylphenyl, 3-5-di(*tert*-butyl)phenyl). The interaction between the polyoxometalate cluster and the organic conjugated system is particularly apparent from the strong red-shifted absorption in the UV/Vis spectrum.



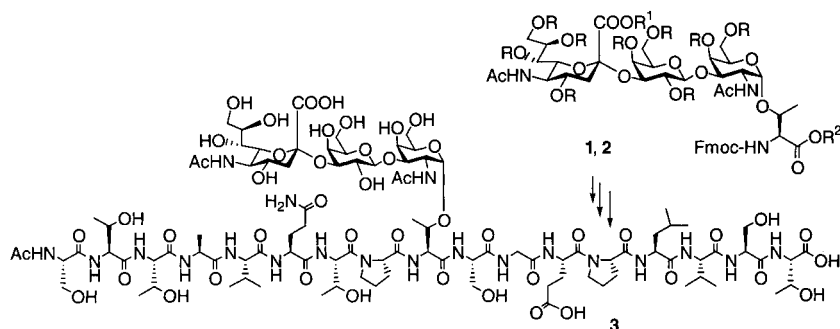
Angew. Chem. **2001**, *113*, 2353–2356

B. Xu, Y. Wei, C. L. Barnes,
Z. Peng* 2290–2292

Hybrid Molecular Materials Based on
Covalently Linked Inorganic
Polyoxometalates and Organic
Conjugated Systems

Keywords: molybdenum • organic–
inorganic hybrids • palladium •
polyoxometalates

Protection of all functional groups of the carbohydrate portion of the chemoenzymatically synthesized sialyl T threonine ester **1** (R = R¹ = H, R² = *t*Bu, Fmoc = 9-fluorenylmethoxycarbonyl) and subsequent acidolysis of the *tert*-butyl ester afforded the building block **2** (R = Ac, R¹ = Me, R² = H). The latter is a useful tool in the solid-phase synthesis of the N-terminal sequence **3** of the leukemia-associated leukosialin.



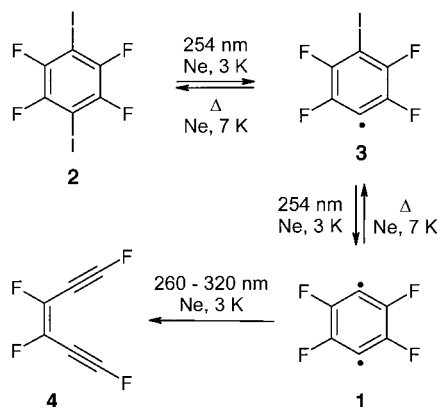
Angew. Chem. **2001**, *113*, 2350–2353

N. Bézay, G. Dudziak, A. Liese,
H. Kunz* 2292–2295

Chemoenzymatic-Chemical Synthesis of
a (2-3)-Sialyl T Threonine Building Block
and Its Application to the Synthesis of the
N-Terminal Sequence of Leukemia-
Associated Leukosialin (CD 43)

Keywords: amino acids • carbohydrates •
chemoenzymatic synthesis • leukosialin •
solid-phase synthesis

As the first isolated derivative of 1,4-didehydrobenzene, 1,4-didehydro-2,3,5,6-tetrafluorobenzene (**1**) was generated from 1,4-diiodotetrafluorobenzene (**2**) by photolysis at 254 nm in a neon matrix at 3 K. The 4-iodo-2,3,5,6-tetrafluorophenyl radical **3** is formed as an intermediate in this reaction. Both **1** and **3** were characterized by their IR spectra. Compound **1** is photolabile and undergoes a photochemical retro-Bergman reaction to 1,3,4,6-tetrafluorohex-3-ene-1,5-diyne (**4**) upon broad-band UV irradiation (260–320 nm).



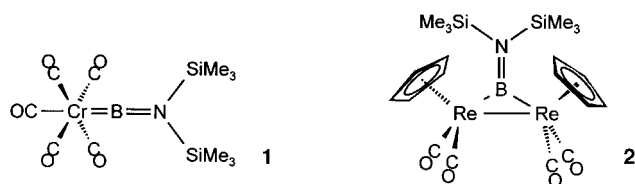
Angew. Chem. **2001**, *113*, 2356–2359

H. H. Wenk, A. Balster, W. Sander,*
D. A. Hrovat, W. T. Borden 2295–2298

Matrix Isolation of Perfluorinated
p-Benzynes

Keywords: 1,4-didehydrobenzene •
enediynes • IR spectroscopy •
matrix isolation

Upon irradiation of $[(OC)_5W=B=N(SiMe_3)_2]$ the complexes **1** and **2** were obtained by intermetallic transfer of $BN(SiMe_3)_2$, thus demonstrating the potential of terminal borylene complexes as a source for borylenes at low temperatures and in the condensed phase. Compound **1** is the first structurally authentic chromium complex of boron.



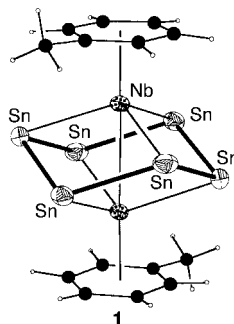
Angew. Chem. **2001**, *113*, 2359–2361

H. Braunschweig,* M. Colling,
C. Kollann, H. G. Stammer,
B. Neumann 2298–2300

Terminal Borylene Complexes as a
Source for the Borylene $B=N(SiMe_3)_2$:
Alternative Synthesis and Structure of
 $[(OC)_5Cr=B=N(SiMe_3)_2]$

Keywords: B ligands • boron •
chromium • ligand transfer • rhenium

Sitting in a tin chair: the compound $[Nb(\eta-C_6H_5Me)]$ reacts with the Sn_6^{4-} ion in ethylenediamine to give the $[(\eta-C_6H_5Me)NbSn_6Nb(\eta-C_6H_5Me)]^{2-}$ ion, **1**. The complex contains a new Zintl ion, Sn_6^{12-} , with a chair cyclohexane-like structure and 2c-2e bonds.



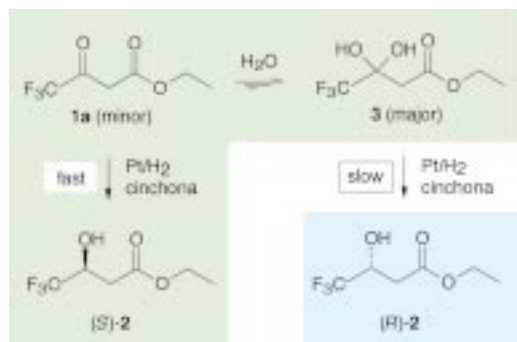
Angew. Chem. **2001**, *113*, 2364–2366

B. Kesanli, J. Fettingner,
B. Eichhorn* 2300–2302

The $[(\eta-C_6H_5Me)NbSn_6Nb(\eta-C_6H_5Me)]^{2-}$ Ion: A Complex Containing a
Metal-Stabilized Sn_6^{12-} Cyclohexane-Like
Zintl Ion

Keywords: arenes • cyclohexane
structure • niobium • structure
elucidation • tin • zintl anions

Two competing reaction pathways, which lead to opposite enantiomers (see scheme), occur in the hydrogenation of **1** over chirally modified platinum, as revealed by catalytic and NMR spectroscopic experiments: the fast reduction of the ketoform **1a** (minor species) and the slow hydrolysis of the hydrate **3** (major species).



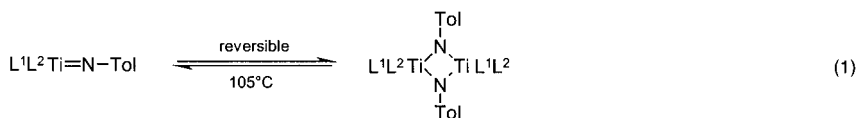
Angew. Chem. **2001**, *113*, 2369–2372

M. von Arx, T. Mallat,
A. Baiker* 2302–2305

Inversion of Enantioselectivity during the
Platinum-Catalyzed Hydrogenation of an
Activated Ketone

Keywords: asymmetric hydrogenation •
chiral auxiliaries • heterogeneous
catalysis • hydrates • platinum

A complex interplay between the catalyst concentration and the reaction rate exists, as shown by kinetic studies, for the $[Cp_2TiMe_2]$ -catalyzed intermolecular hydroamination of alkynes. The reason for this is a reversible dimerization of the catalytically active species [Eq. (1)]. $L^1, L^2 = Cp$ (cyclopentadienyl), Tol = NH (Tol = 4-MeC₆H₄, tolyl).



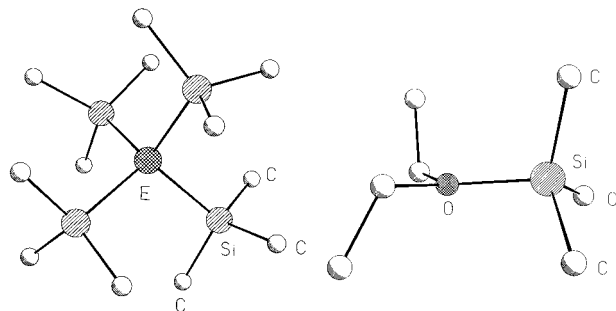
Angew. Chem. **2001**, *113*, 2361–2364

F. Pohlki, S. Doye* 2305–2308

The Mechanism of the
 $[Cp_2TiMe_2]$ -Catalyzed Intermolecular
Hydroamination of Alkynes

Keywords: alkynes • amination •
homogeneous catalysis • metallocenes •
titanium

Only strong Lewis acidic, arene-solvated Me_3Si^+ ions react with $\text{E}(\text{SiMe}_3)_3$ compounds ($\text{E} = \text{P}, \text{As}$) to give the crystallographically characterized $\text{E}(\text{SiMe}_3)_4^+$ onium ions **1** (left hand picture), which contain highly negative polarized P and As atoms, respectively. The masked Me_3Si^+ ions in **1** can be easily transferred to Et_2O , to give the first structurally characterized planar silyloxonium ion $[\text{Et}_2(\text{Me}_3\text{Si})\text{O}]^+$ **2** (right hand picture).



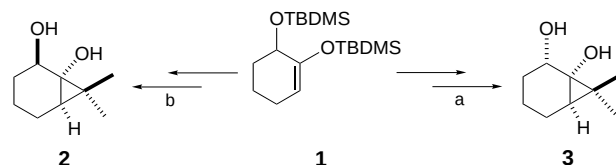
Angew. Chem. **2001**, *113*, 2366–2369

M. Driess,* R. Barmeyer, C. Monsé,
K. Merz 2308–2310

$\text{E}(\text{SiMe}_3)_4^+$ Ions ($\text{E} = \text{P}, \text{As}$): Persilylated
Phosphonium and Arsonium Ions

Keywords: arsenic • onium ions •
phosphonium salts • silicon

The diastereocomplementarity of halo- and alkylcarbenes (paths a and b, respectively) was shown in the cyclopropanation reaction of **1**. The conversion of **1** into 7,7-dimethylbicyclo[4.1.0]heptan-1,2-diols ($\pm$)-**2** and ($\pm$)-**3** represents an important transformation in a synthetic strategy towards phorbol derivatives. TBDMS = *tert*-butyldimethylsilyl.



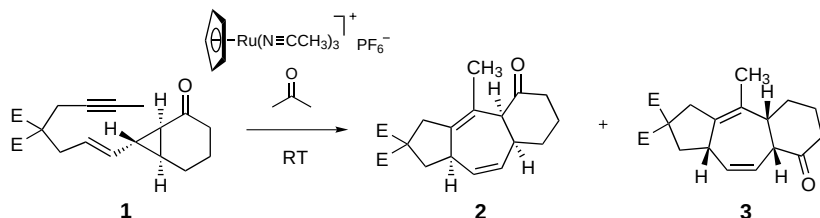
Angew. Chem. **2001**, *113*, 2373–2375

M. G. B. Drew, L. M. Harwood,*
A. J. Macías-Sánchez, R. Scott,
R. M. Thomas, D. Uguen .. 2311–2313

Diastereocontrol in the Synthesis of
Models of Rings C and D of Phorbol:
Directing Effect of an Ether Substituent
on Lithium Carbenoid Mediated
Cyclopropanation

Keywords: carbenoids •
cyclopropanations • diastereoselectivity •
enol ethers • synthetic methods

Efficient access to tricyclic compounds such as **2** and **3**, which contain a seven-membered ring, is provided by the ruthenium-catalyzed intramolecular [5+2] cycloaddition of a 1,2,3-trisubstituted cyclopropyl enyne such as **1**. Improved regioselectivity is observed when $\text{In}(\text{OTf})_3$ is used as the cocatalyst. (No cocatalyst: **2**:**3** 6:1; cat. $\text{In}(\text{OTf})_3$ (10%): **2**:**3** > 20:1; Tf = trifluoromethanesulfonyl).



Angew. Chem. **2001**, *113*, 2375–2378

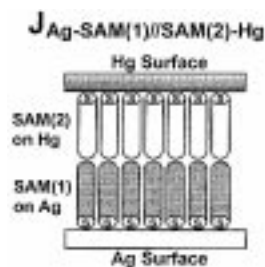
B. M. Trost,* H. C. Shen ... 2313–2316

Constructing Tricyclic Compounds
Containing a Seven-Membered Ring by
Ruthenium-Catalyzed Intramolecular
[5+2] Cycloaddition

Keywords: cycloaddition •
diastereoselectivity • enynes •
homogeneous catalysis • ruthenium

A convenient experimental system is described, with which electron transport through structurally well-defined, 2–5 nm-thick, organic films can be examined. Two types of junction **J** have been studied in which self-assembled monolayers (SAMs, for example, SAM(1) formed on Ag from aliphatic and aromatic thiols, and SAM(2), formed on Hg from hexadecanethiol) are in contact through either van der Waals interactions (see picture) or through covalent, hydrogen, or ionic bonds.

Angew. Chem. **2001**, *113*, 2378–2382



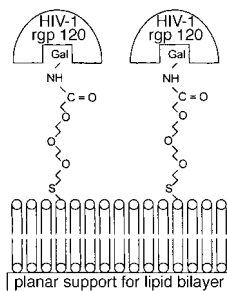
R. E. Holmlin, R. F. Ismagilov, R. Haag, V. Mujica, M. A. Ratner, M. A. Rampi,* G. M. Whitesides* 2316–2320

Correlating Electron Transport and Molecular Structure in Organic Thin Films

Keywords: electron transfer • monolayers • self assembly • thin films

A critical spacer arm length necessary to promote efficient binding of the HIV-1 surface glycoprotein rgp120 to several synthetic galactosyl-conjugated lipids, reconstituted into planar lipid bilayers, was identified (see figure). This should aid the design of anti-HIV-1 agents based on membrane-tethered, carbohydrate-based receptors for gp120.

Angew. Chem. **2001**, *113*, 2382–2384



Y. Gu, R. LaBell, D. F. O'Brien,* S. S. Saavedra* 2320–2322

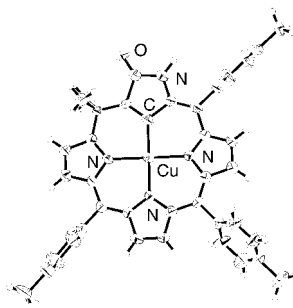
Quantitative Studies of Binding between Synthetic Galactosyl Ceramide Analogues and HIV-1 Gp120 at Planar Membrane Surfaces

Keywords: fluorescence spectroscopy • glycoproteins • HIV • sphingolipids • structure–activity relationships



Rare organometallic complexes can be stabilized by using an N-confused system as a carbon ligand. A stable organocopper(II) compound of N-confused calix[4]phyrin has been characterized by X-ray crystallography (see picture). Complete π conjugation was found not to be a prerequisite for the formation of the metal–carbon bond.

Angew. Chem. **2001**, *113*, 2385–2387



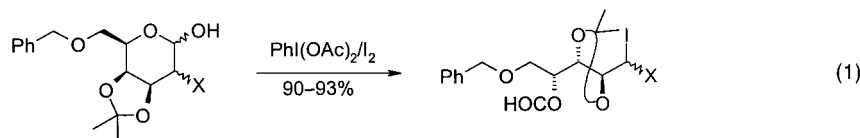
H. Furuta,* T. Ishizuka, A. Osuka,* Y. Uwatoko, Y. Ishikawa* .. 2323–2325

Metal Complexes of an N-Confused Calix[4]phyrin Derivative—The First X-ray Structure of an Organometallic Compound of Divalent Copper

Keywords: C ligands • copper • macrocycles • nickel • porphyrinoids



One less carbon atom is found in 1-halo-1-iodo compounds obtained by C1–C2 radical fragmentation of carbohydrate 1,2-halohydrins. This fragmentation is achieved via the anomeric alkoxy radicals of the halohydrins, formed upon reaction with (diacetoxyiodo)benzene and iodine [Eq. (1); X = Cl, Br, I].



Angew. Chem. **2001**, *113*, 2388–2390

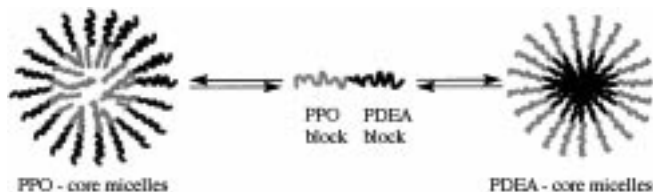
C. C. González, A. R. Kennedy, E. I. León, C. Riesco-Fagundo, E. Suárez* 2326–2328

Fragmentation of Carbohydrate Anomeric Alkoxy Radicals: A New Synthesis of Chiral 1-Halo-1-iodo Compounds

Keywords: carbohydrates • chirality • halides • iodine • radical reactions



Two micellar states are possible for a novel PPO–PDEA diblock copolymer synthesized by atom-transfer radical polymerization. Subtle variation of the solution pH value and temperature is all that is needed to form both conventional micelles (with the PDEA block in the core) and reverse micelles (with the PPO block in the core) in aqueous media (shown schematically). DEA = 2-(diethyl-amino)ethyl methacrylate, PO = propylene oxide.



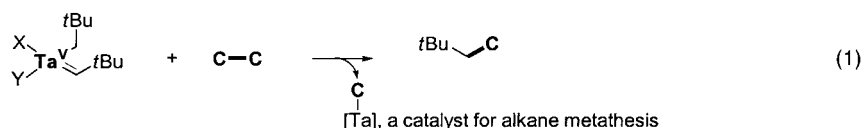
Angew. Chem. **2001**, *113*, 2390–2393

S. Liu, N. C. Billingham,
S. P. Armes* 2328–2331

A Schizophrenic Water-Soluble Diblock
Copolymer

Keywords: copolymerizations •
micelles • polymerizations • polymers •
self-assembly

C–C activation of unactivated alkanes on a silica-supported neopentyl neopentylidene Ta^V complex [Eq. (1)] affords the alkane cross-metathesis products *t*BuCH₂R and an alkane-metathesis catalyst. Since the activity and product distributions are similar to those obtained with a silica-supported Ta^{III} hydride, these results are a first step in understanding alkane σ-bond metathesis on metal hydrides.



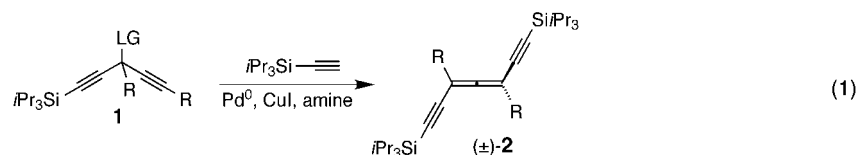
Angew. Chem. **2001**, *113*, 2393–2396

C. Copéret, O. Maury, J. Thivolle-Cazat,*
J.-M. Basset* 2331–2334

σ-Bond Metathesis of Alkanes on a Silica-
Supported Tantalum(V) Alkyl Alkylidene
Complex: First Evidence for Alkane
Cross-Metathesis

Keywords: C–C activation • C–C
coupling • metathesis • tantalum

Regioselective Pd⁰-catalyzed cross-coupling of bispropargylic precursors **1** with silyl-protected alkynes gave rise to the first 1,3-diethynylallenes **2** [Eq. (1), LG = leaving group]. In enantiomerically pure form, these novel carbon-rich modules could provide access—by oxidative oligomerization—to a fascinating new class of helical oligomers and polymers.



Angew. Chem. **2001**, *113*, 2396–2399

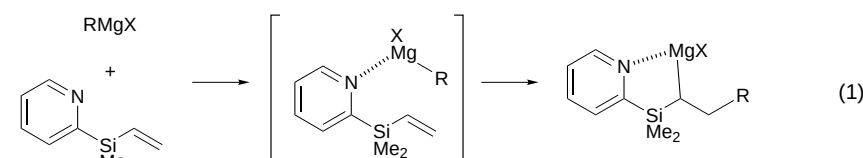
R. C. Livingston, L. R. Cox, V. Gramlich,
F. Diederich* 2334–2337

1,3-Diethynylallenes: New Modules for
Three-Dimensional Acetylenic
Scaffolding

Keywords: alkynes • allenes • cross-
coupling • oligomerization • synthetic
methods



Facile addition of primary alkyl Grignard reagents to vinylsilanes has been realized for the first time by exploiting the directing effect of a 2-pyridyl group on silicon [Eq. (1)]. Three-component coupling reactions of a Grignard reagent, the vinylsilane, and an electrophile, followed by oxidative removal of the 2-pyridyl-dimethylsilyl group with H₂O₂ furnishes various secondary alcohols in excellent overall yields.



Angew. Chem. **2001**, *113*, 2399–2401

K. Itami, K. Mitsudo,
J.-i. Yoshida* 2337–2339

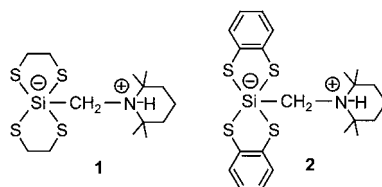
Directed Intermolecular
Carbomagnesation across Vinylsilanes:
2-PyMe₂Si Group as a Removable
Directing Group

Keywords: alcohols • magnesium •
multicomponent reactions • silicon •
synthetic methods

The zwitterionic compounds 1 and 2

are the first pentacoordinate silicates with covalent Si₄C skeletons. They were characterized by crystal-structure analyses and NMR spectroscopic studies. Although pentacoordination of silicon is usually favored by ligand atoms of high electronegativity, the structural data of both **1** and **2** are consistent with the presence of five covalent bonds to the silicon atom.

Angew. Chem. **2001**, *113*, 2401–2403



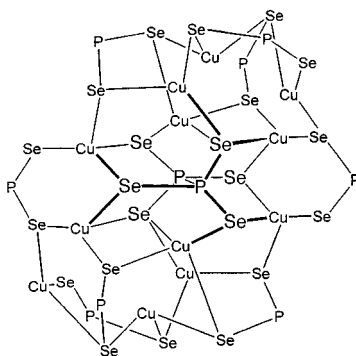
R. Tacke,* M. Mallak,
R. Willeke 2339–2341

Pentacoordination of Silicon by Four Covalent Si–S Bonds and One Covalent Si–C Bond

Keywords: chelates • hypervalent compounds • silicon • S ligands • zwitterions

The coexistence of P⁴⁺ and P⁵⁺ in one complex and the presence of an ethane-like hexaselenodiphosphato ligand, P₂Se₆^{4–}, are the novel features of the title compounds (see structure, in which R = Et or *i*Pr; OR groups omitted for clarity). The coordination mode of P₂Se₆^{4–} in these dodecanuclear copper species is unprecedented and has not even been identified in any mixed ligands containing Group 15/16 elements.

Angew. Chem. **2001**, *113*, 2404–2406

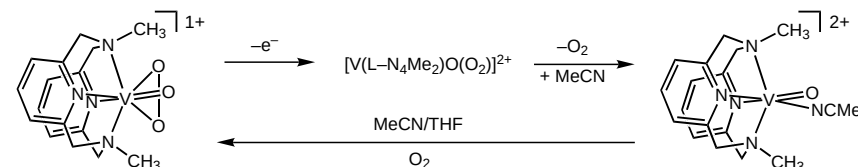


C. W. Liu,* H.-C. Chen, J.-C. Wang,
T.-C. Keng 2342–2344

[Cu₁₂(P₂Se₆){Se₂P(OR)₂}]₈: Discrete Copper Clusters Containing an Ethane-Like Hexaselenodiphosphate(IV)

Keywords: cluster compounds • coordination modes • copper • phosphorus • selenium

A missing link: A superoxovanadium(V) complex is the first reaction intermediate in the oxidative conversion of a peroxovanadium(V) complex into a vanadyl(IV) complex and molecular oxygen (see scheme). The superoxo species appears also to play an essential role in the formation of the peroxovanadium(V) complex from the vanadyl(IV) complex and molecular oxygen.



Angew. Chem. **2001**, *113*, 2406–2410

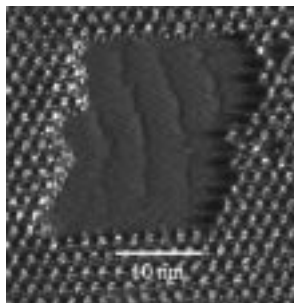
H. Kelm, H.-J. Krüger* 2344–2348

A Superoxovanadium(V) Complex Linking the Peroxide and Dioxygen Chemistry of Vanadium

Keywords: oxidation • oxygen • peroxides • radicals • vanadium

Two “face-on” phases and one “edge-on” lamellar phase comprised of self-assembled structures of phthalocyanines have been visualized by scanning tunneling microscopy (STM) at the gel–graphite interface. The switching between the phases can be stimulated with the microscope tip with a resolution on the molecular scale. The STM image shows the manipulated area consisting of π – π stacked phthalocyanines forming the lamellar phase, which is embedded in a hexagonally packed “face-on” phase.

Angew. Chem. **2001**, *113*, 2410–2412



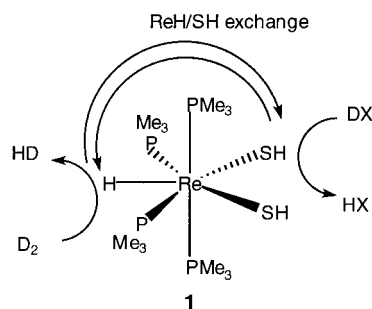
P. Samorí, H. Engelkamp, P. de Witte,
A. E. Rowan, R. J. M. Nolte,
J. P. Rabe* 2348–2350

Self-Assembly and Manipulation of Crown Ether Phthalocyanines at the Gel–Graphite Interface

Keywords: crown compounds • nanostructures • phthalocyanines • scanning tunneling microscopy • self-assembly

Not a poison! In contrast to the high reactivity of **1**, the corresponding trihydride $[\text{ReH}_3(\text{PMe}_3)_4]$ is kinetically inert. Thus, the usual view that sulfur poisons catalysts is clearly inappropriate in this case. The catalytic properties of **1** result from its difunctional nature with both protic (SH) and hydridic (ReH) sites; these sites communicate by an intramolecular exchange process (see scheme; X = OMe, SH).

Angew. Chem. **2001**, *113*, 2413–2415



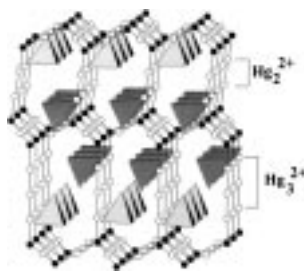
D. E. Schwarz, J. A. Dopke,
T. B. Rauchfuss,*
S. R. Wilson 2351–2353

$[\text{ReH}(\text{SH})_2(\text{PMe}_3)_4]$: A Catalyst for
Fundamental Transformations Involving
 H_2 and H_2S

Keywords: homogeneous catalysis •
hydrodesulfurization • hydrogen •
P ligands • rhenium • sulfur

Pyramids in a mercury tunnel (see picture): Hg_3^{2+} and Hg_2^{2+} units form the tunnel walls of the novel inorganic supramolecular compound $[\text{Hg}_{11}\text{As}_4](\text{GaBr}_4)_4$. This is the first three-dimensional framework that incorporates the subvalent mercury cluster Hg_3^{2+} as a structural unit. Each of the two types of tunnel that extend along the *b* axis of the unit cell contains two columns of GaBr_4^- ions.

Angew. Chem. **2001**, *113*, 2415–2416



A. V. Olenov,
A. V. Shevelkov* 2353–2354

The Hg_3^{2+} Group as a Framework
Unit in a Host–Guest Compound:
 $[\text{Hg}_{11}\text{As}_4](\text{GaBr}_4)_4$

Keywords: host–guest systems •
mercury • solid-state structures •
subvalent compounds



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

* Author to whom correspondence should be addressed

The cover picture was prepared by Rainer Haag, University of Freiburg, Germany.



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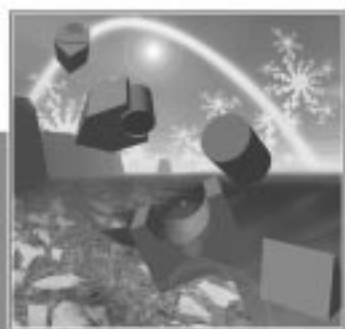
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ASPECTS OF MODERN CHEMISTRY

Fritz Vögtle · J. Fraser Stoddart · Marikatsu Shibasaki

STIMULATING CONCEPTS IN CHEMISTRY



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Stimulating Concepts in Chemistry

2000. XVI, 396 pages, 428 figures, 29 tables. Hardcover.
DM 98.00 | € 50.11 | sFr 89.00 | ISBN 3-527-29978-5

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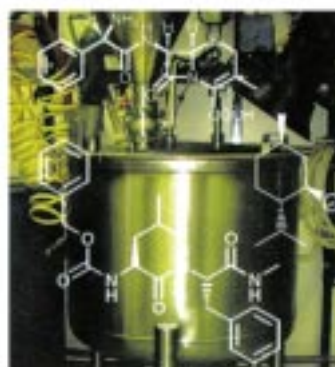
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**Protein
Crystals**



Biopharmaceuticals



Biocatalysts

Protein Crystals as Novel Catalytic Materials

Alexey L. Margolin* and Manuel A. Navia*

In this era of molecular biology, protein crystallization is often considered to be a necessary first step in obtaining structural information through X-ray diffraction analysis. In a different light, protein crystals can also be thought of as materials, whose chemical and physical properties make them broadly attractive and useful across a larger spectrum of disciplines. The full potential of these protein crystalline materials has been severely restricted in practice, however, both by their inherent fragility, and by strongly held

skepticism concerning their routine and predictable growth, formulation, and practical application. Fortunately, these problems have turned out to be solvable. A systematic exploration of the biophysics and biochemistry of protein crystallization has shown that one can dependably create new protein crystalline materials more or less at will. In turn, these crystals can be readily strengthened, both chemically and mechanically, to make them suitable for practical commercialization. Today, these novel materials are used

as industrial catalysts on a commercial scale, in bioremediation and “green chemistry” applications, and in enantioselective chromatography of pharmaceuticals and fine chemicals. In the near future, their utility will expand, to include the purification of protein drugs, formulation of direct protein therapeutics, and development of adjuvant-less vaccines.

Keywords: biotransformations • drug research • enzyme catalysis • medicinal chemistry • protein crystals

1. Introduction

For most people, protein crystals are strongly associated with structural biology, as a necessary first step—or a necessary evil—in the course of X-ray diffraction experiments. This focus of attention is well justified, given the remarkable advances in our understanding of biological processes at the molecular level that have been brought about by macromolecular crystallography. As of May 15th 2001, there were 12 514 structures posted on the Protein Data Bank internet site that were determined by X-ray diffraction analysis.^[1] These structures include membrane proteins, enzymes, nucleic acids and protein–nucleic acid complexes, hormones and their receptors, carbohydrates, peptides, and viruses. Many of these structures describe complexes of specific ligands with target proteins of therapeutic interest at atomic resolution. In a number of instances, that information

has led to approved drugs on the market—drugs developed through the application of structure-based drug design.^[2] Some aspect of this vast and comprehensive panorama is constantly under review in the literature.^[3]

One of the earliest practical applications of macromolecular crystallization methods involved the purification of jack bean urease by Sumner in 1926,^[4] which was done as a prelude to further biochemical studies of that enzyme.^[5] Sumner's work predates the demonstration in 1934 by Bernal and Crowfoot that crystals of the enzyme pepsin could diffract X-rays at atomic resolution.^[6] Sumner's crystallization experiments, in turn, were themselves predated by a series of nineteenth century crystallizations on hemoglobins, seed proteins, and other nonenzymatic proteins, as reviewed by Fruton^[7] and more recently by McPherson.^[8]

Protein crystals have not been widely exploited in the past, apart from their use in structure determination and (to a more limited extent) in protein purification. This neglect may be attributed, in part, to the peculiar conditions under which protein crystals are usually grown and maintained, conditions that are largely incompatible with most practical applications that one might consider. In addition, macromolecular crystals are inherently quite fragile and prone to dissolution or shattering under relatively benign conditions.

Against this backdrop, we sought to create cross-linked enzyme crystals (CLECs)^[9] and later, more generally, cross-linked protein crystals (CLPCs) with greatly enhanced

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stability and performance characteristics that would allow for the routine use of such enzymes and other proteins under the harsh conditions found in chemical manufacturing.^[10] CLECs have now been used in the synthesis of fine chemicals, chiral intermediates, and peptides. These transformations have now been carried out not only on the lab bench, but also on a commercial scale that involves multiple kilograms of catalyst and thousands of kilograms of product.

In the subsequent course of our investigations, we have expanded our interests to encompass other practical applications for crystals and further improvements in crystallization and cross-linking methods. The applications, discussed in detail below, have included:

- 1) crystallization as a “routine” purification tool for proteins and other macromolecules,
- 2) stabilization of protein therapeutics to facilitate drug delivery and extend shelf-life prior to use,
- 3) use of CLPCs as novel microporous materials to be used as “bioorganic zeolites” and as chiral chromatographic media,
- 4) environmental applications, including the destruction of nerve agents for bioremediation and civil defense, and
- 5) biomedical applications including luminal therapies (see Section 4.4.1), self-adjuvanting vaccines, and biosensors.

What is remarkable in all of these considerations, is the fact that nature provides us with such precisely constructed arrays

of macromolecules for a relatively modest effort on our part. As Bernal and Crowfoot state in their historic paper, “the arrangement of atoms inside the protein molecule is...of a perfectly definite kind”. The protein molecules in a crystal are “relatively dense globular bodies, perhaps joined together by valency bridges, but in any event separated by relatively large spaces which contain water”. The regularity, uniformity, and precision of the crystal lattice—properties which are exploited so effectively in diffraction experiments—imply other properties and effects whose practical application has not yet been as aggressively pursued. By what other means, for example, could one hope to precisely position atomic-scale objects, such as a cofactor or prosthetic group in a protein, in a given orientation in space, using only one’s fingers!

2. Beyond Crystallography

2.1. Crystallogenesis: Order from Chaos

The science of crystallogenesis has been extensively and comprehensively reviewed.^[11] Under conditions of supersaturation at high protein concentration, or in the presence of reagents or conditions that reduce protein solubility, protein molecules will aggregate. According to the extent to which solution conditions have been suitably manipulated, those

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A. L. Margolin



M. A. Navia

Manuel A. Navia, born in Havana, Cuba, received his B.A. in physics from New York University in 1967 and his M.S. in biophysics from the University of Chicago in 1969, after which his studies were interrupted by military service. He received his Ph.D. in biophysics in 1974 from the University of Chicago, where he worked with Prof. Paul Sigler on the structure of tRNA. Postdoctoral studies with Dr. David Davies on the structures of an intact antibody and antibody fragments followed at the National Institutes of Health in Bethesda, Maryland. From 1980 to 1989, Dr. Navia worked at Merck Research Laboratories, where he engaged in the structure-based drug design of enzyme inhibitors that resulted in approved and marketed drugs. From 1989 to 1997, he was at Vertex Pharmaceuticals in Cambridge, Massachusetts, where he solved the structures of calcineurin, the IL-1 beta converting enzyme (Caspase-1), and the HIV protease, in support of structure-based drug design programs against immunosuppression, inflammation, and HIV infection. The latter program led to discovery and development of amprenavir, now approved for the control of AIDS. While at Vertex, Dr. Navia was a co-inventor of the CLEC technology and founder of what is now Altus Biologics. In 1997, he cofounded The Althexis Company, in Waltham, Massachusetts, where he serves as Executive Vice President. Althexis is dedicated to the structure-based drug design of novel antibiotics.

early intermolecular associations (Figure 1 a–c) will reflect the interactions that will later propagate through the body of the macroscopic crystal ultimately formed (Figure 1 d).^[12] The global physico-chemical characteristics of such early complexes will differ from those of the resulting crystal; this is reflected, for example, in the different conditions that often are required for the formation of crystal nuclei on the one hand, and crystal growth from those nuclei on the other.

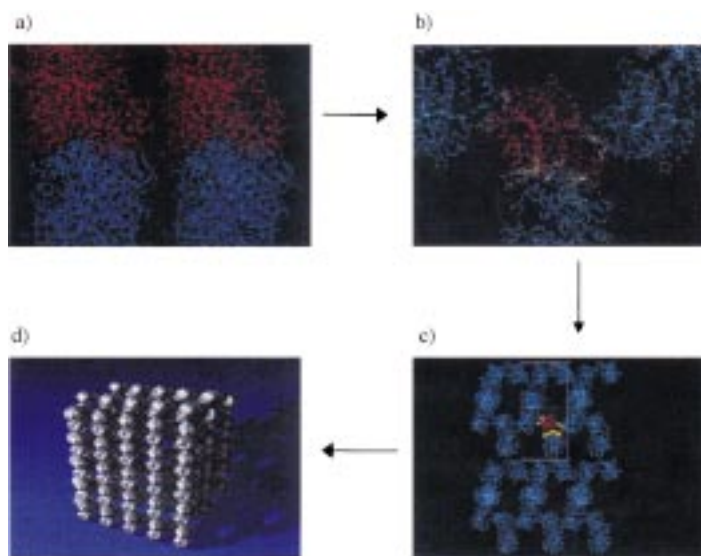


Figure 1. Serine carboxypeptidase II in the $P4_2,2$ crystal form. a) Stereoview of a contact region.^[13] b) Cross-sectional view of an interior molecule (red) in the unit cell. Regions involved in intermolecular contacts are highlighted in yellow, and include the region of extensive contacts shown in (a), as well as two other regions of lesser contact. c) Cross-sectional view of a hypothetical prenuclear complex structure. d) Representation of a crystallization nucleus (see Table 2).

Prenuclear complexes can be quite small in size, and may consist of as few as five or ten repeating cells. In Figure 1 c, we see a model cross-section of what such a prenuclear complex might look like for the enzyme serine carboxypeptidase II in its tetragonal crystal form, which was solved by Liao et al.^[13] In turn, Figure 1 d shows a much larger crystalline aggregate of approximately thirty unit cells that might represent a nucleus for further crystallization through the regular accretion of proteins under supersaturating crystal growth conditions. Further growth may subsequently lead to a large, macroscopic crystal suitable for X-ray diffraction analysis. Both crystal nucleation and growth occur in supersaturated solutions where the concentration of protein exceeds its equilibrium solubility value. Recently, atomic force microscopy has been used to directly visualize the structure of prenuclear complexes of the protein apoferritin and the transition of such complexes to crystal nuclei.^[14] An extension of these studies to a broader sample of macromolecules could greatly enhance our understanding of the critical early steps in crystal formation.

The methods and mechanisms of the formation of protein crystals that are suitable for X-ray diffraction analysis have been extensively reviewed.^[15] For the purpose of CLEC preparation, however, batch crystallization is clearly the

method of choice. This technique is quite attractive because it is simple and can ultimately be scaled up.^[16] Indeed, with this technique we have been able to crystallize more than forty proteins, including glycoproteins, enzymes, antibodies, and hormones, with different molecular weights (1–500 kDa) and from a variety of sources. Some of these crystals are shown in Figure 2.

Controlling the kinetics of crystallization can change the size of the crystals. Normally, faster crystallization processes yield smaller particles. For many chemical applications that require multiple reuse of the catalyst, crystals of 50–150 μm are preferred, since they offer a combination of good filtration properties and high activity. Smaller particles (<5 μm) are better suited for biomedical and other applications, when recycling is not necessary. In some instances, smaller crystals can be aggregated into larger porous particles to enhance their sedimentation properties without compromising substrate/product diffusion characteristics.

2.2. Crystallization as a Means of Purification

Crystallinity has always been associated with purity. Indeed, the aim of the early protein crystallization work was the purification of pure homogeneous proteins from complex extracts. The fact that protein crystals could be grown from relatively crude mixtures was proven by the very first crystallization of a protein, hemoglobin, by Hünefeldt in 1840 and later by Reichert and Brown.^[17] Other dramatic examples, such as crystallization of ferritin from fresh slices of horse spleen by simply adding divalent ions,^[18] crystallization of lysozyme directly from egg white,^[19] and crystallization of albumins, plant proteins, and enzymes, have recently been reviewed by McPherson.^[20] Many of these crystallizations were conducted on a gram scale and resulted in high protein yields.

The advent and use of X-ray crystallography brought significant changes to the science of protein crystallization. The focus of the protein crystallization had shifted from developing reliable purification processes to preparation of diffraction quality single crystals. Nowadays, the purification of proteins and other macromolecules by crystallization is relatively rare.^[21] In an age when chromatography dominates as the principal approach to the purification of proteins and other macromolecules, the crystallization methods pioneered more than a hundred years ago may seem quaint and hopelessly outdated.

Crystallization as a method of purification has also suffered, by extension, from the mystique that surrounds the growth of diffraction-quality macromolecular crystals suitable for X-ray structural analysis. In this regard, one has to be sensitive to the differences between crystals needed for diffraction purposes and those that would otherwise be perfectly suitable for protein purification or for further elaboration into cross-linked protein crystals. The former need to be quite large, if the X-rays scattered from them are to be detected by our instruments. In addition, diffraction-quality crystals must also be suitably ordered and free of internal flaws (such as twinning) in order to provide the level of resolution that

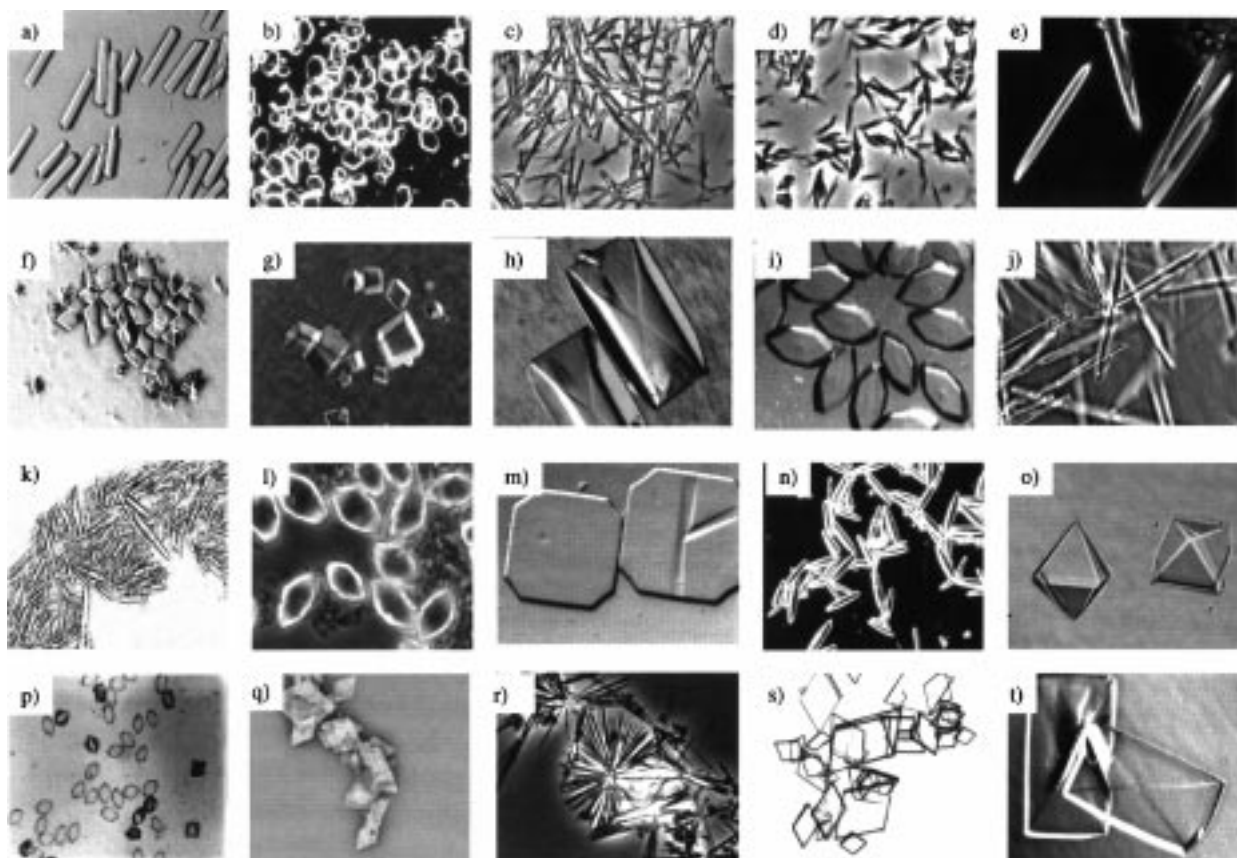


Figure 2. Selected enzyme crystals. a) and b) Lipase from *Pseudomonas cepacia* (enlargement: $\times 360$). c) Alcohol dehydrogenase from *Thermoanaerobacter ethanolicus* ($\times 720$). d) Glucose oxidase from *Aspergillus niger* ($\times 720$). e) Porcine liver esterase ($\times 720$). f) and g) Everlase ($\times 360$ and $\times 180$, respectively). h) and i) Savinase ($\times 180$). j) Subtilisin from *Bacillus licheniformis* ($\times 720$). k) Human serum albumin ($\times 720$). l) and m) Lipase from *Candida antarctica* ($\times 360$ and $\times 180$, respectively). n) Thermolysin from *Bacillus thermoproteolyticus* ($\times 180$). o) Urease from jack beans ($\times 360$). p) H254R organophosphorus hydrolase ($\times 360$). q) Organophosphorus acid anhydrolase from *Alteromonas* sp. ($\times 360$). r) Rituximab ($\times 720$). s) Lipase from *Candida rugosa* ($\times 360$). t) Penicillin acylase from *E. coli* ($\times 180$).

would make the resulting structural images biologically relevant. The crystals produced for purification purposes need only be large enough to facilitate their separation from solute and their isolation. The goal in this case is to make the process high yielding, fast, and, ultimately, economical.

These requirements have been met in several large-scale crystallizations of industrial enzymes.^[22] Judge et al. have crystallized a model protein ovalbumin out of a mixture containing 2 % w/w ovalbumin, 0.167 % w/w conalbumin, and 0.167 % w/w lysozyme in $>99\%$ purity.^[23]

High yield and purity has been achieved in bulk crystallization of thermolysin^[24] and *Candida rugosa* lipase (CRL).^[25] The latter example is instructive. The pure CRL was first obtained by ion-exchange chromatography and a crystallization procedure was developed. This procedure was then applied to crystallization from an impure commercial mixture containing 5–6 % w/w CRL and at least three additional enzymes (less than 2 % w/w).

These and other examples demonstrate that large-scale protein crystallization is a powerful alternative to classical purification techniques, since it can streamline the purification procedures and yield highly concentrated slurries of pure protein ready for further formulation.

2.3. Cross-Linking

While crystallization of proteins creates a precise spatial arrangement of molecules, subsequent cross-linking inside the crystal “locks” the proteins in the crystalline state outside of the conditions that led to crystallization. Historically, glutaraldehyde has been by far the most popular cross-linking agent for enzyme crystals.^[26] Glutaraldehyde is safe, inexpensive, and easy to work with. However, the mechanism of its action is not fully understood.^[27] It is clear, however, that the cross-linking is irreversible even in the presence of exogenous amines and cannot be explained by simple Schiff base formation. The ability of glutaraldehyde to form a mixture of oligomers of different lengths and structures^[28] makes the use of this cross-linker somewhat unpredictable. The cross-linking conditions (pH, temperature, concentrations, and time) must be carefully optimized (excessive cross-linking may lead to formation of protein precipitates and loss of activity) to ensure both high stability and activity of CLEC catalysts. Nevertheless and despite all the shortcomings, glutaraldehyde-mediated cross-linking yielded enzyme crystals that retained almost full activity toward smaller molecules and were much more stable than the corresponding soluble enzymes.

In addition to glutaraldehyde, we have used several homo- and heterobifunctional agents with spacer arm lengths ranging from 3–30 Å for the cross-linking of enzyme crystals. (Figure 3) Among the cross-linkers used, cleavable agents deserve special attention. In situations when the activity of fully cross-linked crystals toward macromolecular substrates remains low (see Section 3.2), one can design CLPCs that remain intact and stable under one set of conditions, but dissolve with release of activity with time when the environment changes. This can be achieved by varying the degree of cross-linking or by using cleavable cross-linkers.

An interesting example of the latter strategy is shown in Figure 4.^[29] First, the crystals of *Candida rugosa* lipase (CRL) were modified by Traut's reagent (Figure 3) in order to introduce additional SH groups. Then the SH groups were cross-linked with a cleavable homobifunctional agent DPDPB (Figure 3). The fully cross-linked crystals of CRL (CRL-CLECs) have very low specific activity (2.3 U mg^{-1}) compared to the activity of the native soluble enzyme (732 U mg^{-1}) in the olive oil assay. However, after the CRL-CLECs were incubated for one hour with cysteine, the crystals completely dissolved to "release" 85% of the initial activity. The principle of controlled dissolution of CLPCs has been successfully applied in the preparation of subunit vaccines, detergent enzymes, and cosmetics (see Section 4.4.2).

3. Properties of Protein Crystals

3.1. Stability

Chemically cross-linked protein crystals are significantly more stable against denaturation by heat, organic solvents, and proteolysis than the corresponding soluble proteins (Table 1).^[10a, 30] However, the source of protein stabilization remains unclear: it may be a result of the crystallinity of the material, the chemical modification of proteins, or a combination of both. We have recently addressed the question of the physical stability of powder formulations of proteins and have found that crystalline powders of CRL and glucose oxidase are considerably more stable than amorphous proteins.^[31] The crystalline proteins better maintain their native conformation at elevated temperature (see Section 4.4.3) and demonstrate a lower tendency to aggregate. The reason why proteins better maintain their native structure in crystalline

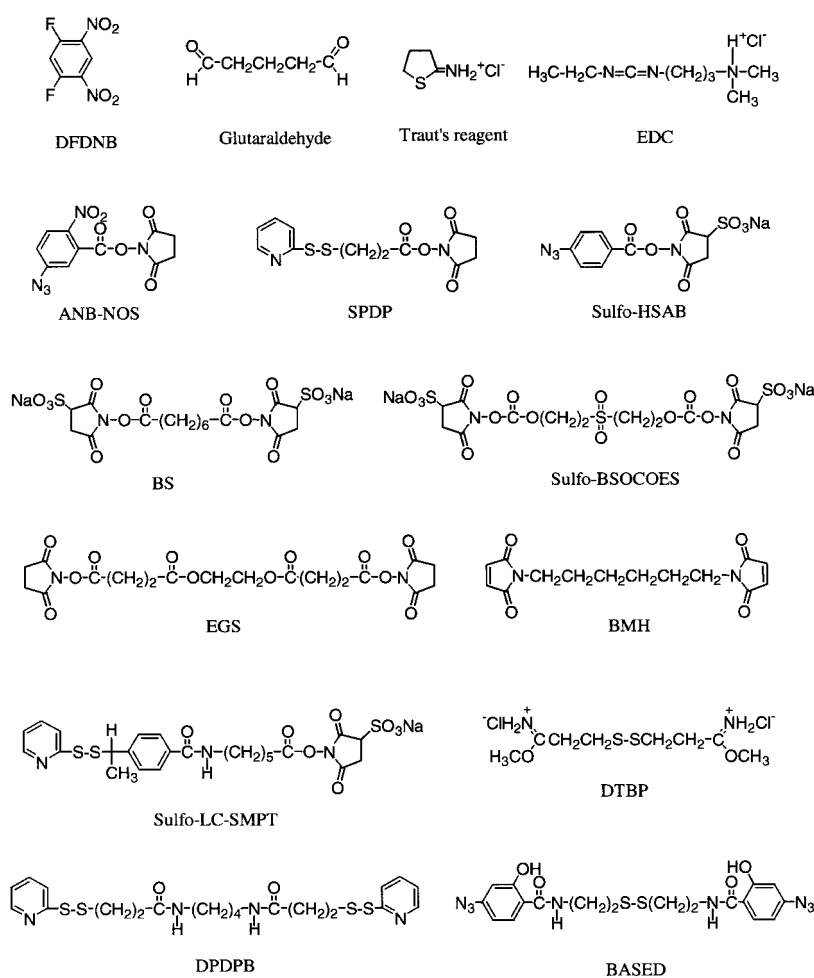


Figure 3. Typical reagents used for cross-linking of protein crystals. DFDNB = 1,5-difluoro-2,4-dinitrobenzene, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, ANB-NOS = *N*-5-azido-2-nitrobenzoyloxysuccinimide, SPDP = *N*-succinimidyl-3-(2-pyridyldithio)propionate, Sulfo-HSAB = *N*-hydroxysulfosuccinimidyl-4-azidobenzoate, BS = bis(sulfosuccinimidyl)suberate, Sulfo-BSOCOES = bis[2-(sulfosuccinimidooxycarbonyloxy)ethyl]sulfone, EGS = ethyleneglycol bis(succinimidylsuccinate), BMH = bis(maleimido)hexane, Sulfo-LC-SMPT = sulfosuccinimidyl-6-[α -methyl- α -(2-pyridyldithio)toluamido]hexanoate, DTBP = dimethyl-3,3'-dithiobispropionimidate $\cdot$ 2 HCl, DPDPB = 1,4-di-[3'-(2'-pyridyldithio)propionamido]butane, BASED = bis-[β -(4-azidosalicylamido)ethyl]disulfide.

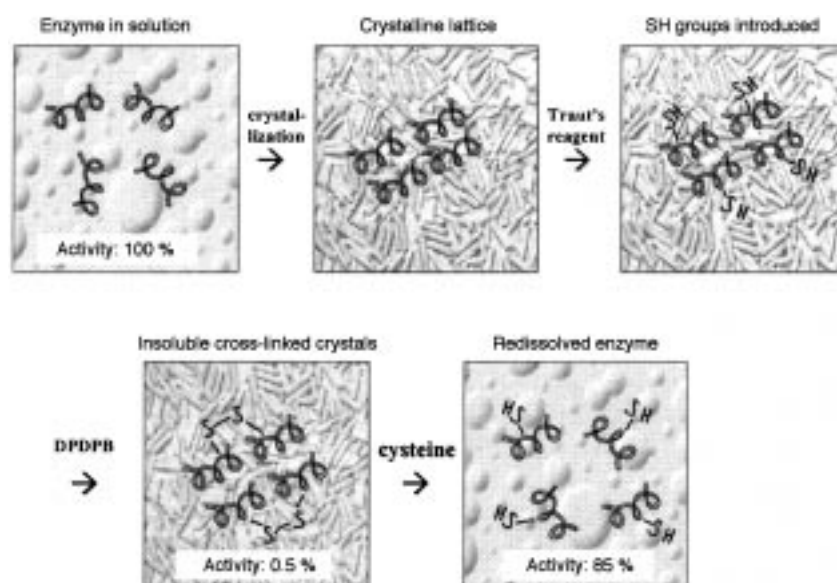


Figure 4. Controlled dissolution of a CLPC that was cross-linked with a cleavable reagent.

Table 1. Stability of cross-linked enzyme crystals.^[a]

Enzyme	Conditions	$t_{1/2}$ (soluble)	$t_{1/2}$ (CLEC)	Ref.
thermolysin	Tris buffer (pH 7.0), 65 °C	6 h	no loss of activity after 5 days	[9]
	50 % THF, DMSO, acetone, 25 °C	1.5–8 h	no loss of activity after 5 days	
	pronase	< 5 min	retains > 95 % activity after 4 days	
alcalase	acetate buffer (pH 5.7), 60 °C	11 h	no loss of activity after 7 days	[110]
	50 % acetone, 40 °C	4 days	no loss of activity after 7 days	
subtilisin	acetate buffer (pH 5.7), 70 °C	< 1 min	> 1 hr	[111]
	autodigestion (pH 8.0), 30 °C	20 h	< 1 % loss after 20 h	[112]
	acetonitrile, 45 °C	0.35 days	31 days	
selenosubtilisin	50 % acetone, 40 °C	< 1 day	no loss of activity after 10 days	[113]
carboxypeptidase A	8 M urea	full inactivation	no inactivation	[114]
<i>Candida rugosa</i> lipase	50 % THF, DMF, DMSO	< 1 h	> 150 h	[25]
penicillin acylase	50 % <i>i</i> PrOH/water, 25 °C	2 h	20 % activity loss after 4 days	[115]
rabbit muscle aldolase	phosphate buffer, RT	1–5 days	no loss of activity after 6 months	[116]
lactate dehydrogenase	buffer, 25 °C	2.5 days	< 10 % loss of activity after 25 days	[117]
alcohol dehydrogenase	buffer (pH 6–8), 30 °C	< 15 days	no loss of activity after 90 days	[118]
glucose isomerase	45 % glucose/fructose solution (pH 7), 77.5 °C	71 min	407 min	[119]

[a] Tris = tris(hydroxymethyl)aminomethane, DMSO = dimethylsulfoxide, THF = tetrahydrofuran, DMF = *N,N*-dimethylformamide.

form lies in the unique properties of the crystalline state. Protein crystals are highly ordered three-dimensional arrays of molecules where the position of each molecule in space is well defined.^[32] In contrast, typical amorphous solids do not possess a long-range order and, thus, have physical properties quite different from the crystalline state. The greater free volume and molecular disorder of amorphous materials make them more similar to the liquid state and result in overall lower stability relative to the crystalline state.^[33]

When a protein transfers from a solution to a crystalline environment a significant part of its surface becomes inaccessible to solvent. The loss in accessible surface area depends on the size of a protein and varies from roughly 10 to 60 %.^[34] These buried parts of protein molecules form additional intermolecular contacts. Protein–protein contacts in crystals have been analyzed for hundreds of proteins and many crystal forms.^[35] A typical pairwise interface for a monomeric protein has an area of 570 Å², involves 10 amino acid residues of each partner, and contains 30 van der Waals contacts.^[36] The numbers vary widely according to the protein size and its crystal form, but the buried surface area may reach more than 2000 Å² and there may be 100 amino acid residues per contact. These new intermolecular contacts that are formed between proteins on crystallization, whether they present hydrogen bonds, hydrophobic interactions, or salt bridges, will reduce mobility and slow down the unfolding of a protein molecule. Indeed, it is widely accepted that there is only a marginal preference (of roughly 40 kJ mol^{−1}) for the native conformation of a protein over the unfolded one. As such, a single additional hydrophobic interaction (2–26 kJ mol^{−1}) or several polar contacts can increase the half-life of a protein by several orders of magnitude.^[37]

It is worth mentioning that the size of the crystal rarely affects the protein stability. This can best be rationalized by considering the relative proportion of “internal” unit cells in the small prenuclear complexes, in a typical crystalline nucleus, in a small crystal suitable for formulation as a CLEC, and finally, in a macroscopic crystal suitable for X-ray diffraction analysis. An internal unit cell would be one that is entirely surrounded by the full complement of intermolecular interactions used to assemble a macroscopic crystal.

Other, “external” unit cells would be missing one or more of those interactions; this would be the case for unit cells on the surface of a nascent crystal. Table 2 shows the relative proportion of internal versus external unit cells in the four stages of crystal growth mentioned.

Table 2. The effect of crystal size on the proportion of repeating unit cells in the crystal interior.^[a]

Object	Size	Number of unit cells		
		total	interior	fraction
unit cell	1 nm × 1 nm × 1 nm	1	1	0 %
prenuclear complex	3 nm × 3 nm × 3 nm	27	26	3.7 %
crystalline nuclei	5 nm × 5 nm × 10 nm	125	75	40 %
small crystal	1 μm × 1 μm × 2 μm	2 × 10 ⁹	3 × 10 ⁶	> 99.9999 %
large crystal	100 μm × 100 μm × 200 μm	2 × 10 ¹⁵	3 × 10 ¹⁰	> 99.9999 %

[a] The calculations are based on the tetragonal unit cell of the serine carboxypeptidase II structure (space group: *P*4₁2₁2; unit cell dimensions: *a* = *b* = 98.6 Å, *c* = 210 Å, $\alpha = \beta = \gamma = 90^\circ$).^[13]

Unit cells in the interior of a crystal are fully engaged in the intermolecular interactions observed through the crystal and are optimally stabilized by those interactions. Once one gets past a modest number of unit cells, most of the protein material in the crystal is internal, and the characteristics of that state would then presumably dominate the observed character. For even the smallest CLECs, the proportion of stabilized unit cells approximates 100 %, for all intents and purposes, as is the case for the much larger crystals that are used in macromolecular structure determination by X-ray diffraction.

3.2. Enzyme Activity

The specific intermolecular interactions that account for increased stability of proteins in the crystalline state may also limit the flexibility and “breathing” of protein molecules and dramatically reduce their activity.^[38] Three major factors—size of the crystal, size of the substrate, and conformation of the enzyme in the crystal—control enzymatic activity in the crystalline state.

In many cases the full activity of an enzyme crystal cannot be realized because of mass-transfer limitations. The problem of diffusional limitations in the crystalline state has been addressed in several publications.^[39] The critical crystal thickness (d_c ; the crystal thickness below which diffusional limitations are not significant)^[40] depends, as given by Equation (1), on the kinetic parameters k_{cat} and K_m of the enzyme, the enzyme concentration $[E]$, and the diffusion coefficient of the substrate D_{eff} in the crystal.

$$d_c = (D_{eff}K_m/k_{cat}[E])^{1/2} \quad (1)$$

The critical thickness for crystals of relatively slow-acting hydrolases was found to be of the order of several microns. For the fast reactions, however, d_c is estimated to be close to the thickness of the unit cell.^[41] One has to keep in mind that while even relatively large crystals may be free of diffusion limitations, normally there is a good correlation between the crystal size and reaction rate (Table 3).

Table 3. The effect of particle size on enzyme activity.

Enzyme	Particle size [μm]	CLEC activity [μmol min ⁻¹ per mg of protein]	Activity ^[a] [%]
alcalase	40	5	24
	1.2	16	76
penicillin acylase	142	5	21
	57	17	71

[a] Activity relative to the native enzyme.

From a practical standpoint it is important to realize that there are no diffusional limitations as long as the substrate concentration is higher than K_m , which is often the case at the beginning of the enzyme-catalyzed process. As the substrate concentration drops below K_m during the course of the reaction, mass-transfer effects lead to reduced activity of the crystal.^[42]

The size of a substrate may dramatically affect the reaction rate. While in principle large molecules, such as casein (M_r 24 000), the insulin B chain (M_r 3500^[24]), cytochrome c (M_r

12 000^[43]), and polyethylene glycol (M_r up to 10 000^[74]), may, at least partially, diffuse through the pores of protein crystals, the reaction rates are normally lower (Table 4).

The third major parameter affecting the activity of crystalline catalysts is the enzyme's conformational flexibility in the crystalline state. In many cases the activity of crystalline enzymes was significantly lower than that of enzymes in solution even when diffusion limitations had been excluded (Table 5). It is possible that in some crystal forms the active sites of enzyme molecules are occluded and, therefore, inaccessible to the substrate. These problems can, in principle, be addressed by producing different crystal forms of the same enzyme.

Lipases present an interesting example in this regard. Lipases are considered to have two important states, defined by the position of the "lid"—a flexible structural element that moves to allow substrate binding to the active site.^[44] Although it is well known that lipases exhibit 10³–10⁴-fold increases in activity when their natural substrates, such as lipids, are present as an emulsion,^[45] the need for interfacial activation does not seem to be necessary in the hydrolysis of more water-soluble or small synthetic substrates.^[12] We prepared CRL-CLECs in both "open"^[46] and "closed"^[47] crystal forms and compared their activity and enantioselectivity in the resolution of ketoprofen (Figure 5). The activity of the "open" form was almost three times higher than that of the "closed" form. In addition, the "open" form exhibited higher enantioselectivity.

In certain cases the enzyme crystal may even be more active than the same enzyme in solution. For example, CLECs of lipases and subtilisin formulated with surfactants exhibited specific activity in organic solvents higher than that of native enzymes.^[48] An even more striking result has recently been achieved in our laboratory. Crystals of CRL cross-linked with sulfo-LC-SMPT (Figure 3) were five to seven times more active than pure native CRL in the olive oil assay.^[49] Interestingly, the same modification of the soluble enzyme did not produce an increase in enzyme activity. Apparently, the chemical modification of CRL in a crystal occurs differently from that in solution.

Table 4. Activity of cross-linked enzyme crystals towards large substrates.

Enzyme	Substrate	Particle size [μm]	CLEC activity [μmol min ⁻¹ per mg of protein]	Activity ^[a] [%]
subtilisin	azocasein	1.2	9.2	35
thermolysin	oxidized insulin B-chain	35	0.44	4

[a] Activity relative to the native enzyme.

Table 5. Activities of cross-linked enzyme crystals.

Enzyme	Substrate	k_{cat} ratios ^[a]	K_m ratios ^[a]	k_{cat}/K_m ratios ^[a]	Ref.
carboxypeptidase A	BzGly-Phe ^[b]	17	0.11	155	[120]
	BzGly-OPhe ^[b]	48	0.04	1200	
carboxypeptidase B	BzGly-Arg ^[b]	17	0.03	570	[121]
	BzGly-OArg ^[b]	150	0.17	1470	
phosphorylase A	glucose-1-P	179	1.2	149	[122]
phosphorylase B	glucose-1-P	57	1	57	[122]
subtilisin	tosylArg-OMe (TAME) ^[b]	4.5	2.2	2.1	[111]

[a] Ratios given for native enzyme/CLEC enzyme. [b] Bz = benzyl, tosyl = toluene-4-sulfonyl.



Figure 5. Stereoview of the Ca tracing of *Candida rugosa* lipase (CRL). The serine, histidine, and glutamic acid residues that constitute the catalytic triad for CRL are labeled as S209, H449, and E341 in the figure. The helical lid is depicted in thick lines, with the closed conformer in white lines and the open one in grey. Produced from data supplied in refs. [13] and [14] and the Brookhaven Protein Data Bank (P. Grochulski and M. Cygler, <http://www.pdb.bnl.gov/>, files "1crl" (open form) and "1trh" (closed form)). Reprinted with permission from ref. [124]. Copyright (1997) Academic Press.

4. Applications

After protein crystals are prepared, they may be formulated in three major ways (Figure 6). First, they may be fully cross-linked by multifunctional reagents to produce CLPCs or CLECs that remain completely insoluble in various media and can be recycled many times. Second, protein crystals may

be cross-linked in such a way that they will dissolve in response to a change in the environment, such as a pH, temperature, or concentration change. Finally, protein crystals may be transferred to a different solvent where they remain insoluble without chemical modification, or they can simply be dried. This formulation flexibility allows for several interesting applications. The first applications we will consider are those for CLECs.

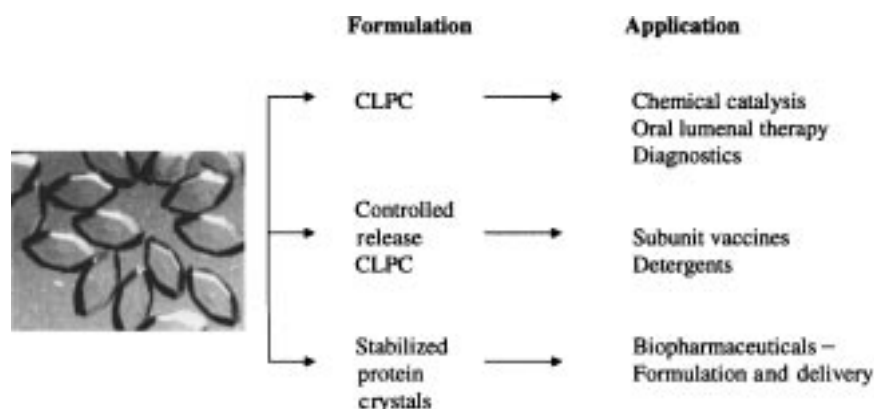


Figure 6. Three major routes for protein crystal formulation and their most important areas of application.

be cross-linked in such a way that they will dissolve in response to a change in the environment, such as a pH, temperature, or concentration change. Finally, protein crystals may be transferred to a different solvent where they remain insoluble without chemical modification, or they can simply be dried. This formulation flexibility allows for several interesting applications. The first applications we will consider are those for CLECs.

4.1. Synthetic Chemistry

Among the often-cited explanations for poor acceptance of enzymes by the chemical industry, such as high cost, limited substrate specificity, and low enantioselectivity for unnatural synthetic substrates, the main reason is clearly the lack of enzyme stability at elevated temperatures and under process conditions. The well-known strategies for stabilizing enzymes include protein engineering, use of enzymes from extreme environments (extremozymes),^[50] immobilization,^[51] chemical modification,^[52] and CLECs.^[30]

One of the advantages of CLEC catalysts is that, in many cases, the enhancement of enzyme stability can be achieved without loss of the specific activity. At the same time, CLEC catalysts may have significantly enhanced stability and productivity in both aqueous and organic media. CLECs remain insoluble throughout the process and can be recycled many times, which increases the productivity of the catalysts. In addition, in some cases the CLEC catalysts can be significantly more enantioselective than the crude mixture of enzymes, an effect that was demonstrated in the resolution of profen drugs.^[25]

4.1.1. Resolution of Racemates with Hydrolases

Several substrates for CLEC-catalyzed enantioselective transformations are presented in Figure 7. The protease subtilisin is broadly used in organic synthesis for enantio- and regiospecific reactions, amide bond syntheses, and hydrolyses in both aqueous and organic solvents.^[53] The synthetic utility of this catalyst in organic chemistry is limited by two major problems: 1) low stability in water (mostly due to autolysis) and water-miscible organics,^[54] and 2) low activity in neat organic solvents. Autolysis not only reduces the life of the catalyst, but it also makes separation and purification of the reaction

products time consuming and expensive. This problem is especially serious in the synthesis of peptides and pharmaceuticals, where the requirements for product purity are very high. In turn, the low activity of subtilisin in neat organic solvents makes various processes too slow and economically unfeasible.^[55]

Subtilisin-CLECs have shown high enantioselectivity in the resolution of amino acid esters and many organic molecules.

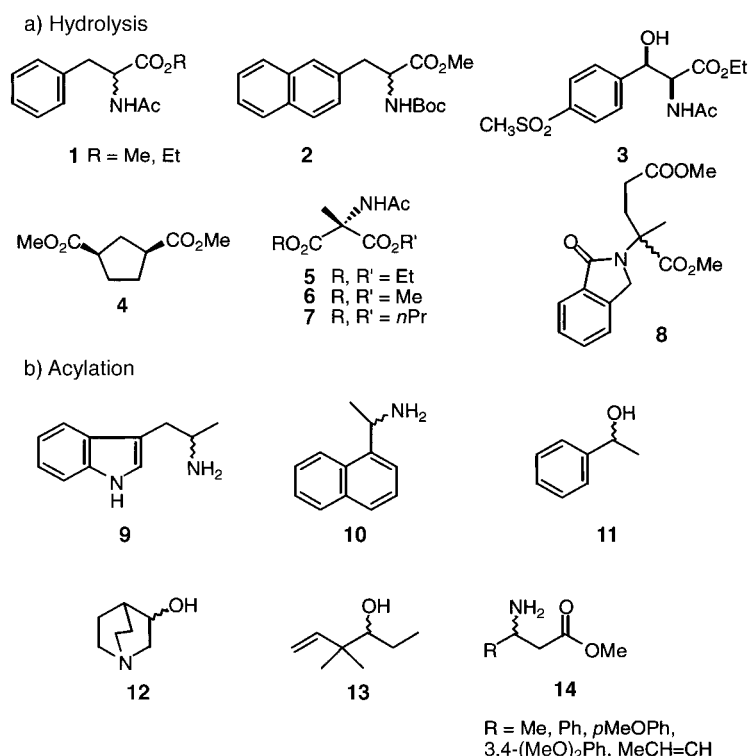


Figure 7. Substrates for CLEC-catalyzed enantioselective hydrolyses (a) and acylations (b). Ac = acetyl, Boc = *tert*-butoxycarbonyl.

Both natural and unnatural amino acids were effectively resolved by this catalyst (Figure 7).^[110] The *N*-Acetyl phenylalanine methyl ester (**1**, R = Me) was hydrolyzed to give L-acid product and D-ester residue with enantiomeric excess (*ee*) values of 96% and >99%, respectively. The unnatural amino acids, *N*-Boc-3-(2'-naphthyl)alanine methyl ester (**2**) and *threo*-*N*-acetyl- β -hydroxy-*p*-methylsulfonylphenylalanine ethyl ester (**3**) were also resolved by this catalyst with high enantioselectivity. The *meso*-diester **4** was enantioselectively hydrolyzed to give the monoester with an *ee* value of 96%. The prochiral diethyl ester **5** was enantioselectively hydrolyzed to give the corresponding monoacid in 97% yield and with 81% *ee*. It is well known that the size of the group near the stereogenic center affects the enantioselectivity in the enzymatic resolution. Therefore, methyl ester **6** and propyl ester **7** were prepared from **5** and hydrolyzed with subtilisin-CLECs. The enantioselectivities for the formation of the corresponding monoacids of **6** and **7** were not significantly different to the result obtained in the hydrolysis of **5**. Another interesting example of enantioselective hydrolysis with the subtilisin-CLEC catalyst was the preparation of analogues of thalidomide (**8**). Both enantiomers were isolated with 95% *ee*.^[56]

Since the subtilisin-CLECs were active and stable in neat organic solvents, the catalyst was used to perform the resolution of alcohols and amines in such solvents (Figure 7).^[110] α -(1-Naphthyl)ethylamine (**10**) was resolved to give corresponding butyramide and remaining amine with *ee* values of 98% and >98%, respectively.^[18b] α -Methyltryptamine (**9**) was resolved to give the *R* amine with an *ee* value of >98% at 53% conversion; the enantiomeric excess of the

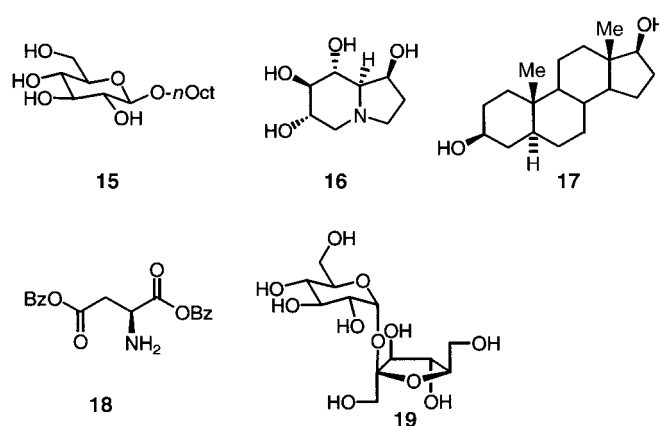
amide product was 94% at 20% conversion. When 1-phenylethanol (**11**) was transesterified by this catalyst, the enantiomeric excesses of the ester product and remaining alcohol were 92% and 40%, respectively, at 30% conversion. The same catalyst was successfully used in enantioselective acylation with vinyl butyrate of racemic 3-quinuclidinol (**12**) in 2-methyl-3-butanol. The *R* enantiomer was obtained in 68% yield and with 96.2% *ee* after crystallization.

The natural products epothilones A and B are structurally very different from taxol but have similar anticancer activity. Significantly, they have been reported to be much more active against cell lines exhibiting multidrug resistance.^[57] Taylor et al. have recently published an elegant, formal total synthesis of epothilone A.^[58] In this work the authors used the cross-linked crystals of *Pseudomonas* (now *Burkholderia*) *cepacia* lipase (ChiroCLEC-PC) to resolve a key alcohol intermediate **13** by selective acylation with vinyl acetate in *tert*-butyl methyl ether. The enantioselectivity was >20:1 at 47% conversion and efficiently provided gram quantities of the desired *R* alcohol. Since the unreacted *S* alcohol can easily be epimerized by a simple oxidation/reduction sequence and the catalyst reused without significant loss in activity, the method is ideally suited for scale-up.

Among other catalysts, CLECs of penicillin acylase were used for the resolution of racemic β -amino acid esters **14** for the preparation of peptidomimetics. The desired *S* enantiomers were obtained with >95% *ee* in 2% aqueous toluene.^[59]

4.1.2. Regioselective Reactions

Subtilisin-CLECs exhibited excellent regioselectivity toward many polyfunctional molecules.^[110] The 6-hydroxy group of *O*-*n*-octyl- β -D-glucopyranoside (**15**) was selectively reacted



with *N*-Cbz-Phe-OBz to give the peptido-sugar (Cbz = benzyloxycarbonyl, Bz = benzyl). The 3-hydroxy group of castanospermine (**16**) and 17-hydroxy group of 5 α -androstane-3 β ,17 β -diol (**17**) were selectively esterified to give their corresponding monoesters. On the other hand, the α -ester

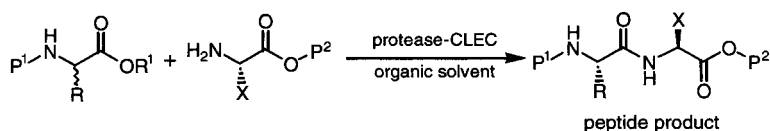
of aspartic dibenzyl ester (**18**) was selectively hydrolyzed to give the corresponding monoacid in 97% yield. Linhardt and co-workers recently published the synthesis of a series of 1'-*O*-acyl sucrose derivatives **19** with use of the same catalyst.^[60] The authors prepared 1'-*O*-lauryl sucrose, 1'-*O*-myristyl sucrose, and 1'-*O*-stearyl sucrose in 80–90% yields. Their method represents a “green” alternative to the organotin chemistry previously used.^[61]

4.1.3. Synthesis of Peptides and Peptidomimetics

Several protease-CLECs have been successfully used for the synthesis of peptides and for mild hydrolysis of amino acid and peptide amides.^[62, 110] Subtilisin-CLECs effectively catalyzed the synthesis of peptides with > 90% yield by accepting both L- and D-amino acid amides as nucleophiles. Thermolysin-CLECs were efficient in the synthesis of several peptides in 90% EtOH and were used in a multicycle preparation of aspartame in ethyl acetate.^[24]

One of the most interesting applications of protease-CLECs is in the synthesis of chiral alkyl amides. Chiral alkyl amides of peptides and amino acids are important building blocks of many marketed and potential pharmaceuticals, such as HIV protease inhibitors, enkephalins, and antibiotics. In chemical procedures, the processes of coupling and resolution are usually separated: First optically pure components are prepared, then the coupling is performed. Despite significant recent advances in both solution- and solid-phase peptide chemistry,^[63] the preparation of peptides on large scale often suffers from partial racemization, modest yield, and the difficulties of removing by-products produced during coupling reactions; dicyclohexyl urea, which arises from the commonly used dicyclohexylcarbodiimide (DCC), is a particularly troublesome example.^[64, 65]

We found that the use of optically pure substrates was not necessary. The high enantioselectivity of the catalyst toward L-amino acids and S-amines resulted in formation of the *S,S*-alkylamide regardless of the optical purity of the substrates (Scheme 1). Indeed, optically pure alkylamides were obtained by in situ resolution when *R,S*-amines, or even both *R,S*-amines and *R,S*-amino acids, were used. In the latter case, the diastereomeric excess of product was greater than 98% (Table 6).^[62, 110] The same approach was used in the synthesis of single-isomer matrix metalloprotease inhibitors (MMPis) D1927 and D2163 with thermolysin-CLECs. In these cases, the key molecular structure and a final element of asymmetry were introduced through a PeptiCLEC-TR-mediated amide bond formation between a free carboxylic acid ($R^1 = \text{H}$ in Scheme 1) and an amine.^[66]



Scheme 1. Synthesis of peptides and peptidomimetics catalyzed by protease-CLECs.

4.1.4. Dehydrogenases

One of the major advantages of enzyme-catalyzed reduction of carbonyl groups in ketones and aldehydes over the use of hydrolases in the synthesis of chiral compounds is the potentially higher product yields. Indeed, by exploiting the prochiral character of carbonyl groups, the formation of racemic intermediates can be avoided.^[67]

Unlike hydrolytic enzymes, dehydrogenases require cofactors, such as NAD(P)H, flavins, or PQQ, that need to be regenerated in situ (NAD(P)H = nicotinamide adenine dinucleotide (phosphate), reduced form; PQQ = pyrroloquinolinequinone tricarboxylic acid). Unlike other cofactors, nicotinamide cofactors are not tightly bound to dehydrogenases and can easily dissociate into solution. If, however, NADH is cocrystallized with a dehydrogenase, the cofactor remains tightly bound to the enzyme and can be recycled inside the complex by a coupled substrate system. This idea was first introduced by Lee et al.,^[68] who demonstrated good activity (26% of that in solution) for crystals of horse liver alcohol dehydrogenase (HLADH) and increased stability of the cross-linked crystals in the presence of zinc salts. By using this system we demonstrated that the HLADH-NAD(H)-CLEC system exhibited high activity (64% of that in solution) without addition of exogenous NADH.^[118] This complex was applied to the reduction of additional ketones **20–24** (Figure 8). The enantioselectivity and stereochemical preference

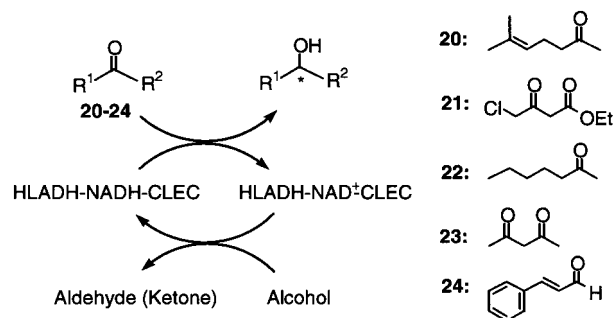


Figure 8. HLADH-catalyzed transformations.

of the HLADH-NAD(H)-CLEC complex were the same as those of the soluble enzyme. Given the fact that the HLADH-NAD(H)-CLEC complex is significantly more stable than

Table 6. Synthesis of peptidomimetics.^[a]

Carboxylate	Amine	Product	Solvent	Yield [%]	de [%]
(<i>S</i>)-Z-PheOBz	(<i>R,S</i>)-Me-tryptamine	(<i>S,S</i>)-Z-Phe-Me-tryptamine	MeCN	> 98 %	> 98
(<i>R,S</i>)-Z-PheOBz	(<i>R,S</i>)-Me-tryptamine	(<i>S,S</i>)-Z-Phe-Me-tryptamine	MeCN	95	> 98
(<i>S</i>)-NAcLeuOMe	(<i>R,S</i>)-NapEt	(<i>S,S</i>)-NAcLeuNapEt	3MP	66	91
(<i>S,S</i>)-Z-AlaSerOMe	(<i>R,S</i>)-NapEt	(<i>S,S,S</i>)-Z-AlaSerNapEt	MeCN	98	> 98

[a] NapEt = 1-naphthylethylamine, 3MP = 3-methylpyridine.

either HLADH or NADH, we concluded that not only the enzyme but also the cofactor was protected by the crystal environment. Further work will show whether the cofactor will stay tightly bound in the CLEC of other dehydrogenases without dissociation.

A different approach (crystallization of lactate dehydrogenase without a cofactor) was used by Sobolov et al. to prepare L-lactic acid from pyruvic acid in an electrolytic cell.^[69] This catalyst maintained constant activity over 25 days and was much less sensitive to pH than the soluble enzyme.

4.1.5. Other Enzymes

In addition to hydrolases and dehydrogenases, several other enzymes, such as glucose isomerase,^[70] fructose diphosphate aldolase,^[116] and hydroxynitrile lyase^[71] have been crystallized, cross-linked, and used as catalysts for chemical transformations. The synthetic potential of the aldolase and hydroxynitrile lyase was demonstrated by the preparation of a series of model compounds.

4.1.6. Productivity

A deciding factor in the evaluation of any catalyst is its productivity—how many kilos of product can one make with one kilo of catalyst? High specific activity and stability of CLEC catalysts in challenging environments, such as in organic solvents, in aqueous–organic mixtures, at elevated temperature, or under high-shear conditions, result in increased catalyst productivity. A good example of the high productivity of CLEC catalysts in organic solvents is the resolution of 1-phenylethanol with vinyl acetate in toluene catalyzed by cross-linked enzyme crystals of *Pseudomonas cepacia* lipase (LPS-CLECs).^[72] In this reaction 1 mg of catalyst produces more than 4.6 g of product (with 98.5% ee), to give a volumetric productivity of 30 g L⁻¹ and a substrate to catalyst ratio of 4600. The high productivity of low molecular weight synthetic catalysts is thought to be their key advantage over high molecular weight enzymes.^[73] This example clearly demonstrates that, despite the high molecular weight and quite unusual reaction medium for an enzyme, a CLEC can be highly productive and can compare favorably even with the best synthetic asymmetric catalysts.

In the very important therapeutic class of antibiotics, both 6-aminopenicillanic acid (6-APA) and 7-aminodeacetoxycephalosporanic acid (7-ADCA) are being produced today on a multiton scale using the cross-linked crystal form of penicillin-G amidase (SynthaCLEC-PA). The stability of enzymes in

the cross-linked crystal form is again clearly demonstrated by the multicycle pilot reaction run for the hydrolysis of penicillin-G (Figure 9). Other examples of CLEC recycling are presented in Table 7.

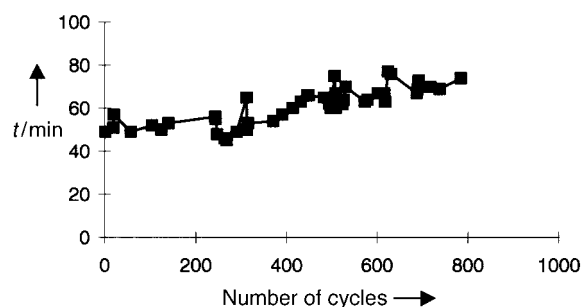


Figure 9. Multicycle hydrolysis of penicillin G. Penicillin G (8%) was hydrolyzed at pH 8 and 28 °C with stirring in a 150-mL filtration cell equipped with 10- μ m filter. After completion of each cycle the reaction mixture was drained and fresh substrate was added to the cell. A constant pH value was maintained by addition of NH₄OH.

4.2. Protein Crystals as Bioorganic Zeolites

Protein crystals have several common features with inorganic crystalline materials such as zeolites. Both are crystalline microporous materials with a uniform pore-size distribution that is fixed by arrangement of their unit cells.

With the method of macromolecular porosimetry we have estimated the apparent pore sizes and pore-size distributions in solid and soft hydrated porous sorbents directly from size exclusion chromatography (SEC) results. According to this method, CLPCs offer a wide range of pore sizes (15–100 Å), porosities (0.5–0.8), and pore surface areas (800–2000 m² g⁻¹).^[74] The experimental data on the porosities of CLPCs are in good agreement with theoretical estimates of solvent content that are based on available crystallographic information for thermolysin and lipases. The solvent content of typical protein crystals is comprised of solvent-filled channels that take up 30–65% of the total crystal volume.^[75] Pore-size calculations based on a cylindrical pore model gave a narrow and symmetrical pore-size distribution for all the CLPCs studied, with a calculated range of pore diameters that differ by less than 10% from the average. One should keep in mind, however, that the channels within protein crystals have quite complicated structures and can hardly be described by a simple cylindrical model. Indeed, as a stereo image of the crystalline lattice of CRL (Figure 10) suggests, a net of

Table 7. Recycling of cross-linked enzyme crystals.

Enzyme	Reaction	Medium	Number of cycles	Reference
subtilisin	resolution of α -methyltryptamine	3-methyl-3-pentanol	7	[110]
selenosubtilisin	reduction of hydroperoxides	aqueous	10	[113]
<i>Candida rugosa</i> lipase	resolution of ketoprofen	50% PEG 1000	18	[25]
alcohol dehydrogenase	reduction of cinnamaldehyde	aqueous	column	[118]
glucose isomerase	production of high-fructose corn syrup	aqueous	column	[123]
hydroxynitrile lyase	synthesis of cyanohydrins	butylether	5	[71]
penicillin acylase	hydrolysis of penicillin G	aqueous	1000	[115]

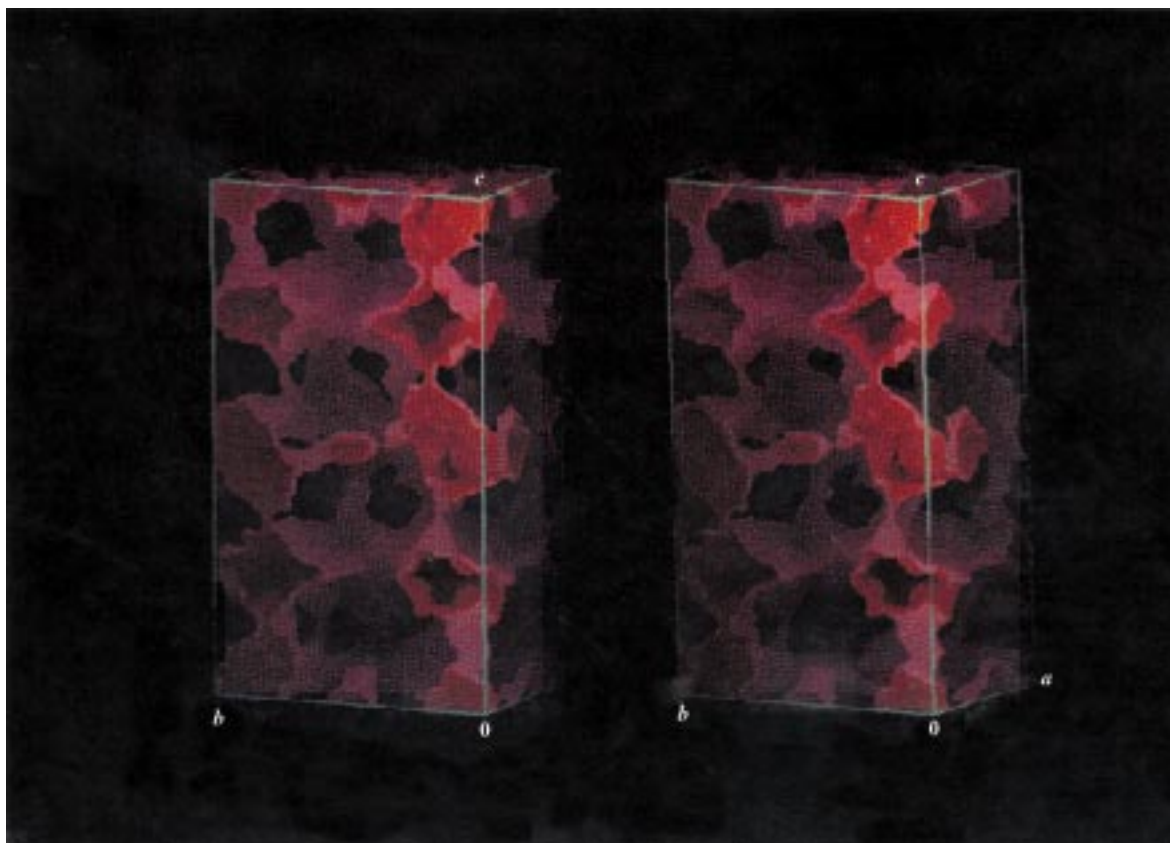


Figure 10. Stereoimage of one unit cell of the crystal lattice of *Candida rugosa* lipase (open form).^[46] In this picture, the enzyme molecules that constitute the lattice, have been removed and only the surface of the solvent channels has been contoured, with the solvent side of the channels in orange and the protein side in violet. Reprinted with permission from ref. [74]. Copyright (1998) American Chemical Society.

channels with narrow connecting necks is seen to traverse the crystal unit cell (and hence, the crystalline macroscopic sorbent particles). The channels are predominantly in the direction of the crystallographic *a* axis, with significant cross-channels along the crystallographic *b* axis. Far narrower channels can be seen along the *c* axis.

In a sense, protein crystals represent a distinct and unique class of molecular sieves, with a pore-size range from 20 to more than 100 Å in diameter (Figure 11). The width and linearity of the solvent channels depends in large part on the way the molecules pack in a particular space group. For example, crystals of human superoxide dismutase (Figure 11F) have wide solvent channels that directly traverse the crystal, whereas molecules of superoxide dismutase from *Xenopus laevis* form crystals with tighter packing and solvent channels that are relatively narrow and convoluted (Figure 11A).

While zeolites are much more stable thermally, protein crystals may offer more control over pore size, porosity, and chemical properties of the pore surface. A distinct advantage of protein crystals over other porous materials is the inherently chiral nature of protein molecules. The L-amino acids that make up proteins create an asymmetric environment that can be exploited in the separation of enantiomers and in catalysis. Furthermore, one can modify the micro-environment of these crystal channels (with respect to both charge and hydrophobicity) by well-known techniques of

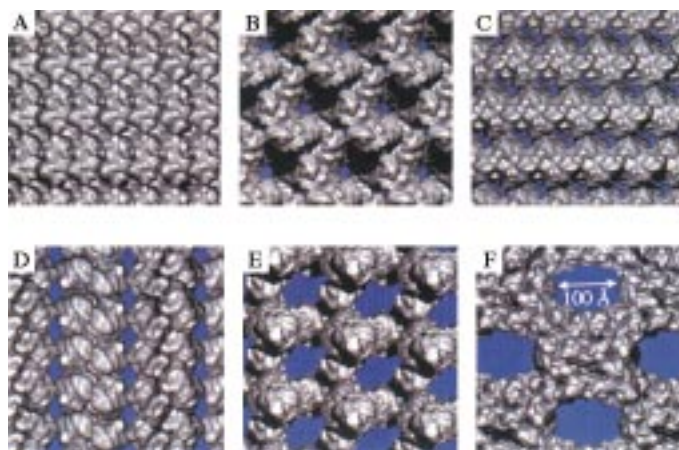


Figure 11. Computer-generated images of six enzyme crystal lattices. The surface representation for each was computed from the electron density that was calculated using coordinates from the corresponding solved crystal structures, which are deposited in the Brookhaven Protein Data Bank.^[103] The contouring isovalues were chosen to yield a surface whose enclosed volume approximates that of the molecule. The solvent channels are shown in blue. The corresponding coordinate file name and reference are given for each entry: A) 1XSO, superoxide dismutase (*Xenopus laevis*); B) 8TLN,^[104] thermolysin (*Bacillus thermoproteolyticus*); C) 1PNL,^[105] penicillin acylase (*Escherichia coli*); D) 1CRL^[28] lipase (*Candida rugosa*); E) 1WHS,^[106] carboxypeptidase W (wheat germ); F) 1SOS,^[107] superoxide dismutase (human recombinant). All structures are shown on the same scale; the bar corresponding to 100 Å establishes the absolute scale of the figure. Reprinted with permission from ref. [74]. Copyright (1998) American Chemical Society.

protein chemistry or by crystallization of modified recombinant proteins expressly designed for this purpose.

In addition to catalysis, one of the most direct and immediate applications of CLPCs is in the area of chromatography.^[74] For example, thermolysin-CLECs (rodlike particles, 7 μ in length) provide good separation capability through at least three different mechanisms: size exclusion (Figure 12A), adsorption (Figure 12B), and enantiomeric separation (Figure 12C–D). As discussed above, CLPCs

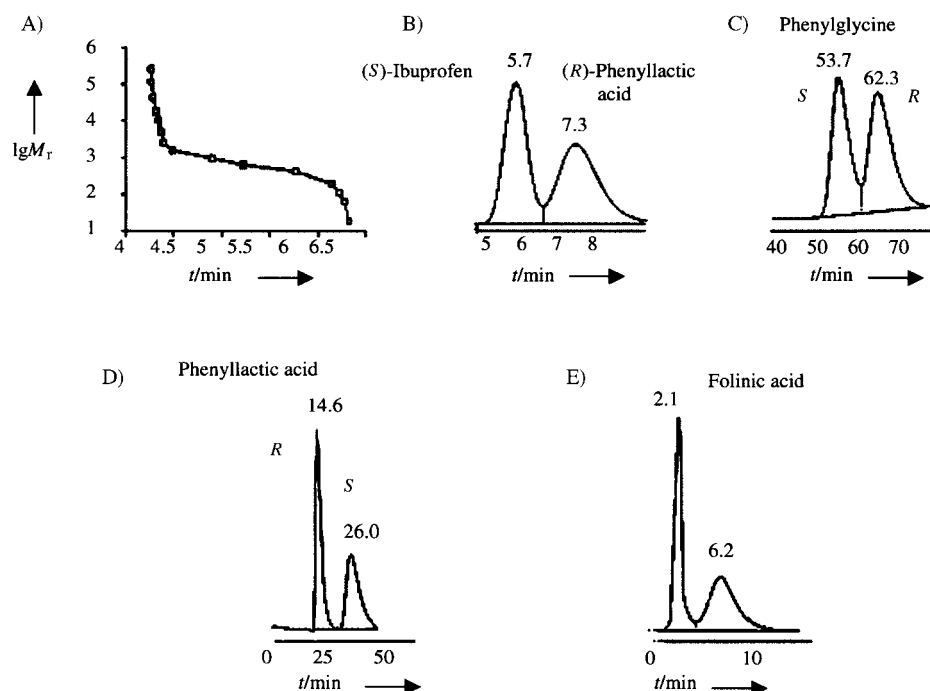


Figure 12. CLPC as a separation medium. Size-exclusion chromatography with PEG samples ($M_r = 64$ –245 000 Da) (A), and chiral separations on thermolysin-CLEC (B–D) and HSA-CLPC (E) packed columns. PEG = polyethylene glycol. Reprinted with permission from ref. [74]. Copyright (1998) American Chemical Society.

can be considered to be a novel type of bioorganic zeolites. The ability of CLPCs to separate molecules by size may stem from the porous structure of the crystals (Figure 11). In contrast, separation of small molecules by their chemical structure and chirality can be attributed, in turn, to the intrinsic structural diversity and chirality of the protein in the stationary phase. Both thermolysin-CLECs and CLPCs of human serum albumin (HSA-CLPCs) were found to be fairly stable both in column packing (a packing pressure of 1500 psi was applied) and in the chromatography experiments themselves (more than 500 injections were performed without loss of separation efficiency). Furthermore, the repeated changes of eluent from water to 50 % acetonitrile did not influence the efficiency of chiral separations, which also indicates high stability of the stationary phase.

Another interesting example is the purification of xylitol by cross-linked crystals of glucose isomerase.^[76] The authors used the principle of affinity chromatography and demonstrated a separation capacity of approximately 1 kg of xylitol per 500 kg of crystals.

4.3. Environmental Catalysis

One potentially significant application of CLEC-catalyzed processes is the detoxification of pesticides and chemical warfare agents. An efficient biocatalyst for this process, organophosphorous hydrolase (OPH) has been identified,^[77] but its stability and specific activity may not be adequate for these applications. OPH is a homodimeric zinc metalloenzyme with unusually broad substrate specificity. It is capable of hydrolyzing P–O, P–F, P–S, and P–CN bonds in a variety of insecticides and chemical nerve agents and thus making them nonhazardous. The enzyme's activity varies widely from extremely high for the pesticide paraoxon (P–O bond; $k_{\text{cat}} > 5000 \text{ s}^{-1}$) to very low for the chemical warfare agent VX (P–S bond; $k_{\text{cat}} = 0.3 \text{ s}^{-1}$).^[78] Despite its low activity in the latter reaction, OPH is the only VX detoxifying enzyme identified to date.^[79]

Practical applications of OPH in the remediation of chemical warfare agents and other hazardous compounds require enzymes with markedly improved activity and stability in the most challenging media. Given the poor solubility of many of the OPH substrates in water, the high stability of OPH against organic solvents will be particularly desirable.^[80] We have demonstrated that OPH-CLECs in fact provide such stability and are quite active against several model substrates.

The active site of OPH consists of a binuclear metal center that can bind any of several metals including Zn^{2+} , Co^{2+} , Mn^{2+} , Cd^{2+} , or Ni^{2+} .^[81] The nature of the metal in the active site of the enzyme profoundly affects its catalytic activity.^[82] We have demonstrated that metal replacement in the active site of OPH can be successfully accomplished in the CLEC form (Figure 13). The facile metal exchange process supports the notion that CLECs are essentially porous materials with channels traversing the entire body of the crystal to facilitate the transport of small molecules in and out of the crystal. Both Zn^{2+} and Co^{2+} OPH-CLECs were shown to have significant activity towards the common pesticide Demeton-S^[83] and the chemical warfare agent VX.^[84]

4.4. Biomedical Applications

The combination of purity, high stability, and activity that makes enzyme crystals so useful in many chemical applications provides new opportunities in biomedical fields and diagnostics^[125] as well. We will consider three applications that

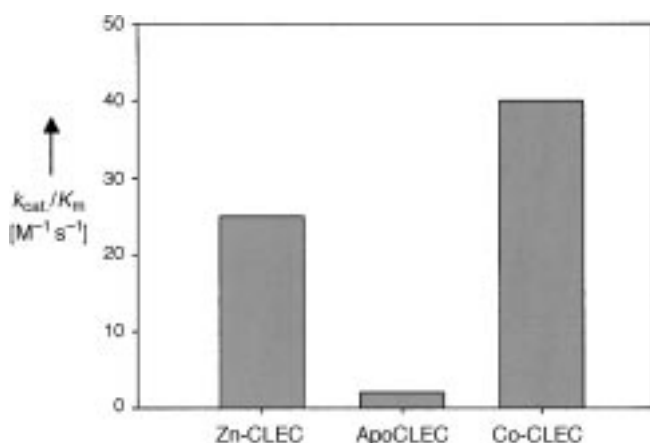


Figure 13. Metal exchange in the active site of OPH-CLECs. Apo-CLEC = the cross-linked enzyme crystals without a metal present.

are based on conventional CLPCs (Figure 6, top), controlled-release CLPCs (Figure 6, middle), and un-cross-linked, stabilized protein crystals (Figure 6, bottom).

4.4.1. Oral Luminal Therapy

Metabolic or gastrointestinal diseases often result from impaired or missing enzyme or protein function at a critical point in a biochemical pathway. For example, some digestive disorders observed with cystic fibrosis or pancreatitis patients can be traced to improper levels of lipase enzymes in the duodenum. Further examples can be found in the disorders resulting from in-born errors in the metabolism. The amino acid metabolism disorder phenylketonuria (PKU) limits patients to a dietary regime that consists largely of phenylalanine-free protein hydrolysates.^[85]

The human gastrointestinal tract presents a challenging environment for proteins due to the acid conditions in the stomach ($pH < 2$) and high concentrations of proteases in the stomach and the gut. For example, less than 1 % of lipolytic activity secreted into the duodenum reaches the ileum.^[86, 87] It is not surprising that porcine pancreatic lipase, the lipase in currently available commercial preparations, rarely abolishes pancreatic steatorrhea caused by chronic pancreatitis or cystic fibrosis.^[88] By virtue of the excellent stability and activity displayed by proteins in the CLEC formulation, such proteins are capable of performing therapeutically beneficial chemistry in the gut lumen without being degraded by extremes of pH or endogenous protease action. Thus, a CLEC therapeutic agent can be orally ingested by a patient and perform the desired therapeutic chemistry in the gut lumen, and then the undegraded CLEC therapeutic agents can be excreted in the stool. Our preliminary results indicate that several lipase-CLECs are at least 100-fold more active and significantly more stable than commercial lipase products. We have also demonstrated the efficacy of certain lipase-CLECs in dogs with pancreatic insufficiency.^[89] In principle, lipase-CLECs could lead to more attractive dosing regimens for these conditions that could significantly reduce the total protein pill and greatly improve patient compliance.

4.4.2. Subunit Vaccines

Subunit vaccines that consist of well-characterized molecules are extremely attractive due to their superior safety profile and ease of manufacture through chemical synthesis or recombinant DNA technology. However, the price one has to pay for these advantages is significant: Subunit vaccines are generally poorly immunogenic and in many cases cannot compete with attenuated and inactivated whole virus or pathogen counterparts.^[90] To enhance the immune response subunit vaccines universally require improved adjuvants and delivery vehicles.

We recently proposed using CLPCs as antigens and compared the immunogenicity of HSA-CLPCs with that of the soluble protein. Crystalline forms induce and sustain 6–10-fold increases in antibody titer for highly cross-linked crystals and approximately 30-fold increase for lightly cross-linked crystals, relative to the soluble protein, in a study of six months duration in rats.^[91] We hypothesized that the depot effect, the particulate structure of the CLPC, and the highly repetitive nature of protein crystals may play roles in the enhanced production of circulating antibodies. Indeed, the highly repetitive structure of a protein crystal results in multiple copies of the antigen presented to the immune system as a part of a relatively large particle (Figure 14). In

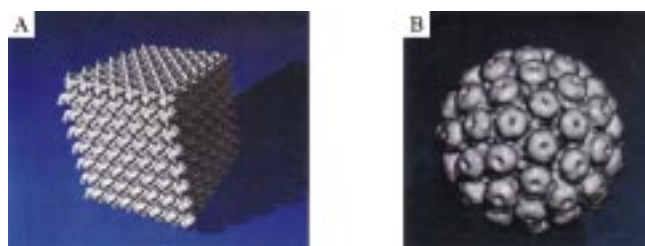


Figure 14. a) Computer-generated image of a three-dimensional HSA crystal. The individual enzyme molecules ($M_r = 66000$) are shown in silver. The crystal has seven unit cells along each edge, hence the dimension of the crystal size is $41.2 \times 62.2 \times 42.5$ nm, and contains 686 HSA molecules in total. The surface representation was computed from the electron density that was calculated using atomic coordinates of the reported structure^[108] obtained from the Brookhaven Protein Data Bank. B) Computer-generated image of a virion of polyomavirus (50 nm) containing 360 VP1 molecules.^[109] Reprinted with permission from ref. [91]. Copyright (1999) National Academy of Sciences, USA.

this respect, CLPCs strikingly resemble polyvalent particulate structures of the hepatitis B surface antigen (HbsAg),^[92] *Helicobacter pylori* urease,^[93] and virus-like particles (VLP).^[94] Several features of CLPCs, such as their remarkable stability, purity, biodegradability, and ease of manufacture make them highly attractive for vaccine formulations. This work paves the way for a systematic study into the effect of protein crystallinity and cross-linking on the enhancement of humoral and cellular responses.

4.4.3. Un-Cross-Linked Protein Crystals

Since dry protein crystals can be quite stable even without cross-linking, they can be used as a unique formulation for drug delivery. Indeed, the value of crystallinity is well

understood for small molecules. The majority of small-molecule drugs are produced in crystalline form. This is not surprising since crystallinity normally results in higher storage stability, purity, and reproducibility in terms of a drug's physical, chemical, and therapeutic properties.^[33] For macromolecule therapeutics the situation is quite different. Among almost 400 biopharmaceuticals^[95] that are either approved or in advanced clinical trials, there is only one product—insulin—that is produced and administered in crystalline form. Yet crystallization of macromolecule pharmaceuticals, particularly proteins, can offer significant advantages:

- protein crystallization can be used to streamline manufacturing process, as in the case with small-molecule drugs,
- a crystal is the most concentrated possible form of protein and can be beneficial for drugs, such as antibodies, which require high doses at the delivery site,
- since the rate of crystal dissolution depends on its morphology, size, and the presence of excipients, crystalline proteins may serve as a convenient carrier-free slow release dosage form (insulin is a good example), and
- the stability of proteins in crystalline form is higher than that of corresponding soluble or amorphous materials.

The inactivation of proteins often starts with a reversible unfolding of a protein molecule followed by an irreversible inactivation that leads to protein aggregation^[96] and, as a consequence, the loss of biological activity.^[97] In order to compare the extent of aggregation in different preparations of glucose oxidase (GO) and CRL, these preparations were incubated at elevated temperatures and reconstituted into aqueous buffers. The insoluble precipitate was filtered out, and the residual soluble protein was investigated by size-exclusion chromatography. The results of these experiments indicate that soluble proteins aggregate quickly by producing poorly soluble precipitates. The comparison of solid formulations indicates that crystalline proteins are less prone to aggregation than their amorphous counterparts. After two days of GO incubation at 50 °C, 73 % of crystalline protein (71 % activity) remains soluble, to give a specific activity for the soluble fraction of 118.6 U mg⁻¹. The amorphous formulation yields a slightly higher amount of the soluble protein (76 %) under the same conditions, but only 27 % activity to give a low specific activity of 57.3 U mg⁻¹. These data point to significant inactivation of amorphous GO under storage. Unlike the soluble GO, which upon reconstitution predominantly consists of a native dimer form (higher insoluble aggregates were removed by ultrafiltration), solid formulations give a mixture of a native dimer and higher soluble aggregates. However, this intermolecular protein aggregation is more profound in the amorphous formulation (36 % native form) than in the crystalline one (67 % native form). The lower tendency of crystalline formulations to aggregate was further confirmed by an experiment with the much more hydrophobic protein, CRL. Indeed, 91 % of the native CRL form (monomer) is preserved in the crystalline formulation versus only 26 % in the amorphous sample (Figure 15).

One potentially significant application of protein crystals lies in protein drug delivery. Inadequate protein stability during encapsulation, storage, and release is one of the major obstacles for successful formulation of polymeric micro-

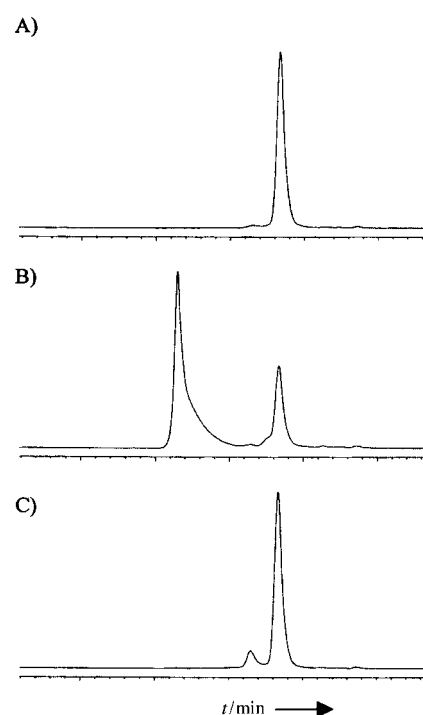


Figure 15. Size-exclusion chromatography of reconstituted CRL formulations. A) Soluble untreated CRL (control). B) Amorphous and C) crystalline CRL formulated with sucrose after 200 days at 40 °C and 75 % RH. The samples were dissolved in phosphate buffered saline (pH 7.4). Reprinted with permission from ref. [31]. Copyright (2001) Wiley Interscience.

spheres.^[98] The high stability of the protein and lower tendency to aggregate in crystalline form of the protein crystals, for example, allow them to better survive the harsh conditions of microencapsulation and to yield polymeric microspheres with higher loading (Figure 16).

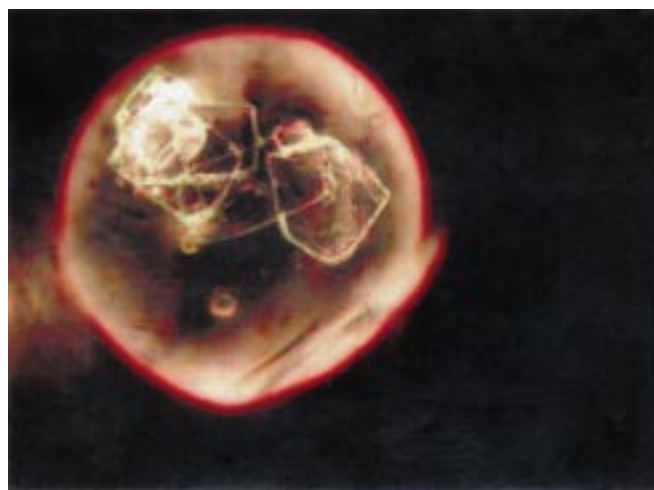


Figure 16. Crystals of penicillin acylase incorporated in the PLGA microspheres.

5. Conclusions and Future Prospects

As is the case with many other developments in technology and science, one can readily identify, in retrospect, roots and

precedents for the cross-linked enzyme crystal technology first outlined in 1992,^[9] and for the further extensions and new implementations of that concept reported since. With hindsight, there are few, if any, technical reasons why Sumner himself could not have developed some of the above-mentioned applications around a jack bean urease in 1926.

One factor that may explain the rapid development and commercialization of CLECs and CLPCs since 1992 is our strongly held view of protein crystals as materials that needed—first and foremost—to be significantly optimized in terms of their underlying chemical and mechanical stability. Having achieved such stability in our cross-linked crystalline materials, we have been free to focus our attention on the introduction of the practical functionality that has proven itself useful in significant real-world applications.

Enzyme catalysts were the logical first step in this development, given that they could bring unprecedented selectivity and specificity to important chemical processes at minimal cost. CLECs have since been developed for a large and diverse panel of uses, as we have discussed in this review.

The theme of stabilized protein crystals as materials extends naturally to their use as novel chromatographic materials that can function repeatedly under the harsh conditions typical of HPLC experiments and that can express the exquisite chirality of their underlying protein matrix. Similarly, the rapid, effective, and economical formulation of protein drugs with unprecedented levels of purity and shelf-life stability is greatly facilitated by this technology, as is the production of vaccines whose immunogenicity is not dependent on the addition of adjuvants and other complicating factors. Additional therapeutic uses for stabilized protein crystalline materials abound and range from protein drug delivery schemes to their use in enzyme replacement therapy.

As we consider the flood of information being produced by the minute through human genome sequencing, we also need to be attuned to the opportunities implicit in the thousands upon thousands of new proteins that will be created for the first time through the expression of that information by proteomics.^[99] This information explosion will undoubtedly speed up the development of massively parallel measurement strategies including high-throughput X-ray crystallography.^[100] Clearly, the ability to crystallize tens of thousands of proteins quickly and inexpensively may lead to a bottleneck in the whole structural genomics initiative.^[101] To this end, advanced methods of robotic automation that are currently being developed will play a key role in monitoring and optimization of crystallization trials.^[102] While the major outcome of this effort will be creation of new structural information, the high-throughput crystallization techniques will benefit the crystallization and formulation methodologies reviewed here.

This nascent science of “crystalomics” provides us with a general strategy for putting proteins, both old and new, to work—rapidly and efficiently—in the harsh conditions typical of most practical industrial processes and in therapeutic interventions of unprecedented power and benefit. Future developments will hopefully be at least as exciting as the advances already achieved with these technologies.

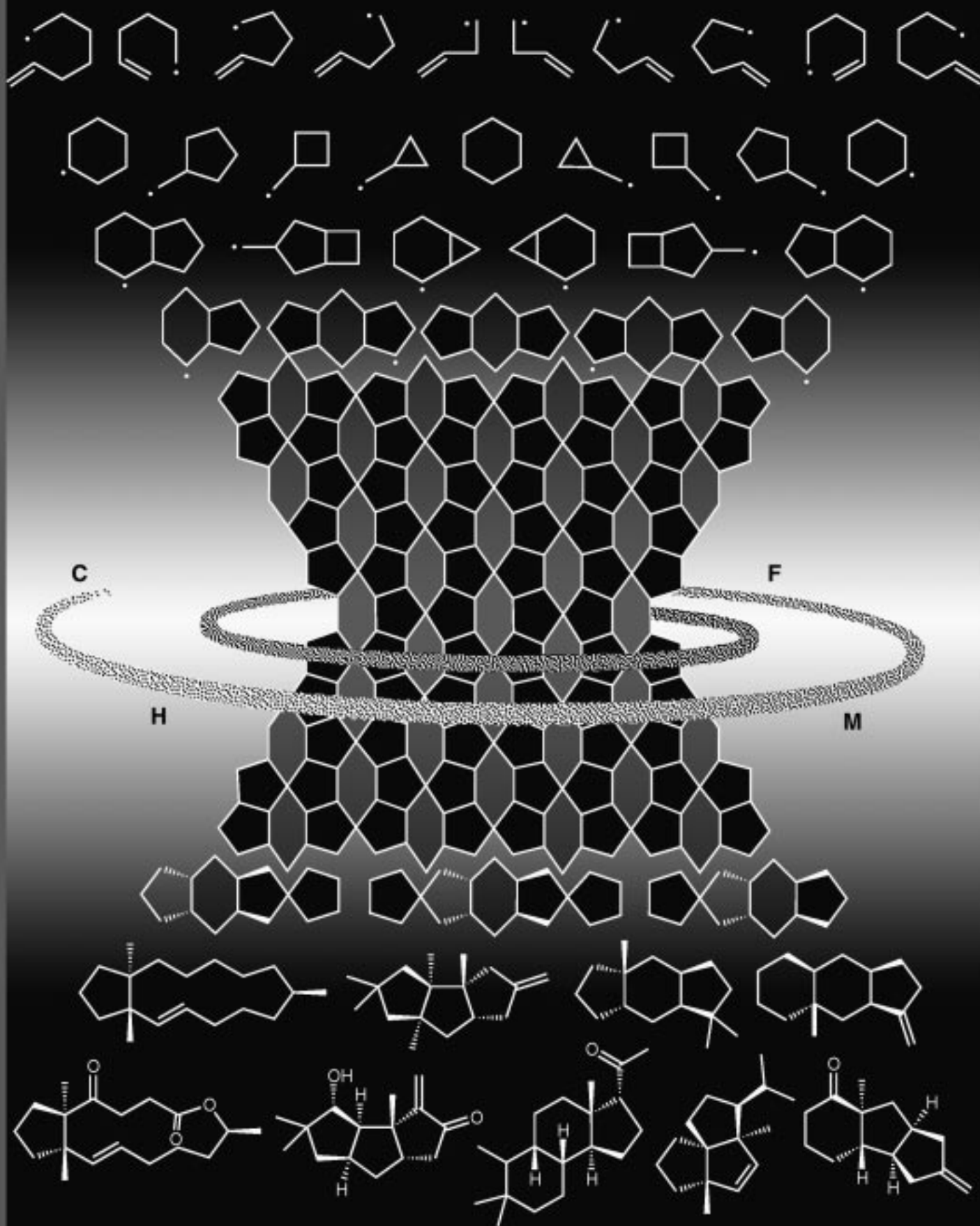
We thank our many colleagues at Altus Biologics who played a crucial role in development of the CLEC technology and whose names are listed in the respective references. Additional thanks go to Jim Griffith (Althexis), Kirill Yakovlevsky, and Yi-Fong Wang for their help in the preparation of the manuscript and for useful discussions. We are also grateful to the NIH, NSF, and Department of Defense who generously supported our work through their SBIR programs.

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Programming Organic Molecules: Design and Management of Organic Syntheses through Free-Radical Cascade Processes

Andrew J. McCarroll and John C. Walton*

Cascade, domino, or tandem processes, that link together two or more transformations in one pot, are increasing in popularity because they lead to improvements in synthetic efficiency and decreases in environmental impact. Not only do these cascades contain choice mechanistic gems but they also deliver compact and elegant syntheses of complex natural products. Longer cascades require more functional groups precisely configured within carefully designed initial molecular architectures. Such “purposeful” molecules can be thought of as chemical algorithms. This article surveys the phenomenal range of unimolecular free-radical cascades. A convenient system for classifying free-radical cascades is described that is useful for evaluating

and comparing cascades and aids the design of synthetic routes to polycyclic structures. Double cyclization cascades lead to cyclopentylcyclopentane or bicyclo[3.3.0]octane derivatives. Precursors that contain a ring as a template have been used to control stereochemistry in syntheses of triquinanes and many related compounds. Of the cascades containing ring-cleavage steps, the most useful are the ring expansions which have opened up new synthetic routes to medium ring polycycles. The key design features of three-stage unimolecular free-radical cascades that yielded steroid structures, are linear arrays of radical acceptor units associated with methyl groups distributed every fifth C-atom in the precursor polyenes. Ring cleav-

age is the reverse of cyclization. In special, symmetrical structures, therefore, this led to sequences that were reversible, thus launching endlessly repeating cascades supported by delightfully fluxional structures. The science of “programming” organic molecules to achieve particular target structures is maturing rapidly. Coordination and classification of the welter of information in this area is intended to facilitate design and hence to extend the range and complexity of attainable structures.

Keywords: cyclizations • domino reactions • radical reactions • rearrangements • synthetic methods

1. Introduction

1.1. Description, Scope, and Uses of Cascade Reactions

Chemical processes in which two or more consecutive molecular transformations are intimately linked together in time and space, (that is, in “one pot”), have been variously dubbed cascade, domino, tandem, or sequential reactions. Perception and chemical understanding of such processes is still immature, but the pace of development has conspicuously quickened recently because of an emerging realization of the actual and potential advantages they possess. By means of cascade methodology, the number of discrete laboratory manipulations required for the construction of a complex

target molecule can be reduced, with consequent savings in hardware, operator, and instrument time. Affiliated with this are reductions in the amounts of solvents and reagents needed and in the amounts of unwanted by-products. These factors can lead to significant improvements in synthetic efficiency and decreases in environmental impact. This potential to streamline laboratory and large-scale preparations guarantees a bright future for cascade processes.

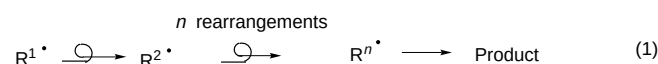
The more steps there are in a cascade process the more functional groups must be precisely located within a carefully designed initial molecular architecture. This requirement may well offset some of the potential benefits of cascade methodology. The structure of the precursor molecule(s) must be carefully “programmed” to enable a complex, scripted, reaction coordinate to be followed, predictably bringing about a drastic configurational change, and ending in the target molecular design. Such pre-adapted precursor molecules can be described as “chemical algorithms” or, in more anthropomorphic terms, as “purposeful molecules”. The precise structural information built into a precursor molecule

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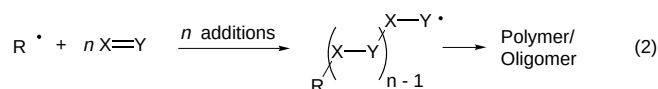
often leads to high stereoselectivity, a very desirable characteristic in synthetic organic chemistry. Well designed cascades are noted for their simplicity and elegance and have provided some of the most exquisite examples of synthetic art.

Choice cascades are also impressive specimens of complex mechanisms that test theories of bonding and reactivity to the limits. However, their main use has been in synthetic organic chemistry, particularly in the preparation of complex polycyclic molecules, including many natural products. Cascade processes occur in nature, particularly in the biosynthesis of alkaloids, terpenes, and steroids, and several illustrative examples were described by Tietze et al. in their valuable reviews of sequential transformations.^[1] Cascade sequences may incorporate two or more cationic, anionic, radical, or pericyclic steps, as well as several more exotic reaction types. A broad framework for classifying these sequences in a systematic manner, based on the reaction type of the first two steps, was devised by Tietze and Beifuss.^[1a] Several reviews and compilations of synthetic applications,^[2] and other aspects of cascade processes,^[3–5] have appeared in recent years.

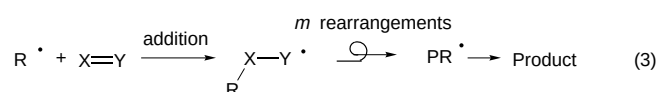
This article focuses on the snowballing number of multistep processes that feature only free-radical reactions as individual steps. Cascades may, of course, encompass reactions that are intermolecular and/or intramolecular. In substitution and bond-forming processes, the latter type usually possess an inbuilt entropic advantage. Moreover, if more than one intermolecular step is incorporated into a cascade, additional reactants and/or reagents need to be introduced. Most likely this will lead to difficult if not insoluble problems of selectivity. Thus, the great majority of free-radical cascades involve sequences of intramolecular steps, the overall propagation coordinate being unimolecular (excluding initiation and termination steps) [Eq. (1)]. This review coordinates



information on this particular unimolecular type of cascade. The most important alternative radical cascades are: first, comparatively unsophisticated oligomerizations and polymerizations in which many radical additions to a limited range of alkenes (or other acceptors) [Eq. (2)] take place and second,



processes for which one step, usually the first, is radical addition to a suitably functionalized acceptor [Eq. (3)]. Many instances of this latter type of radical cascade can be found in the recent literature, but for reasons of space they will not be systematically covered here.



For programming purposeful molecules, suitable for target syntheses, knowledge is needed of the allowed steps, their regio- and stereoselectivity, valid ways of coupling them together in a sequence, and preferably of individual rates. The propagation steps of a generalized intramolecular free-radical cascade process are illustrated in Scheme 1. The configured precursor molecule (S^b) is converted into the first free-radical intermediate ($R^{1\cdot}$) by the initiation step(s) (In), which may be abstraction(s) or substitution(s), as with organotin hydrides or tris(trimethylsilyl)silane (TTMSS), or redox processes, as with transition metal initiators. Radical intermediate $R^{1\cdot}$ then undergoes a unimolecular rearrangement that converts it into intermediate $R^{2\cdot}$ with or, better, without production of side-product B^1 . The cascade can proceed through any number ($n-1$) of unimolecular rearrangements until the final inter-

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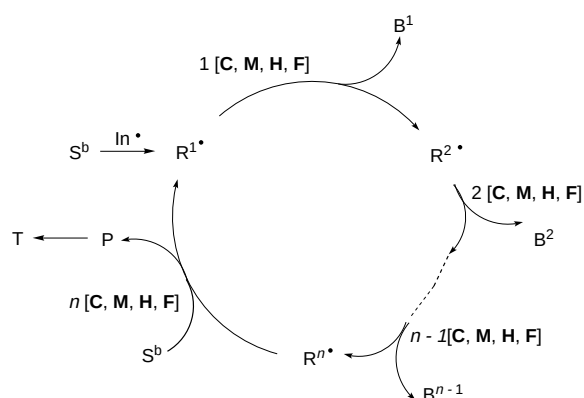


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Scheme 1. Generalised intramolecular free-radical cascade. See Scheme 2 for an explanation of the abbreviations.

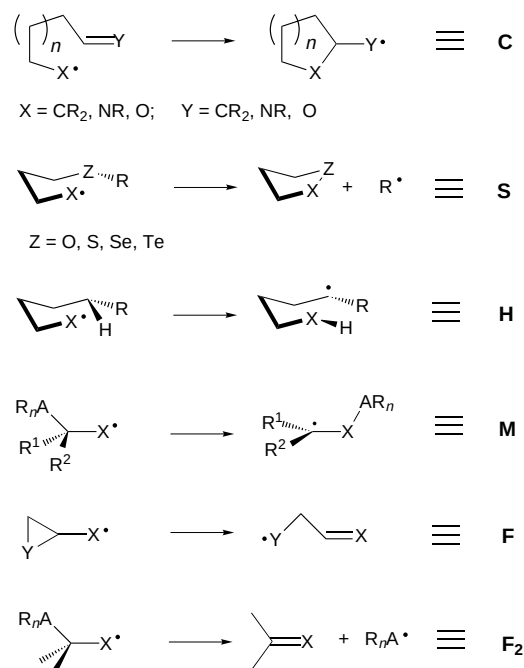
mediate $R^n\cdot$ converts into the desired product (P) that can itself be commuted into the target molecule (T) by means of extraneous functional group transformations which do not form part of the cascade. For many cascades the final step also regenerates the first intermediate, by reaction with more precursor, as shown in Scheme 1 (or otherwise), and the whole cascade is then a chain reaction. This chain character is not an absolute requirement for cascade status.

For a cascade to function efficiently, the rates of the individual rearrangements must be fast in comparison with termination reactions (combination, disproportionation, redox) of the $R^x\cdot$ intermediates and in comparison with their reactions with solvent, precursor S^b and initiator molecules. It is desirable that the final intermediate $R^n\cdot$ react selectively with S^b , while the rest of the intermediate radicals do not. To achieve this, the final rearrangement step needs to bring about a major change in polarity or reactivity of the propagating radical, for example, by generating an *O*-centered radical or perhaps a vinyl-type radical.

1.2. Classification of Unimolecular Homolytic Cascades

Radical rearrangements are comparatively well understood^[6, 7] enabling the four major classes of unimolecular processes that take place at appropriate rates for incorporation into homolytic cascades ($k \geq 10^3 \text{ s}^{-1}$ at 25°C) to be pinpointed. The main archetype cyclizations are summarized by the generalized equation in Scheme 2 where the symbol **C** is introduced to label them. Superscripts will be added to make individual rearrangement symbols more informative. For cyclizations, the size of ring formed, and whether ring closure is *exo* (**x**) or *endo* (**n**), will be included. The scope of this reaction is huge, but the most prevalent ring closure is 5-*exo-trig* (**C^{5x}**). Radical 6-*endo* (**C⁶ⁿ**), and 6-*exo* cyclizations (**C^{6x}**) are not unusual and medium and macrocyclizations are also readily accomplished. Baldwin's rules give helpful guidance as to allowed and disfavored cyclization modes.^[6, 8] The chain may contain many types of heteroatoms and be configured in many different ways.^[9–11]

Intramolecular homolytic substitutions (S_{Hi} or **S**; Scheme 2) also result in cyclization.^[12] The scope of this type

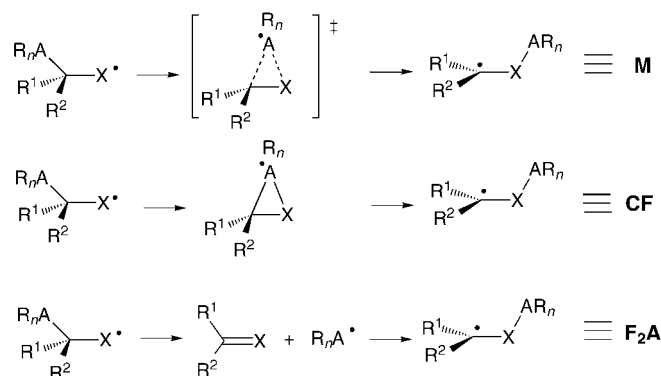


Scheme 2. Classes of unimolecular free-radical rearrangements. See text for full details.

of reaction is limited because, except for a few exotic cases, the attacked center Z cannot be carbon and is usually either oxygen or an element from the second or subsequent rows of the periodic table. Furthermore, the radical center does not remain with the main ring, but is ejected with the displaced radical. Hence these **S** type rearrangements can normally only be the final step in a cascade. The released radical $R\cdot$ may lead to (deleterious) branching of the cascade. For these reasons very few cascade sequences incorporating **S** type processes are known.

The third type of process allowed in homolytic cascades is intramolecular hydrogen abstraction (**H** in Scheme 2). 1,5-Hydrogen migrations (**H⁵**) are the most common, and 1,6-migrations (**H⁶**) are also very well known. Occasional 1,4-shifts (**H⁴**) can be found in the literature,^[6, 13] but it should be noted that what may appear to be a single hydrogen shift, may in reality be two sequential shifts.

1,2-Group migrations (designated **M**) are mechanistically more enigmatic.^[6] The process is akin to a homolytic substitution in which the attacked center is adjacent to the radical center. The distinction between **S** and **M** is appropriate, however, because conventional **S** reactions require “linear” transition states.^[12] Carbon-centered groups, $R_3C\cdot$, with sp^3 hybridization do not usually undergo 1,2-migrations. Most migrations involve groups that contain some unsaturation such as in aryl, vinyl, or carbonyl, or are otherwise able to make available a low lying orbital to accept the unpaired electron during the migration. A 1,2-migration may take place as a single concerted step via a transition state (true **M** Scheme 3). It may also occur as a cyclization **C** to afford a discrete intermediate radical, followed by a fragmentation step (**CF**, Scheme 3). Another alternative is fragmentation followed by re-addition (**F₂A**, Scheme 3). This is favored by

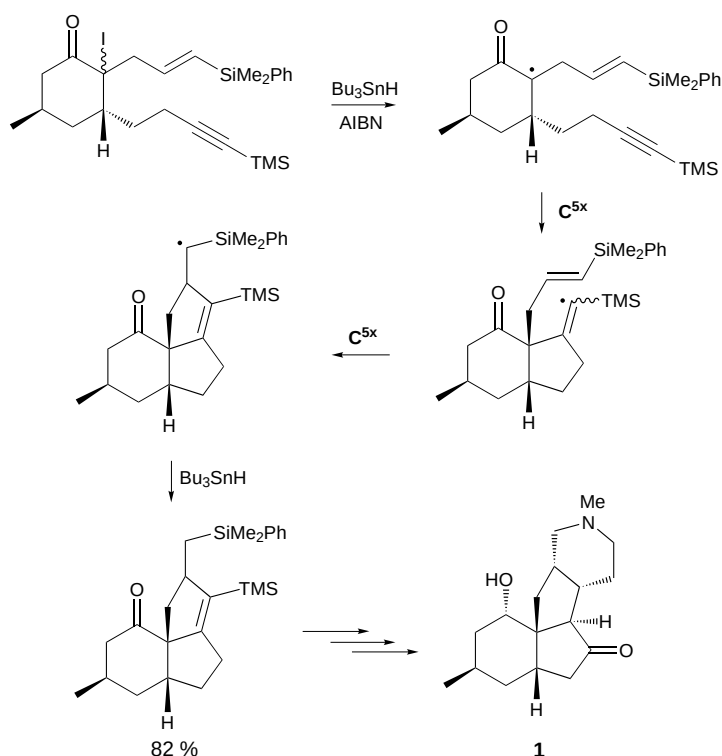


Scheme 3. Radical processes that result in overall 1,2-group migration.

halogen, sulfenyl (RS), organostannyl, and related groups. Often the exact mechanism of a “migration” will not be known, and informed guesswork may have to be used to arrive at a tentative classification for the process. In general, steps for which the overall result is group migration will be classified as **M**, unless evidence specifically points to one of the other mechanisms.

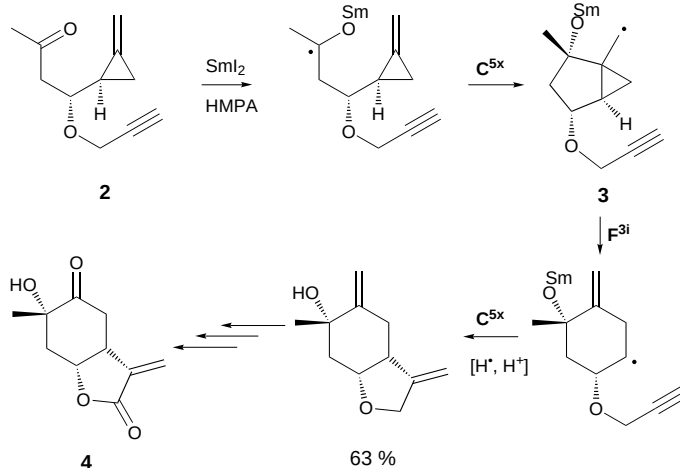
The final category of isomerization is fragmentation. Ring opening, in which a single unsaturated radical is produced (**F** in Scheme 2) is the most important manifestation of this type. This is the reverse of cyclization. Ring opening (i.e. fragmentation by β -scission) of cyclopropylmethyl and oxiranylmethyl radicals (**F³**) is an extremely rapid process. Ring opening of cyclobutylmethyl and related radicals (**F⁴**) is also rapid. However, for cycloalkylmethyl radicals containing larger rings β -scission is normally thermodynamically unfavorable and unimportant in solution. Alkoxy radicals, however, fragment with ease at moderate temperatures and therefore ring-opening of cycloalkyloxy radicals with small, and large ring sizes to yield carbonyl compounds is common. If an intermediate radical cleaves into two or more fragments this will usually start cascade branching. Such degradative fragmentation processes, for example, decarboxylations, can be useful in certain circumstances, and will be designated **F₂** (Scheme 2).

Various exotic rearrangements are known, such as Stevens-type radical-pair combinations, but these processes are not currently included in cascades and will not be examined here. Cascades are terminated by hydrogen or halogen transfer, by β -scission, by electron transfer, and in other ways. In classifying free-radical cascades only the propagation steps which form the cycle (see Scheme 1) will be considered as strict integral parts of the cascade. The initiation and termination steps do not form part of the central chain process; the same cascade can often be initiated in several different ways. In metal hydride mediated cascades the initial intermolecular halogen abstraction (or SePh displacement, etc.) that starts the sequence and the hydrogen abstraction from R_nMH that ends it, are not classed as part of the cascade. For example, the synthesis^[14] of the (+)-paniculatin (**1**) precursor shown in Scheme 4 will be classified as a two stage, **C^{5x}C^{5x}**, cascade because propagation involves two cyclization steps. The initial iodine atom abstraction, and the final H abstraction from


 Scheme 4. Double cyclization cascade route to a precursor of (+)-paniculatin **1**.

Bu_3SnH that terminates the cascade, are not included in the classification.

Consider also the partial synthesis^[15] of paeonilactone B (**4**) (Scheme 5). This three-step cascade was launched by treatment of methylenecyclopropane derivative **2** with samarium


 Scheme 5. Three-step cascade synthesis of the skeleton of paeonilactone B **4**.

diiodide. The first intermediate radical ring closed via a 5-*exo*-cyclization to generate (bicyclo[3.1.0]hexyl)methyl radical **3**. The latter selectively underwent β -scission of its inter-ring bond (**i**), rather than the outer cyclopropane bond (**o**), for stereoelectronic reasons^[6, 7, 16] and was thus transformed into a substituted cyclohexyl radical. A further 5-*exo*-cyclization

assembled the 7-oxabicyclo[4.3.0]nonane skeleton, ready for conversion into lactone **4**. The designation $C^{5x}F^{3x}C^{5x}$ is therefore appropriate for this cascade.

When a cascade does not proceed by a regular chain process it may be fitting to include the initial and final steps in the classification.

Matrices containing the codes for all 16 possible two-stage unimolecular cascade sequences and all 64 theoretical unimolecular three-stage cascade sequences, that can be obtained by combining the four rearrangement types **C**, **H**, **F**, and **M**, are shown in Schemes 6 and 7. Each individual two-letter code represents a range of possible cascades within a particular subtype. Further matrices could be constructed, based around the superscripts outlined above, to elaborate possibilities within each subtype. However, additional symbols to indicate heteroatoms, configurational details etc. would be needed for a thorough description. Such elaboration would probably stretch the classification beyond its limits of usefulness and will not be attempted here.

Initial step	Second step			
	C	M	H	F
C	CC	CM	CH	CF
M	MC	MM	MH	MF
H	HC	HM	HH	HF
F	FC	FM	FH	FF

Scheme 6. The codes for two-step unimolecular free-radical cascades.

Initial step	Second step				Final step
	C	M	H	F	
C	CCC	CMC	CHC	CFC	C
	CCM	CMM	CHM	CFM	M
	CCH	CMH	CHH	CFH	H
	CCF	CMF	CHF	CFF	F
M	MCC	MMC	MHC	MFC	C
	MCM	MMM	MHM	MFM	M
	MCH	MMH	MHH	MFH	H
	MCF	MMF	MHF	MFF	F
H	HCC	HMC	HHC	HFC	C
	HCM	HMM	HMH	HFM	M
	HCH	HMH	HHH	HFH	H
	HCF	HMF	HHF	HFF	F
F	FCC	FMC	FHC	FFC	C
	FCM	FMM	FHM	FFM	M
	FCH	FMH	FHH	FFH	H
	FCF	FMF	FHF	FFF	F

Scheme 7. The codes for three-step unimolecular free-radical cascades.

Cyclization processes are bond forming and are therefore the most significant for organic syntheses. Thus the **CC** and **CCC** cascade types in the top left-hand corners, together with types clustering in the top rows, and left-hand columns of the matrices are particularly important. The central areas of the matrices mainly represent cascades in which translocations of the radical center, and associated hydrogen atoms or functional groups, occur. Degradative cascades in which original programmed structure is largely lost by sequences of ring-opening β -scissions are represented by **FF**, **FFF**, and associated subtypes in the lower right-hand corners of the matrices.

Several subtypes, particularly the multiple cyclizations, have been intensively studied, but some cascade subtypes remain unknown in reality.

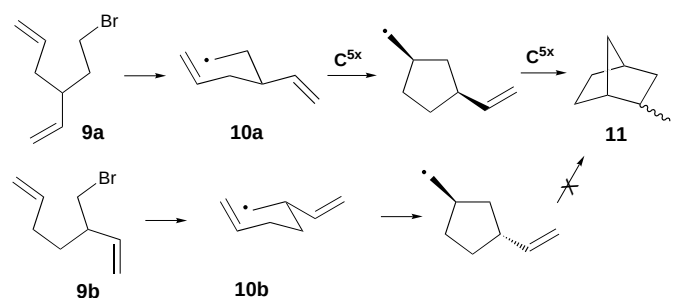
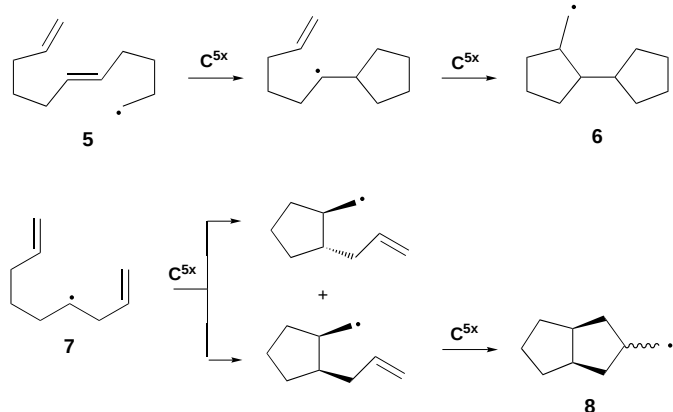
This system provides a short means of classifying the scattered and mixed array of cascade chemistry dispersed in the literature. It is intended to help in storing, displaying, evaluating, and comparing cascades. It should also assist in inferring the reaction mechanisms of radical cascades and in the design of target directed syntheses. The system is easily extendible to cascade types not included in this review, for example, to cascades containing intermolecular addition steps (**A**).

2. Two-Stage Unimolecular Free-Radical Cascades

2.1. The Acyclic Approach to Double Cyclizations

Starting structures may contain undeca-, nona-, or octadiene units, and the radical center may be generated within the diene chain, or in a branch attached to the diene chain. For example, if the radical is generated at the end of an undeca-5,10-dien-1-yl radical (**5**) the $C^{5x}C^{5x}$ cascade produces a cyclopentylcyclopentane derivative **6** (Scheme 8). Heterocyclic and alkyne analogues are also known, as are the corresponding processes for double cyclizations via the C^{6x} and C^{6n} modes.

Alternatively, if the radical center is generated within the chain of a nonadiene **7** then the $C^{5x}C^{5x}$ cascade leads to bicyclo[3.3.0]octane structures **8** (Scheme 8). Generally, the first cyclization produces a mixture of *cis* and *trans* cyclo-



Scheme 8. Double 5-*exo* cyclizations of linear and branched dienyl radicals.

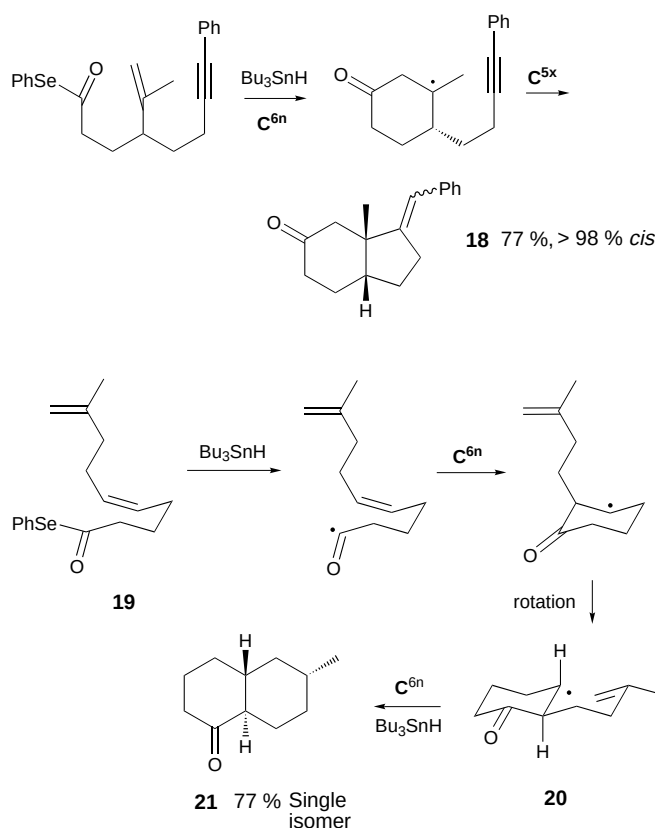
alkylalkyl radicals and only the *cis* radical can undergo a second ring closure. For efficient syntheses, therefore, it is necessary to include some substituent which will induce *cis* selectivity in the first step. This “acyclic approach”^[17] to CC cascades, in which there are no rings already present to direct stereoselectivity, shows great diversity. Furthermore, stereoselectivity is often extremely good.^[18] The first cyclization of branched octadienyl radical **10a**, generated from bromodiene **9a**, was found to be *cis* selective permitting efficient occurrence of the second ring closure to a bicyclo[2.2.1]heptane skeleton **11** (Scheme 8). Radical **10b** on the other hand cyclized to give predominantly the cyclopentylmethyl radical with a *trans* configuration, which could not undergo a second cyclization to give bridged bicycle **11**.^[19, 20]

Parsons et al. provided an early example of an acyclic system being used in the synthesis of the natural product framework, avermectin A_{2b}.^[21] Likewise, Kilburn used a CC cascade in a synthesis of isoridomycin (**12**) demonstrating the high degree of stereoselectivity that can be obtained (Scheme 9).^[22] Morikawa et al. established that “awkward” angular trifluoromethyl substituted bicyclic systems such as **13** could be synthesized by a C⁶ⁿC^{5x} sequence that started with a 6-*endo* cyclization (Scheme 9).^[23]

The synthesis of heteroannular acetals, for example, **15** and **17**, by radical double cyclization cascades starting from enynes was studied by Hoffmann et al.^[24] Enyne **14**, and related precursors with the *R* configuration, underwent a C^{5x} cycliza-

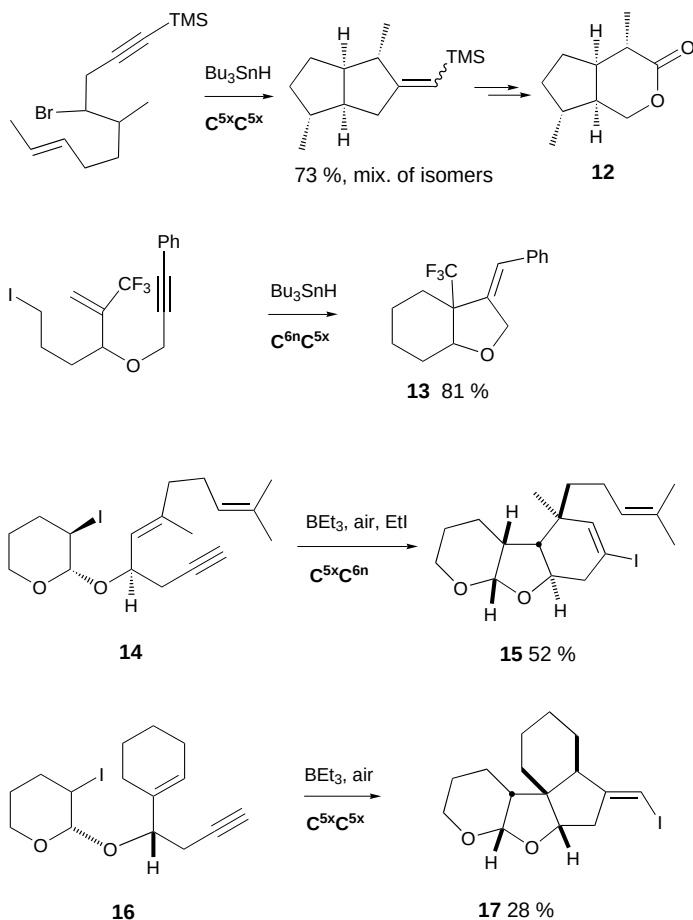
tion, followed by a C⁶ⁿ process that was dictated by ring strain. For the diastereomeric enyne containing the *S* configuration, and related precursors such as **16**, the cascade was largely diverted into the more normal C^{5x}C^{5x} mode, especially if a quaternary carbon center was established during the first cyclization (Scheme 9). These and related cascades were remarkable in that they allowed the construction of four or more chiral centers in a single convergent step. Another attractive feature was the avoidance of organotin compounds, because use of triethylborane/air as initiator worked well.

The chemistry of acyl radicals, including cascade reactions, has recently been comprehensively reviewed^[25] so only a couple of illustrative sequences will be described. Boger and Mathvink demonstrated an acyl-radical mediated C⁶ⁿC^{5x} cascade sequence that led to bicyclo[4.3.0]nonanone derivative **18** (Scheme 10).^[26] Related reactions involving 6-*exo* cyclizations displayed much poorer stereoselectivity.



Scheme 10. Preparation of bicyclic ketones by double cyclizations of acyl radicals.

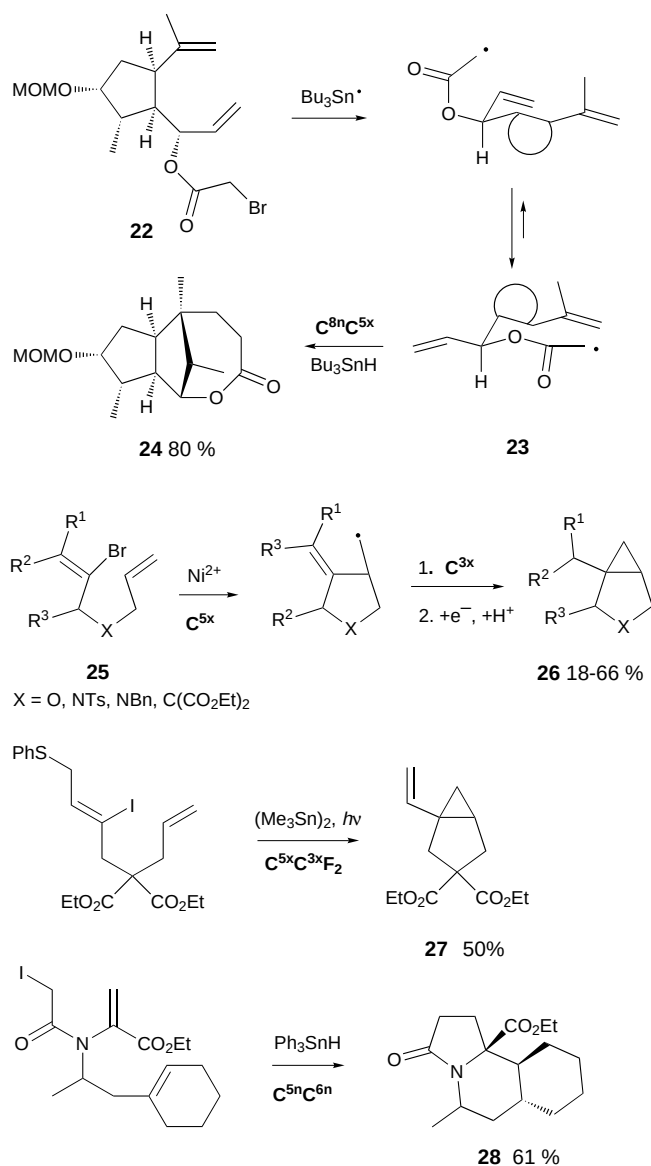
Many cascades starting from acyl radicals have featured consecutive 6-*endo* cyclizations (C⁶ⁿC⁶ⁿ) to afford decahydronaphthalen-1-ones, that is, generate the A and B steroid rings.^[25] The initial acyl radicals are more likely to cyclize in a 6-*endo* fashion, either directly or by ring expansion. The C⁶ⁿC⁶ⁿ cascade shown in Scheme 10^[27] was initiated by treatment of a selenoester **19** with tributyltin hydride. The starting acyl radical preferentially cyclized in the C⁶ⁿ mode and the second cyclization was biased in favor of C⁶ⁿ closure because the intermediate hex-5-enyl-type radical **20** contained a



Scheme 9. Synthesis of oxapolycycles by CC cascades.

methyl substituent at C(5). Overall this resulted in a good yield of *trans*-6-methyldecahydronaphthalen-1-one **21** as a single isomer. Other sequences, including cyclizations disfavored according to Baldwin's rules,^[8] are possible.

Having made guaianolide with a $C^{5x}C^{7n}$ sequence,^[28] Lee et al. were optimistic that tricyclic γ -lactone **24** could be synthesized by a similar sequence.^[29] Instead, the initial (alkoxycarbonyl)methyl radical preferred to cyclize in an 8-*endo* fashion, and underwent a $C^{8n}C^{5x}$ sequence (Scheme 11). The intermediate (alkoxycarbonyl)methyl radical preferred conformation **23** that favored closure to an eight-membered ring lactone in the first step. 3-*Exo* cyclizations may sometimes be rendered irreversible by stabilizing the product radical. This tactic was used to prepare bicyclo[3.1.0]hexane derivatives **26** in $C^{5x}C^{3x}$ sequences starting from bromodienes **25**, initiated electrochemically, but mediated by a nickel complex (Scheme 11).^[30] It was necessary for

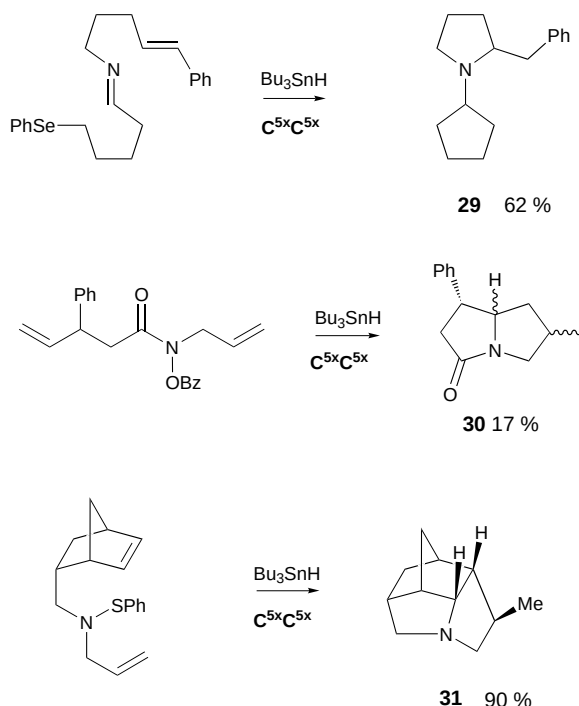


Scheme 11. Double cyclizations embodying unusual steps, Ts = 4-methylphenylsulfonfyl.

R^1 and R^2 to be radical stabilizing groups that also facilitated a rapid electron transfer (ET) reaction and the best yield (66 %) was obtained when $R^1 = R^2 = R^3 = Ph$ and $X = O$.

Two different radical cascades were used to prepare bicyclo[3.1.0]hexane derivatives, both of which involved the initial cyclization of a vinyl radical.^[31] In one of these sequences the three-membered ring was trapped by following the reversible 3-*exo* cyclization with an effectively irreversible fragmentation to yield **27** (Scheme 11).^[31b] The presence of heteroatoms can sometimes enable “disfavored” 5-*endo* ring closures to take place. For example, appropriately substituted α -carbamoylmethyl radicals were used in cascade reactions to give indolizidinones such as **28** via $C^{5n}C^{6n}$ sequences (Scheme 11).^[32] Attempts at pyrrolizidine synthesis, from similar compounds with appropriately placed electron-withdrawing groups, failed. The presence of the carbonyl group in the precursor was vital. Analogous enamines merely underwent decomposition, presumably because the carbonyl group crucially affects the geometry of the α -carbamoylmethyl moiety.

Nitrogen-centered radicals cannot be easily generated by halogen abstraction. However, aminyl radicals have been produced by cyclization onto an imine (Scheme 12). The system was designed such that a further cyclization occurred to yield cyclopentylpyrrolidines **29**.^[33] Sometimes a Lewis acid was beneficial, because this generated a much more nucleophilic aminium radical, but yields were variable.



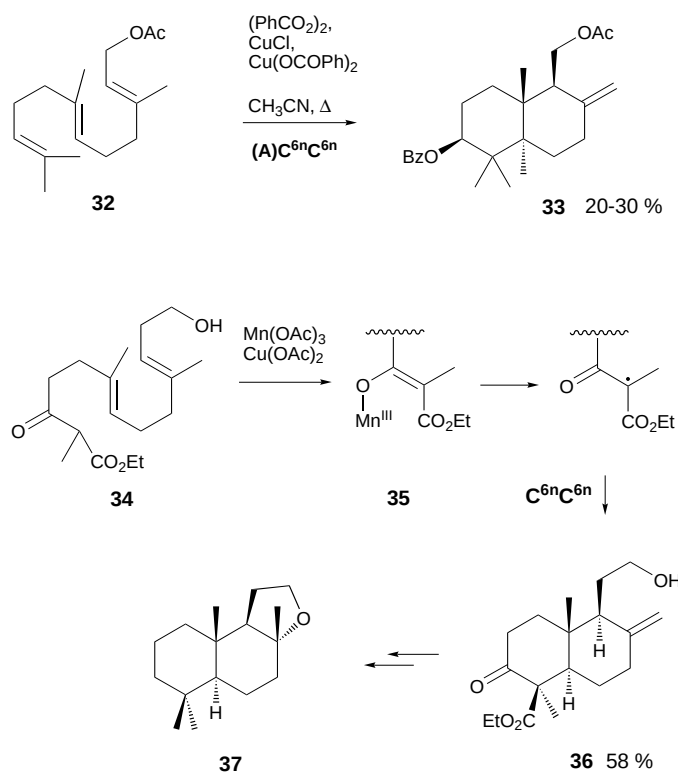
Scheme 12. Domino double cyclizations involving *N*-centered radicals. In **30** the isomer ratio is 3:2:1.

Apart from the above, the geminal donor/acceptor *N*-aziridinylimine method of Kim et al.,^[34] and the synthesis of ($\pm$)- γ -lycorane by Zard et al. (Section 2.2) are additional examples of the exploitation of *N*-centered radicals. Amidyl radicals have been obtained from *N*-hydroxypyridine-2-thi-

one imidate esters (PTOC imidate esters)^[35] and from *O*-acyl hydroxamic acid derivatives,^[36] and used in $C^{5x}C^{5x}$ cascade cyclizations resulting in hexahydropyrrolizin-3-ones such as **30** (Scheme 12), containing bridgehead nitrogen atoms.

Aminyl radicals are less electrophilic than amidyl radicals, and seem to be less well behaved, but can still undergo cascade cyclizations. They too can be generated from PTOC imidate esters, and have been used in a domino fashion.^[37] Bowman et al. have described a series of syntheses in which aminyl radicals generated from phenylsulfenamides have undergone cascade cyclizations, (such as the formation of polycyclic amine **31**) though $C^{5x}C^{5x}$ sequences in excellent yields.^[38]

As long ago as 1968 Breslow reported an oxidative tandem cyclization (Scheme 13) that was initiated by the addition of a benzoyloxyl radical to triene **32** and consisted of a $C^{6n}C^{6n}$ sequence followed by an oxidative termination step.^[39] Although this method appears not to be generally applicable, it was followed by reports of numerous related oxidative annulations, mostly mediated by Mn^{III} acetate as one-electron oxidant.^[40, 41]



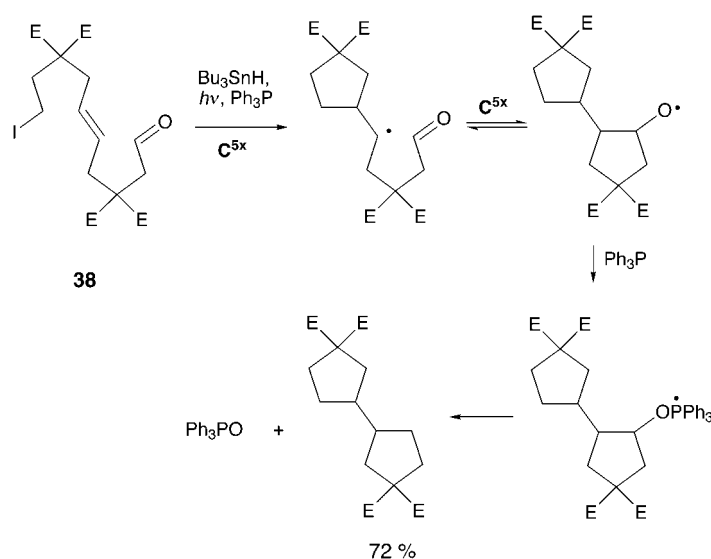
Scheme 13. Double cyclization cascades mediated by transition metal oxidants.

The synthesis of (–)-norlabdane oxide (**37**),^[42] which is highly valued in the fragrance industry, serves to illustrate the use of the Mn^{III} acetate method (Scheme 13). The initial electrophilic carbon-centered radical was formed from β -keto ester **34** via enolate **35** and underwent a double cyclization ($C^{6n}C^{6n}$) followed by oxidation,^[43] in this, as in most other cases, by a Cu^{II} salt, to form the decalone derivative **36**. Natural products that have been synthesized utilizing Mn^{III}

initiated two-step cascades include aloesaponol III and okicenone,^[44] and the CD ring system of gibberellic acid.^[45]

Unfortunately, the Mn^{III}/Cu^{II} ET system is not suitable as a general replacement for organotin hydrides, because only hydrogens on enolizable carbons are (effectively) abstracted, but it provides a neat, complementary method. Many of the CC cascades performed using Mn^{III} acetate were models for longer sequences (see Section 3).

Kim and Oh showed that cyclizations onto aldehydes could precede deoxygenation with organophosphorus compounds, and that this method was feasible for $C^{5x}C^{5x}$ cascades as well (Scheme 14).^[46, 47] This gambit facilitates the use of precursors **38** and others for which a terminal aldehyde may be easier to introduce than a terminal alkene.

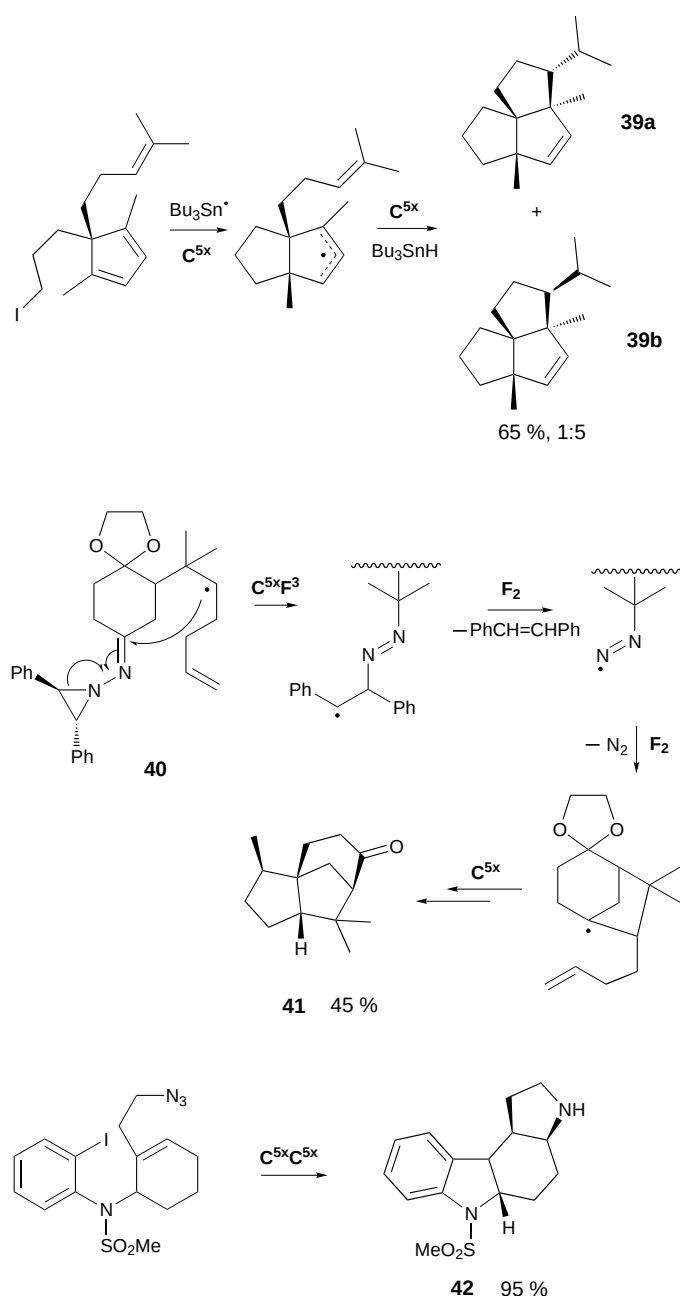


Scheme 14. Cascade featuring a cyclization onto a carbonyl group; E = CO_2Et .

2.2. The One-Ring Template Strategy for the Synthesis of Triquinanes and Related Tricyclics

This template strategy utilizes precursors that already contain a ring to control the stereochemistry of two subsequent cyclizations. The presence of a ring in the preadapted precursor, to which chains containing unsaturated centers and incipient radical centers are attached in a specific way, “bias(es) the stereochemical outcome of the cyclization.”^[17] Integration of a five-membered ring template with two C^{5x} steps leads to perhydrocyclopenta[*a*]pentalenes or perhydrocyclopenta[*c*]pentalenes (angular triquinanes). Six-membered ring templates have also been popular. The majority of these types of cascades have used organotin hydrides to mediate the reactions.

The one-ring template strategy was used by Curran and co-workers in admirable CC syntheses of (±)-silphiperfol-6-ene, (±)-9-episilphiperfol-6-ene,^[48] (±)-modhephene, (±)-epi-modhephene,^[49] and the BCD ring section of crinipellin A (**39a**).^[50] These preparations all required the cyclization of an allylic radical, which worked well, but gave the “wrong” isomer **39b** in a 5:1 ratio with **39a** (Scheme 15). The main



Scheme 15. One-ring template strategies for the stereocontrolled synthesis of triquinanes and related compounds.

points of note were the 1,3-delocalization of the unpaired electron in the intermediate allylic radical and the preference for *cis* ring junctions in both cyclization steps. Curran's "PRT" method (see Section 2.5) was also used with acyl radicals generated from selenoesters. Unfortunately the unnatural isomer was always the major product.

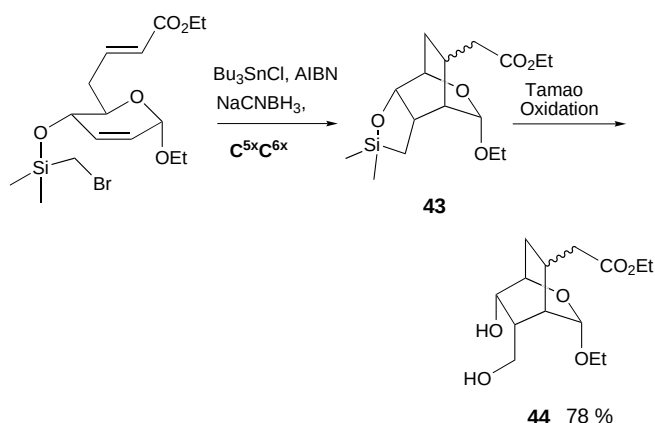
The "one-ring template strategy", was combined with CC cascades in syntheses of lysergic acid derivatives,^[51] a model for pseudocopsinine,^[52, 53] and aspidosperma (6% yield).^[53] Morphine,^[54] ($\pm$)- α -cedrene,^[55] α - and β -biotol,^[56] and (+)-paniculatin^[57] have also been targeted using these techniques.

The above rearrangements were all fairly standard organotin mediated $C^{5x}C^{5x}$ sequences. Radical cascades can, how-

ever, be remarkably diverse, even within the limits of "one-ring template" CC sequences. One of the many syntheses of α -cedrene **41** provided an illustration of the potential value of *N*-aziridinyliumines **40** in radical cascades (Scheme 15).^[34] *N*-Aziridinyliumines act as geminal radical donors/acceptors.^[58] In effect, the carbon onto which addition has taken place will also be the carbon from which the subsequent addition will occur. The process that results in the radical center appearing on the same carbon as the radical acceptor is a triple $F^3F_2F_2$ cascade accompanied by loss of stilbene and nitrogen (Scheme 15). The overall cascade is therefore a five-stage $C^{5x}F^3F_2F_2C^{5x}$ process. Kim et al. used the same technique in syntheses of *dl*-pentalenene,^[59] *dl*-zizaene, and *dl*-khusimone,^[60] and a similar cascade was also used in the synthesis of (+)-7-deoxypancratistatin.^[61]

Cyclization onto an azide moiety results, after a fragmentation, in the formation of a cyclic aminyl radical.^[62] This sequence has been incorporated into an attractive CC cascade, which results in the formation of **42** (95%) containing the [6.5.6.5] ABCE ring system of aspidospermidine and related indole alkaloids (Scheme 15).^[63]

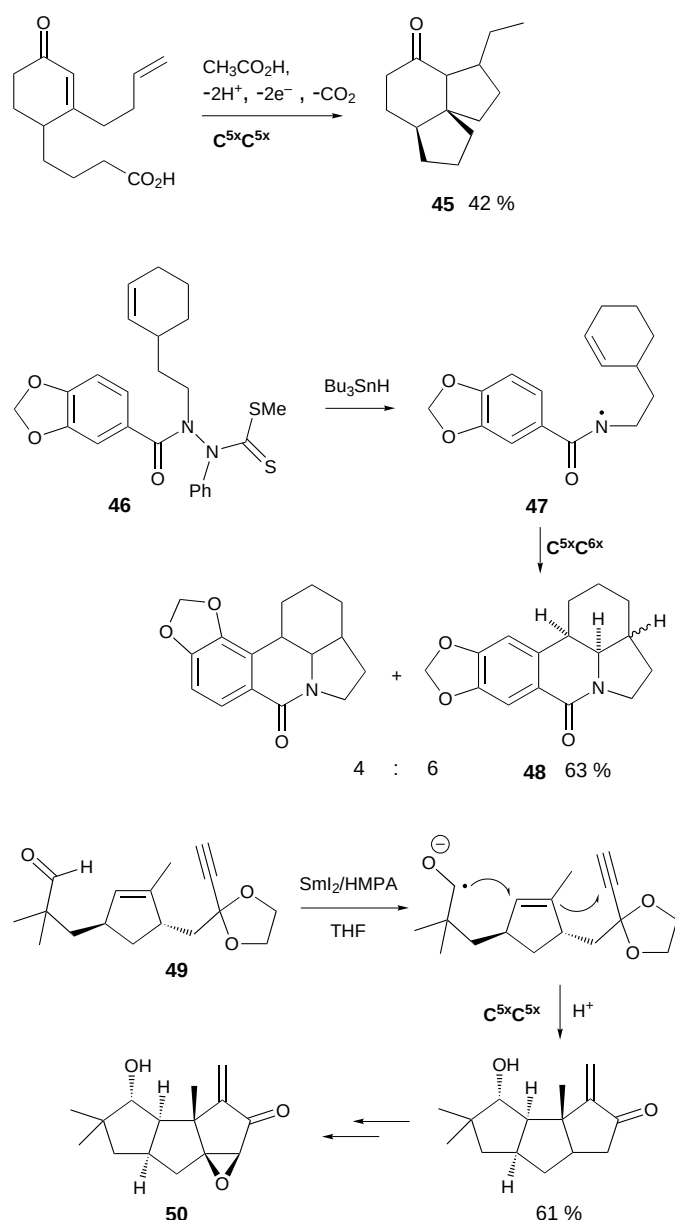
(Bromomethyl)dimethylsilyl allyl ethers have been the subject of extensive studies.^[17, 64] The silicon is employed as a tether, enabling the increased stereocontrol inherent in cyclization reactions to be utilized. Tamao oxidation^[65] of the 1,2-oxasiloles (**43**) formed in the first ring closure results in the production of 1,3-diols in a stereoselective manner. The technique, which originated from the work of Nishiyama et al.,^[66] was used by the Fraser-Reid group in a $C^{5x}C^{6x}$ cascade preparation of **44**, the precursor to reserpine in the total synthesis by Woodward, in enantiomerically pure form^[67] (Scheme 16), and more recently by Belval et al. as a synthetic route to an isoprostanoic precursor.^[68]



Scheme 16. Preparation by a double cyclization cascade of one of the intermediates employed by Woodward in the reserpine synthesis, AIBN = 2,2'-azobis[(2-methyl)propanenitrile].

An electrochemically initiated sequence commenced from an unsaturated carboxylic acid and led by a $C^{5x}C^{5x}$ cascade to the inden-4-one derivative **45** (Scheme 17).^[69] Reaction conditions were crucial, with current density being the important factor.

The key step in the synthesis of ($\pm$)- γ -lycorane by Zard et al. involved generation of amidyl radical **47** from precursor



Scheme 17. Ring-templated cascade syntheses of **45**, the γ -lycorane precursor **48**, and ($\pm$)-hypnophilin **50**, HMPA = hexamethyl phosphoramide.

46. Subsequent $\text{C}^{5x}\text{C}^{6x}$ double cyclization led to a 6:4 mixture of the desired **48** and undesired regioisomers (Scheme 17).^[70] The major isomer **48** was reduced to ($\pm$)- γ -lycorane with lithium aluminum hydride.

Curran et al. employed SmI_2 to generate a ketyl radical in their cascade syntheses of ($\pm$)-hypnophilin **50** (total synthesis, Scheme 17) and the key intermediate in the formal synthesis of ($\pm$)-coriolin.^[71]

2.3. Transannular Double Cyclizations

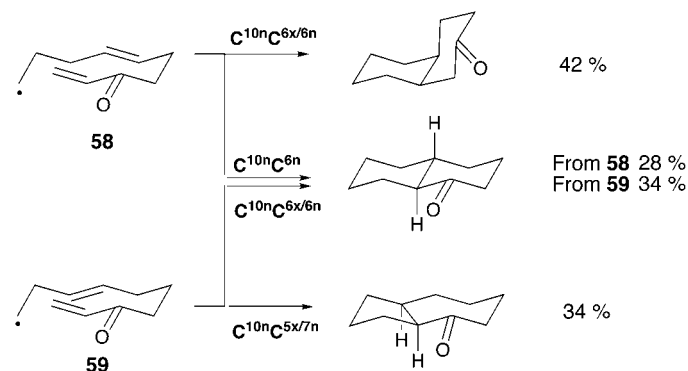
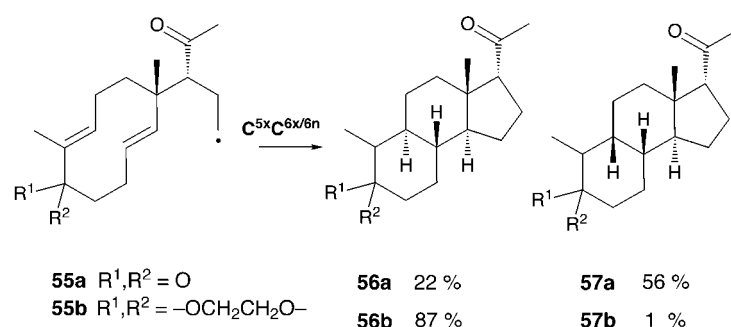
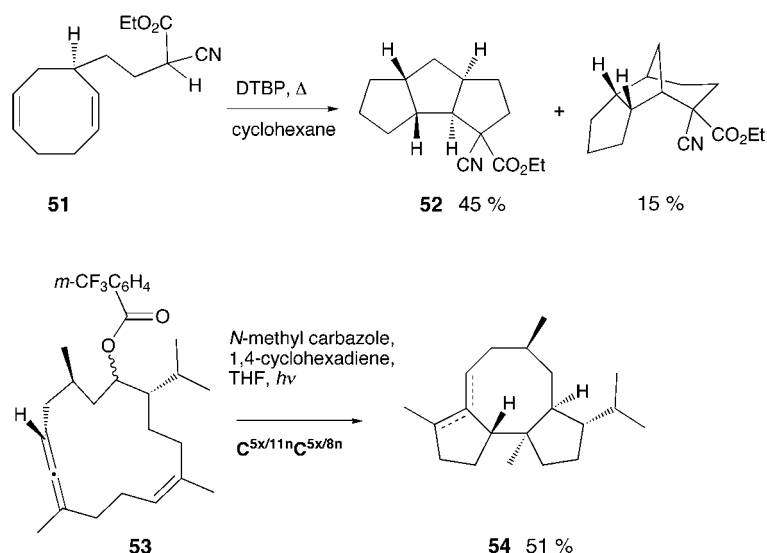
Transannular cyclizations constitute a distinct type of rearrangement that is potentially very useful in cascade reactions,^[72] but that has been neglected for some years

because of perceived difficulties in syntheses of the medium and large rings of the precursors. Generally, the two rings that form in a transannular cyclization can be viewed as arising from two different modes. The superscript notation has therefore been expanded to display both possible modes, separated by a forward slash. A study by Winkler and Sridar on the formation of linear fused cyclopentanoids from double cyclization of 3-(cycloocta-2,6-dien-1-yl)propyl radicals revealed that the first cyclization occurred mainly in a *trans* fashion, which prevented a second cyclization from taking place. However, the presence of stabilizing groups at the radical center generated from the cyclooctadienyl precursor **51** rendered the cyclization reversible. Thermodynamic control encouraged formation of the more stable *cis* ring system, resulting in triquinane **52** as the major product from a $\text{C}^{5x}\text{C}^{5x/5n}$ cascade (Scheme 18).^[73] Conformational studies indicated that a substituent at the 4-position *trans* to the alkyl chain ought also to improve the proportion of *cis*-fusion, and this was found to be the case, although the effect was fairly small.^[74]

In the $\text{C}^{5x/11n}\text{C}^{5x/8n}$ cascade devised by Myers and Condroski as the key step in their synthesis of ($\pm$)-7,8-epoxy-4-basmen-6-one, both cyclizations were transannular.^[75] Stannane-based radical-generation methods were unsuccessful, because of the tendency of tin-centered radicals to add to the allene moiety in the precursor (cf. **53**). The successful method (Scheme 18) involved illumination of the 14-membered ring trifluoromethylbenzoyl ester **53** in the presence of *N*-methylcarbazole and 1,4-cyclohexadiene in THF, and resulted in formation of the target tricyclic **54** in a 51% yield.

Recently, the progesterone BCD ring system was synthesized using transannular cascade methodology.^[76] MM2 transition-state models predicted that ketone **55a** would favor the undesired product **57**, whereas acetal **55b** would almost exclusively favor the desired stereoisomer **56**. Use of the acetal led, via a $\text{C}^{5x}\text{C}^{6x/6n}$ cascade, to the expected product **56b** (Scheme 18).

Pattenden et al. have employed an impressive range of transannular cyclization cascades in their syntheses of steroids. They have taken the method a stage further by forming macrocycles in radical *endo* cyclizations as well, thus avoiding the difficulty of forming medium-sized rings in a separate step. Early applications were their syntheses of the taxane ring system in low yield by $\text{C}^{12n}\text{C}^{6x}$,^[77] and $\text{C}^{12n}\text{C}^{8n}$ sequences,^[78] (alternatives to the tin method, such as TTMSS, were tried, and found to be less successful) and the method was also used to make fused lactones and lactams.^[79] A detailed investigation of the scope of the reaction has been published.^[80] The macrocyclization needed to be onto an enone but it was shown that the reactions with **58** and **59** followed different pathways (Scheme 18), which were ascribed to the different conformations adopted by the two macrocyclic radicals. A variety of CC reactions were investigated,^[80a] mainly with success, although it was noted that 5-*exo* cyclizations would occur “given half a chance” in preference to macrocyclization. Another surprising limitation was discovered when a 3-*exo* cyclization occurred instead of a macrocyclization, and was rendered irreversible by a sequential 5-*exo* cyclization to give a stabilized α -keto radical.^[81]



Scheme 18. Two-step cascades involving transannular cyclizations, DTBP = di-*tert*-butylperoxide.

2.4. Cyclization/Ring Opening as a Versatile Ring-Expansion Methodology

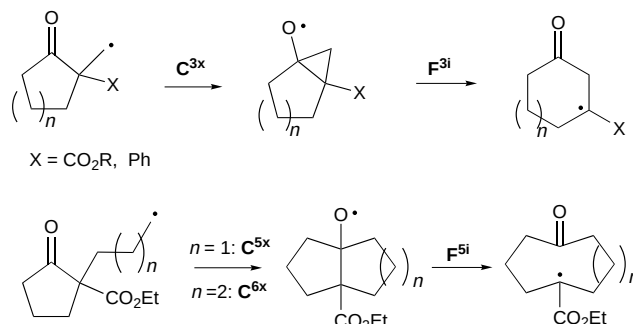
“Dowd-type” ring expansions take place by **CF** cascades and hence this sequence has become common. Ring enlargements have, however, been reviewed^[7, 82, 83] so only some illustrative and recent examples will be included. Recurring types are the one- (**C^{3x}F³ⁱ**), three- (**C^{5x}F⁵ⁱ**), and four-carbon (**C^{6x}F⁶ⁱ**) expansions shown in Scheme 19. Similar **CF** ring expansions have been reported for heterocyclic compounds containing O, S, and N atoms, various polycyclic compounds,

medium-sized rings, and the method has been extended to **CCF** and similar cascades.^[84] The ring expansion phenomenon may explain (or partly explain) other anomalous reactions, such as the preference of acyl radicals to cyclize in 6-*endo*, rather than 5-*exo* fashion.

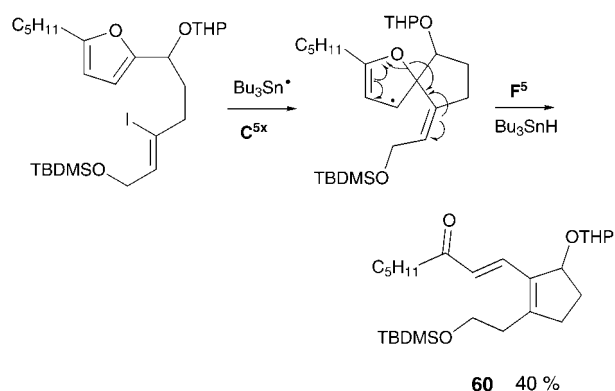
Parsons et al. utilized a different type of cascade (**C^{5x}F⁵ⁱ**) for the formation of enone **60**.^[85] Cyclization of a vinyl radical onto a furan ring (Scheme 20) produced an allylic radical that fragmented to an enone. This was another example of the allyl system being used to “translocate” a radical center. Replacement of the silyl protected alcohol with a phenyl-sulfanyl group (which could be eliminated in the final step) resulted in a product suitable for an *in situ* Cope-type rearrangement.

2.5. Sequences Containing Hydrogen Migrations; Protecting/Radical Translocating Reactions

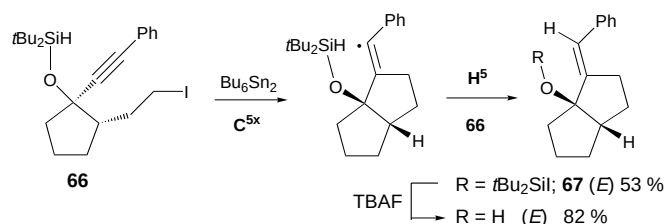
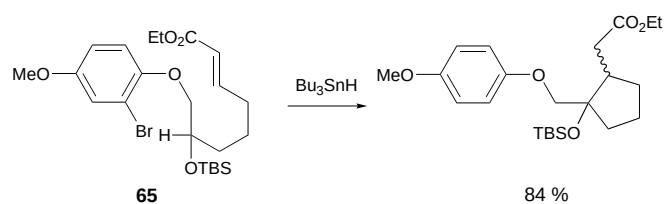
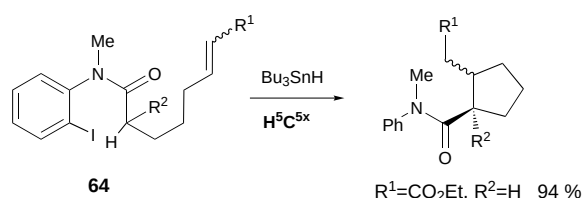
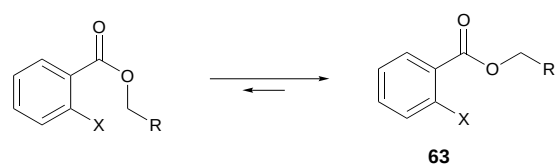
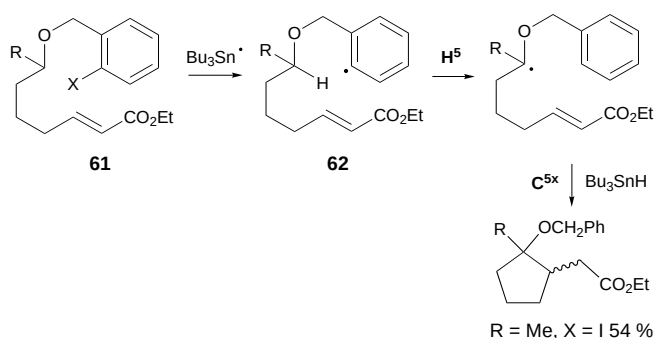
Sequences launched by a 1,5-hydrogen migration (**H**) generally include a cyclization as the second step. A special case, which automatically results in a radical lined up for a 5-*exo* cyclization, involves 1,5-H transfer to an initial vinyl (or aryl) radical. Such sequences have been extensively studied by the Curran group,^[86] who described examples in which the initial species were aryl radicals.^[87] The starting materials were benzyl ethers **61** prepared from alcohols containing hex-5-enyl-type chains (Scheme 21). These precursors contained C–H bonds, α to the oxygen atom, that were consequently weak and activated towards 1,5-hydrogen transfer. On generation of aryl radicals **62**, rapid 1,5-hydrogen transfer selectively generated α -alkoxyalkyl radicals^[87, 88]. The resulting intermediates could ring close onto a suitably situated unsaturated group to yield cyclic benzyl ethers, that is, protected cycloalkanols, after the final hydrogen transfer from tin hydride. Curran dubbed these **H⁵C^{5x}** sequences “Protecting/Radical Translocating Reactions” (PRT). He found that the (2-bromophenyl)dimethylsilyl group was often a more efficient hydroxyl protecting group.



Scheme 19. Ring enlargement by cyclization/fragmentation sequences.



Scheme 20. Preparation of enones by cyclization/fragmentation with furan-containing radicals.



Scheme 21. Radical cascades embodying 1,5-H shifts and cyclizations; TBSO = tri-*tert*-butylsiloxy, TBAF = *N,N,N*-tributyl 1-butanaminium fluoride.

The PRT method enabled tin-centered radicals to be used for what was effectively a hydrogen abstraction.

The PRT method has been deployed with protected amides (or amines),^[88a, 89] and carboxylates.^[90] When an amide or ester group was present the preferred conformation of this functional group had to be taken into account. Esters exclusively adopted *syn* configurations **63** (Scheme 21), that precluded 1,5-H transfer, so esters could not be used as PRT groups for carboxylic acids.^[90b] Anilides were predominantly in the desired configuration (for example **64**) especially in benzene, the normal reaction medium, and hence 2-iodoanilides functioned well as PRT groups and mediated cyclizations of unsaturated carboxylic acids (Scheme 21).^[90a]

Curran deduced that the strength of the C–H bond was not as crucial to the success of 1,5-H migrations as was the geometry of the system.^[86, 90b] He and J. Xu developed 2-bromo-4-methoxyphenyl ethers **65** as PRT groups that would generate radicals β to oxygen atoms in benzyl ether protected alcohols (Scheme 21).^[91] 1,5-H Transfer was most efficient (80–85 %) when a tertiary alkyl radical was generated. Deprotection was accomplished using ceric ammonium nitrate.

The rapidity of these H migrations enabled them to be coupled with intermolecular addition reactions, as was shown early on by Snieckus et al.^[88a] The method has recently been used in stereoselective syntheses. For example, β -substituted β -amino acids were synthesized enantioselectively in this way,^[92] stereoselective allylations were accomplished,^[93] and *N*-(2-iodobenzyl) protected 1,3-oxazolidines were used to stereoselectively functionalize the 2-position of β -amino alcohols.^[94]

HC sequences which do not involve the PRT process^[95] have been used in the synthesis of bicyclic β -lactams,^[96] and as routes to ($\pm$)-helistridane and (6*S*,7*S*)-dihydroxy-helistridane.^[97] Acyl radical equivalents, derived from vinyl radicals, have also been used in **HC** processes.^[98] 1,2-Group migration and 1,5-hydrogen migration steps also form parts of longer domino sequences (Section 3).

Sequences in which a cyclization is followed by a 1,5-hydrogen migration have also proved useful in preparations of bicyclo[3.3.0]octane derivatives and related polycyclics. For example, Curran et al. showed that silicon hydrides, functionalized as shown in **66**, on treatment with hexabutylditin, initially underwent a C^{5x} cyclization to generate a vinyl radical. This was followed by intramolecular hydrogen shift from the SiH group, that is, the C^{5x}H^5 sequence amounted to a unimolecular chain transfer (the **UMCT**) process.^[99] This cascade specifically gave the *E* alkene **67** which was readily hydrolyzed with *N,N,N*-tributyl 1-butanaminium fluoride (TBAF) to the corresponding (*E*)-hexahydro-1*H*-pentalenol (Scheme 21). A similar principle involving homolytic substitutions was recently developed by Studer et al.^[100]

2.6. Cascades Containing Ring-Opening Steps

Ring-opening processes result in the formation of double bonds and hence are often followed, at some point in a sequence, by a cyclization.

Motherwell et al. studied in detail $F^{3o}C^{5x}$ sequences of butenyl- and butynylbicyclo[4.1.0]heptane derivatives (Scheme 22).^[101] The ketyl radical that started the sequence was generated in four different ways but the best yield of spiro product **68** (79 %) was obtained using SmI_2 with 1,3-dimethyl hexahydro-2-pyrimidinone (DMPU).

In a very similar system (containing a terminal rather than a silylated alkyne) the ketyl radical was generated by illuminating the initial bicyclo[*n*.1.0]alkanone in triethylamine and acetonitrile,^[102] and a yield of 23 % was obtained. Kim et al. uncovered a cascade of this general type in their investigations of cyclizations onto azide moieties (an FCF_2 sequence).^[62] Motherwell et al. also examined very similar reactions of C-centered radicals generated from thiocarbonylimidazoles **69** using tin hydride.^[103] The reaction proceeded in an analogous manner ($F^{3o}C^{5x}$), forming spiro[5.6]decene derivative **70** in 71 % yield (Scheme 22). In both this, and the ketyl

radical study, an FCC cascade was also described. Enholm and Jia put this type of FC cascade to good use in tin hydride mediated preparations of linear and angular triquinanes, which were obtained in excellent yields.^[104]

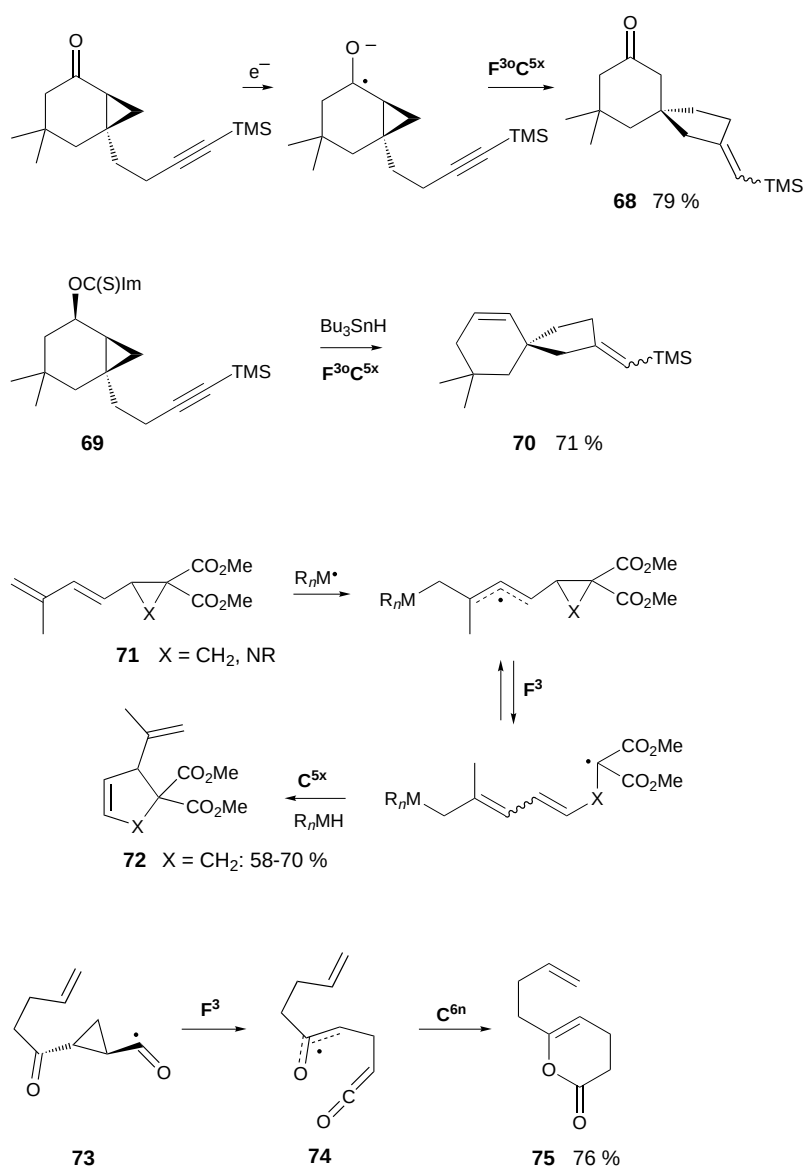
The “outer” mode cyclopropyl ring opening, giving primary radicals in the above sequences, resulted from stereoelectronic control. In contrast, the “Dowd type” ring expansions occurred in the “inner” mode because of the inclusion of substituent X (Section 2.4, Scheme 19) that stabilized the secondary radical.^[105, 106]

Reactions started by fragmentations of three-membered rings that are not fused to another ring have also been reported. Bertrand et al. described FCC processes as routes to bicyclic lactones, lactams, and ketones.^[107] Feldman et al. adapted their [3+2] cycloaddition strategy for intramolecular use in the synthesis of ($\pm$)-rocaglamide^[108] and brefeldin.^[108b] Miura et al. described an F^3C^{5x} sequence starting with diencylcyclopropane **71** ($X = CH_2$) and involving allyl radical translocation to yield functionalized allylcyclopentene **72** ($X = CH_2$; Scheme 22).^[109] The design was such that the radical that added intermolecularly ($R_nM^\bullet$) was also the radical that was eliminated to terminate the sequence (and hence could hypothetically be used as a catalyst). Different radical sources were tested, and triphenyltin hydride generally gave the best results. The authors also applied the method with a dienzylaziridine, thus forming a five-membered nitrogen heterocycle.^[109]

Oxiranylmethyl and aziridinylmethyl radicals also ring open efficiently to yield heteroatom-centered radicals, except when phenyl or other product-stabilizing substituents, are present. A cascade consisting of ring opening of a butenyl epoxymethyl radical followed by cyclization of the resulting alkoxy radical onto the butenyl bond (F^3C^{5x}) has been used for the preparation of vinyl tetrahydrofurans.^[110, 111] A second cyclization onto the vinyl group took place with the *cis*-isomer of the intermediate vinyl tetrahydrofuranylmethyl radical ($F^3C^{5x}C^{5x}$) opening the way to 7-oxabicyclo[2.2.1]heptane derivatives. More recently, another FC reaction involving a homoallylic aminyl radical derived from an aziridinylmethyl radical has been described.^[112]

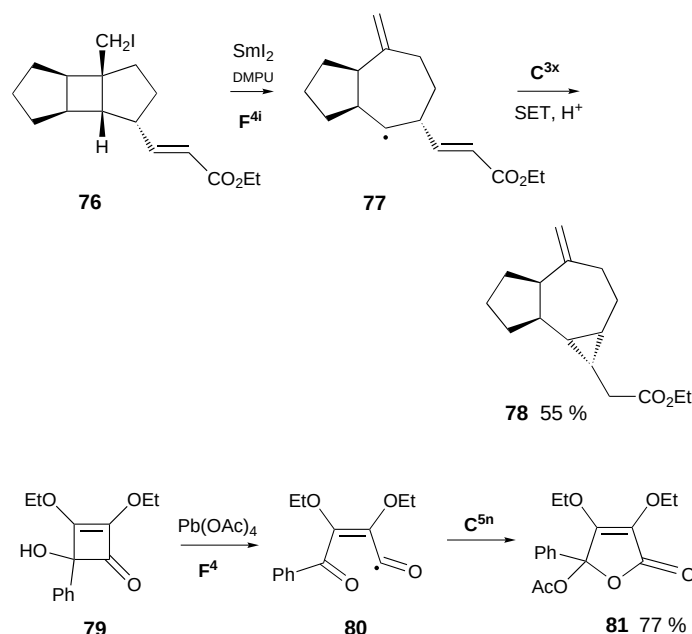
Pattenden et al. communicated a surprising and unusual sequence starting from cyclopropylacyl radical **73** (which was generated from a selenide) and leading to unsaturated lactone **75** by an F^3C^{6n} cascade (Scheme 22).^[113] The ring-opening step produced ketylmethyl radical **74** which, after radical delocalization onto oxygen, underwent a 6-*endo* cyclization to afford lactone **75** in good yield.

Photochemical [2+2] cycloadditions have been widely applied for the preparation of functionalized bicyclo[3.2.0]heptanes that un-



Scheme 22. Cascades starting with three-membered-ring opening reactions; TMS = trimethyl silyl.

dergo radical-mediated opening of their four-membered rings to produce methylenecyclopentanes. For example, a cascade synthesis of the aromadendrane carbon skeleton was started by treatment of tricyclic iodide **76** with SmI_2 (Scheme 23).^[114] Cleavage of the cyclobutylmethyl-type radical produced intermediate **77** which subsequently ring closed, underwent a rapid single electron transfer (SET), and picked up a proton to yield tricycle **78** containing the desired skeleton (Scheme 23). The cascade amounted to an F^4C^{3x} process and cyclopropane ring formation was favored by the radical-stabilizing ester group.



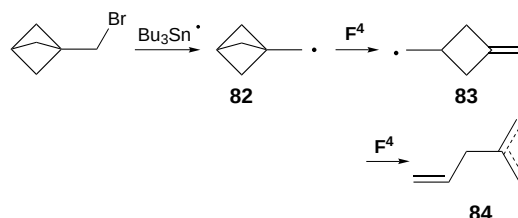
Scheme 23. Cleavage of four-membered rings followed by cyclization. DMPU = 1,3-dimethyl hexahydro-2-pyrimidinone.

An unusual series of reactions commencing with the squaric acid derivative **79** was described by Eguchi et al. (Scheme 23).^[115] The alkoxyl radical, generated from alcohol **79** by lead tetraacetate, ring opened to give acyl radical **80**. Subsequent *endo* cyclization back onto the oxygen atom of the newly generated carbonyl group yielded unsaturated lactone **81** by an F^4C^{5n} sequence the overall effect of which was ring expansion. A similar sequence was also reported by O'Dell et al. for a reaction in which an alkoxyl radical was generated using mercuric oxide/iodine.^[116]

Precursors programmed for successive ring opening of two three-membered rings must contain structures such that the but-3-enyl-type radical formed in the first F^3 step will unmask a cyclopropylmethyl-type of radical. Several examples of F^3F^3 sequences in, for example, quadricycl-3-yl radicals, dispiro-[2.2.2.2]decadiene-derived radicals and various biradicals have been reported in the older literature.^[7] Most recent instances of F^3F^3 types have formed parts of more complex cascades (Section 3.3).

The (bicyclo[1.1.1]pentyl)methyl radical **82** undergoes a unique double fragmentation involving two four-membered rings (F^4F^4). The first β scission occurs at low temperatures

transforming the molecule into the (3-methylenecyclobutyl)-methyl radical **83** that itself undergoes a second ring cleavage yielding the 2-allylallyl radical **84**^[117, 118] (Scheme 24). This cascade is a rare instance where all three of the intermediates were individually characterized by EPR spectroscopy and the rate constants of both steps were determined.



Scheme 24. Double ring opening of (bicyclo[1.1.1]pentyl)methyl radicals.

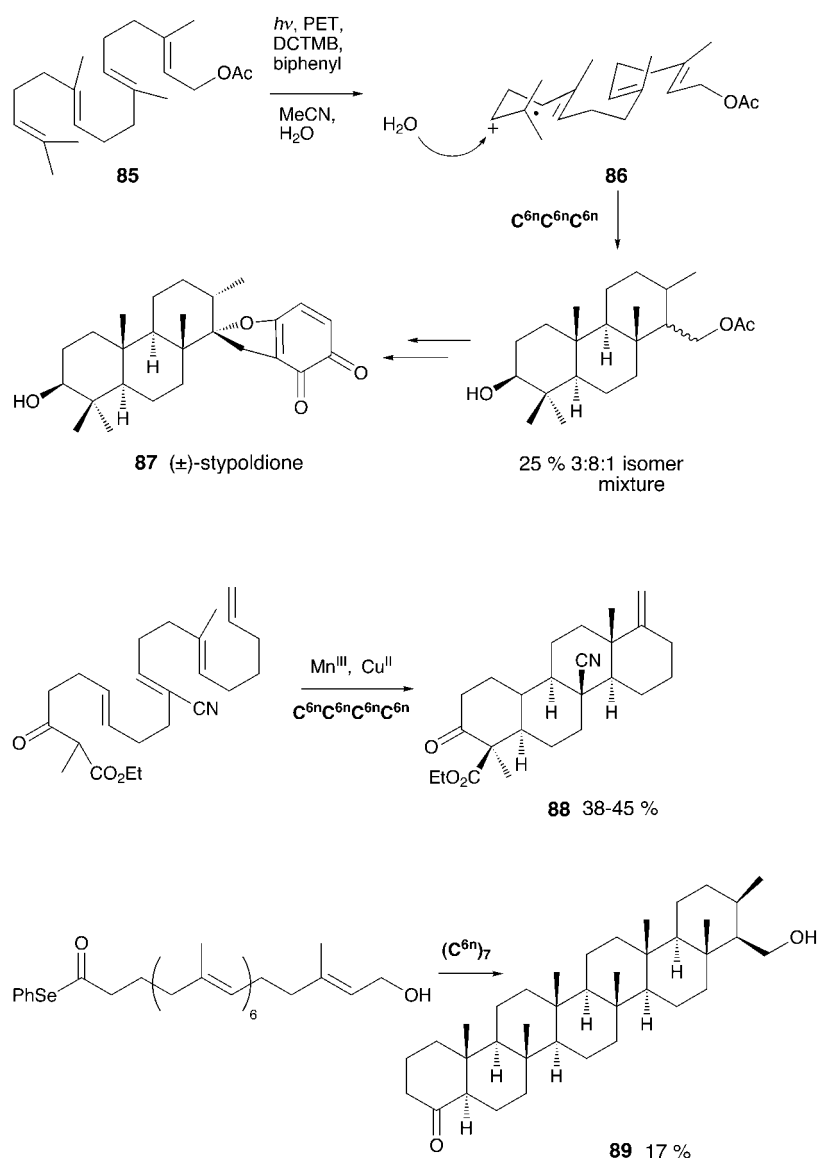
3. Three-Stage and Longer Unimolecular Cascades

3.1. Triple Cyclization Sequences

From the standpoint of organic synthesis, the triple cyclization (CCC) is the most important of the 64 sub-types of unimolecular three-stage cascades. Beginning with an initial acyclic radical, three C^{5x} steps lead to triquinane-type structures. However, many other polycyclic structures are accessible from initial designs that permit closures to different ring sizes. Longer cascades of cyclizations are more likely to involve precursors that contain repeating units, as exemplified by the cascade initiated by an unusual photoelectron transfer (PET) method (Scheme 25, top).^[119] Although this cascade was started by initial formation of radical cation **86** from tetraene **85**, the domino cyclization was purely a radical process,^[120] and was applied to the synthesis of ($\pm$)-stypoldione **87**. The three *endo* cyclizations were constrained by the three strategically placed methyl substituents in the original tetraene.

A large number of remarkable triple-C sequences mediated by Mn^{III} and Cu^{II} salts have been invented, and those in Scheme 25 are typical. The defining features were the linearity of the precursor polyene containing the radical acceptor units within the same chain, not branched or interrupted by the initial radical site, and the methyl groups, usually necessary to direct cyclizations *endo*, were distributed every fifth C-atom from the start of the polyene system. These cascades contributed to notable syntheses of *dl*-isopongiadial,^[121] *dl*-spongiatriol,^[122] and to even more remarkable quadruple $\text{C}^{6n}\text{C}^{6n}\text{C}^{6n}\text{C}^{6n}$ extensions in which complete homosteroid skeletons, for example, **88** were constructed (Scheme 25).^[123]

Good use has been made of the preference shown by acyl radicals for the 6-*endo* mode of cyclization; the perhydrophenanthrene and -decalone ring systems were constructed^[27, 124] and the method was extended to triple-C cascades and superb CCCC sequences leading to steroid ring systems. Yields were generally 60–80% and just two D ring epimers



Scheme 25. Formation of steroidal structures by multiple *endo*-cyclizations; DCTMB = 1,4-dicyan-2,3,5,6-tetramethylbenzol, PET = poly(oxy-1,2-ethanedioxydicarbonyl-1,4-phenylene-carbonyl).

were formed. More recently this methodology was applied to the synthesis of spongian-16-one by a CCC sequence.^[125] The range of cascade cyclizations was dramatically extended by the realization of a phenomenal seven-step all *endo* $C^{6n}C^{6n}C^{6n}C^{6n}C^{6n}C^{6n}C^{6n}$ sequence (Scheme 25) that accomplished the one-pot synthesis of novel steroidal heptacycle **89** in a very acceptable yield of 17%.^[126]

Pattenden et al. have also studied three-stage and longer macrocyclization–transannulation sequences;^[80b] although unexpected or undesired reactions often served to highlight some of the drawbacks of these systems. For example, an ambitious attempt to assemble the steroid ring system by a macrocyclization–transannulation reaction consisting of a CCCC sequence failed.

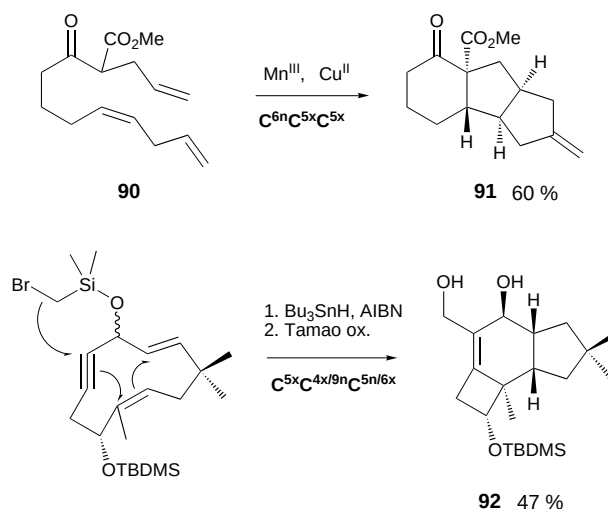
The triple cyclization of “interrupted” polyene **90** produced the tricyclic ketone derivative **91** (Scheme 26) in good yield as a single diastereoisomer^[127] by a $C^{6n}C^{5x}C^{5x}$ cascade. The ester substituent stabilized the initial radical and promoted the first

6-*endo* cyclization. In the absence of additional directing substituents, however, the next two ring closures took place in the usual 5-*exo* mode (Scheme 26). Snider et al. recently synthesized a precursor of (±)-isosteviol and (±)-beyer-15-ene using this “interrupted” method which showed that it was more likely to suffer from lower yields because of alternative cyclizations taking place.^[128]

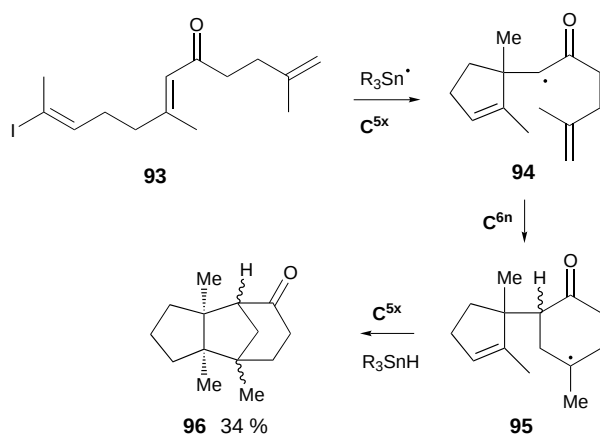
Of the few examples of triple and longer cyclizations, starting from structures that were very irregular in the disposition of radical acceptors, most involved silicon-tether methodology. One such cascade was a remarkable transannular $C^{5x}C^{4x/9n}C^{5n/6x}$ sequence, that was used in the synthesis of *epi*-illudol (Scheme 26) which is shown in protected form (**92**).^[129] Other CCC sequences have been described in a review.^[17]

Triple cyclizations that amount to a “round trip”, that is, are “isomerisations in which an intermediate radical ultimately adds back to the initial site of radical generation” have been investigated by several groups.^[130] Treatment of the trione derivative **93** with tin hydride led to production of a mixture of isogymnomitrene (major) and gymnomitrene (minor) precursor ketones **96** (Scheme 27). An initial C^{5x} cyclization afforded radical **94**, which preferred to cyclize in the C^{6n} mode, as is normal for α -keto radicals, although considerable coaxing was needed.

Sugar-based dodeca-1,6-dien-11-yne and dodeca-6-en-1,11-diynes sustained triple $C^{5x}C^{5x}C^{6n}$ round-trip cascades to yield diastereomerically pure 1,6-dioxahydrindacenes on treatment with triphenyltin hydride.^[131] These tetracycles were only minor products, because cascade propagation stopped after two cyclizations for the majority of intermediates.



Scheme 26. Triple cyclizations of interrupted and irregular triene and dieneyne units.



Scheme 27. "Round trip" triple cyclization leading to isogymnomitrene and gymnomitrene precursor ketones.

However, the reactions were noteworthy because of their stereospecificity and because the radical-promoted triple cyclization was equivalent to a [2+2+2] cycloaddition.

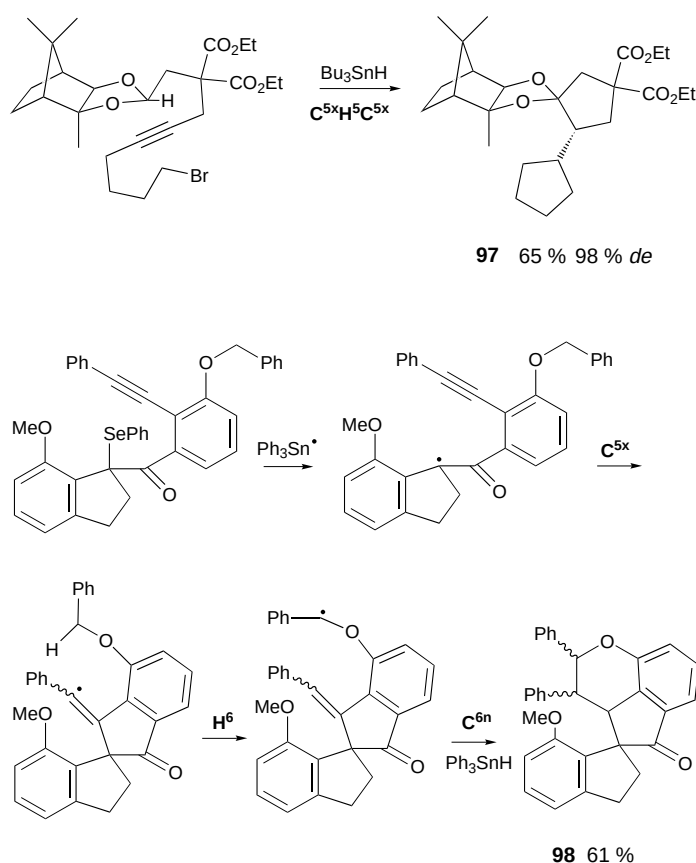
3.2. Other Multiple-Step Cascades Containing Cyclizations

Premature hydrogen transfers are one way that multiple-cyclization sequences can be diverted from their original design. For example, attempts by Malacria and co-workers to synthesize a steroid skeleton by means of a multiple-cyclization sequence was deflected into a **CCH** cascade,^[132] and H migration from supposedly passive ether protecting groups may lead to the formation of dehydroxylated products.^[133] However, hydrogen migrations can also be beneficial as in the **CCCCHC** process (followed by elimination of a trimethylsilyl radical) which aided the development of syntheses of linear triquinanes.^[134]

CHC sequences are comparatively common, and have proved to be of some utility. Stien et al. published a report concerning a chiral acyl-radical equivalent that included the interesting **C^{5x}H⁵C^{5x}** sequence shown in the top part of Scheme 28.^[98] The same alkyne group was the acceptor for both cyclizations, and the product **97** was formed in good yield, and high diastereomeric excess. The large acyl-group equivalent was important for the stereoselectivity and for increasing the population of the conformer that promoted fast 1,5-H migration.

Radicals are useful for forming quaternary centers in spiro ring systems and this property was exploited in syntheses leading eventually to (±)-fredericamycin. Initially, spirocycle **98** was obtained by a **C^{5x}H⁶C⁶ⁿ** cascade (Scheme 28).^[135]

Many **CHC** sequences involving [(bromomethyl)dimethylsilyl] allyl and propargyl ethers have been reported,^[17, 136] including a **C^{5x}H⁵C⁵ⁿ** cascade terminating in a rare 5-*endo* cyclization involving no ring heteroatoms.^[136b] More extended cascades were uncovered including various **CHCF** types,^[136c] but the most impressive was probably the **C^{5x}H⁶C⁶ⁿC^{4x}H⁶** sequence sustained by diyne **99** (Scheme 29).^[136e] The initial



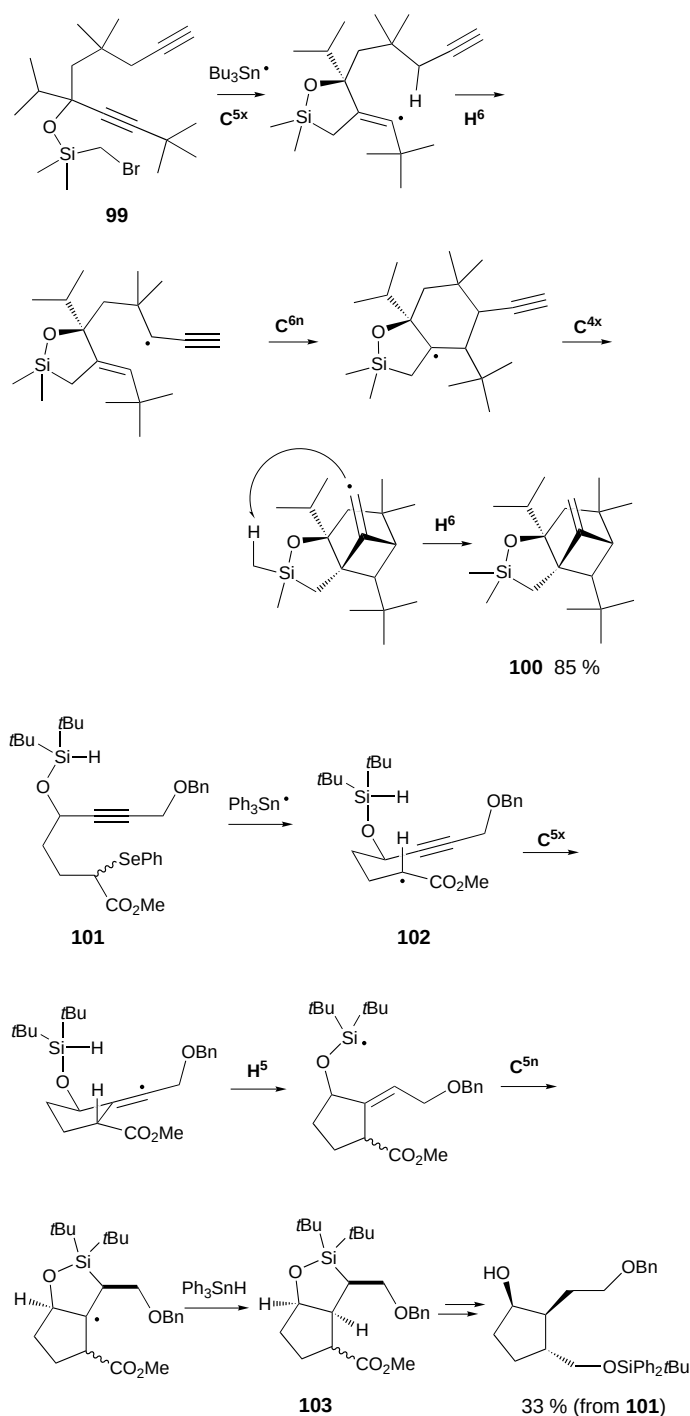
Scheme 28. Cascades starting with cyclization/H migration steps.

5-*exo* cyclization/1,6-H shift/6-*endo* cyclization sequence was not too surprising, but this was followed by an exceptional 4-*exo* cyclization, which was trapped by the sequential 1,6-H shift. The 85% yield of tricyclic product **100** was also remarkable, and the reaction occurred with good stereoselectivity.

A **C^{5x}H⁵C⁵ⁿ** cascade starting from acetylenic selenide **101** and leading to a methyl *epi*-jasmonate precursor has also been reported (Scheme 29).^[137] The first cyclization took place from the preferred conformer (**102**) of the initial radical in which the ester group was *trans* to the O–Si unit. The second cyclization to give **103** was a normally disfavored **C⁵ⁿ** type, but presumably *endo* approach was permitted because of the longer Si–O and Si–C bonds associated with the Si-centered radical.

The radical Brook rearrangement involves a concerted 1,2-shift of a silicon group from a carbon atom to an oxygen centered radical. Tsai et al. developed this into an effective synthetic method, in which an acylsilane (e.g. **104**; Scheme 30) acts as a geminal radical acceptor/donor.^[138] The basic process is a **CM** cascade, that transforms a cycloalkyloxy radical to a cycloalkyl radical. The advantage occurs when further reactions take place such as a subsequent cyclization leading, after hydrolysis, to diol production (Scheme 30).

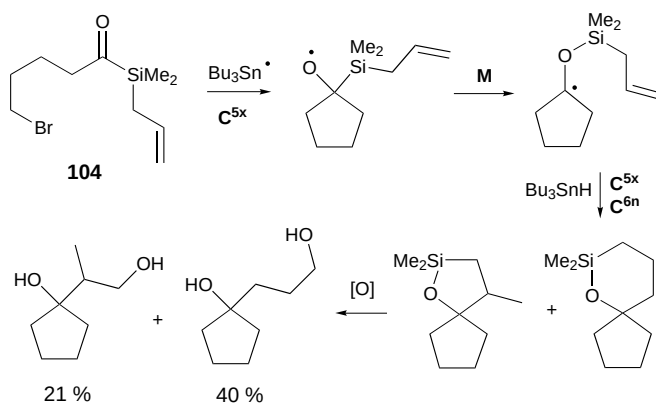
Extensions of the **CF** (Dowd) type of ring-expansion sequence take various directions including **CCF** processes,^[139] and a rare **C^{6x}F⁴ⁱH⁵** sequence (Scheme 31) resulting in the intermediate bicyclo[6.3.0]undecanone radical **106** (an α -acyl



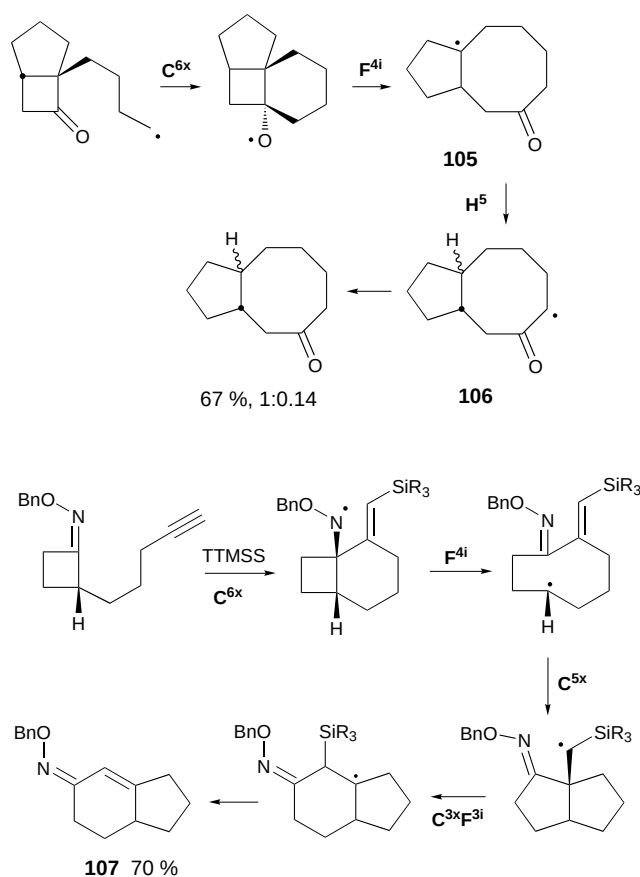
Scheme 29. Cascade transformations of silyl ethers.

radical).^[84c] The hydrogen shift in **105** is permitted because of the mainly *trans* configuration of the ring junction.

The scope of **CFC** sequences, including the effects of varying ring size and competing hydrogen transfers, have been studied,^[139] and one was employed in a synthesis of *cis*-decalins.^[140] Many permutations of an ingenious theme embodying cyclization onto a methylenecyclopropane unit, with subsequent ring opening, have been explored.^[141] The consequent **CFC** cascades mediated by tin hydride have produced bicyclic systems^[141c] and spirocycles,^[141d] and the



Scheme 30. Cyclic diol production by a radical Brook rearrangement.



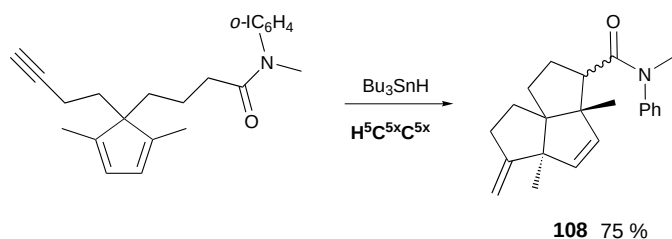
Scheme 31. Synthesis of bicyclic systems by sequences starting with cyclization/ring cleavage.

reaction has been extended to **CFCC** sequences for the synthesis of tricycles,^[141e] and, notably, in the diastereoselective synthesis of paeonilactone B (see Scheme 5, Section 1.2).^[141b]

Unusual cascades involving cyclization onto an oxime ether followed by fragmentation to a medium-sized ring and subsequent transannular cyclization, were investigated by Pattenden et al. The processes that occurred sequentially, depended on subtle structural differences in the systems used. A remarkably intricate **C^{6x}F⁴ⁱC^{5x}C^{3x}F³ⁱ** sequence, that contained two separate ring expansions, ended in the formation of

bicyclic oxime ether **107** (Scheme 31).^[142] Other syntheses involving **CF** sequences have been reported.^[143, 144]

The usefulness of PRT sequences has been referred to (see Section 2.5), and an **HCC** sequence that afforded angular triquinane **108** based on this methodology has been reported (Scheme 32).^[90a] The technique has been further developed: for example the method was used in the formation of γ -lactams.^[132, 145]



Scheme 32. Triple cascade involving protection/translocation (PRT) methodology.

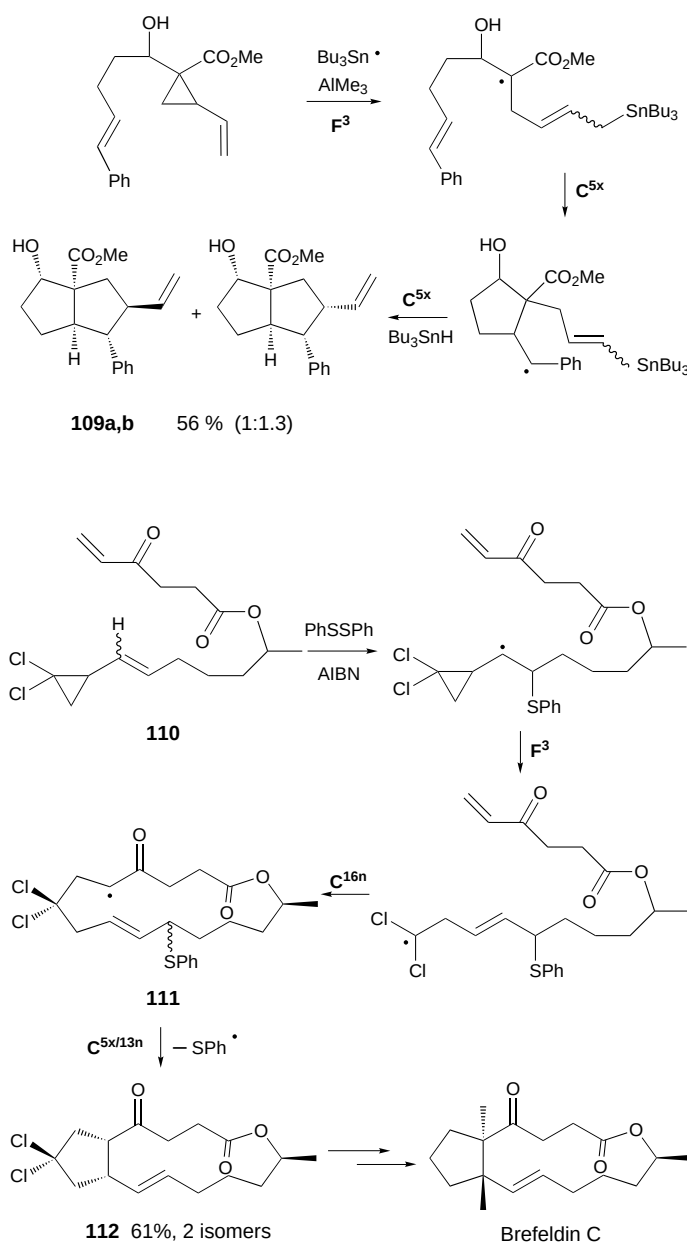
3.3. Multiple-Step Cascades Starting with Ring Cleavage

The butenyl unit, generated on cleavage of a cyclopropylmethyl radical, may eventually act as the acceptor in a subsequent cyclization. Consequently, cascades of the **FCC** type have been quite popular. A recent example demonstrated the excellent stereoselectivity that a Lewis acid can induce: Renaud et al. designed an **F³C^{5x}C^{5x}** cascade that produced functionalized bicyclo[3.3.0]octanes **109a, b** (Scheme 33).^[146] In the absence of trimethylaluminum at least eight stereoisomers were obtained, however, addition of this Lewis acid controlled the stereochemical outcome so that only two isomers were formed in a combined yield of 56 %.

The brefeldin skeleton was obtained by addition of phenylsulfenyl radicals to the vinylcyclopropane **110**.^[147] Ring opening was followed by an *endo* macrocyclization to intermediate **111** which underwent a further cyclization and final loss of a phenylthiyl radical. The complete **F³C¹⁶ⁿC^{5x/13n}** sequence led to 13-membered cyclic lactone **112** (Scheme 33).

The tricyclic core structure (**113**) of laurenene was prepared using the **F⁶ⁱC^{5x}C^{5x}** process shown in Scheme 34.^[148] Stereochemical control was critical to the success of this reaction; a *cis* arrangement of the allylic side chain and the hydroxyl group occasioned unwanted 1,5-migration of the allylic hydrogen. Axial substituents were also found to render the final cyclization unfavorable. Crimmins et al. described a series of cascades comprising a ring opening, followed by a ring expansion, that is, **FCF** sequences, as exemplified by the **F^{4o}C^{3x}F³ⁱ** transformation leading to tricyclic ketone **114** (Scheme 34).^[149]

Iminyl radicals were generated by treatment of polycyclic imines (such as **115**) with tributyltin radicals. Cleavage of the four-membered rings started cascades that, for certain stereochemical arrangements, promoted 1,5-hydrogen migrations.^[150] For example, radical **116a** underwent a 1,5-H shift followed by rapid cleavage of the four-membered ring (**F⁴H⁵F⁴**) whereas isomeric radical **116b** underwent no further

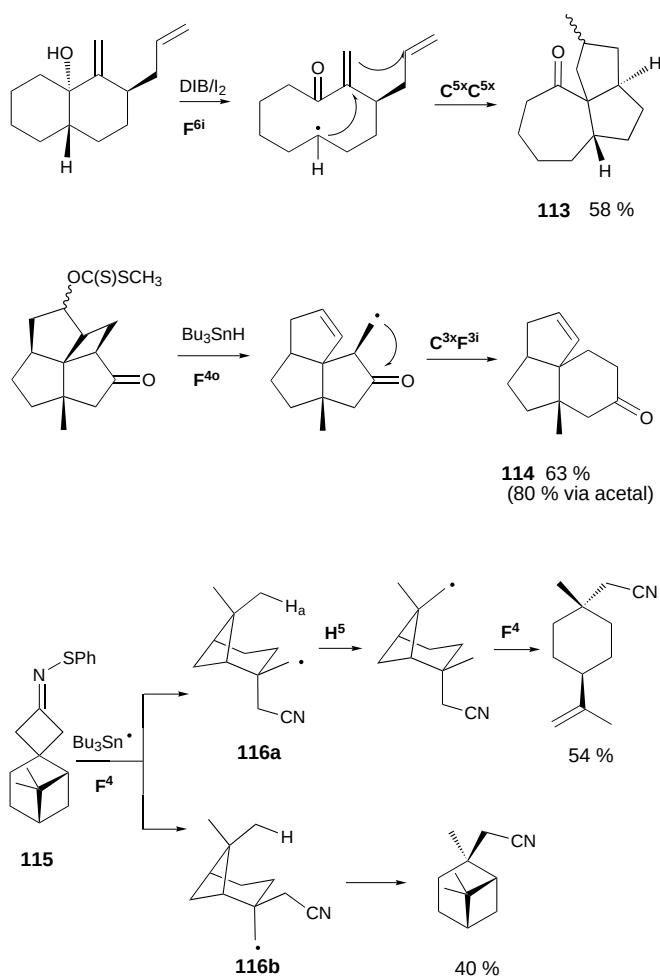


Scheme 33. Cascades involving ring cleavage followed by cyclization.

rearrangement (Scheme 34). Remarkably, abstraction of H_a in **116a** appeared to be facile, despite the fact that the resulting radical was primary.

Elegant **FHC** sequences were executed as routes from bicyclic epoxides to both linear and angular triquinanes (**117**, Scheme 35).^[151, 152] Catalytic amounts of diphenyl disulfide were used to mediate the reactions.

Ziegler and Peterson described an unusual sequence starting with epoxide **118** and leading by an **F^{3o}F³H⁵** cascade to formation of the prostaglandin B₁ skeleton **120** (Scheme 35).^[153] Two three-membered ring openings resulted in the formation of radicals **119a** and **119b**, which were in rapid equilibrium (presumably because of reversible closure/opening of the epoxide ring). Only the *cis* isomer **119b** could undergo the 1,5-H transfer. Synthesis of prostaglandin B₁ from **120** was straight forward.



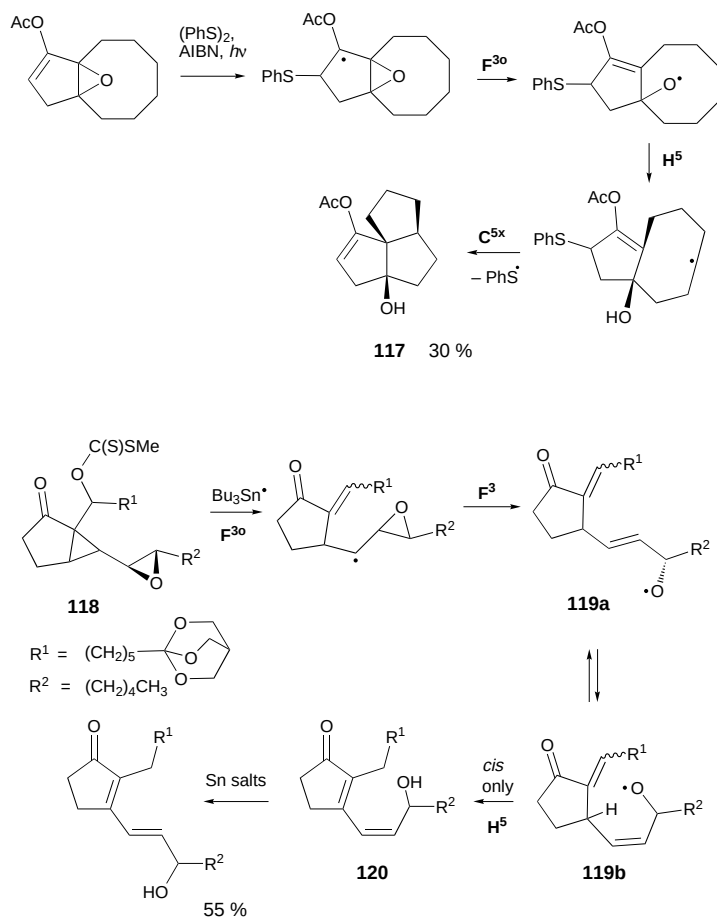
Scheme 34. Cascades involving ring cleavage, cyclization and H-migration; DIB = (diacetoxyiodo)benzene.

The potential for a short two-carbon ring expansion of cycloalkanones by **FFC**-cascade rearrangements of spiroepoxides **121** has been thoroughly examined (Scheme 36).^[154, 155] The reactions all had the same premise; initial ring opening of the epoxide to generate an alkoxy radical **122** that would ring open a second time to generate an alkyl radical **123**, ready for the final cyclization (Scheme 36). This cascade entails changes in hybridization at five of the original atoms yet the molecules were found to traverse this complex reaction coordinate with ease. The enone system in intermediate **123** was expected to enhance *endo*-cyclization but, although this predominated for most ring sizes, closure was not selective enough for the cascade to function as a general and efficient two-carbon ring expansion. Furthermore, it was found that for the larger rings, 1,5-H transfer was competitive with ring opening of the alkoxy radicals.^[154a] For example, radical **124** ($n=5$) underwent ring opening and H migration to produce vinylcyclooctyl radical **125**, that took part in a final cyclization process to yield bicyclo[4.2.1]nonanol derivative **126**. Overall this amounted to an **F³H⁵C^{5x}** process.

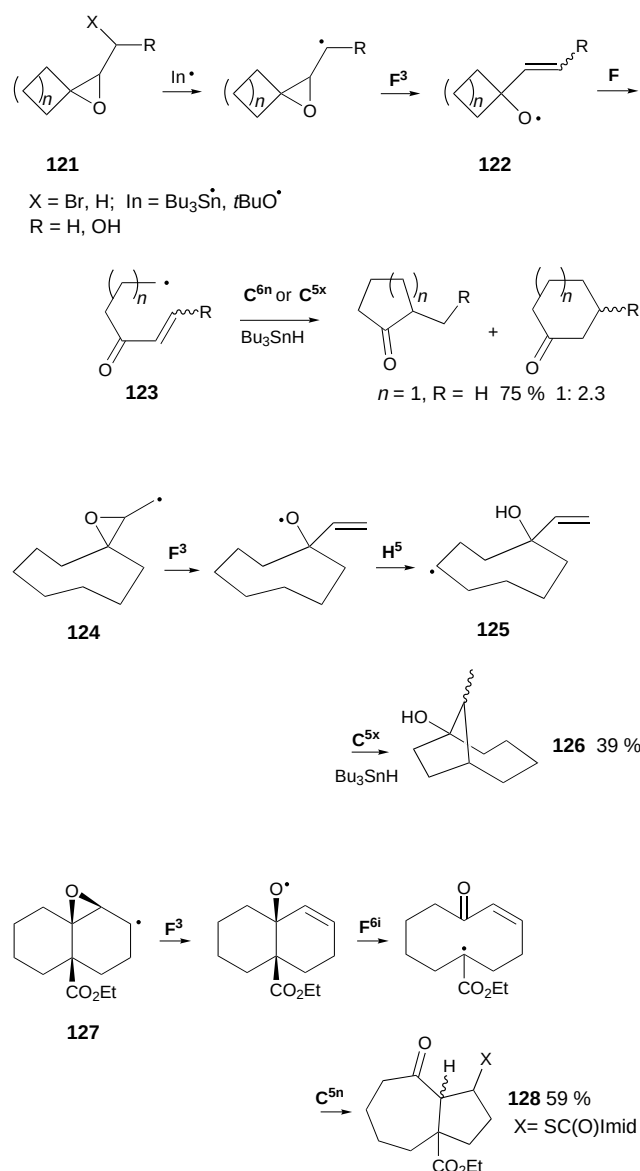
Suárez et al. have taken advantage of the ready ring cleavage of cyclohexyloxy radicals by means of a series of cascades in which an alkoxy radical was generated from

the corresponding alcohol using (diacetoxyiodo)benzene and iodine.^[156] Most of these sequences incorporated intermolecular addition of oxygen, but an **FF** process in which the second fragmentation involved the ring opening of a cyclopropyl ring was described.^[156] A combination of these rearrangements was utilized in syntheses of medium-sized, fused-ring polycyclics **128** (Scheme 36).^[157] The overall sequences were **F^{3o}F⁶ⁱ** or **F^{3o}F⁶ⁱC⁵ⁿ**, depending on conditions, which could be adjusted to favor either sequence.

Most fragmentations found in cascade sequences embody cleavage of three- or four-membered rings. It follows that cascades of three or more fragmentations are rare because of severe problems in the preparation of precursors containing so much strain. Moreover, such cascades are essentially degradative, unraveling laboriously assembled structure and symmetry, and hence are usually of mechanistic interest only. Nevertheless, a few triple-fragmentation sequences have been investigated, notably those based around precursors with cubane and related structures. The cubylmethyl radical **129** was generated in several ways and found to rearrange very rapidly by a series of three **F⁴** ring-opening steps (Scheme 37). Under appropriate conditions, just two isomeric methylenedicyclobutenes **130** were obtained as products, although by use of good hydrogen donors most of the intermediate radicals could be trapped,^[158] and several were characterized by EPR spectroscopy.^[159] The ring-opening steps were strictly



Scheme 35. Cascades starting with epoxide ring-cleavage processes.



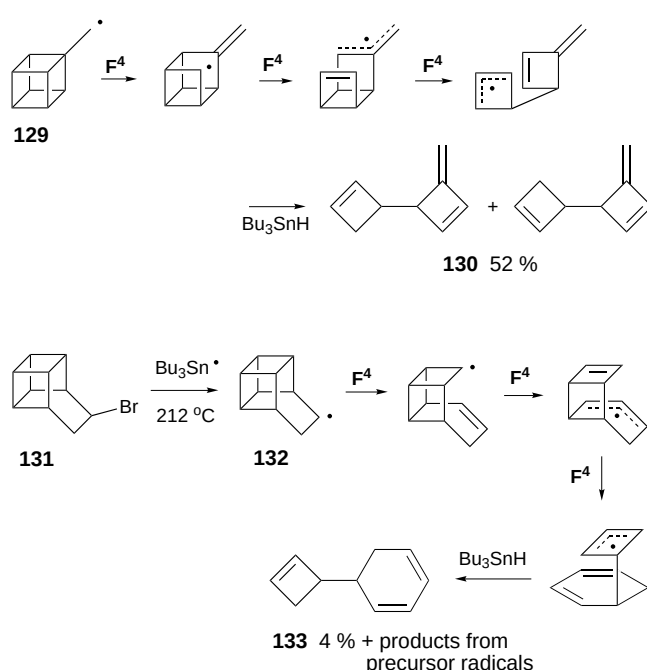
Scheme 36. Cascade expansion/rearrangement of spiro and tricyclo epoxides.

stereoelectronically controlled and rate constants were estimated for each.

Remarkably, the 9-bishomocubyl (basketyl) radical **132** did not rearrange at 150 °C even though it contained approximately 470 kJ mol⁻¹ strain. However, at 212 °C the tributyltin hydride mediated reaction of basketyl bromide **131** resulted in 5-(cyclobut-2-enyl)cyclohexa-1,3-diene **133** by a triple **F⁴F⁴F⁴** cascade (Scheme 37) analogous to that sustained by radical **129**.^[160] Impressively, considering its internal strain, the 9-homocubyl radical did not follow suit even at 220 °C.

4. Repeating and Infinite Free-Radical Cascades

In certain circumstances the rate of a **C**, **M**, **H**, or **F** rearrangement may be similar or even equal to that of its reverse rearrangement. As indicated in the introduction, ring

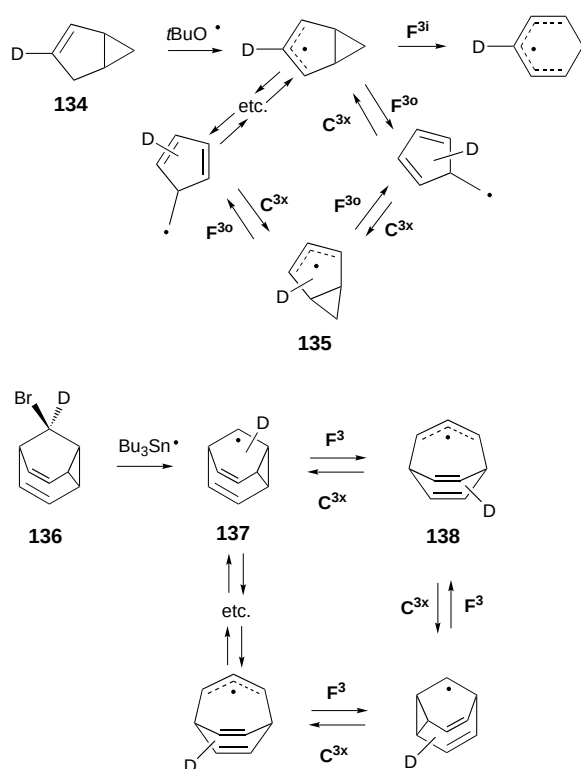


Scheme 37. Triple-fragmentation cascades of cubylmethyl and basketyl radicals.

opening is the reverse of cyclization and hence partial, or total, reversals of cascades containing **CF** sequences are permitted. In particular, the **F³** ring opening is the reverse of the **C³** cyclization and hence, in special cases that usually involve symmetric bi- and polycyclic species, cascades can occur that are degenerate, that is, return a radical to its original structure.

One such cascade is the “walk” or “circumambulation” established for the bicyclo[3.1.0]hexenyl radical (Scheme 38, top). Initial hydrogen abstraction from bicyclo[3.1.0]hex-2-ene gave the expected bicyclo[3.1.0]hexenyl radical, which rearranged by scission of its inter-ring bond (**F³ⁱ**) to give a cyclohexadienyl radical and hence to the product benzene. Experiments with deuterium labeled precursors (**134**) showed that the label was statistically scrambled to every possible site in the intermediate cyclohexadienyl radical (**135**). This was rationalized by a cascade involving an infinite sequence of β scission (**F^{3o}**) and cyclization reactions (**C^{3s}**), the products being bled off by the competing **F³ⁱ** ring cleavage (Scheme 38).^[161, 162] Various substituted examples were studied spectroscopically.^[162] Delicate balances of rearrangement possibilities can easily be redirected by structural changes. This was illustrated by the fact that the vinylogous bicyclo[5.1.0]octa-2,4-dienyl radical did not undergo an analogous walk.^[163, 164]

A three dimensional analogue of the “walk” rearrangement has also been discovered. Tributyltin hydride reduction of 9-bromotricyclo[3.3.1.0^{2,8}]nona-3,6-diene (9-bromobarbaralane) gave bicyclo[3.2.2]nona-2,6,8-triene (83 %) together with unrearranged barbaralane (2 %).^[165] Spectroscopic and deuterium-labeling (**136**) studies established that a remarkable series of ring-opening/cyclization steps rendered the structure fluxional and distributed the unpaired electron to



Scheme 38. Repeating cascades involving infinite sequences of ring-cleavage/cyclization steps.

every carbon (Scheme 38, bottom).^[166] The tricyclo[3.3.1.0^{2,8}]-nona-3,6-dienyl radical **137** was transformed to the bicyclo[3.2.2]nona-2,6,8-trienyl radical **138** by an F^3 ring cleavage. The process could be reversed by means of four possible C^{3x} cyclizations. However, radical **138** was stabilized by allyl-type electron delocalization and hence was the predominant partner in the equilibrium. Series of $(C^{3x}F^3)_n$ sequences (part shown in Scheme 38) scrambled deuterium to every site.

5. Summary and Outlook

The science of “programming” organic precursor molecules to achieve particular target structures by multiple step sequences of radical rearrangements is maturing steadily. A phenomenal variety of unimolecular radical cascades exist in which a single molecule undergoes a complete metamorphosis by means of combinations of four fundamental rearrangement types, with occasional assists from more exotic processes. These cascades are mainly responsible for dramatic skeletal reorganizations, rather than functional-group manipulations, although every cascade involves some functional-group alterations, usually in the initiation and/or termination stages. Multiple cyclization sequences build up polycyclic structures while hydrogen and group migrations transfer (translocate) radical centers. Ring cleavage processes undo prearranged structure but, because they usually introduce unsaturation, make subsequent cyclizations possible.

A convenient system for classifying free-radical cascades has been devised, based on combining the mechanisms of individual steps in such cascades. Every cascade can be

represented by a multiletter that indexes the process. These codes display the component steps, give clues about the reaction course, and are useful for relating cascades to each other, for evaluating and comparing cascades and for inferring their mechanisms.

3-Step cascades of C^{5x} cyclizations typically produce linear and angular triquinanes and related polycycles. Many natural products containing all or parts of these skeletons, and analogues with one, two, or three six-membered rings, have been synthesized by this method. Acyl radicals preferentially cyclize in the C^{6n} mode to produce six-membered rings, and this mode can also be programmed by inclusion of methyl groups, five atoms away from incipient radical centers, at unsaturated bonds. By these means many partial and complete steroidal skeletons have been assembled. Stereoselectivity is often good even for acyclic precursors, but several strategies have been developed to facilitate closer stereochemical control. The one-ring template strategy starts with precursors containing five- or six-membered rings that then direct the stereochemistry of two or more cyclizations. Combinations of all these parameters have enabled impressive syntheses of many types of terpenoid, steroid, and alkaloid natural products.

Of the many intricate cascades containing ring-cleavage steps, the most useful synthetically are the ring expansions which have opened up synthetic routes to various types of medium-ring cycles and polycycles. Ring cleavage is the reverse of cyclization. In special, symmetrical structures, therefore, this can lead to sequences that are reversible, thus launching endlessly repeating cascades supported by delightfully fluxional structures.

Of the 64 possible three-stage cascades only about 16 have so far been investigated, with interest concentrating heavily on **CCC**, **CHC**, **CFC**, and **FCC** sequences. Cascades starting with hydrogen or group migrations have hardly been touched. The discovery field for four-stage and longer cascades is even more vast because fewer than 10 such sequence types have been examined to date. Of course, multiple cyclization cascades, particularly longer ones, are likely to maintain their priority of interest because they rank amongst the most powerful strategies for rapid syntheses of polycyclic structures. Cascades ending in heterocycle production currently represent quite a small proportion of the total and there is obviously major scope for expansion into, for example, nitrogen-containing heterocycles and alkaloids as well as oxygen- and sulfur-containing heterocycles. So far only a few cascades have been subject to detailed mechanistic and kinetic analysis. The unique structural distributions of rings, unsaturated bonds, and radical centers achievable in polycyclic intermediates invites disfavored steps and enhances favored ones. The doorway to kinetic and thermodynamic quantification of unusual and esoteric steps is therefore enticingly open.

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TNA as a Potential Alternative to Natural Nucleic Acids

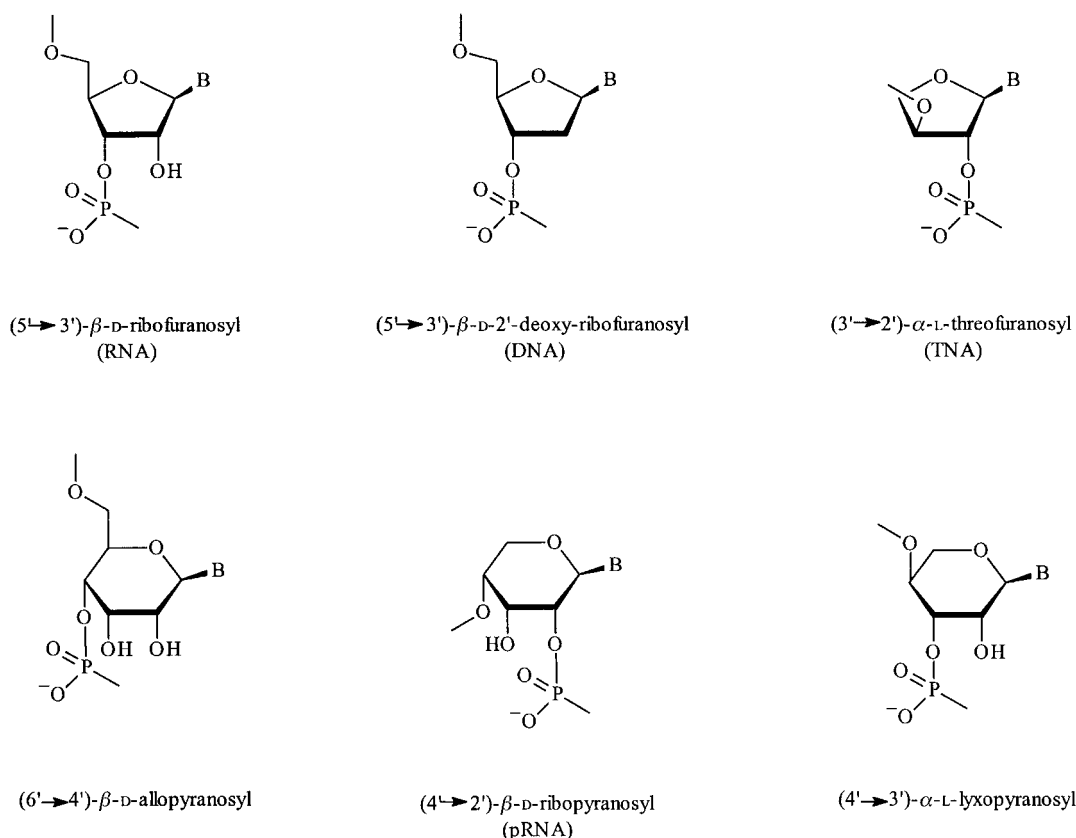
Piet Herdewijn*

One of the intriguing questions related to the origin of life concerns the understanding of the chemical etiology of the present-day nucleic acids: RNA and DNA. This problem has been systematically approached by Eschenmoser and co-workers by analyzing several nucleic acid alternatives that might have been obtained under prebiotic conditions. Their analysis focused on the chemical properties that are fundamental to the biological functions of RNA and DNA, and has now led to the synthesis and the exploration of the properties of (3' → 2')-α-L-threofuranosyl oligonucleotides (TNA; Scheme 1).^[1] The selection of TNA as a model system was

based on previous investigations on the diastereoselective aldol condensation of glycolaldehyde phosphate, which has a kinetic preference for the formation of allose 2,4,6-triphosphate in the absence of formaldehyde and for ribose 2,4-diphosphate in the presence of formaldehyde. Significant amounts of racemic erythrose 2,4-diphosphate and threose 2,4-diphosphate are formed as intermediates of the hexoaldehyde synthesis, particularly in the absence of formaldehyde.^[2] It is, therefore, not unrealistic to consider threofuranosyl nucleic acids as an ancestor to RNA or as an RNA alternative. The potential of TNA for base pairing was

deduced from its structural analogy with (4' → 3')-α-L-lyxopyranosyl oligonucleotide that was known to show cross-pairing with DNA and RNA.^[3] Previously, the β-aldohexose nucleic acids were ruled out as nucleic acid alternatives based on their functional inferiority to RNA. This conclusion was based on their lower base-pairing strength and base-pairing selectivity compared to RNA. The (4' → 2')-pentopyranosyl oligonucleotides, with pRNA as the prototype, have a stronger and more selective pairing system than RNA and have the potential for nonenzymatic replication,^[4] which makes them potential RNA alternatives. The study with pRNA led to the conclusion that nature did not select RNA

according to the criterion of maximal strength of base pairing. The quasi-linear structure of the thermodynamically more stable double-stranded pRNA shows only a weak left-handed twist, which is very different from the helical structure of natural nucleic acids. Since pRNA does not cross-pair with



Scheme 1. Various oligonucleotide building blocks.

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RNA, a direct exchange of information between these oligonucleotides seems difficult. However, the absence of cross-pairing between pRNA and RNA does not preclude the possibility of pRNA being an ancestor of RNA, but only suggests that it is very unlikely. A nucleic acid that can adopt several conformations and that in this way can hybridize equally with pRNA and RNA, might be considered as an evolutionary intermediate between them.^[5]

Analysis of the properties of TNA might answer the question why TNA could have, but did not, become nature's genetic system, and it may add to our understanding of the functional superiority of RNA over its potential alternatives. Eschenmoser and co-workers demonstrated that this tetrose-based oligonucleotide shows base pairing which is similar to that of pentose-based RNA in regard to specificity, strand orientation, and pairing strength. Moreover, TNA hybridizes with the natural nucleic acids RNA and DNA, and informational transfer based on complementary (presumed) Watson–Crick base-pair recognition between these furanosyl oligonucleotides has been demonstrated. This finding is unique because the previously studied nucleic acid alternatives (excluding pentofuranosyl nucleic acid analogues such as arabinofuranosyl nucleic acids^[6]) do not demonstrate this characteristic. It is also innovative because it demonstrates that one of the bonds responsible for nucleic acid flexibility (the repeating unit of the TNA backbone has five bonds instead of the usual six) can be removed without abolishing the capacity of furanosyl nucleic acids for functional selection by base pairing. This observation has its precedent in the field of artificial nucleic acids. Carbocyclic 5'-nor oligonucleotides (five bonds)^[7] and carbocyclic oxetanocin oligonucleotides (seven bonds)^[8] both hybridize with RNA.

Cross-pairing between TNA and RNA is possible because of the stretched conformation of TNA, in which all the substituents on the furanose ring are quasi-axially oriented (3'-endo conformation). This is an interesting example of nucleoside conformation mainly being determined by stereo-electronic effects (gauche and anomeric effects). β -D-Xylofuranosyl nucleosides have a similar conformation, which makes (3' $\rightarrow$ 2')- β -D-xylofuranosyl nucleic acid another candidate for cross-pairing with RNA (assuming that the 5'-CH₂OH group does not cause steric hindrance).^[9] An important observation is that TNA is able to form hairpin structures and, thus, does not restrict its conformational diversity to classical duplex formation.

The criteria which have been put forward for selecting potentially natural (transient) nucleic acid alternatives as genetic material for a primitive life are:^[10]

- 1) a potential natural type of molecular structure,
- 2) a capacity for informational base pairing,
- 3) a capability for self-replication,
- 4) a capacity to express a chemical phenotype (reactivity and catalytic properties), and
- 5) a potential for evolution.

Which of these criteria are met by TNA? TNA could be considered as a structural alternative for RNA as it can be potentially formed by self-organization of organic material (first requirement). The question of whether RNA or TNA is most easily available under prebiotic conditions (simplicity of

synthesis) can only be answered when nitrogenous systems are included in the experiments for investigating constitutional self-assembly.^[1] It has also been demonstrated that TNA survives the second requirement, that is, a thermodynamic functional selection procedure based on base pairing. If TNA is to be regarded as either a precursor or an alternative to RNA then it must be demonstrated that TNA is inferior to RNA on the basis of functional criteria, since TNA was not selected by nature as its genetic system. It may be doubted that non-enzymatic replication of TNA will work as well as with pRNA because of the lower base-pairing strength, but (based on this single criteria) its potential for replication should be similar to (or even exceed) that of RNA. Both RNA and TNA have pairing capabilities which seem to be optimal for nature's purposes as a functional nucleic acid.

The absence of a free hydroxyl function (the equivalent of the 2'-OH group in RNA) restricts the catalytic potential of TNA (for example, for self-splicing), and from the point of view of catalysis, TNA can be considered as an analogue of DNA. It is clear, however, that the increasing efficiency and diversity of catalytic activities is an important evolutionary driving force towards RNA, and therefore that ancestral RNA might have had less catalytic activity combined with a higher chemical stability. In this respect, TNA and pRNA are both candidates for a precursor RNA, although it is not clear how the catalytic potential of TNA and pRNA can be translated into RNA catalysis. Although TNA could be an excellent candidate for the storage of genetic information, nature preferred instead to use complicated chemistry for the conversion of RNA into DNA. However, as creation of life most probably precedes storage of information, this does not exclude TNA from being a precursor of RNA or an RNA alternative. Indeed, in a primitive life the same molecular structure might be required to play both roles: information storage and structure-specific reactivity and catalysis.^[10] Although TNA might have evolved its own characteristic functionalities as a genetic model, evolution is conservative in such a way that it might re-use substances from one primitive life form for different purposes. From this point of view, it is interesting to note that pentopyranose nucleosides have been isolated from nature (that is, out of culture medium of *Streptomyces griseochromogenes*), but the extraction of threofuranosyl nucleosides from natural sources is not known.

As previously discussed, "life" implies the potential for information storage, for self-replication, and for exponential growth, and it has been speculated that threose, furanose, and (pento)pyranose nucleic acids may all have this potential. Evolution (and survival) implies the potential for the transfer of information and for making selection (maybe in a combinatorial way), first by evolution of one system into another and thereafter by recombination and mutation to explore new functions. In evolution, conformational diversity might be a substitute for structural diversity since extensive structural diversity might not be available in a primitive world, and also not sufficiently available in more complex systems. Conformational diversity is, likewise, required for catalysis—the essential factor in every living organism. One possible conclusion might be that the selection of furanose nucleic acids rather than pyranose nucleic acids is more a

question of evolution than a question of the creation of life. As an example, replication and transcription (information transfer) assumes that the double-stranded nucleic acid opens and recloses. The strength of the duplex is defined by the degree of interstrand and intrastrand stacking interactions. In the thermodynamically more stable A form of double-stranded nucleic acids (3'-endo-furanose conformation) interstrand stacking is more pronounced than in the less stable B form (2'-endo-furanose conformation). Conformational transformation from A type to B type might facilitate the opening of double-stranded nucleic acids and, hence, replication and transcription; this transformation implies conformational flexibility. Such considerations together with the increased chemical stability of DNA might make DNA a better candidate than RNA for information storage (in the way information storage was conceived by nature) and exclude the use of pyranosyl nucleic acids. Similar considerations concerning the catalytic reactivity of RNA restricts considerably the choice of potential structural alternatives for nature's nucleic acid. The reduced conformational flexibility (absence of the 5'-CH₂OH group) might make TNA both an inferior candidate to DNA for storage of information and an inferior candidate to RNA for catalysis.

There is at this moment no indication (or suggestion) that either TNA or pRNA were precursors or former evolutionary competitors of RNA (the opposite cannot be demonstrated either). The investigation of Eschenmoser and co-workers on TNA and its properties provides an additional piece of information to be added to the puzzle which might eventually

lead to a general understanding of the genesis of present day life and to the proposition of alternative models of life. It has also become clear that the power of natural selection cannot be understood fully solely on the basis of information generated by the synthesis and analysis of the properties of RNA alternatives.

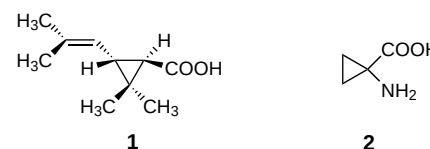
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Fascinating Natural and Artificial Cyclopropane Architectures

Rüdiger Faust*

The various facets of the chemistry of cyclopropane derivatives are amazingly diverse and continue to fascinate scientists from a broad range of backgrounds, among them theoreticians, synthetic or structural chemists, and researchers with interests in natural product and/or medicinal chemistry. The challenges posed by the intriguing cyclic arrangement of only three tetravalent carbons are multitudinous, ranging from fundamental aspects of bonding, over the synthesis of highly strained molecules to an understanding of the mode of action of biologically active cyclopropyl derivatives. Selected examples of cyclopropane architectures encountered in compounds either derived from natural sources or prepared for the first time in the laboratory are highlighted below.

That nature has chosen to use a cyclopropane skeleton to design a defense mechanism for certain pyrethrum flowers against insect attack has been known since 1924, when Staudinger and Ruzicka isolated and characterized (+)-*trans*-chrysanthemic acid **1** from the petals of these plants.^[1] The active insecticidal ingredients in these plants are in fact

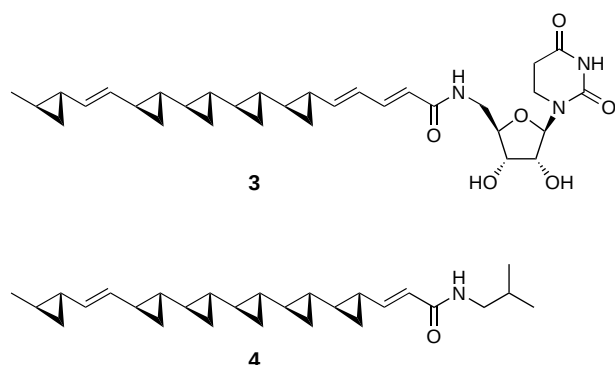


[*] Dr. R. Faust

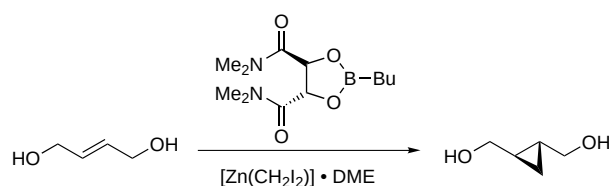
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esters of **1**, which can be easily modified and have been commercially exploited to give birth to one of the most successful classes of biomimetic insecticides, the pyrethroids. In 1997, the market value of this class of insecticides amounted to a staggering 1.5 billion US dollars.^[2]

Chrysanthemic acid derivatives are by far not the only examples of cyclopropane-containing structures in nature. In fact, the highly strained three-membered carbocycle is virtually ubiquitous. It occurs, for example, in every green plant in the form of 1-aminocyclopropanecarboxylic acid (ACC) **2**, a direct precursor to the plant hormone ethylene.^[3] In addition, the cyclopropane unit is found in a variety of other natural products, including terpenes and various cyclopropanated fatty acids.^[4] The biochemical precursors of the latter are unsaturated fatty acids, and in view of the existence of polyunsaturated fatty acids it is perhaps not too surprising that multiply cyclopropanated analogues also occur in nature, and indeed in 1990 Yoshida et al. were able to isolate the potent antifungal agent FR-900848 (**3**) from the fermentation

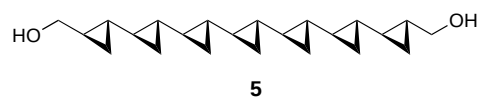


broth of *Streptoverticillium fervens*.^[5] The unusual architecture of **3**, ultimately proven by total synthesis and X-ray crystallographic analysis,^[6, 7] consists of four contiguous and one isolated cyclopropane unit, all of which are arranged on the same face of an all-*trans*-configured carbon backbone. But the amazing array of five cyclopropane units in **3** is not unique. Shortly before the structure of **3** was unequivocally established, chemists at the company Upjohn isolated U-106305 (**4**) from *Streptomyces* sp.^[8] This compound had aroused the scientist's interest because it acts as an effective inhibitor of the cholesteryl ester transfer protein in the blood and can thus be envisioned to slow the progression of atherosclerosis. The remarkable structural similarity between compounds **3** and **4**, the latter endowed with five contiguous out of a total of six cyclopropane units, suggests that they are synthesized along the same biochemical pathway. As with **3**, the structure and the absolute configuration of **4** was established by a total synthesis^[9, 10] that made use of an enantioselective cyclopropanation reaction of allylic alcohols originally developed by Charette et al. in 1995^[11] (Scheme 1). Indeed, Charette and

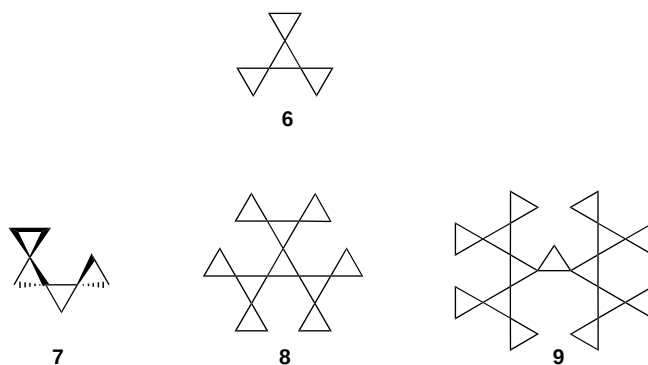


Scheme 1. Enantioselective cyclopropanation of allylic alcohols developed by Charette et al.^[11]

Lebel published the enantioselective synthesis of the non-natural enantiomer of U-106305 shortly thereafter.^[12] The cyclopropanation procedure they devised involves the complex $[\text{Zn}(\text{CH}_2\text{I}_2)] \cdot \text{DME}$ (DME = 1,2-dimethoxy ethane) and the presence of a chiral dioxaborolane ligand derived from tartaric acid diamide (see Scheme 1). The same methodology was used to make the non-natural, all-*trans* septicyclopropane derivative **5**,^[10] the most highly cyclopropanated linear structure prepared to date.



Multiple cyclopropyl groups can also be arranged in a spiro-fused fashion around a core carbocycle, giving rise to the structurally fascinating classes of the so-called rotanes and triangulanes.^[13] These hydrocarbons have been investigated extensively by the groups of Conia and de Meijere. In 1973, Fitjer and Conia prepared the smallest system in this series, the highly strained [3]rotane **6**.^[14] More recently, de Meijere's team presented a succession of milestones in this area, including the first synthesis of an enantiomerically pure [4]triangulane **7**,^[15] the stunning perspirocyclopropanated [3]rotane **8**,^[16] and even the [15]triangulane **9**,^[17] a record-breaking arrangement of fifteen spiro-linked cyclopropane rings.



Compound **7**, prepared to test the hypothesis that chiral, unfunctionalized and completely saturated hydrocarbons can show optical activity if sufficiently rigid, was found to have a remarkably high specific rotation ($[\alpha]_{365}^{20} = -648.2$), which the authors attribute to the helical arrangement of the σ C–C bonds in **7**. It was therefore suggested that **7** is a σ bond analogue of the aromatic [*n*]helicenes, a class of compounds with similarly large optical rotations resulting from a helical arrangement of their π -bond backbone.^[18]

Most recently, de Meijere and co-workers have climbed yet another mountain in cyclopropane architecture and prepared tetracyclopopylmethane **10** (Figure 1).^[19] Many organoelement derivatives with the maximum number of cyclopropyl groups are known, and in fact the heavier (and larger) homologues of **10**, namely tetracyclopopylsilane, -germane, and -stannane had been made before.^[20] However, the

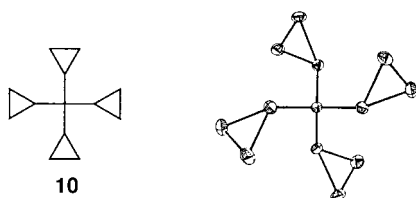
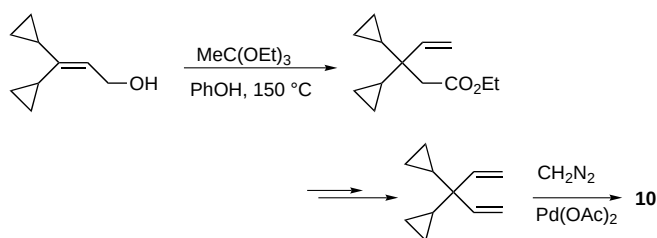


Figure 1. Molecular structure of tetracyclopropylmethane.^[19]

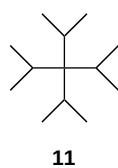
corresponding hydrocarbon has remained elusive until now, and earlier attempts to generate the compound using standard cyclopropanation methods failed. The key steps in the successful synthesis of **10** are the formation of its quaternary center (Scheme 2) by an orthoester Claisen rearrangement



Scheme 2. Synthesis of tetracyclopropylmethane.

and the twofold cyclopropanation of dicyclopropylpentadiene with diazomethane. The larger steric crowding in **10** compared to that in the higher homologues also affects its conformation in the solid-state. Whereas the molecules in crystals of the corresponding silicon, germanium, and tin derivatives have D_{2d} symmetry, **10** has S_4 symmetry (Figure 1).

Compound **10** is not only of structural interest, it also serves as a starting point to make one of the most sterically congested methane derivatives prepared to date: palladium-catalyzed selective hydrogenolysis of the least-substituted cyclopropane bonds in **10** furnishes tetraisopropylmethane **11** in almost quantitative yield. X-ray crystallographic analysis of



11 reveals that the shortest nonbonded $H \cdots H$ distances are 2.008 Å, significantly shorter than those observed in **10** (shortest $H \cdots H$ distance 2.135 Å). The elegance of the synthetic route to the highly crowded **11** becomes apparent when one ponders the fact

that the sterically even more fraught tetra-*tert*-butylmethane remains elusive.

This short excursion into the diverse field of natural and artificial cyclopropane architectures highlights the fact that cyclopropanes continue to provide stimuli for, and challenges to, current concepts of synthesis, structure, and theory. It is amazing what three carbons can do!

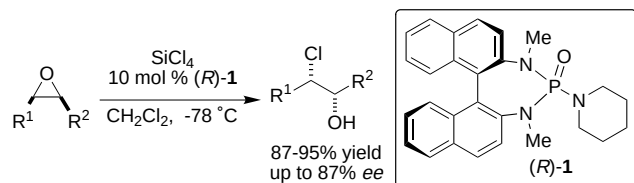
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Beneficial Effect of *ortho*-Methoxy Groups in the Asymmetric Ring Opening of *meso* Epoxides with Silicon Tetrachloride Catalyzed by Chiral *ortho*-Methoxyphenyldiazaphosphonamide Lewis Bases

Response to the Communication by G. Buono et al.**

Scott E. Denmark,* Thomas Wynn, and Bradley G. Jellerichs

A 1998 report from these laboratories disclosed the enantioselective opening of *meso* epoxides with silicon tetrachloride in the presence of a catalytic amount of a chiral phosphoramidate (Scheme 1).^[1] The resulting chlorohydrins

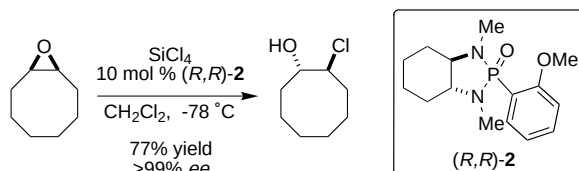


Scheme 1.

were formed in good yield and variable enantioselectivities which depended on the structure of the epoxide. For example, whereas *cis*-stilbene oxide afforded 2-chloro-1,2-diphenylethanol in 87% ee, the opening of cyclopentene oxide produced the chlorohydrin in nearly racemic form. Moreover, we found that the reaction rate was also highly structure-dependent; for example, cyclohexene oxide required 20 min at -75 °C for complete conversion (52% ee), whereas cyclooctene oxide required 5.5 days under the same conditions and produced the racemic chlorohydrin.

We were therefore surprised to read the recent report by Buono et al. in this journal which described the use of a phosphoramidate-type catalyst for the same transformations that gave generally much higher enantioselectivities and at enhanced rates.^[2] Although there was no reason a priori to question the results, we were particularly struck by the

remarkable facility and selectivity reported for opening of cyclooctene oxide which was used to optimize the conditions and catalyst structure. The authors claimed that catalyst (R,R)-2 gave a 77% yield of the 2-chlorocyclooctanol in >99% ee after 4 h at -78 °C (Scheme 2).



Scheme 2.

If true, these results represent a significant advance in the asymmetric synthesis of enantiopure chlorohydrins. However, the claims were so contrary to our own experience that we felt compelled to repeat the experiments as described by Buono et al. We describe herein the details of that exercise. Despite multiple repetitions with different experimentalists we have been unable to authenticate the results published by those authors.

We first prepared the catalyst (R,R)-2 according to the published procedures.^[2] The phosphoramidate was purified to microanalytical standards and has been fully characterized spectroscopically.^[3] Although there was a small discrepancy in the optical rotations, the enantiomeric purity of (R,R)-2 we employed was assured by chiral stationary phase (CSP) supercritical CO₂ chromatographic (SFC) analysis of the bis(*p*-toluamide) derivative of the cyclohexane-1,2-diamine employed.

To evaluate the experimental results, we selected three substrates, namely *cis*-stilbene oxide (3), cyclohexene oxide (4) and cyclooctene oxide (5), which represented a range of structural classes and also corresponded to those results that were most at variance with our experience. Although we had previously described in detail the analytical methods employed in our work, we repeated this task to be certain of the veracity of our claims. Thus, freshly prepared samples of authentic racemic products were prepared by opening the

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

epoxides with silicon tetrachloride in the presence of HMPA. As described previously, 2-chloro-1,2-diphenylethanol (**6**) could be analyzed directly by CSP-SFC with baseline separation (Chiralpak AS column).^[3] However, both *trans*-2-chlorocyclohexanol (**7**) and *trans*-2-chlorocyclooctanol (**8**) were first derivatized to their trifluoroacetates which gave baseline separation by CSP GC analysis (Chiraldex G-TA and B-PH columns).

The first attempts to reproduce the results using *cis*-stilbene oxide immediately raised our concerns. Three independent runs, rigorously following the conditions reported by Buono et al.,^[3] did indeed produce **6**, but in nearly racemic form (Table 1, entries 1–3) and not 60% *ee* as reported. In all three

Table 1. Attempted opening of *meso* epoxides with silicon tetrachloride and **2**.^[a]

Entry	Epoxide	<i>t</i> [h]	Product	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	3	3.5	6	87	5
2	3	3.5	6	75	5
3	3	3.5	6	65	8
4	4	0.33	7	90	5
5	4	0.33	7	90	6
6	4	0.33	7	75	5
7	5	3.5	8	3 ^[d]	1
8	5	3.5	8	3 ^[e]	3
9	5	72	8	6 ^[f]	8

[a] Reactions all performed on 1.2 mmol scale. See Supporting Information for full experimental details. [b] Yield of chromatographically homogeneous material. [c] Enantiomeric excess determined by CSP-SFC or CSP-GC as described in the Supporting Information. [d] 83% recovery of epoxide **5**. [e] 81% recovery of epoxide **5**. [f] 70% recovery of epoxide **5**.

runs, the products were isolated in a highly pure state by chromatography (as judged by 500 MHz ¹H NMR analysis), and no other signals were seen in the CSP-SFC traces.^[3] The next case, cyclohexene oxide, behaved similarly (Table 1, entries 4–6) producing the chlorohydrin **7** in good yield, but again in nearly racemic form, not 82% *ee* as reported. Finally, we found the behavior of cyclooctene oxide to be completely disparate from the published results. In two independent experiments exactly following the experimental description (–75 °C, 3.5 h), we obtained only 3% of the chlorohydrin **8** along with 81–83% recovery of the epoxide (Table 1, entries 7 and 8). Derivatization of this small quantity revealed an essentially racemic product. In a third experiment, the reaction time was extended to three days in an attempt to increase conversion. Once again, we secured only 6% of **8** along with a 70% recovery of **5**. The enantiomeric compo-

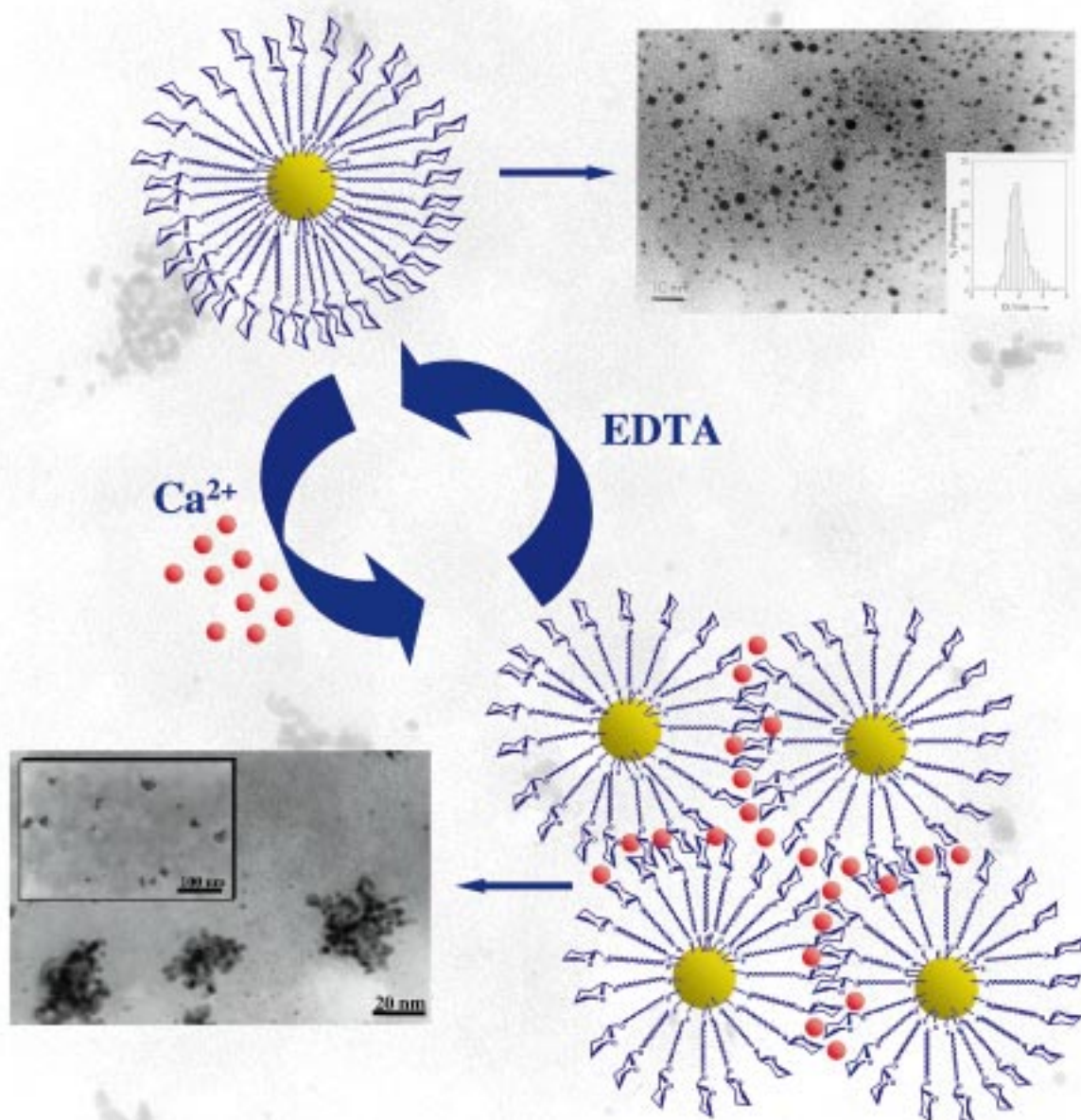
sition of **8** from this experiment was only marginally improved suggesting that the small amount of **8** obtained in entries 7 and 8 may have arisen from ring opening upon workup.

Clearly there is a serious discrepancy between the results reported by Buono et al. and what we have found. Although we have made no attempt to adumbrate the origin of the problems, the data given in their Supporting Information provide reason for concern. For example, the determination of enantiomeric composition of **7** is described as being done by ¹³C analysis of the derived fluorolactate according to Heumann et al.^[4] This is most disturbing since the original authors use ¹⁹F NMR spectroscopy; it is difficult to accurately integrate ¹³C{¹H} spectra.^[5] Also of concern is the analytical method employed for determination of the enantiopurity of **8**. The authors describe their sample of **8** as having >99% *ee* on the basis of CSP-GC analysis (Lipodex E) of the trifluoroacetate of **8**. It is remarkable that the enantiomers of this compound are reported to have retention times that differ by nearly 8 min. Whereas one would assume that this method would have been calibrated with the racemate, these data are not provided.

In conclusion, the reported ability of chiral phosphonamide **2** to effect the enantioselective opening of *meso* epoxides with silicon tetrachloride has not withstood experimental verification. Although we have not attempted to repeat all of the examples in which this catalyst (or others claimed in the paper) is purported to give enantiomerically enriched chlorohydrins, until the questions raised herein are appropriately addressed, all the results described by Buono et al. should be viewed with skepticism.^[6,7]

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- [6] Since the time these control experiments were completed, the same group has published “further developments” in which they claim, *inter alia*, the ability to use a variety of chlorosilanes to open cyclooctene oxide (S. Reymond, J. M. Brunel, G. Buono, *Tetrahedron: Asymmetry* **2000**, 11, 4441). Among the most incredible of the results is the report that *tert*-butyldimethylchlorosilane can open this epoxide in 4 h at –78 °C with 60% *ee*. In our first communication, we explicitly state that other chlorosilanes were competent reaction partners, but all of the products were racemic.
- [7] **Note added in proof** (May 8, 2001): The inability of (*R,R*)-**2** to enantioselectively promote the opening of cyclooctene oxide as we describe, has been independently confirmed by Professor Gregory Fu and Beata Tao (MIT) with catalyst samples provided by both us and Professor Buono. We thank Professor Fu and Miss Tao for their gracious assistance.

Glycosphingolipid clustering and interactions at the cell membrane can be modeled by gold glyconanoparticles prepared with biologically significant oligosaccharides.



For more information see the following pages.

Gold Glyconanoparticles as Water-Soluble Polyvalent Models To Study Carbohydrate Interactions**

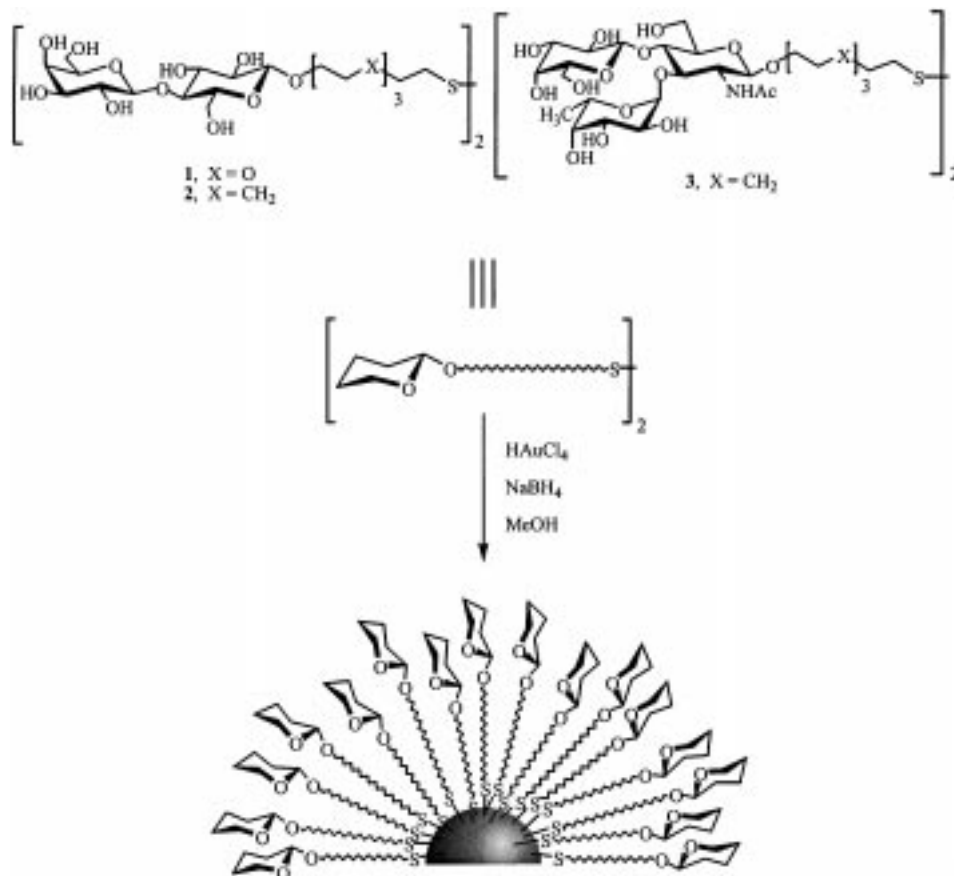
Jesús M. de la Fuente, Africa G. Barrientos, Teresa C. Rojas, Javier Rojo, Javier Cañada, Asunción Fernández, and Soledad Penadés*

Dedicated to Professor Manuel Martín-Lomas on the occasion of his 60th birthday

There is now evidence that in addition to protein–protein and protein–carbohydrate interactions, cells use attractive interactions between glycosphingolipid (GSL) microdomains as an initial step for adhesion and recognition.^[1] GSL microdomains are functional units associated with cell adhesion, signal transduction, and other normal and pathological processes.^[2] A homophilic carbohydrate–carbohydrate interaction between the Lewis^x antigen seems to be responsible for morula compaction,^[3] and a heterotopic interaction between glycosphingolipid patches of GM3 and Gg₃ is involved in metastasis of melanoma cells in mice.^[4] Characteristic features for this interaction are its strong dependency on divalent cations and its extremely low affinity, which is compensated in Nature by polyvalent presentation of the ligands.^[5] These features make the study such interactions a real challenge. Herein we present a new water-soluble three-dimensional (3D) polyvalent model system for the study of carbohydrate interactions, this system consists of gold nanoclusters functionalized with neoglycoconjugates of biologically significant oligosaccharides. We illustrate the usefulness of these models with the preparation of gold nanoparticles functionalized with the disaccharide lactose or the trisacchar-

ide Lewis^x determinant and also demonstrate the selective self-recognition of the Lewis^x functionalized glyconanoparticles by carbohydrate–carbohydrate interactions. These glyconanoparticles provide a glycocalyx-like surface with globular shapes and a chemically well-defined composition to intervene in the cell–cell adhesion processes.

Recently several groups have prepared multivalent carbohydrate model systems,^[6–8] that have been used to study carbohydrate–protein interactions. Of special interest are the two-dimensional (2D) arrays of glycoconjugates on gold surfaces using self-assembled monolayers.^[9, 10] Spherical arrays of carbohydrates, as represented by glycodendrimers,^[11] and liposomes^[12] have also been employed as useful tools to investigate carbohydrate recognition processes.



Scheme 1. Preparation of gold (gray hemisphere) glyconanoparticles.

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We now report a simple and versatile approach by which carbohydrates are linked to gold nanoparticles as a method for tailoring highly polyvalent water-soluble carbohydrate surfaces with globular shapes (Scheme 1). This approach opens the way to tailoring glyconanoparticles with a variety of carbohydrate ligands and with differing ligand density, providing a controlled model for investigating the influence of carbohydrate clustering^[13, 14] and orientation effects^[15] on their interactions with specific receptors.

Thiol-derivatized neoglycoconjugates **1–3** of two biologically significant oligosaccharides, the disaccharide lactose (Galβ(1→4)Glcβ1-OR) and the trisaccharide Le^x (Galβ(1→4)[Fucα(1→3)]GlcNAcβ1-OR), have been pre-

pared to functionalize gold nanoparticles in situ. The synthesis of the disulfides **1–3** was carried out by glycosidation of the conveniently protected lactose and Le^x derivatives with 11-thioacetate-3,6,9-trioxa-undecanol (for **1**) and 11-thioacetate undecanol (for **2** and **3**) by using the trichloroacetimidate method.^[16] Both linkers have been used to test the versatility of the method in the preparation of glyconanoparticles with different spacers. Compounds **1–3** were isolated as disulfide forms, and used in this form for the formation of the water-soluble gold-protected glyconanoparticles **1-Au**, **2-Au**, and **3-Au** which were obtained in methanol by using the procedure of Brust et al.^[17] for the synthesis of monolayer-protected gold nanoclusters. A series of gold-protected nanoparticles, soluble in organic solvents, has recently been prepared,^[18–20] however, few examples have been reported of water-soluble gold nanoclusters.^[21–23] The *lacto*-Au and Le^x-Au glyconanoparticles are stable, water soluble, and can be manipulated as a water-soluble biological macromolecule. They were purified by dialysis or centrifugal filtering and characterized by ¹H NMR, UV/Vis, and FT-infrared (IR) spectroscopy, elemental analysis, and transmission electron microscopy (TEM).

Figure 1 shows TEM images and core size-distribution histograms for **2-Au** and **3-Au**. A mean diameter of 1.8 nm was found for the gold core of the functionalized nanoparticles. Elemental analyses for **1-Au**, **2-Au**, and **3-Au** confirm a ratio of 63 (*lacto*-**1**), 70 (*lacto*-**2**), and 97 (Le^x-**3**) molecules per 201 gold atoms, in accord with data from previous work^[21] for alkanethiol-protected nanoclusters of 2 nm mean diameter. These analyses correspond to molecular weights of 73, 76, and 109 kD, respectively. The aqueous solutions of the nanoparticles remained transparent for months and no agglomeration was detected by the naked eye and TEM examination.

An important point for the application of our model to the investigation of the in vivo cell-adhesion processes, is the stability to enzymatic degradation. The steric crowding of the carbohydrate moiety on the nanoparticle surface may inhibit its recognition and degradation by enzymes.^[24] We have tested the enzymatic hydrolysis of **1** and **2** and their corresponding nanoclusters, **1-Au** and **2-Au**, with β -galactosidase of *E. coli*. The enzyme processes **1** and **2** at a level comparable to that of lactose itself, while the hydrolysis of the **1-Au** and **2-Au** nanoparticles, under the same conditions, was barely detectable (<3% relative to the enzymatic activity with the free ligands **1** and **2**).

The glyconanoparticles have been used as 3D models to mimic GSL clustering at the cell surface and to investigate the

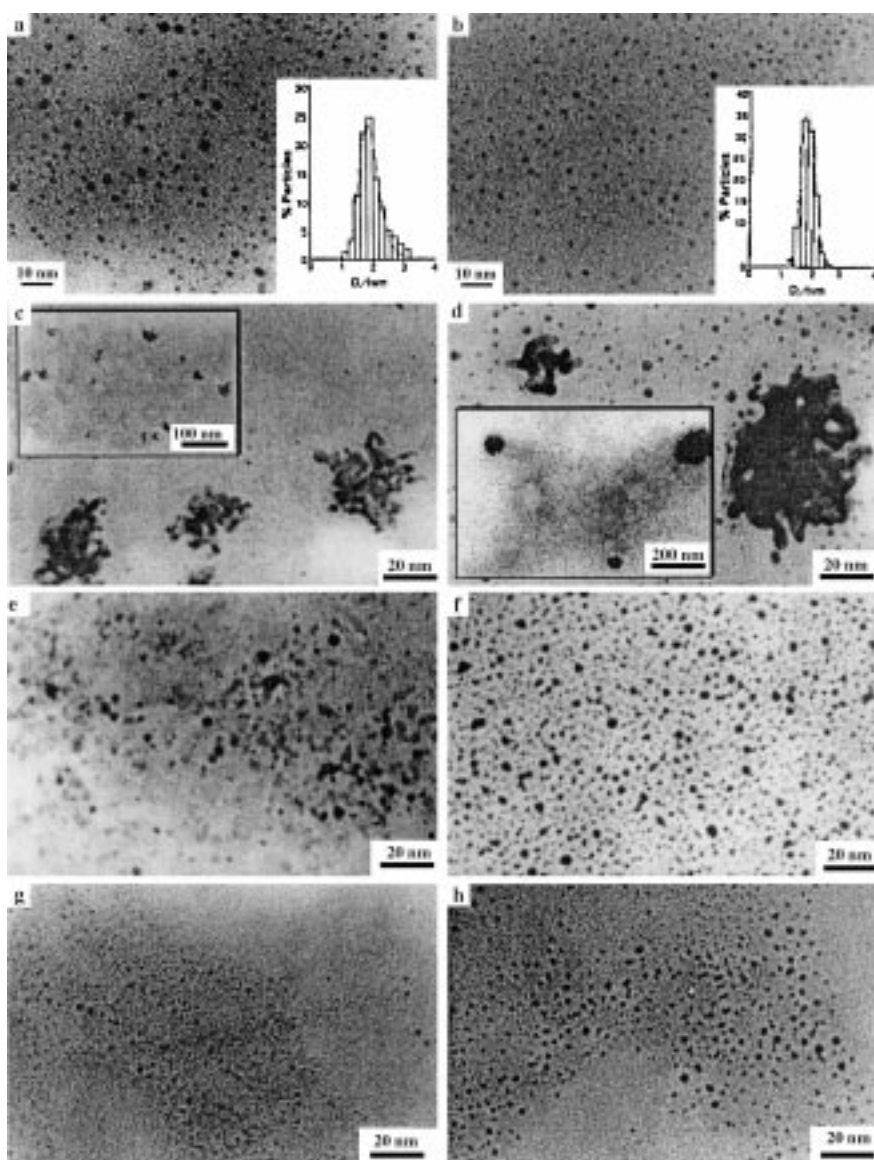


Figure 1. Transmission electron micrographs and core size-distribution histograms (insets in a, b) of: a) **3-Au** (0.1 mg mL⁻¹ in water); b) **2-Au** (0.1 mg mL⁻¹ in water); c) **3-Au** (0.1 mg mL⁻¹ in 10 mM CaCl₂ solution); d) **3-Au** (0.9 mg mL⁻¹ in 10 mM CaCl₂ solution); e) the same as (c) + EDTA; f) the same as (d) + EDTA; g) **2-Au** (0.1 mg mL⁻¹ in 10 mM CaCl₂ solution); h) **2-Au** (0.9 mg mL⁻¹ in 10 mM CaCl₂ solution); EDTA = ethylenediaminetetraacetate.

existence of carbohydrate–carbohydrate interactions in solution. Divalent cations seem to be essential in this interaction.^[1] The aggregation of the *lacto*-**2-Au** and Le^x-**3-Au** nanoparticles has been studied in the presence and absence of calcium cations. TEM has also allowed us to observe the self-interaction events between the glyconanoparticles in water and calcium solutions. The *lacto*-Au and the Le^x-Au nanoparticles were dissolved at different concentrations (0.1 mg and 0.9 mg mL⁻¹ for the *lacto*- and 0.1, 0.3, 0.5, and 0.9 mg mL⁻¹ for the Le^x-Au nanoparticles) in 10 mM CaCl₂ solution, left overnight and aliquots of the solutions were then observed under the microscope. Comparison of the TEM micrographs obtained in water (Figure 1a, b) with those in calcium solution (Figure 1c, d, g, h) reveals clear differences between the *lacto* and the Le^x samples. The Le^x-Au nanoparticles in calcium solution show 3D aggregates at all

concentrations (Figure 1 c, d), while the *lacto*-Au nanoparticles remain dispersed as in the water solution (Figure 1 g, h). The interaction of two Le^x-Au nanoparticles will result in the presentation of more carbohydrate epitopes at the surface allowing further aggregation in the presence of calcium. At a concentration of 1 mg mL⁻¹ of **3**-Au the mean diameter of the aggregates reaches 100 nm.

Le^x-antigen aggregates arise from self-recognition between Le^x molecules in the presence of Ca²⁺ ions and not the result of nonspecific interactions with the salt. This notion is supported in that: first, salts usually induce flocculation processes in gold nanoclusters. However, neither the Le^x-Au nor the *lacto*-Au nanoparticles flocculate in water or calcium solution even after several months. Second, the *lacto*-Au nanoparticles under the same conditions did not show any aggregation. Third, removal of the calcium cations from the Le^x solution by adding EDTA results in the dispersion of the Le^x aggregates and the isolated nanodots were once again observed by TEM (Figure 1 e, f).

These results indicate that only specific binding events between Ca²⁺ ions and the Le^x molecules dictate the self-aggregation process and confirm the Le^x determinant as a homophilic adhesion molecule. Measurements by atomic force microscopy (AFM) of the adhesion forces between self-assembled monolayers of the Le^x derivative **3** have also confirmed the Le^x antigen as an adhesion molecule.^[28]

In conclusion, the glyconanoparticle approach presented here provides a versatile strategy to prepare a great variety of water-soluble highly polyvalent carbohydrate arrays with globular shapes by using a simple synthetic method. The simplicity of the preparation makes the glyconanoparticles a competitive tool in the study of polyvalency in carbohydrate interactions in solution. This strategy also allows us to prepare hybrid glyconanoparticles made up of carbohydrates and other molecules (biotin, fluorescent probes, peptides, etc.).

We have demonstrated the selective ability of the Le^x determinant for self-recognition in aqueous solution,^[30] supporting the proposal that specific interactions between carbohydrates are possible and may represent an additional mechanism for cell adhesion and recognition. Previously, by the use of synthetic receptors, we have also demonstrated that stabilizing interactions between carbohydrate surfaces exist in water.^[25, 26] The glyconanoparticles may also be considered to be a convenient tool to intervene in cell-cell adhesion and recognition processes where carbohydrates are involved. We are presently preparing other glyconanoparticles with other carbohydrate antigens. The application of the *lacto*-Au and Le^x-Au nanoparticles to interfere anti-adhesion therapy is presently underway. Preliminary results indicate that the *lacto*-nanoparticles inhibit in vivo lung metastasis of melanoma cells in mice.^[29]

Experimental Section

Preparation of glyconanoparticles: A solution of disulfide **1**, **2**, or **3** (0.012 M, 5.5 equiv) in MeOH (5 mL) was added to a solution of tetrachloroauric acid (0.025 M, 1 equiv) in water (0.4 mL). An aqueous solution of NaBH₄ (1 M, 22 equiv) was added in small portions with rapid stirring. The black suspension formed was stirred for an additional 2 h and the solvent then removed under vacuum. The glyconanoparticles are insoluble in MeOH

but soluble in water (more than 1 mg/100 µL). Purification was performed by centrifugal filtration: crude product (50 mg) was dissolved in water (5 mL) NANOpure. This solution was loaded into a centrifugal filter device (CENTRIPLUS YM30, MICROCON, MWCO = 30000), and was subjected to centrifugation (3000 × g, 40 min). The dark glyconanoparticle solution was washed with MeOH and the process repeated several times until the starting material could no longer be detected by thin layer chromatography (TLC). The glyconanoparticles were dissolved in water and lyophilized. The products obtained were free of salts and starting material (absence of signals from disulfide and Na⁺ ions in ¹H and ²³Na NMR spectroscopy).

Transmission electron microscopy: Examination of the samples was carried out with a Philips CM200 microscope working at 200 kV. A single drop of the aqueous solutions of the gold glyconanoparticles was placed onto a copper grid coated with a carbon film. The grid was left to dry in air for several hours at room temperature. Particle size distribution of the Au clusters was evaluated from several micrographs using an automatic image analyser. The number of particles selected for consideration was around 400, which resulted in stable size-distribution statistic. The same procedure was used for the calcium solutions. To remove calcium cations, EDTA solution was added to samples (final concentration in EDTA 50 mM). Solutions were loaded into a centrifugal filter device and were subject to centrifugation. The residues were dissolved in water (the original concentrations were kept) and a drop was placed onto a copper grid.

Enzyme assays: Solutions of **1**, **2**, or the corresponding glyconanoparticles **1**-Au and **2**-Au (2 mM lactose equivalents) in a buffer solution (pH 7.2, sodium phosphate 50 mM, MgCl₂ 1 mM) were treated with *E. coli* β-galactosidase (SIGMA, 0.01 to 0.1 mg protein per mL). The galactose produced was measured by means of a standard enzymatic coupled assay with galactose deshydrogenase.^[27]

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Electronic Transduction of Polymerase or Reverse Transcriptase Induced Replication Processes on Surfaces: Highly Sensitive and Specific Detection of Viral Genomes**

Fernando Patolsky, Amir Lichtenstein, Moshe Kotler, and Itamar Willner*

Dedicated to Professor André M. Braun on the occasion of his 60th birthday

The detection of pathogens or autosomal recessive diseases is one of the future challenges of medicine and diagnostics.^[1] Sensitive gene detection is accomplished by the polymerase chain reaction (PCR) amplification or secondary signal amplification routes.^[2, 3] Major goals in future gene analysis include the parallel detection of a variety of pathogens and their quantitative assay. Inherent limitations of PCR prohibit the application of the method for quantitative and parallel high-throughput analyses. Microarrays of DNA have attracted substantial research efforts for the simultaneous analysis of genetic materials. In most of these systems the analyte samples are amplified by PCR cycles, and the microarrays act as a sensing interface that lacks amplification capabilities.^[4, 5] Herein we address the development of ultrasensitive DNA-detection methods where in situ amplification proceeds

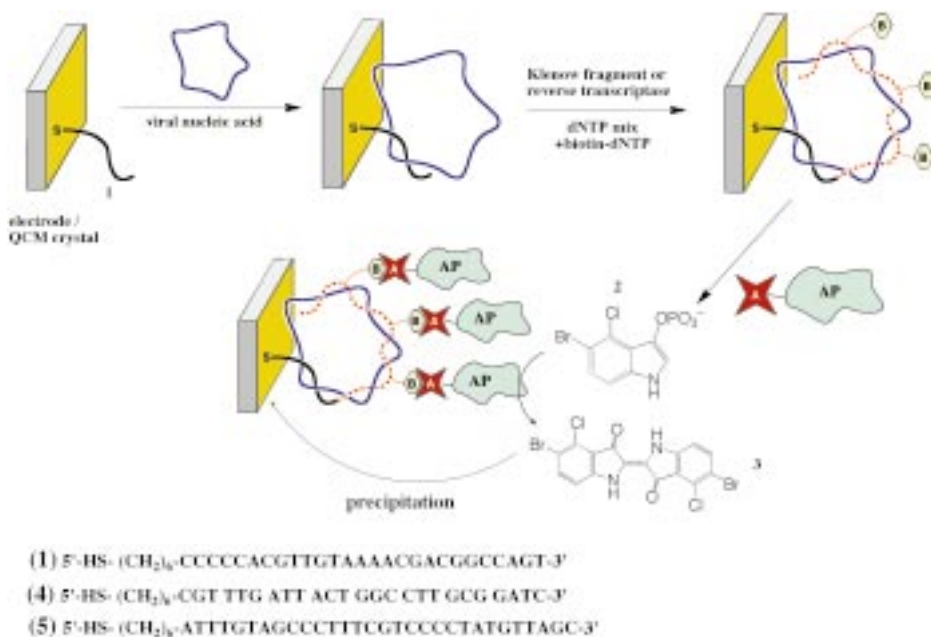
on functionalized surfaces (electrodes or piezoelectric crystals) and the detection process is electronically transduced. The method enables the quantitative analysis of viral DNA and may be adopted for parallel analyses on arrays. Previous reports addressed the electrochemical^[6–9] or microgravimetric,^[10] quartz-crystal microbalance detection (QCM) of DNA. Several recent studies reported attempts to amplify DNA sensing processes: Dendritic, hyperbranched, oligonucleotides were employed to enhance the binding of DNA to electrodes.^[11] The biocatalyzed precipitation of an insoluble product on the electronic transducer, that follows the primary hybridization between the analyte DNA and the probe oligonucleotide, was used to amplify the sensing event.^[12] Also, labeled liposomes were employed as micromembrane interfaces that amplify the primary DNA-sensing events by their association to the probe-oligonucleotide/DNA-analyte complex generated on the transducer.^[13, 14] Similarly, dendritic-type amplification of the analysis of a target DNA was accomplished by the use of oligonucleotide-functionalized Au-nanoparticles.^[15] Faradaic impedance spectroscopy or frequency changes of the piezoelectric crystal, were used to transduce the different amplified sensing processes. Here we report a novel ultrasensitive method for the electronic transduction of the detection of viral nucleic acids. We demonstrate the surface polymerase-induced or reverse transcriptase stimulated formation of double-stranded DNA or RNA on the transducer, and the secondary amplification of the sensing process by the biocatalyzed precipitation of an insoluble product. Electrochemical and microgravimetric QCM methods are used as electronic transduction means for the DNA detection. The process is exemplified by the analysis of the M13 mp8 (M13 ϕ) DNA (ca. 300 copies per 10 μ L) and of the RNA of vesicular stomatitis virus (VSV; ca. 60 copies per 10 μ L).

The method for analysis of the target is depicted in Scheme 1. The primer thiolated oligonucleotide **1**, complementary to a segment of the target M13 mp8 DNA, is assembled on an Au-electrode or an Au-quartz crystal through a thiol functional group.^[16, 17] The sensing interface is then treated with the analyte DNA of M13 mp8 (+) strand, and the resulting complex on the transducer is treated with dATP, dGTP, dTTP, dCTP, and biotinylated-dCTP (ratio 1:1:1:2/3:1/3, nucleotides concentration of 1 mM) in the presence of DNA polymerase I, Klenow fragment (20 U mL^{−1}).^[18] Polymerization and the formation of a double-stranded assembly with the target DNA is anticipated to provide the first amplification step of the analysis of the viral DNA. Polymerase introduces biotin tags to the double-stranded assembly, thus providing a high number of docking sites for the binding of the avidin–alkaline-phosphatase conjugate. The associated enzyme biocatalyzes the oxidative hydrolysis of 5-bromo-4-chloro-3-indolyl phosphate (**2**) to form the insoluble indigo product **3**, that precipitates on the transducer, thus providing a second amplification step for the analysis of the target DNA.^[19] The synthesized strand on the electrode is anticipated to attract a positively charged redox label that can be assayed by chronocoulometry.^[20] This approach enables us to monitor the polymerization process continuously. The negatively charged double-stranded assem-

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Scheme 1. Amplified electronic transduction of viral DNA/RNA by the polymerase-induced replication or reverse transcription and the biocatalyzed precipitation on an insoluble product of the transducer; AP = alkaline phosphatase, dNTP = mixture of dGTP, dATP, dTTP, and dCTP, broken red line = replicated nucleic acid, B in hexagon = biotin, A in red star = avidin.

bly is anticipated to repel a negatively charged redox probe, and to enhance the electron-transfer resistance on the transducer surface. The barrier for electron transfer to a negatively charged redox label in solution can be assayed by the Faradaic impedance spectroscopy technique.^[21] Furthermore, hybridization, formation of the double-stranded assembly, polymerization, and precipitation of the insoluble product **3** alter the mass on the transducer. Thus, the entire set of detection steps of the target DNA may be assayed by microgravimetric analysis of the frequency change of a piezoelectric crystal.

The coverage of the probe oligonucleotide on the transducer was determined by microgravimetric QCM analysis and chronocoulometric experiments, using the [Ru(NH₃)₆]³⁺ ion as redox label.^[20] The surface coverage of the probe oligonucleotide on the transducer is controlled by the primer concentration and by the time of incubation of the transducer with the primer solution. Upon interaction of the Au-electrode with the primer **1**, 4.2×10^{-6} M, for 60 min, a surface with optimal surface coverage, corresponding to $6.3(\pm 0.3) \times 10^{-11}$ mol cm⁻², for the sensing of M13φ was generated.

Figure 1 shows the chronocoulometric transients, in the presence of [Ru(NH₃)₆]³⁺, of the probe-oligonucleotide-functionalized-electrode and of the sensing interface after hybridization with the analyte DNA. After 4 h hybridization, the charge associated with the linked redox probe was estimated to be 54 μC. Assuming that all of the [Ru(NH₃)₆]³⁺ ions linked to the hybridized analyte DNA communicate electrically with the electrode, the surface covered by M13 mp8 DNA is about 9.0×10^{-13} mol cm⁻². Thus, only 1.5% of the sensing oligonucleotide units underwent hybridization with the viral DNA. This surface coverage of the hybridized DNA is supported by microgravimetric QCM measurements that reveal a frequency change of $\Delta f = -445$ Hz upon binding

of the viral DNA to the surface. This frequency change translates to a surface coverage of the hybridized DNA of 1.1×10^{-13} mol cm⁻², which corresponds to hybridization to about 1.7% of the sensing interface.

The increase in the charge associated with [Ru(NH₃)₆]³⁺ ions linked to the double-stranded assembly (Figure 2) is a result of the polymerase-induced formation of the double-stranded assembly with the analyte DNA which acts as template. The charge increases with time, implying that polymerization occurs on the surface, and levels-off after about 60 min of polymerization. Note that the charge associated with the analyte DNA is 29.2 μC, but the polymerization did not reach this value. Thus, the replication led only to 54% formation of the double-stranded assembly (on average

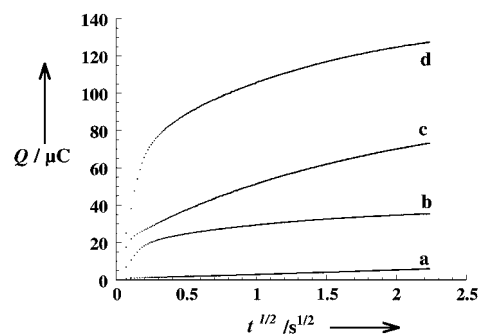


Figure 1. Chronocoulometric transients for: a) bare Au-electrode; b) **1**-modified Au-electrode; c) **1**-modified Au-electrode after hybridization with M13φ (2.3×10^{-9} M) for 1.5 h, and d) after hybridization with M13φ (2.3×10^{-9} M) for 4 h. All transients were recorded in the presence of [Ru(NH₃)₆]³⁺, 5×10^{-5} M, in 10 mM Tris buffer, pH 7.4. The hybridizations were conducted in 0.1 M phosphate buffer, pH 7.5, that included 30% formamide, at room temperature.

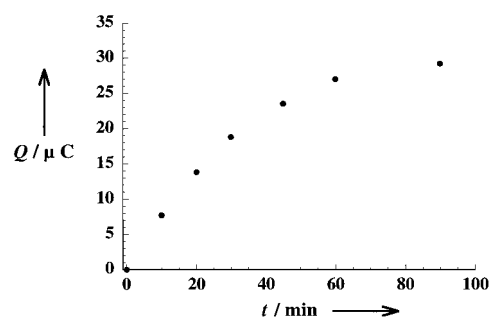


Figure 2. The time-dependent changes of the charge associated with the polymerase-induced polymerization and measured by chronocoulometry using [Ru(NH₃)₆]³⁺ ions as the redox label in 10 mM Tris buffer, pH 7.4. The polymerization conditions are in ref. [18].

3900 bases were incorporated over each analyte DNA). This is attributed to steric constraints for the formation of the fully replicated double-stranded assembly on the surface or to the interruption of the Klenow fragment induced polymerization that is known to occur at specific sites during M13 ϕ replication.^[22] The partial polymerization on the surface is further reflected by QCM experiments that indicate that polymerization yields a frequency change of $\Delta f = -195$ Hz, whereas the attachment of the analyte DNA to the surface results in a frequency change of $\Delta f = -445$ Hz.

Figure 3 shows the Faradaic impedance spectra of the probe-oligonucleotide-functionalized electrode. The electron-transfer resistance R_{et} (diameter of the semicircle on the x axis)

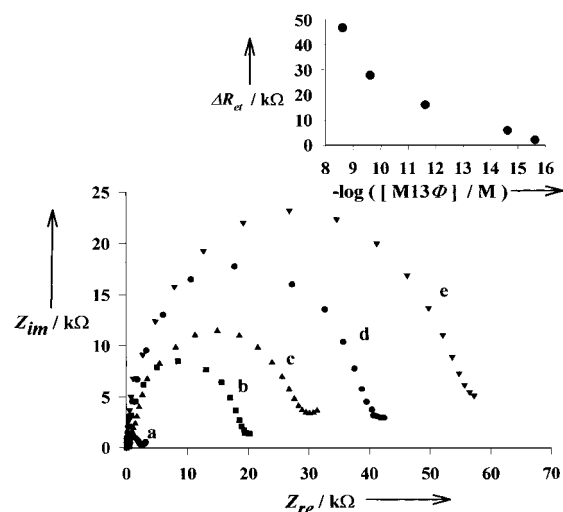


Figure 3. Faradaic impedance spectra (Nyquist plots) of: a) 1-functionalized electrode; b) after hybridization with M13 ϕ , 2.3×10^{-9} M; c) after the polymerase-induced replication and formation of the double-stranded assembly for 45 min; d) after the binding of the avidin–alkaline phosphatase conjugate to the surface; e) after the biocatalyzed precipitation of **3** for 20 min in the presence of **2** (2×10^{-3} M) in 0.1 M Tris buffer at pH 7.2. The hybridization and polymerization conditions are in the caption of Figure 1 and ref. [18]. Inset: The changes in the electron-transfer resistance ΔR_{et} upon the sensing of different concentrations of M13 ϕ by the amplified biocatalyzed precipitation of **3** onto the electrode. The ΔR_{et} is the difference in R_{et} at the electrode after the precipitation of **3** for 20 min and R_{et} at the 1-functionalized electrode.

increases upon the binding of the virus DNA from 3 k Ω to about 20 k Ω . This is consistent with the fact that binding of the high molecular weight DNA electrostatically repels the negatively charged redox label, $[\text{Fe}(\text{CN})_6]^{3-}/[\text{Fe}(\text{CN})_6]^{4-}$, from the electrode surface. The DNA polymerase-mediated synthesis of the complementary strand further increases the electron-transfer resistance to about $R_{\text{et}} = 33$ k Ω . Note that the polymerization does not double the interfacial electron-transfer resistance, consistent with the partial replication of the complementary strand on the target DNA molecule. The binding of the conjugate avidin–alkaline phosphatase and the subsequent biocatalyzed precipitation of **3** onto the electrode, results in an insulating layer that introduces a barrier for the interfacial electron transfer, and the R_{et} increases to ≈ 55 k Ω . Similarly, microgravimetric QCM experiments reveal that at this concentration of the analyte DNA, the biocatalyzed

precipitation of **3** on the crystal yields a decrease of $\Delta f = -1300$ Hz as a result of the mass increase on the transducer. The extent of the biocatalyzed precipitation of **3** on the transducers, and consequently the ΔR_{et} and Δf transduced signals, are controlled by the concentration of the M13 mp8 DNA in the sample, Figure 3 (inset) and Figure 4, respectively. Note that at concentrations of M13 mp8 corresponding to

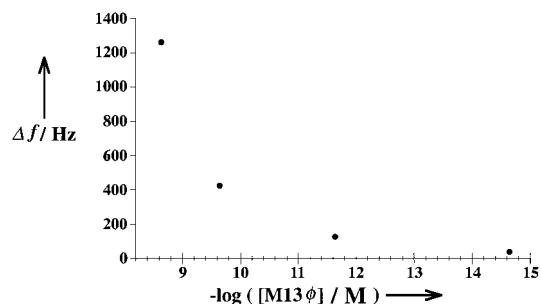


Figure 4. Frequency changes of the 1-functionalized Au-quartz crystal upon the sensing of different concentrations of M13 ϕ DNA as a result of the biocatalyzed precipitation of **3** onto the transducer. The conditions are in the caption of Figure 3.

2.3×10^{-15} M and 2.3×10^{-16} M, the hybridization of the analyte DNA with the sensing interface, and the subsequent polymerization, cannot be detected by Faradaic impedance spectroscopy or QCM, because of the low coverage of the hybridized analyte DNA on the respective transducers. In the electrochemical transduction, a change in the R_{et} of 2.8 k Ω is observed upon the analysis of the DNA, 2.3×10^{-16} M, as a result of the precipitation of **3**. In the microgravimetric analysis of the target DNA (2.3×10^{-15} M) a change of -36 Hz is observed as a result of the precipitation of **3** on the transducer.

A series of control experiments were performed to reveal the high specificity of the developed approach for sensing the targeted virus DNA: The foreign oligonucleotide **4** (see Scheme 1) that is not complementary to M13 mp8, was assembled on the electrode or Au-quartz crystal, but it failed to analyze the target DNA. Also, the 1-functionalized electrode or QCM crystal were treated with denatured calf-thymus DNA (2.3×10^{-9} M) and the resulting transducers were subsequently subjected to polymerization, association of avidin–alkaline phosphatase, and the biocatalyzed precipitation of **3**. No binding of calf-thymus DNA with the sensing interfaces could be detected by impedance spectroscopy or QCM measurements. After the attempt to stimulate the biocatalyzed precipitation of **3**, a change of $\Delta f = -7$ Hz was observed, a value that may be considered as the noise level as a result of the nonspecific binding of avidin–alkaline phosphatase to the sensing interface. In another experiment the 1-functionalized electrode or QCM crystal was treated with denatured calf-thymus DNA (2.3×10^{-9} M) mixed with an extremely low concentration (2.3×10^{-15} M) of M13 ϕ DNA. The resulting assembly was subjected to polymerization and biocatalyzed precipitation. The observed change was $\Delta f = -31$ Hz, very close to the frequency change obtained with the target DNA only, implying that the sensing of M13 ϕ is specific in the presence of DNA contaminants.

A similar approach was used for the amplified sensing of the 11161 base RNA of vesicular stomatitis virus (VSV),^[23] using reverse transcriptase as the replication biocatalyst.^[24] The oligonucleotide **5** (see Scheme 1) was immobilized as the primer sensing interface on an Au-electrode or an Au-quartz crystal, surface coverage about 1.4×10^{-11} mol cm⁻².^[16] Figure 5A shows the Faradaic impedance spectra of the **5**-functionalized electrode and the results observed upon the

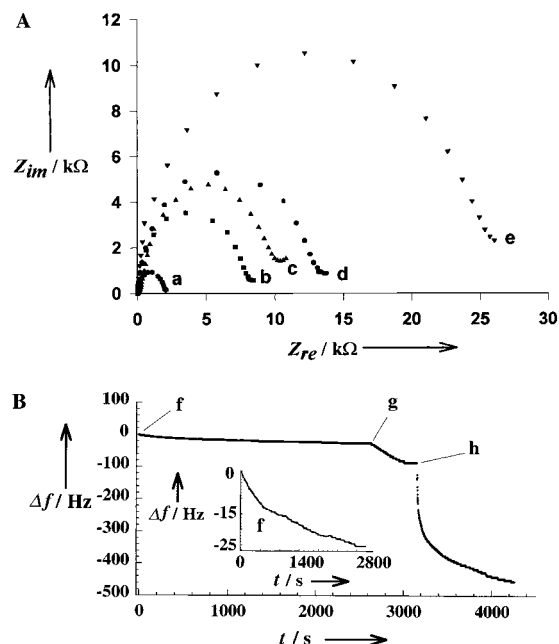


Figure 5. A) Faradaic impedance spectra (Nyquist plots) upon the amplified sensing of VSV RNA: a) the **5**-functionalized electrode; b) after hybridization with the VSV RNA, 1×10^{-12} M, in a solution consisting of 40 mM PIPES, 1 mM EDTA, 400 mM NaCl, 80% formamide, pH 7.5; c) after the reverse transcription for 45 min (80 U mL^{-1}) in the presence of dGTP, dATP, dTTP, dCTP, and biotinylated dCTP (1:1:2/3:1/3 base concentration 1 mM) in a solution consisting of 50 mM Tris buffer, 40 mM KCl, 8 mM MgCl₂, pH 8.3 at room temperature; d) after the association of the avidin–alkaline-phosphatase conjugate, bulk concentration 1 mM; e) after the biocatalyzed precipitation of **3** for 20 min in the presence of **2** (2×10^{-3} M) in Tris buffer pH 7.5. B) Time-dependent frequency changes of an Au-quartz crystal upon the analysis of the VSV RNA (1×10^{-12} M); f) frequency changes as a result of the replication of the bound RNA in the presence of reverse transcriptase and dGTP, dATP, dTTP, dCTP, and biotinylated-dCTP; g) upon the association of the avidin–alkaline-phosphatase conjugate; h) Upon the biocatalyzed precipitation of **3**. The conditions for the polymerization and biocatalyzed precipitation of **3** are detailed in Figure 5A. Inset: Magnification of curve f.

analysis of VSV–RNA according to the sequence outlined in Scheme 1. As expected, each of these steps increases the R_{et} at the electrode surface. For example, upon the analysis of 1×10^{-12} M VSV RNA the reverse transcription increases the interfacial R_{et} by $\Delta R_{et} = 4.5 \text{ k}\Omega$, the association of avidine–alkaline phosphatase further increases the R_{et} by $5.0 \text{ k}\Omega$, and the precipitation of the insoluble product **3** onto the electrode increases the R_{et} by $14.0 \text{ k}\Omega$. The viral RNA could be analyzed with a detection limit that corresponds to 1×10^{-17} M. At this concentration, the hybridization process and the reverse transcription of the VSV RNA were undetectable, yet the alkaline phosphatase precipitation of **3**

onto the electrode resulted in an amplification path and the interfacial R_{et} increased by $2.2 \text{ k}\Omega$. Control experiments revealed that the interaction of the sensing interface with a foreign RNA (1×10^{-9} M)^[25] followed by an attempt to stimulate the reverse-transcription and the biocatalyzed precipitation of **3** resulted in a minute change in the R_{et} at the electrode ($\Delta R_{et} = 0.3 \text{ k}\Omega$) indicating that the amplified detection of the VSV–RNA is selective. Figure 5B shows the microgravimetric, QCM analysis of the RNA. Hybridization with the VSV–RNA, 1×10^{-12} M results in a decrease of $\Delta f = -72 \text{ Hz}$ that indicates a surface coverage of 1% of the sensing interface. The replication of the viral RNA in the presence of dGTP, dATP, dTTP, dCTP, and biotinylated-dCTP (1:1:1:2/3:1/3 base concentration 1 mM) in the presence of reverse transcriptase, 80 U mL^{-1} , results in a decrease of -26 Hz , Figure 5B, curve f. This frequency decrease translates to an average replication of the surface-associated analyte RNA of 36%. Binding of the avidin–alkaline phosphatase conjugate onto the surface is shown in curve g ($\Delta f = -52 \text{ Hz}$) and the biocatalyzed precipitation of **3** results in a significant decrease in the crystal frequency that corresponds to around $\Delta f = 400 \text{ Hz}$, curve h, Figure 5B.

In conclusion, we highlight novel methods for the rapid and sensitive electronic transduction of viral DNA/RNA by bioelectronic devices. These methods would find broad applicability in clinical diagnostics, environmental control, and food analysis. We have demonstrated highly sensitive detection methods for long nucleic acids, based on the polymerization or reverse transcription of the double-stranded assembly of the primers with the target viral DNA or RNA on surfaces, followed by the amplification of the sensing event by the biocatalyzed precipitation of an insoluble product on the transducer. Detection limits of 2.3×10^{-15} M and 2.3×10^{-16} M for the analysis of the virus-target DNA, were achieved by using microgravimetric and impedance transduction, respectively. The RNA detection limit was found to be 1×10^{-17} M (ca. 60 copies in $10 \mu\text{L}$). This approach for the amplification of DNA/RNA sensing has broad and general potential applicability in biochip array technologies. By using redox-labeled nucleotides or fluorophore-labeled nucleotides as polymerization probes, amplified electrochemical or optical detection of viral DNA/RNA may be accomplished.

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- [17] Quartz crystals, 9 MHz AT-cut sandwiched between two Au-electrodes (area 0.196 cm², roughness factor ca. 3.5) were used in the studies.
- [18] The M13 mp8 (+) strand, nucleotides, biotinylated-dCTP and Klenow fragment were all provided by Sigma. Polymerization was performed in a 10 mM Tris buffer solution, pH 7.5, that contained 50 mM of KCl, 5 mM MgCl₂, and 20 U mL⁻¹ of the enzyme, dGTP, dATP, dTTP, dCTP, and biotinylated-dCTP (1:1:1:2/3:1/3, each base 1 mM).
- [19] The avidin–alkaline phosphatase conjugate was coupled to the biotinylated surface by treating the electrodes or the quartz crystal with avidin–alkaline phosphatase conjugate (10 nmol mL⁻¹) in 0.1 M Tris buffer for 20 min. The resulting electrodes were treated with 2 × 10⁻³ M 5-bromo-4-chloro-3-indolyl phosphate (Aldrich) in a Tris buffer for 20 min.
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- [23] HeLa cell cultures were inoculated with vesicular stomatitis virus-NJ. The culture medium was collected after 24 h, and clarified by centrifugation at 4 °C at 3000 g for 20 min. The supernatant solution was overlaid upon a 20% sucrose cushion in TNE buffer (TNE: 10 mM Tris buffer, pH 7.8, 100 mM NaCl, 1 mM EDTA; EDTA = ethylenediaminetetraacetate) and subject to centrifugation for 60 min at 27000 rpm with a SW 27 Beckmann ultracentrifuge. The pellet was dissolved in a mixture of 1:1 of phenol and TNE buffer that included 0.1% sodium dodecyl sulfate (SDS). Following extraction, the RNA was precipitated in ethanol that was incubated at –70 °C for 20 min and then subject to centrifugation for 20 min at 10000 rpm at 4 °C. The RNA was dissolved in TNE buffer.
- [24] Enhanced avian reverse transcriptase product of Sigma.
- [25] Yeast RNA of heterogeneous length of 2–7 kb (Boehringer Mannheim).

Cesium- and Rubidium-Selective Redox-Active Bis(calix[4]diquinone) Ionophores**

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Michael G. B. Drew, and Paul D. Beer*

The synthesis of redox-active molecular receptors designed to selectively recognize and electrochemically sense charged or neutral guest species of biological and environmental importance is an area of intense current interest.^[1] A number of research groups have incorporated redox-active transition metal and organic centers into a variety of macrocyclic structural frameworks based on crown ethers, cryptands, and calixarenes, and shown some of these systems to be selective and electrochemically responsive to the binding of metal cations, particularly lithium,^[2] sodium,^[3] and potassium.^[4] However, the construction of redox-active ionophores for the selective recognition of the larger cesium and rubidium metal cations has not, to our knowledge, been reported. This situation is surprising in view of the environmental concern for monitoring radioactive cesium in nuclear waste solutions^[5] and the potential use of rubidium isotopes in radiopharmaceutical reagents.^[6] We report here the synthesis, coordination, and electrochemical investigations of novel bis(calix[4]-diquinone) receptors L¹ and L², and demonstrate their remarkable ability to selectively complex and electrochemically sense cesium and rubidium cations.

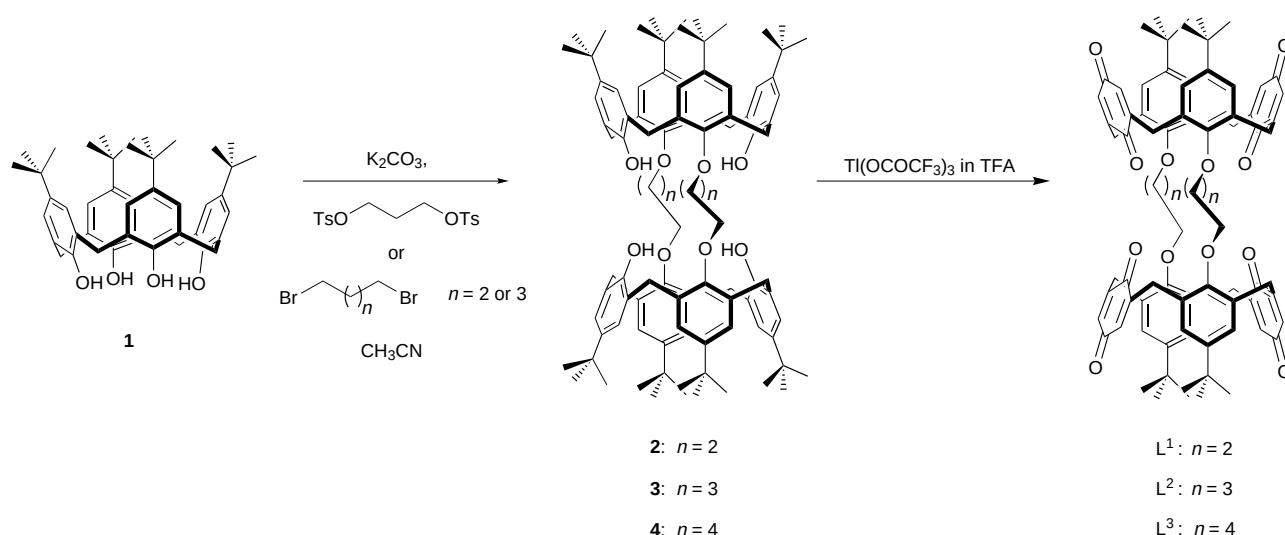
Reaction of a solution of *p*-tert-butylcalix[4]arene (**1**) in acetonitrile with propane-1,3-ditosylate, 1,4-dibromobutane, or 1,5-dibromopentane in the presence of potassium carbonate gave the bis(calix[4]arene) derivatives **2**, **3**, and **4** in 30, 23, and 26% yields, respectively (Scheme 1). Oxidation of these compounds with Ti(OCOCF₃)₃ in trifluoroacetic acid^[4a, 7] gave the new bis(calix[4]diquinone) ionophores L¹, L², and L³ in respective yields of 28, 10, and 9% after column chromatography and recrystallization.^[8]

Electrospray mass spectrometry (ES-MS) competition experiments gave the first qualitative indication that L¹ and L² displayed notable selectivity preferences for Cs⁺ and Rb⁺ ions. The electrospray mass spectra of equimolar Group 1 metal iodides in the presence of solutions of the tetraquinone ligands in DMSO revealed the most intense peaks occurred at

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Scheme 1. Synthesis of the calix[4]diquinones. Ts = toluene-4-sulfonyl; TFA = trifluoroacetic acid.

m/z values of 1293.3 $[\text{L}^1 + \text{Rb}]^+$ and 1369.9 $[\text{L}^2 + \text{Cs}]^+$. In contrast, analogous competition ES-MS experiments with L^3 suggested only weak binding of Group 1 metal cations in DMSO solutions. UV/Vis titrations were undertaken on L^1 and L^2 in a mixture of DMSO and H_2O (99:1) by monitoring the perturbation of the $n \rightarrow \pi^*$ electronic transition of the quinone moiety on addition of the cationic Group 1 metal guest. The stability constants for 1:1 complexes were then calculated using the Specfit program.^[9] The data obtained (Table 1) reveals that L^1 forms a very stable complex with Rb^+

Table 1. Stability constant data for the alkali metal complexes.

	$K [\text{M}^{-1}]^{\text{[a]}}$	
	L^1	L^2
Na^+	— ^[b]	— ^[b]
K^+	7.9×10^3	— ^[b]
Rb^+	6.3×10^4	40
Cs^+	1.3×10^4	1.6×10^3

[a] Determined in DMSO:H₂O (99:1) at 298 K, errors are estimated to be $\leq 5\%$. The alkali metal cations were added as their perchlorate salts. [b] No evidence of complexation was observed.

ions and exhibits the selectivity trend $\text{Rb}^+ > \text{Cs}^+ > \text{K}^+ \gg \text{Na}^+$. In contrast, L^2 displays a remarkable high selectivity for Cs^+ ions;^[10] in fact in this competitive aqueous DMSO mixture L^2 does not form complexes with either K^+ or Na^+ ions (Table 1). This very high $\text{Cs}^+:\text{Na}^+$ selectivity preference is of real significance for the separation of radioactive cesium nuclear waste, as such solutions typically contain Na^+ ions at high concentrations.^[5] It is noteworthy that the qualitative selectivity trends obtained from the ES-MS competition experiments are in agreement with the stability constant data and shows that the length of the bridging methylene chain between the two calix[4]diquinone moieties crucially dictates the selectivity and strength of binding for Group 1 metal cations.

The cesium complex of L^2 has been characterized by X-ray crystallography (Figure 1). The cation structure has approximate twofold symmetry. Both calix[4]diquinones have the

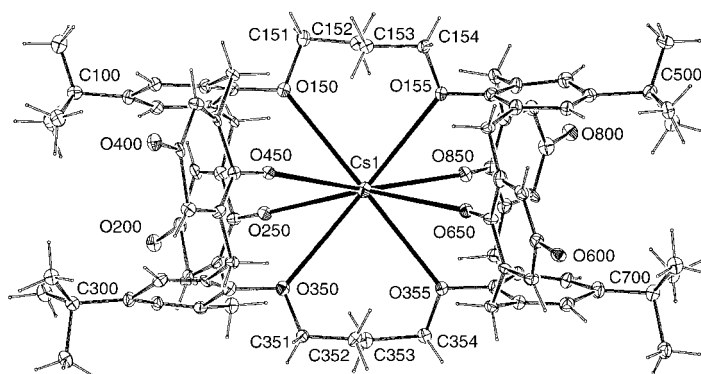


Figure 1. The structure of $[\text{CsL}^2]^+$ with ellipsoids at 10% probability.

well-known C_2 flattened-cone conformation. Thus, the phenyl rings (1, 3, 5, and 7) are almost perpendicular to the plane of the methylene rings, intersecting at angles of 87.5, 86.5, 89.1, and 84.7°, respectively, while the four diquinone rings (2, 4, 6, and 8) intersect at angles of 35.0, 35.0, 29.8, and 32.2°, respectively. The torsion angles for atoms C16–O150–C151–C152–C153–C154–O155–C156 in the butane link between the two oxygen atoms of the calixdiquinones show a *trans*, *–gauche*, *trans*, *–gauche*, *trans* conformation around the five central bonds, respectively, which allows bidentate coordination to the metal center. The cesium atom is bonded to the eight oxygen atoms bordering the central cavity. The shortest Cs–O distances are to the four diquinone oxygen atoms (3.224(8)–3.292(8) Å) with longer distances to the four ethereal oxygen atoms (3.364(9)–3.530(10) Å). In addition, the Cs atom forms two strong bonds to adjacent oxygen atoms from the diquinone oxygen atoms at the top rim of two neighboring molecules (O200: 3.226(8) (–*x*, –*y*, –*z*) and O400: 3.287(8) Å (–*x*, 1–*y*, –*z*)), thus setting up a 1D polymeric chain parallel to the *y* axis (Figure 2).

A preliminary electrochemical investigation of the recognition properties of L^1 and L^2 for Group 1 metal ions was performed in a mixture of dichloromethane and acetonitrile (4:1) by using cyclic voltammetry (CV) and square-wave

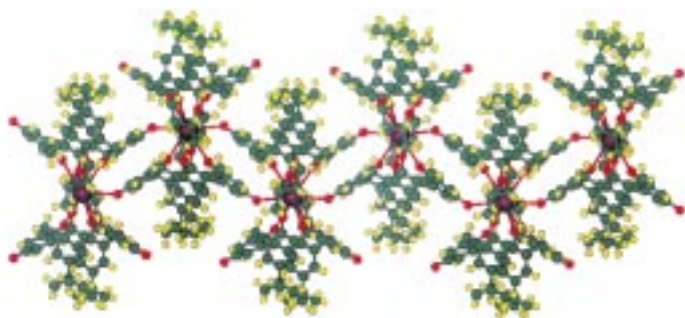


Figure 2. The structure of $[\text{CsL}^2]^+$ showing the polymeric chain in the *b* direction; cesium: purple, carbon: green, hydrogen: yellow, oxygen: red.

voltammetry (SWV, Figure 3). The results, although complicated by protonation of reduced radical anion and dianionic species,^[4a, 11, 12] are summarized in Table 1. Both receptors exhibit essentially two broad redox waves, which implies that there is multielectron transfer. The two redox waves correspond to a quasi-reversible reduction and an irreversible redox process which occurs at a more cathodic potential (Table 2). These CV features are very similar to those of previously reported calix[4]diquinones.^[4a, 11, 12] By taking into account the known voltammetric behavior of a calix[4]diqui-

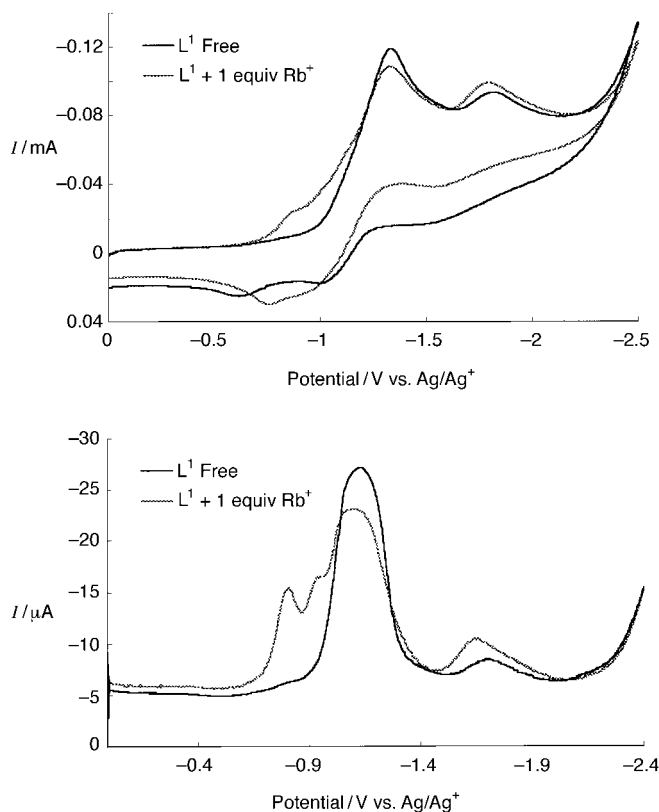


Figure 3. CV (top) and SWV (bottom) of L^1 and L^1 plus one equivalent of Rb^+ in $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{CN}$ (4:1). The anodic peaks at -1.6 V and -1.0 V are coupled with the cathodic peaks at -1.7 V and -1.3 V, respectively. It is noteworthy that the shapes of the two-wave couples are affected by the protonation of the reduced radical anion and dianion. The current wave at approximately -0.8 V on the reverse scan has also been observed in the CV spectra of other calix[4]diquinones, and was ascribed to incompletely protonated dianions (see ref. [11]). This argument is also supported by the fact that the current wave at -0.8 V is not observed when a metal cation is complexed.

Table 2. Electrochemical data^[a] in $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{CN}$ (4:1).

	L^1	L^2
$E_{1/2}$ [V] ^[b]	-1.16	-1.18
E_{pc} [V] ^[c]	-1.71	-1.79
ΔE (Na^+) [mV] ^[d]	440	500
	290	440
ΔE (K^+) [mV] ^[d]	360	440
	210	370
ΔE (Rb^+) [mV] ^[d]	350	330
	210	270
ΔE (Cs^+) [mV] ^[d]	340	310
	210	260

[a] 0.1M Bu_4NBF_4 was added as the supporting electrolyte. The concentration of the receptor in solution was approximately $1 \times 10^{-3}\text{M}$. [b] $E_{1/2}$ values are the averages of the cathodic and anodic peak potentials of the first wave couple referenced to a Ag/Ag^+ electrode at 298K . [c] E_{pc} is the cathodic peak potential of the second wave, which is irreversible. [d] Anodic shifts of the reduction waves relative to the quasireversible first reduction wave of the free receptor on addition of up to five equivalents of alkali metal cations as their perchlorate salts.

none, which can accept a total of four electrons by sequential two-electron reduction processes, the first redox wave may be attributed to a four-electron reduction process in which a one-electron transfer takes place to each of the quinone moieties present in the ligand to form radical anions. The second, more cathodic, irreversible reduction is consistent with another four-electron reduction process which leads to the formation of dianions. It has been suggested that the irreversibility of the second wave could be the result of the formation of insoluble hydroquinone species.^[12] The addition of Group 1 metal cations to electrochemical solutions of L^1 and L^2 led in all cases to the evolution of two new redox waves at potentials that were substantially positive-shifted relative to wave 1, which diminished in current height and shifted anodically concomitant with the growth of the new waves (Figure 3). Surprisingly the growth of the new waves ceased after the addition of one equivalent of metal cation, while wave 1 was still at a significant current height. Wave 1 cannot be simply ascribed to uncomplexed ligand because of its positive shift in reduction potential. Instead the observed metal cation induced electrochemical behavior suggests the metal cation is bound in an unsymmetrical manner, in closer proximity to one of the two calix[4]diquinone moieties. Although the solid-state structure of $[\text{CsL}^2]^+$ (Figure 1) shows the cesium cation is symmetrically located in the center of the ligand, the movement of the complexed cation may occur on reduction, during which electron transfer to one of the calix[4]diquinone groups proceeds earlier in real time than to the second calix[4]diquinone group.^[13] Thus, the resulting negative charge on one of these redox centers could induce movement of the metal cation within the tetraquinone–polyether binding site.^[14, 15] The alkali metal cation induced anodic shift values relative to the first reduction wave of the respective receptor (Table 2) are all substantial in magnitude, with Na^+ ions producing the greatest magnitude of shift ($\Delta E = 500\text{mV}$). It is noteworthy that electrochemical competition experiments with L^2 in a mixture of CH_2Cl_2 and CH_3CN (4:1) in the presence of tenfold excess amounts of Na^+ and K^+ ions did not affect the receptor's selective redox response to Cs^+ ions.

In summary these new bis(calix[4]diquinone) receptors represent a new design of redox-active ionophore which depend upon the length of the bridging methylene chain between the two calix[4]diquinone moieties. Their unique topological cavities can exhibit impressive selectivity preferences and novel electrochemical recognition properties towards the larger alkali metal cations Cs^+ and Rb^+ .

Experimental Section

Experimental details are given in the Supporting Information. Crystal data for $[\text{CsL}^2]\text{ClO}_4$: $\text{C}_{82}\text{H}_{93}\text{ClCsO}_{19.5}$, $M_r = 1558.92$, monoclinic, space group $P2_1/n$, $a = 11.869(15)$, $b = 18.337(25)$, $c = 40.992(44)$ Å, $\beta = 91.00(1)^\circ$, $V = 8920$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.161$ Mg m⁻³, $\mu = 0.506$ mm⁻¹. Intensity data was collected with $\text{MoK}\alpha$ radiation using the MARresearch Image Plate System. The crystal was positioned 90 mm from the Image Plate. 100 frames were measured at 2° intervals with a counting time of 10 mins to give 8091 independent reflections. Data analysis was carried out with the XDS program.^[16] The structure was solved by using direct methods with the SHELX86 program.^[17] In the cesium complex of L^2 there are two independent perchlorate anions with occupancies refined to 0.56, 0.44 and two pairs of overlapping methanol molecules each with common oxygen atoms and occupancies refined to 0.49, 0.51 and 0.49, 0.51, respectively, and two water molecules with occupancies of 1.0 and 0.5. The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The structure was refined on F^2 using SHELXL.^[18] The final R values for the cesium complex of L^2 were $R_1 = 0.0891$, $wR_2 = 0.2398$ for data 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 nos. CCDC-157775 and CCDC-157776. 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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- [14] For redox-active receptors where through-space electrostatic interactions dominate the potential shift, ΔE (mV) can be calculated using the equation $\Delta E = (Q_{\text{redox}} e / 4\pi\epsilon_0 l) (z/r)$, where $Q_{\text{redox}} = ne$, the charge variation in the redox center upon electron transfer; e = charge on an electron; n = number of electrons transferred to or from the redox center; ϵ_0 = permittivity of a vacuum; ϵ = relative permittivity of the solvent; l = distance between the redox center and the complexed cation; z = valence of the complexed cation; and r = radius of complexed cation. (See: Z. Chen, A. J. Pilgrim, P. D. Beer, *J. Electroanal. Chem.* **1998**, *444*, 209.) For 4:1 CH_2Cl_2 : CH_3CN $\epsilon = 14.6$, $r(\text{Cs}^+) = 1.74$ Å, average $\text{Cs}^+\text{--O}$ distance from crystal structure = 3.258 Å, $\Delta E = 173$ mV. (If the distance is taken between the centers of the complexed cation and quinone redox center, the value of ΔE would be smaller in magnitude.) This value is much smaller than the experimentally observed value of 260 mV (Table 2), which suggests the Cs^+ ion is bound closer to one of the two calix[4]diquinone redox centers.
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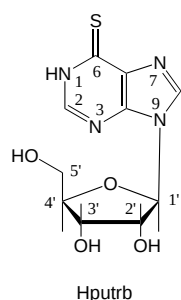
Cyclic Hexamer with a Cubic Cavity: Crystal Structure of $[\{\text{Rh}(\text{6-Purinethione Ribosido})(\text{Cp}^*)\}_6](\text{CF}_3\text{SO}_3)_6$

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The metal–ion binding capability of N⁹-substituted nucleobases such as 9-alkyladenine (R-Hade) and adenosine (Hado) have been studied intensively in the past two decades.^[1] Some cyclic polynuclear metal complexes that include such nucleobases have been synthesized recently based on self-assembling reactions.^[2] Crystal structures have been reported for $[\{\text{Rh}(\text{Me-ade})(\text{Cp}^*)\}_3](\text{CF}_3\text{SO}_3)_3$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$),^[3]

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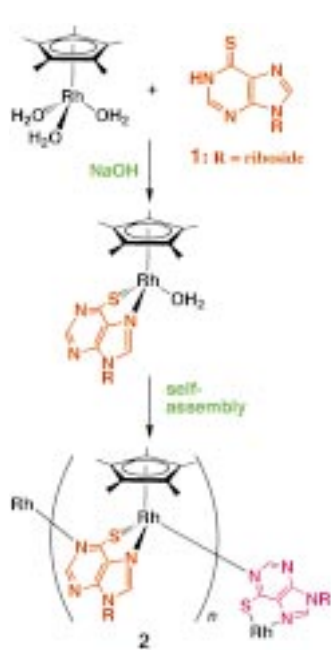
$[\{\text{Ru}(\text{Et-ade})(\text{cymene})\}_3](\text{CF}_3\text{SO}_3)_3$ (cymene = η^6 -*p*-Me- $\text{C}_6\text{H}_4\text{iPr}$),^[4] $[\{\text{Ru}(\text{S'-amp})(\text{cymene})\}_3](\text{CF}_3\text{SO}_3)_3$ (S'-amp = adenosine 5'-monophosphate),^[5] and $[\{\text{Ir}(\text{Et-ade})(\text{Cp}^*)\}_3](\text{CF}_3\text{SO}_3)_3$.^[6] Interestingly, they are all trinuclear species with C_3 symmetry.



Herein we report a similar kind of self-assembling reaction between $[\text{M}(\text{Cp}^*)(\text{H}_2\text{O})_3]^{2+}$ ($\text{M} = \text{Rh}$ and Ir) and 6-purinethione riboside (**1**, Hputrb), which has a similar ligand skeleton as adenosine, except that the NH_2 group in the 6-position is substituted by a thione group.^[7] The

crystal structure in the present system reveals that the isolated complex has a novel cyclic hexanuclear structure. The self-assembling reaction between $[\text{Rh}(\text{Cp}^*)(\text{H}_2\text{O})_3]^{2+}$ and **1** gave $[\{\text{Rh}(\text{putrb})(\text{Cp}^*)\}_6](\text{CF}_3\text{SO}_3)_6$ **2** in high yield (Scheme 1). The ^1H NMR spectrum of **2** showed a single methyl signal for Cp^* and one set of signals for **1** (Figure 1), which indicates that complex **2** is composed of a single species. The electrospray ionization (ESI) mass spectrum^[8] showed four dominant peaks at m/z 521, 655, 856, and 1191, which correspond to the ions of $[6\text{M} - 6\text{X}]^{6+}$, $[6\text{M} - 5\text{X}]^{5+}$, $[6\text{M} - 4\text{X}]^{4+}$, and $[6\text{M} - 3\text{X}]^{3+}$, respectively. This result means that **2** has a cyclic hexanuclear structure.

Figure 2 shows the stereoview of the cation in $[\{\text{Rh}(\text{putrb})(\text{Cp}^*)\}_6](\text{CF}_3\text{SO}_3)_6 \cdot 12\text{H}_2\text{O}$ (**2**). This complex has a novel hexanuclear structure. Six Rh^{III} ions are crystallographically independent and the mean $\text{Rh} \cdots \text{Rh}$ distance is 5.963 Å. The putrb ligand adopts a μ - $1\kappa\text{N}^1:2\kappa^2\text{S}^6, \text{N}^7$ bridging mode: it coordinates to one Rh^{III} ion in a bidentate manner through the S^6 and $\text{N}(7)$ donors, which form a five-membered chelate ring, and bridges to another



Scheme 1. Expected self-assembling process to form cyclic oligomers.

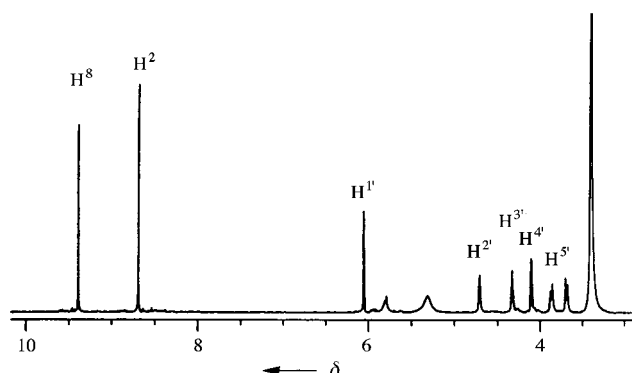


Figure 1. ^1H NMR spectrum of **2** in $[\text{D}_6]\text{DMSO}$.

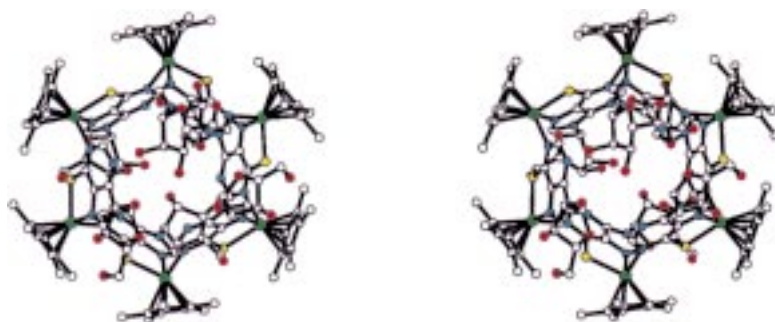


Figure 2. Stereoview of the cation in $[\{\text{Rh}(\text{putrb})(\text{Cp}^*)\}_6](\text{CF}_3\text{SO}_3)_6 \cdot 12\text{H}_2\text{O}$ (**2**): Selected distances [Å] and angles [°]: $\text{Rh}-\text{S}$ 2.431, $\text{Rh}-\text{N}(1)$ 2.155, $\text{Rh}-\text{N}(7)$ 2.132, $\text{C}(6)-\text{S}$ 1.73; $\text{S}-\text{Rh}-\text{N}(7)$ 83.6, $\text{S}-\text{Rh}-\text{N}(1')$ 91.2, $\text{N}(7)-\text{Rh}-\text{N}(1')$ 90.2, $\text{S}-\text{C}(6)-\text{C}(5)$ 116, $\text{Rh}-\text{N}(7)-\text{C}(5)$ 112, $\text{Rh}-\text{S}-\text{C}(6)$ 99.3, $\text{Rh}-\text{N}(1)-\text{C}(6)$ 125, $\text{Rh}-\text{N}(1)-\text{C}(2)$ 117, $\text{S}-\text{Rh}-\text{N}(1')-\text{C}(6) \pm 144$ (all values are averages).

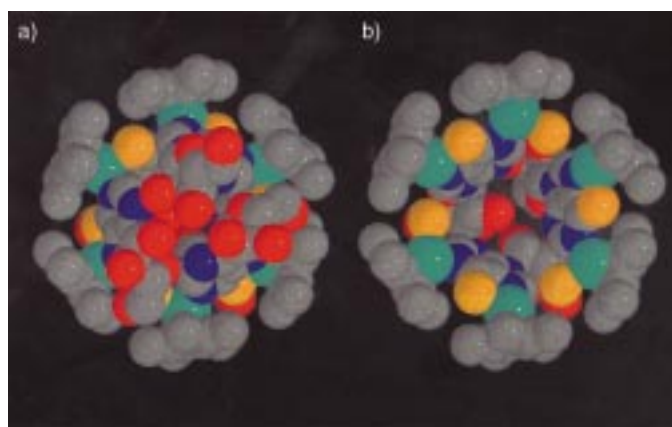


Figure 3. a) Space-filling structure of **2**, and b) the inner cavity structure after removing three putrb ligands from the foreground of **2**: green (rhodium), yellow (sulfur), red (oxygen), blue (nitrogen), gray (carbon).

the present hexanuclear structure with a cubic cavity is unprecedented.

The central Rh^{III} ions are chiral because of the unsymmetrical bridging mode of **1**. The unit Rh^{III} complex can be expressed as an arrow and the arrows must be arrayed in the same direction to form cyclic polynuclear complexes. Each unit complex has C (clockwise) or A (anticlockwise) chirality.^[10] In the cyclic hexanuclear complex, eight geometrical isomers are possible: Figure 4 shows these isomers with their symmetries and the number of sets of NMR signals that are expected. The above structure of **2** corresponds to a S_6 isomer.

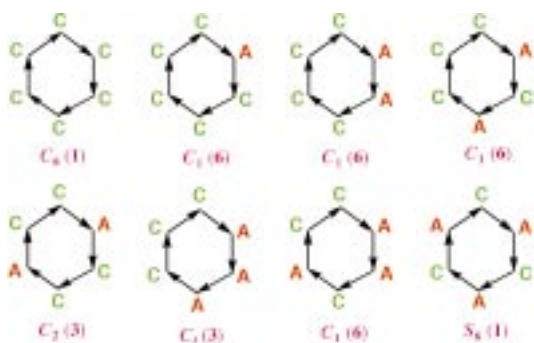


Figure 4. Possible geometrical isomers for a cyclic hexanuclear complex with an achiral bridging ligand. The characters C (clockwise) and A (anticlockwise) denote the chirality of the unit Rh^{III} complex. Each isomer is denoted by its complex symmetry, and the numbers in parentheses show number of sets of NMR signals that are expected.

The S_6 structure has the alternate cyclic array of chiralities CACACA. Hence there is no configurational contribution around metal ions but **2** becomes optically active because of the chiral ribose group of **1**. The circular dichroism (CD) spectrum of **2** shows a strong CD intensity as a vicinal contribution (Figure 5). Some CD spectra of complexes that contain nucleosides have been reported so far. Their CD intensities are, however, relatively weak because these complexes are mixtures of two diastereomers.^[3b] It should be noted that the present Rh^{III} system contains only the pseudo- S_6 isomer, which was formed stereoselectively.

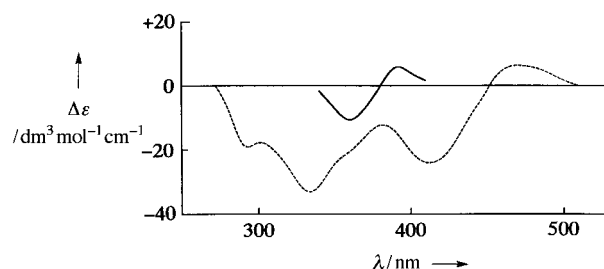


Figure 5. CD spectra of $[\{\text{Rh}(\text{putrb})(\text{Cp}^*)\}_6]^{6+}$ (**2**; dotted line) and $[\{\text{Ir}(\text{putrb})(\text{Cp}^*)\}_6]^{6+}$ (**3**; solid line).

Two cyclic purine hexamers have been reported so far.^[11] $[\{\text{Pt}(\text{thp})(\text{CH}_3)_3\}_6] \cdot 12 \text{CHCl}_3$ (Hthp = theophylline)^[11a] has the same S_6 symmetry as **2**: The thp ligand adopts a $\mu\text{-}1\kappa\text{N}^9\text{:}2\kappa^2\text{O}^6\text{N}^7$ bridging mode. This complex also has the alternate cyclic array of CACACA, but the structure is completely different from that of **2**. We concluded that these two structures are types of conformational isomers, though the bridging modes, N(1) for **2** and N(9) for the Pt^{IV} complex, are different from each other. In the model study, the other pseudo- S_6 structure similar to $[\{\text{Pt}(\text{thp})(\text{CH}_3)_3\}_6]$ can be easily constructed in the present system. The dihedral angle S-Rh-N(1)-C(6) is on average $\pm 144^\circ$ ($+147$ to -146°) in **2** and expected to be near $\pm 35^\circ$ in the other pseudo- S_6 isomer. The two conformational isomers are produced only by the difference of this dihedral angle. The mutual exchange between the two conformational isomers is impossible in solution without breaking bonds.

The corresponding Ir^{III} complex $[\{\text{Ir}(\text{putrb})(\text{Cp}^*)\}_6][\text{CF}_3\text{SO}_3]_6$ (**3**) was prepared in the same manner. Complex **3** gave rise to a very similar ^1H NMR spectrum to that of **2**, and its positive ESI mass spectrum showed dominant peaks at m/z 611, 763, and 991, which correspond to the ions of $[6M - 6X]^{6+}$, $[6M - 5X]^{5+}$, and $[6M - 4X]^{4+}$, respectively. Therefore we concluded that **3** has the same cyclic hexanuclear pseudo- S_6 structure as **2**. The CD pattern at the lower energy side for **3** is similar to that of **2** (Figure 5).

Experimental Section

2 and 3: Silver trifluoromethanesulfonate (0.33 g, 1.3 mmol) was added to a suspension of $[\{\text{Rh}(\text{Cp}^*)\text{Cl}_2\}_2]^{12}$ (0.2 g, 0.32 mmol) in water (30 mL), and the mixture was stirred at 40°C for 1 h. The resulting precipitate of silver chloride was removed by filtration, and an aqueous solution (50 mL, adjusted to about pH 8 by adding aqueous NaOH) of Hputrb (0.18 g, 0.64 mmol) was added to the filtrate. The mixed solution was heated at 80°C for 3 h, then cooled to room temperature and concentrated by using a rotary evaporator to give orange crystals, which were recrystallized from water and ethanol (70–85% yield). ^1H NMR (270 MHz, $[\text{D}_6]\text{DMSO}$, 25°C , TMS): δ = 9.38 (H^8 ; s, 1H), 8.69 (H^2 ; s, 1H), 6.05 (H^1 ; d, 1H), 5.78 (s, 1H), 5.31 (s, 1H), 4.70 (H^2 ; s, 1H), 4.32 (H^2 ; s, 1H), 4.11 (H^4 ; s, 1H), 3.86 (H^5 ; d, 1H), 3.68 (H^5 ; d, 1H), 1.81 (Cp^* ; s, 15H); ^{13}C NMR: δ = 172.43 (C6), 155.40 (C2), 145.51 (C4), 144.42 (C8), 136.18 (C5), 102.18 (Cp^*), 90.01 ($\text{C}1'$), 85.24 ($\text{C}4'$), 73.64 ($\text{C}2'$), 69.09 ($\text{C}3'$), 60.11 ($\text{C}5'$), 9.17 (Cp^*); ESI MS (in acetone): m/z : 521 $[6M - 6X]^{6+}$, 655 $[6M - 5X]^{5+}$, 856 $[6M - 4X]^{4+}$, 1191 $[6M - 3X]^{3+}$; calcd for $[\{\text{Rh}(\text{putrb})(\text{Cp}^*)\}_6](\text{CF}_3\text{SO}_3)_6 \cdot 12\text{H}_2\text{O}$ (**2**): $\text{C}_{126}\text{H}_{180}\text{F}_{18}\text{N}_{24}\text{O}_{54}\text{Rh}_6\text{S}_{12}$ (%): C 35.70, H 4.28, N 7.93; found: C 35.22, H 4.21, N 7.92.

The corresponding Ir^{III} complex was prepared in the same manner (70–80%). ^1H NMR (270 MHz, $[\text{D}_6]\text{DMSO}$, 25°C , TMS): δ = 9.34 (H^8 ; s, 1H), 8.63 (H^2 ; s, 1H), 6.01 (H^1 ; d, 1H), 5.74 (s, 1H), 5.27 (s, 1H), 4.64 (H^2 ; s, 1H), 4.28 (H^2 ; s, 1H), 4.07 (H^4 ; s, 1H), 3.82 (H^2 ; d, 1H), 3.64 (H^5 ; d, 1H), 1.81 (Cp^* ; s, 15H); ESI MS (in acetone): m/z : 611 $[6M - 6X]^{6+}$, 763 $[6M - 5X]^{5+}$, 991 $[6M - 4X]^{4+}$; calcd for $[\{\text{Ir}(\text{putrb})(\text{Cp}^*)\}_6](\text{CF}_3\text{SO}_3)_6 \cdot 9\text{H}_2\text{O}$ (**3**): $\text{C}_{126}\text{H}_{174}\text{F}_{18}\text{Ir}_6\text{N}_{24}\text{O}_{51}\text{S}_{12}$ (%): C 32.06, H 3.71, N 7.12; found: C 32.00, H 3.73, N 7.32.

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were performed by using the TEXSAN^[13] crystallographic software package. 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-153832. 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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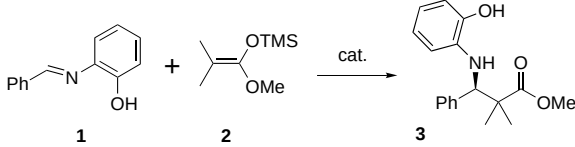
Active Site Design in a Chemzyme: Development of a Highly Asymmetric and Remarkably Temperature-Independent Catalyst for the Imino Aldol Reaction**

Song Xue, Su Yu, Yonghong Deng, and William D. Wulff*

The asymmetric aldol reaction of an enolate or enolate equivalent with an imine is a reaction of established synthetic importance for the synthesis of chiral amines in general and β -amino esters in particular.^[1] The development of chiral catalysts for this reaction has proven to be a difficult task and had eluded all attempts until recently when Kobayashi and co-workers examined imines derived from *o*-aminophenol.^[2–4] Their method involves the catalysis of the reactions of these imines and ketene acetals with a catalyst generated from zirconium(IV) *tert*-butoxide and two equivalents of (*R*)-6,6'-dibromoBINOL (BINOL = 1,1'-binaphth-2-ol). Our interest in the synthesis of chiral amines led us to investigate the use of VAPOL-derived catalysts^[5] (see Figure 1) for this reaction. Here we report the development of a remarkably temperature-independent and highly asymmetric method for this process that was guided by an analysis of models of intermediates that are suspected to be involved in the reaction.

A comparison of catalysts prepared from BINOL, 6,6'-dibromoBINOL and VAPOL ligands on the asymmetric induction in the reaction of the phenyl-substituted imine **1** and acetal **2** is summarized in Table 1. Following the Kobayashi

Table 1. Reactions of imine **1** with acetal **2** with various catalysts.^[a]



Entry	Ligand	mol % cat.	T [°C]	t [h]	Solvent	Yield 3 [%]	% ee
1	<i>S</i> -VAPOL	20	–45	10	CH ₂ Cl ₂	50	80
2	<i>S</i> -VAPOL	20	–45	20	toluene	92	91
3	<i>S</i> -VAPOL	20	25	15	toluene ^[b]	94	89 ^[c]
4	<i>S</i> -VAPOL	2	40	6	toluene ^[b]	100	86 ^[d]
5	<i>S</i> -VAPOL	0.5	41	19	toluene	60	85
6	<i>R</i> -BINOL ^[e]	20	–45	19	CH ₂ Cl ₂	80	36
7	<i>R</i> -BINOL ^[e]	20	25	4	CH ₂ Cl ₂	100	28
8	<i>R</i> -Br ₂ BINOL ^[f]	10	–45	19	CH ₂ Cl ₂	87	86
9	<i>R</i> -Br ₂ BINOL ^[f]	20	25	4	CH ₂ Cl ₂	87	48
10	<i>R</i> -Br ₂ BINOL ^[f]	10	25	18	toluene	95	62

[a] Catalyst generated from Zr(OiPr)₄/iPrOH, (*S*)-VAPOL (2.2 equiv) and 1.2 equiv *N*-methyl imidazole (NMI) in either CH₂Cl₂ or toluene at 25 °C for 1 h. Unless otherwise specified, all reactions were performed with 1.2 equiv of **2** and 0.125 M in imine. [b] 15:1 toluene:CH₂Cl₂. [c] 0.5 M in imine. [d] 1.0 M in imine. [e] Catalyst generated from Zr(OiPr)₄/iPrOH, *R*-BINOL (2.2 equiv) and 1.2 equiv NMI in CH₂Cl₂ at 25 °C for 1 h. [f] Catalyst generated from Zr(OrBu)₄, (*R*)-6,6'-dibromoBINOL (2.2 equiv) and 1.2 equiv NMI in CH₂Cl₂ at 25 °C for 1 h.

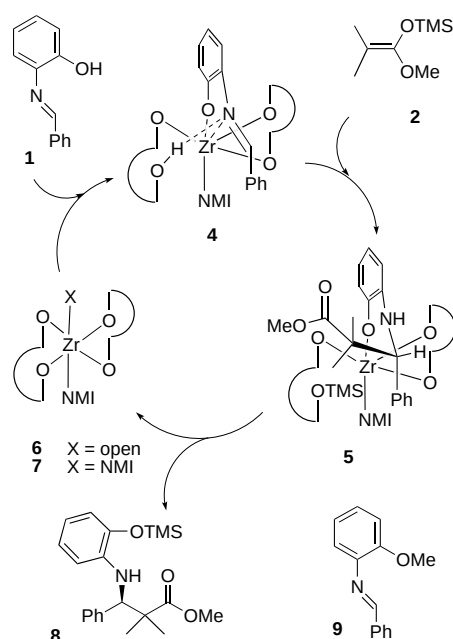
protocol, the catalyst was prepared by reaction of the ligand with 0.5 equivalents of zirconium tetraalkoxide in the presence of 0.6 equivalents of *N*-methyl imidazole at room temperature for 1 h.^[2] The VAPOL catalyst could be prepared in either methylene chloride or toluene, but for solubility reasons, the BINOL catalysts were prepared in methylene chloride. The VAPOL and Br₂BINOL catalysts were superior to the BINOL catalyst at –45 °C. The asymmetric induction dropped for the Br₂BINOL catalyst when the temperature was raised from –45 °C to room temperature, but curiously, the asymmetric induction for the VAPOL catalyst was essentially unchanged over this same temperature range. Only a small drop-off is noted (85 % ee) when the temperature is raised to 41 °C and the substrate-to-catalyst ratio is raised to 200:1 (entry 5). Both the *R* enantiomers of BINOL and Br₂BINOL ligands give the *R* enantiomer of the product **3**, whereas with the VAPOL ligand, it is the *S* enantiomer that gives the *R* product. This reversal is not unexpected given the structures of the ligands where the zirconium is in the minor groove of the BINOL ligands and in the major groove of the VAPOL ligand.^[6, 7]

The mechanism that has been proposed for the catalytic cycle for the Br₂BINOL–zirconium-mediated reaction involves a catalyst bearing two Br₂BINOL ligands on one zirconium and the coordination of the *o*-hydroxyphenylimine to the zirconium as a bidentate ligand.^[2g] It is clear from the examination of space-filling CPK models that it is possible to bind two VAPOL ligands to one zirconium atom but only with a facial arrangement of the four oxygen atoms as is illustrated by structure **6** in Scheme 1. This is supported by ¹H NMR experiments on a catalyst generated from zirconium tetraisopropoxide and VAPOL in the presence of two equivalents of *N*-methyl imidazole. A clean spectrum is only observed with two equivalents of VAPOL relative to zirconium and the spectrum is consistent with a single C₂-symmetrical species

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Scheme 1. Proposed mechanism for the reaction of imine **1** with acetal **2**.

which is tentatively identified as structure **7** bearing mutually *trans* NMI ligands bound to the zirconium.^[8, 9] An approach of imine **1** to the open apical position in intermediate **6** is proposed to lead to intermediate **4** in which a phenol exchange has occurred. In support of this is the observation that the catalysis of the reaction of the O-methylated imine **9** with acetal **2** under the conditions in entry 3 in Table 2 gave **3** in 5% yield and 0% *ee*.^[10] The requirement for NMI then can be explained as that of a monodentate ligand that binds to the other apical site and maintains an octahedral geometry. Reaction of species **4** with the ketene acetal would give intermediate **5** and then release of the product would regenerate the unsaturated species **6** and complete the cycle.

A space-filling CPK model of intermediate **6** is shown in Figure 1 and illustrates the binding cleft that is available for the docking with imine **1**. There are a number of possible

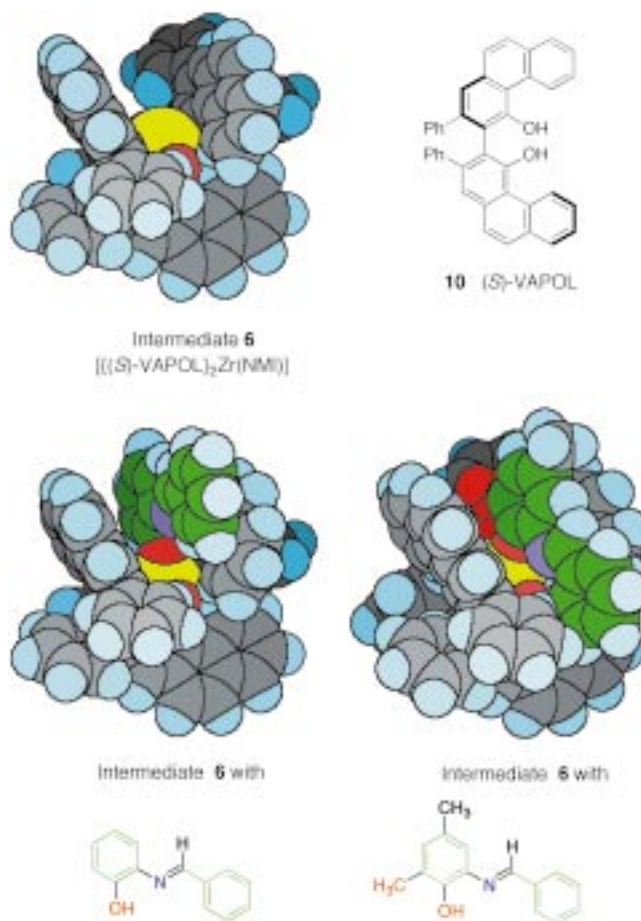


Figure 1. CPK models of intermediate **6** and of two imines complexed with intermediate **6**.

orientations of **1** in the cleft of **6** and these are largely associated with changes in the Zr–O–C bond angle that has the effect of rocking the imine back and forth in the cleft. Rocking the imine down into the cleft should provide a conformation that provides a greater facial selectivity of attack on the imine since it should provide greater shielding of the *re*-face by the phenanthrene unit on the right side of the molecule as viewed in Figure 1. CPK models reveal that a methyl group on the imine *ortho* to the phenol function should be sufficient to push the imine down into the cleft. This methyl group is presented in red in the imine complex with intermediate **6**, and as illustrated in Figure 1 this methyl group makes close contacts with the floor of the cleft even when the imine is rotated down into the cleft and this results in greatly restricted movement about the Zr–O–C unit to the imine moiety. This model thus predicts that imines with a methyl substituent *ortho* to the phenol function in imine **1** should lead to increased asymmetric induction in the imino aldol reaction whereas methyl groups at positions *meta* and *para* to the phenol should not have any effect since they do not make close contacts with any part of the catalyst.

On the basis of the above predictions, a series of seven substituted imines were prepared; data from their reactions with ketene acetal **2** are summarized in Table 2. Indeed, of the four possible monomethyl-substituted imines, the highest induction was observed with a methyl group *ortho* to the

Table 2. Reactions of imines from substituted amino phenols.^[a]

Imine	R ¹	R ²	R ³	R ⁴	Product	Yield [%]	% <i>ee</i>
1	H	H	H	H	3	94 ^[b]	89
11	Me	H	H	H	17	89	≥ 99
12	H	Me	H	H	18	87 ^[c]	91
13	H	H	Me	H	19	93	95
14	H	H	H	Me	20	80 ^[c]	36
15a	Me	H	Me	H	21a	100	≥ 98
16	H	H	Cl	H	22	78	60
15a	Me	H	Me	H	21a	93	47 ^[d]

[a] See Table 1. [b] Reaction performed at 0.5 M imine in 15:1 toluene/CH₂Cl₂. [c] Reaction time of 2 h. [d] Catalyst (10 mol %) generated from (*R*)-6,6'-dibromoBINOL according to footnote [f] in Table 1.

phenol function ($R^1 = \text{Me}$). The asymmetric induction increases from 89% *ee* with imine **1** to >99% *ee* with imine **11** (entries 1 and 2). The induction significantly drops with imine **14** with a methyl group *ortho* to the imine which may be a result of twisting of the imine to expose the *re*-face. The introduction of a methyl group at R^2 has very little effect and the slight increase in induction for the methyl group at R^3 may indicate an electronic effect that results in a shortening of the zirconium–oxygen distance. This is corroborated with the decrease in induction observed for the imine **16** with a chloro substituent at R^3 . The catalyst generated from Br_2BINOL has a completely different response to substituents on the imine; the induction drops with introduction of a methyl group *ortho* to the phenol. The catalyst prepared from this ligand gives an enantiomeric excess of 62% with imine **1** (Table 1, entry 10) and 47% with the dimethyl-substituted imine **15a** (Table 2, entry 8).

The rate of the reaction of imines with ketene acetals with the VAPOL catalyst is slower with imines generated from substituted aminophenols, however, as indicated in Table 3, this effect can be offset by performing the reaction at higher

Table 3. Temperature dependence of the asymmetric induction in **21**.^[a]

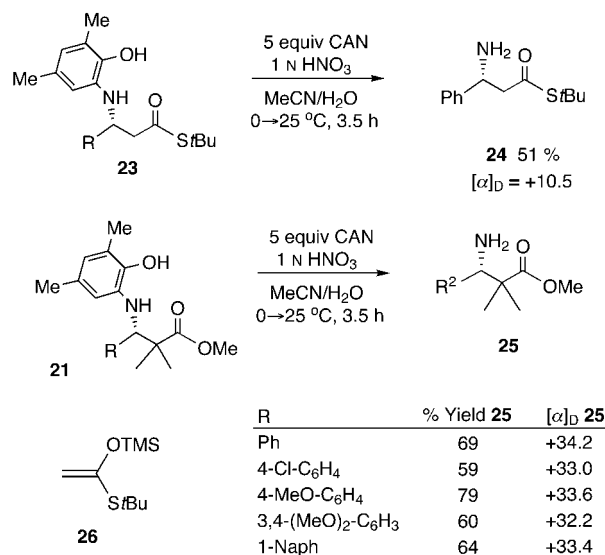
Series	R	mol % cat.	T [°C]	Yield 21 [%]	% <i>ee</i> 21
a	Ph	20	25	100 ^[b]	98.0
		20	65	93 ^[c]	98.4
		20	85	94 ^[c]	98.5
		20	100	91 ^[c]	98.5
		5	100	90 ^[c]	98.4
		2	100	95 ^[d]	98.5
b	4-Cl-C ₆ H ₄	2	100	90 ^[e]	95.4
c	4-MeO-C ₆ H ₄	2	100	85 ^[e]	99.8
d	3,4-(MeO) ₂ -C ₆ H ₃	2	100	85 ^[e]	96.4
e	1-Naph	2	100	83 ^[e]	93.0

[a] See Table 1; reaction time 2–3 h. [b] Reaction time 15 h. [c] (S)-VAPOL used. [d] Reaction time 5 h. [e] Reaction time 24 h.

temperature where greater turnover numbers are observed. It was quite striking to observe that the induction with imine **15a** shows absolutely no temperature dependence over the range of 25 to 100 °C.^[11] Furthermore, the reaction at 100 °C can be performed with an order of magnitude change in catalyst loading with no loss in induction. The turnover numbers have not yet been measured, as the minimum time for these reactions was not investigated. The electronic nature of the imine has a small effect on the induction at this temperature with a slight increase noted for a *p*-methoxy substituent and slight decrease for a *p*-chloro substituent.

The reactions of the imines **15** with the ketene acetal **26** mediated by the VAPOL–zirconium catalyst are slower than those involving the ketene acetal **2** and do not display the same temperature independence. The reaction of imine **15e** with **26** gives **23e** in 91% enantiomeric excess at 25 °C

(20 mol% catalyst) and in 76% enantiomeric excess at 100 °C (5 mol% catalyst). Similarly, the reaction of imine **15a** with **26** gives **23a** in 71% *ee* at 25 °C (20 mol% catalyst) and 60% *ee* at 100 °C (2 mol% catalyst). The deprotection of the amine function in the adduct **23a** can be accomplished by direct treatment with 5 equivalents of ceric ammonium nitrate at 0 °C and then warming to room temperature over 3.5 h. The deprotection of the methyl esters **21a–e** were accomplished with the same conditions in 60–79% chemical yield (Scheme 2).



Scheme 2. Products, yields, and optical rotations of the reactions of imine **15** with the ketene acetal **26** and deprotection of **21** and **23**.

The VAPOL–zirconium catalyst described herein is unusually robust providing very high asymmetric inductions in the Mukaiyama type condensation of ketene acetals with imines. We will report in due course on continuing studies directed toward experimentally probing the mechanism of this reaction as well as further development of the scope and synthetic potential of these reactions.

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Cu^{2+} Inhibits the Aggregation of Amyloid β -Peptide(1–42) in vitro**

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Alzheimer's disease (AD) is the most frequent cause of late-life dementia, with pathological characteristics of extracellular aggregation of amyloid β -peptides ($\text{A}\beta$ s) with 39–43 amino acids, which are proteolytically derived from the transmembrane amyloid precursor protein (APP).^[1] Recent studies indicate that the amyloid β -peptide(1–42) ($\text{A}\beta(42)$) plays a central role in the formation of the β -amyloid fibril (fA β) in vivo among the different coexisting $\text{A}\beta$ species.^[2] Further elucidation of the mechanism of $\text{A}\beta(42)$ aggregation, and the effect of extrinsic or environmental factors such as pH, metal ions, ionic strength, membrane-like surfaces, and solvent hydrophobicity on the aggregation is useful for our understanding of the pathophysiology and treatment of Alzheimer's disease and other similar neurodegenerative diseases.

Some metal ions such as Zn^{2+} , Cu^{2+} , etc., are essential in trace amounts with important fundamental roles in the biochemistry of human life.^[3] It was recently reported that Cu^{2+} , Zn^{2+} , and Fe^{3+} are concentrated in the normal neocortex. The concentrations of these cations are more than doubled in the cerebral amyloid deposits of AD brains compared with the neuropil of normal age-matched brains.^[4] However, the role of Cu^{2+} in neurodegenerative diseases such as Alzheimer's disease is still not clear, although the effect of Zn^{2+} on the aggregation of $\text{A}\beta$ s has been demonstrated by several groups in recent years.^[5] Our recent study indicated that the complexation of peptides with Cu^{2+} is responsible for inducing and enhancing the formation of the α -helix conformation of the alanine-based peptides with a Trp/His pair in different geometrical spacings and positions.^[6] Herein we describe the aggregation of $\text{A}\beta(42)$ and demonstrate for the first time that Cu^{2+} inhibits the aggregation of $\text{A}\beta(42)$ with both thioflavin T (ThT) fluorescence assay and atomic force microscopy (AFM) in vitro.

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At first, we examined the concentration dependence of A β (42) aggregation by using ThT fluorescence assay. The concentrations of the A β (42) solution were changed from 6.25 to 100 μ M. The formation of fA β was monitored with their corresponding ThT fluorescence spectra. The characteristic ThT fluorescence spectra of fA β with an emission peak at 484 nm were obtained with the excitation wavelength at 435 nm (Figure 1a). The intensity of the ThT fluorescence

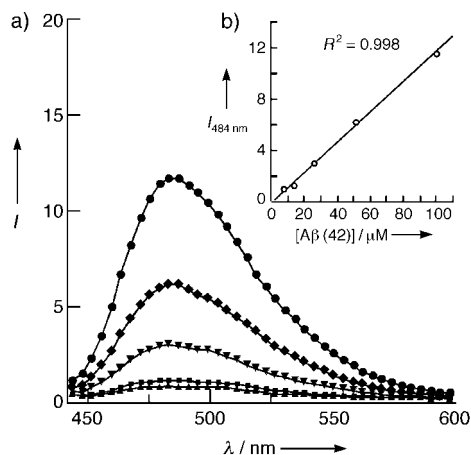


Figure 1. Concentration effect of A β (42) on the formation of amyloid fibril. a) ThT fluorescence spectra of A β (42) solutions incubated in (●) 100 μ M, (◆) 50 μ M, (▼) 25 μ M, (■) 12.5 μ M, and (▲) 6.25 μ M. b) ThT fluorescence emission intensity at 484 nm of A β (42) solutions incubated in different concentrations.

emission at 484 nm varied from 0.84 at 6.25 μ M (▲) to 11.73 at 100 μ M (●) and was a linear function ($R^2 = 0.998$) of the concentration of A β (42) (Figure 1b). It is known that ThT specifically binds to fA β , and this binding results in a fluorescent signal proportional to the mass of the formed fibril.^[7] Therefore, the linear dependence of the ThT fluorescence intensity at 484 nm with the A β (42) concentration indicated that the formation of fA β is directly proportional to the concentration of A β (42) in the range of 6.25 to 100 μ M. On the contrary, the characteristic ThT fluorescence spectrum of fA β was not observed in a solution of 100 μ M A β (42) that was stored for 6 h at 2 °C (data not shown).

It is known that ThT characteristically stains amyloid-like deposits under a number of pathophysiological conditions.^[7–9] They are believed to interact specifically with the crossed- β -sheet structure common to amyloid structures comprised of different materials, although the mechanism is not fully known. This paper examined the interaction between ThT and fA β of A β (42) with a series of ThT concentration dependence experiments. The fluorescence intensity at 484 nm was related to the ThT concentration and reached a saturation state at a high concentration (above 5 μ M; Figure 2a). It is known that the Scatchard plot is useful for identifying the noncovalent binding of one or more ligands to a single macromolecule. The Scatchard plot was performed to evaluate the interaction between ThT and fA β (Figure 2b). The concentration of fA β bound with ThT was recorded with the ThT fluorescence intensities at different ThT concentrations and the bound/free ratio was calculated approximately

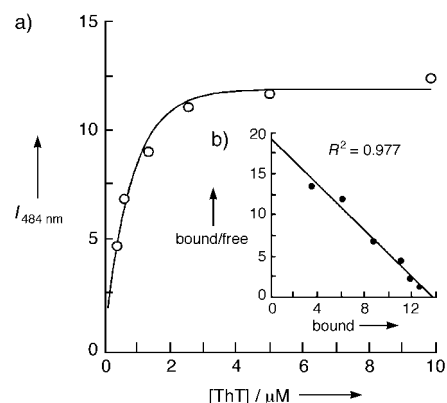


Figure 2. Concentration effect of ThT on the fluorescence assay. a) ThT fluorescence intensities at 484 nm with different ThT concentrations. b) The Scatchard plot of ThT binding to amyloid fibril.

by dividing the ThT fluorescence intensities by the corresponding total ThT concentrations.^[8] A single population of binding sites with a dissociation constant of $K_d = (7.1 \pm 0.6) \times 10^{-7}$ M ($R^2 = 0.977$) was obtained with the characteristic Scatchard plot of ThT binding to fA β . It was revealed that ThT molecules bind fA β of A β (42) in the identical and independent weak binding sites of fA β . A similar linear dependence of the ThT fluorescence intensity was also observed and the Scatchard plot was performed by other researchers. LeVine reported that the K_d values of the ThT binding with fA β s of A β (40) and A β (28) at pH 6.0 were 2×10^{-6} M and 5.4×10^{-7} M, respectively.^[7] Recently, Naiki and Nakakuki described in detail the interaction of ThT binding with fA β of A β (40).^[8] The disassociation constant, $K_d = 8.6 \times 10^{-7}$ M, of the interaction between ThT and fA β was obtained with the corresponding Scatchard plot (pH 8.5). These results, together with the data herein, confirm that the binding of ThT with various fA β s is of lower affinity. The ThT fluorescence assay is useful for monitoring the assembly process of fA β s, especially in Alzheimer's disease and other similar neurodegenerative diseases, as well as for testing agents that might modulate the assembly and disassembly.

To evaluate the effect of Cu²⁺ on the aggregation of A β (42), the incubation of 100 μ M A β (42) for 6 h was performed in the absence and presence of Cu²⁺ with A β (42)/Cu²⁺ 1:5 (molar) at 37 °C. The intensities of the ThT fluorescence emission at 484 nm of A β (42) solutions were incubated at different pH values (Figure 3). It is apparent that the aggregation of A β (42) is dependent on the pH of the A β (42) solution. A high potential of the A β (42) aggregation was observed at neutral and basic pH values in the absence of Cu²⁺. However, it decreased in the acidic solution. On the contrary, the characteristic ThT fluorescence spectra of fA β with an emission peak at 484 nm disappeared in the A β (42) solutions that were incubated at different pH values in the presence of Cu²⁺. The corresponding intensities of the ThT fluorescence emission at 484 nm are also shown in Figure 3. Comparing the intensities of the ThT fluorescence emission at 484 nm between the absence and presence of Cu²⁺, it is demonstrated that Cu²⁺ inhibits the aggregation of A β (42) in vitro.

AFM was also used to evaluate the aggregation of A β (42) and the effect of Cu²⁺ inhibition on the process. The A β (42)

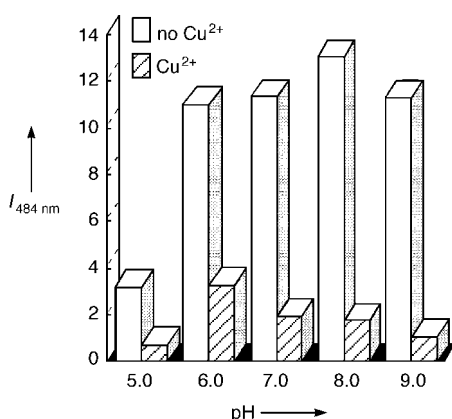


Figure 3. pH effect on the aggregation of Aβ(42) in the absence and presence of Cu²⁺. Fluorescence intensities at 484 nm were used to monitor the aggregation of Aβ(42).

solutions incubated under different conditions were adsorbed on freshly cleaved mica surfaces and imaged in the tapping mode. The advantage of the tapping mode over the contact mode is that the damage to biological samples (protein) is evidently reduced owing to the decrease in the tip-sample forces. The images were simultaneously collected in the height mode, in which increasing brightness corresponded to the increasing height feature. The amyloid fibril was not observed in the sample stored for 6 h at 2 °C in the absence of Cu²⁺, although some small particles were revealed in the figure (Figure 4a). Longer fibrous strands and larger globular particles are evident in the sample incubated for 6 h at 37 °C in the absence of Cu²⁺ (Figure 4b). On the contrary, it is novel that the longer fibrous strands disappeared and that the small particles were reduced in the sample incubated for 6 h at 37 °C in the presence of Cu²⁺ (Figure 4c). The results of the AFM

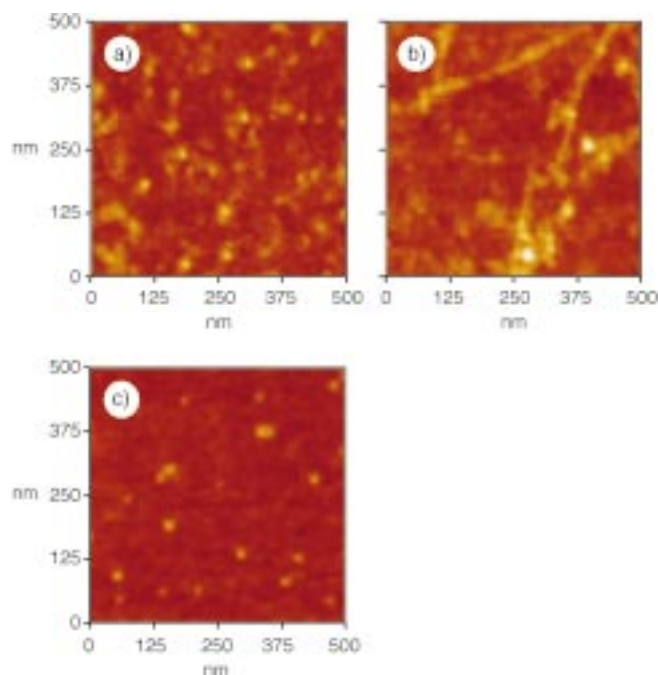


Figure 4. AFM images of Aβ(42) incubated under different conditions. The images were 500 × 500 nm and were collected simultaneously in the height mode; a) at 2 °C in the absence of Cu²⁺, b) at 37 °C in the absence of Cu²⁺, and c) at 37 °C in the presence of Cu²⁺.

imaging confirmed that Cu²⁺ was able to inhibit the aggregation of Aβ(42) in vitro.

As described above, both the ThT fluorescence assay and AFM revealed that Cu²⁺ is an inhibitor in the aggregation of Aβ(42) in vitro. This corresponds well to our recent results that Cu²⁺ is able to induce and enhance the α-helix conformation in short alanine-based peptides.^[6] The formation of Cu²⁺–Aβ(42) complex is responsible for the inhibition of Cu²⁺ because it is useful to stabilize the soluble form of Aβ(42) and to control the conformational transition from the random coil to the β-sheet. The possible mechanism of the inhibition by Cu²⁺ of the aggregation of Aβ(42) will be proposed in our next paper. The distinct biochemical role of Cu²⁺ was not only observed in the aggregation of Aβ(42) as described above, but also in some other bioprocesses. For example, the importance of Cu²⁺ was indicated in the conformational transition of the prion protein (PrP) found in bovine spongiform encephalopathy (BSE).^[10] Finally, it should be mentioned that the biochemical role of Cu²⁺ is still a challenging task. It is not clear in which oxidation–reduction state the involved copper ions are present in vivo or to what extent and in which way copper creates conformational changes of the protein portion. Further work has to be performed to answer these questions.

Experimental Section

Aβ(42) used in this study was purchased from the Peptide Institute, Inc. (Lot No. 491120). The other substances used in this study were purchased from Wako Pure Chemical Industries, Ltd. Aβ(42) was dissolved in dimethyl sulfoxide (DMSO) as a stock solution (1.0 mM) and stored at –30 °C before the aggregation assay. The aggregation solution of Aβ(42) (100 μM) was prepared by diluting the stock solution with the appropriate buffers containing sodium citrate (1 mM), sodium phosphate (1 mM), sodium borate (1 mM), and sodium chloride (10 mM) in an ice-water bath of 2 °C, which were adjusted by HCl or NaOH to different pH values.^[6, 11] Unless otherwise noted, all the incubations for the aggregation of Aβ(42) were performed at 37 °C for 6 h in a B1-515 Block Incubator (ASTEC). The chloride salt of Cu²⁺ was used with Aβ(42)/Cu²⁺ 1:5 (molar) to observe its effect on the aggregation of Aβ(42). The solutions were not agitated during the incubation.

The formation of fAβ was monitored with the ThT fluorescence assay by using a F-3010 Fluorescence Spectrophotometer (Hitachi Co., Ltd.) with a quartz cell (1.0 cm path length) at 2 °C. The fluorescence intensity is shown in arbitrary units. After incubation, an aliquot of the Aβ(42) solution (25 μL) was added to glycine buffer (pH 9.0, 50 mM), containing ThT (5 μM) with a final volume of 1.2 mL in an ice-water bath of 2 °C. Its fluorescence spectrum from 440 to 600 nm was immediately measured at the excitation wavelength of 435 nm. The concentration dependence of Aβ(42) aggregation was monitored by incubating Aβ(42) in different concentrations and examining the corresponding ThT fluorescence intensities at 484 nm with the excitation wavelength of 435 nm. A curve-fitting procedure was performed by MacCurveFit version 1.4 of Kevin Raner Software.^[6]

The formation of fAβ and the effect of Cu²⁺ were also examined by using AFM (JSPM-4200, JEOL). An aliquot of incubated Aβ(42) solution (ca. 5 μL) was transferred to a piece of freshly cleaved mica and dried with nitrogen gas. The buffer salts and loosely bound Aβ(42) were washed from the surface of the mica with distilled water (2 × 10 μL each time) and the mica was dried again with nitrogen gas. The sample was stored in a covered container to protect it from contamination until it was imaged (within 1–2 h). The images shown above were measured in the tapping mode and simultaneously collected in the height mode. All imaging was performed at room temperature (about 25 °C).

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Pure Polymorph C of Zeolite Beta Synthesized by Using Framework Isomorphous Substitution as a Structure-Directing Mechanism**

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Zeolites are crystalline tectoaluminosilicates, whose structure is formed by TO_4 tetrahedra ($\text{T} = \text{Al}, \text{Si}$) and each apical oxygen atom is shared between two adjacent tetrahedra. The main interest of these materials lies on the fact that the TO_4 tetrahedra are organized in such a way that micropores of regular dimensions are formed giving these materials molec-

ular-sieve properties. The regular and shaped pores and cavities could act as microreactors selecting the transition state that better fits to a given particular structure. However, an important prerequisite for supramolecular inorganic host–guest chemistry will be production of tailor-made host systems with designed topologies and adapted surface properties.^[1] Important advances towards this direction have been made by introducing organic cations into the synthesis media. The very relevant work carried out on this field by the groups of Davis and Zones^[2–4] have allowed these authors to conclude that while organic cations play an important role as structure directing agents during the synthesis, very seldom they act as true templates, at least in the sense that this term is used in biological systems.^[5] Therefore, it is not surprising that only in very few cases it can be claimed that the organic cations act as true templates.^[6–8] This implies that, despite the important attempts to carry out “a priori design of zeolites”,^[9,10] the synthesis of new zeolitic structures advances by accumulating knowledge on the influence of the different synthesis variables.

A more sophisticated achievement would be to direct the synthesis of zeolites, which are formed by an intergrowth of polymorphs, towards the production of a single, pure polymorph. As far as we know, this has been done in the case of SSZ-33, which corresponds to an intergrowth of two polymorphs, and one pure polymorph could be obtained by choosing the appropriate organic structure-directing agent (SDA).^[8,11,12]

Zeolite Beta is accepted as a highly faulted intergrowth of two polymorphs, A and B, which are normally found in a 60:40 ratio.^[13] However, it has been proposed that a third polymorph (polymorph C) should also exist even if has not been detected experimentally.^[13] The structure of the proposed polymorph C of Beta is closely related to those of polymorphs A and B and could be generated from polymorph A simply by the recurrent application to the building layers of a shear operation along both *a* and *b* axes. In this way, the space group of polymorph A ($P4_22$) is transformed into the more symmetrical polymorph C ($P4_2/mmc$).

What is interesting is that the hypothetical structure of polymorph C has a three-dimensional pore topology, in which all three 12-membered-ring channels are linear, while in the case of the other two polymorphs one of the channels is sinusoidal.^[13] An additional important structural difference between the different polymorphs is that polymorph C contains double four-membered-ring (D4MR) cages as secondary building units, namely two D4MR cages per unit cell (u.c.), while polymorphs A and B do not contain such secondary building units. If one takes into account that the D4MR cages should be under high tension in this structure, thereby introducing a certain instability, it is not surprising that polymorph C has been elusive under the synthesis conditions of zeolite Beta.

By means of theoretical calculations, we have found (see Supporting Information) that stability is gained in D4MR cages when germanium replaces silicon in the TO_4 tetrahedra.^[14] Indeed, the isomorphous substitution of Si by Ge does not introduce any framework charge but allows angles and distances to vary and thereby stabilizing such a secondary

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building block. This, together with the observed fact that F^- ions located within the D4MR cages increases their stability,^[15] made us to think that it could be possible to synthesize the polymorph C by introducing F^- ions and Ge in the synthesis gel. If our hypothesis were correct, both factors (or even only one of them) should be enough to discriminate polymorph C from polymorphs A and B during the synthesis of zeolite Beta regardless of the organic SDA used in the synthesis media. We will see that indeed this has been the case, and that pure polymorph C can be obtained with a large variety of SDAs which, in the absence of Ge in the media, gives the typical intergrowth of polymorphs A and B of zeolite Beta or even other zeolite structures.

A germanium-containing polymorph C was synthesized by using 1-benzyl-1,4-diazabicyclo[2.2.2]octane (benzyl-DABCO; BD⁺) as an SDA. The resultant calcined sample with a Si:Ge molar ratio of 1.8:1 exhibits the X-ray powder diffraction (XRD) pattern given in Figure 1. This pattern was

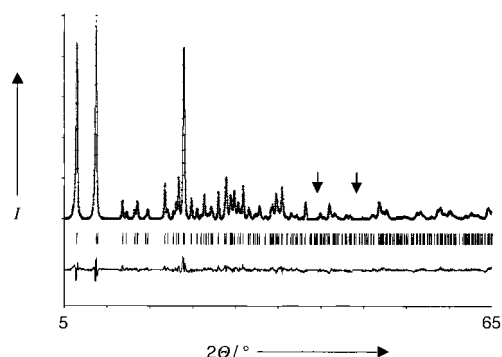


Figure 1. Observed (crosses) and calculated (lines) XRD patterns of polymorph C as well as the difference profile (bottom). The short tick marks below the pattern give the positions of the Bragg reflections. The arrows indicate the two small regions excluded from the Rietveld refinement containing the diffraction lines of the platinum sample holder ($Cu_{K\alpha 1,2}$ radiation).

indexed according to a tetragonal unit cell with the following optimized unit cell parameters: $a = 12.823$ and $c = 13.345$ Å. The Rietveld refinement of the crystal structure of the Si:Ge = 1.8:1 form of polymorph C was successfully performed in space group $P4_2/mmc$, the same space group which has been proposed by Newsam et al.^[13] for the aluminosilicate form (Si:Al = 10:1) of polymorph C of Beta. From the chemical analysis of the sample and assuming that all T sites are filled, the unit cell composition of the calcined sample is close to $Si_{20.6}Ge_{11.4}O_{64}$. Its refined unit cell volume is larger by 61 Å³ than the volume calculated for the aluminosilicate form. This result is consistent with the larger ionic radius of Ge compared to Si and clearly indicates that Ge is located at framework sites replacing isomorphically Si atoms in the structure. The refined atomic coordinates are listed in Table 1, and Figure 1 shows the very good agreement between observed and calculated XRD patterns. The details of the Rietveld refinement are given in the Experimental Section and the averaged values of some relevant distances and angles are compared to those proposed for the aluminosilicate form in Table 2.^[13, 16]

Table 1. Fractional atomic coordinates^[a,b] for polymorph C (Si:Ge = 1.8:1).

Atom	x	y	z	Number of positions	Wyckoff notation
T1 ^[c]	0.3777(4)	0.1259(4)	0.1143(3)	16	<i>r</i>
T2 ^[c]	0.1915(8)	<i>x</i>	$\frac{1}{4}$	8	<i>n</i>
T3 ^[c]	0	0.1229(7)	0.1160(8)	8	<i>o</i>
O1	0	0	0.1303(16)	4	<i>g</i>
O2	0.0994(6)	0.1764(9)	0.1705(6)	16	<i>r</i>
O3	0.3486(12)	0	0.1278(12)	8	<i>o</i>
O4	$\frac{1}{2}$	0.1481(14)	0.1555(11)	8	<i>p</i>
O5	0.3010(6)	0.1772(8)	0.1954(6)	16	<i>r</i>
O6	0.3543(12)	0.1583(11)	0	8	<i>q</i>
O7	0	0.1635(17)	0	4	<i>l</i>

[a] As obtained from Rietveld refinement (space group $P4_2/mmc$; $a = 12.823(2)$, $c = 13.345(3)$ Å). [b] Estimated standard deviations given in parentheses. [c] Refined atomic occupations for site T1: 0.54(2) Si + 0.46(2) Ge; T2: 0.72(2) Si + 0.28(2) Ge; T3: 0.77(2) Si + 0.23(2) Ge.

Table 2. Comparison of relevant averaged distances (*d*) and angles ($\angle$) between the refined polymorph C structure (Si:Ge = 1.8:1) and the corresponding simulated one (Si:Al = 10:1) from a least-squares refinement on distance.

	Si:Ge = 1.8:1 experiment	Si:Al = 10:1 simulated
<i>d</i> (T–O) [Å]	1.614(23)	1.616(1)
$\angle$ (O–T–O) [°]	109.4(3.7)	109.47(3)
$\angle$ (T–O–T) [°]	151.4(8.2)	150(15)

Figure 2 shows the arrangement, along one 4_2 screw axis, of the two structural building units of polymorph C, namely the $[5^4]$ cage consisting of four five-membered rings and the

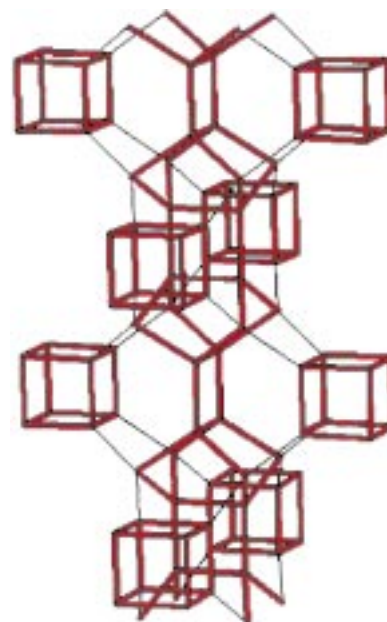


Figure 2. Arrangement along the 4_2 screw axis of the two structural building units of polymorph C, cage $[5^4]$ formed by four five-membered rings and cage D4MR formed by double four-membered rings. The mirror-related $[5^4]$ cages are connected forming four-membered rings and are linked to the $[5^4]$ cages of the neighboring unit cells through the D4MR cages, which are preferentially occupied by Ge. The D4MR cages consist only of T1 sites while each $[5^4]$ cage contains sites of type T2 and T3. To visualize the D4MR building units, the links between T1 and T2 sites have been depicted as single lines.

D4MR cage. The complete structure is plotted in Figure 3 and agrees well with that of polymorph C postulated by Newsam et al.^[13]

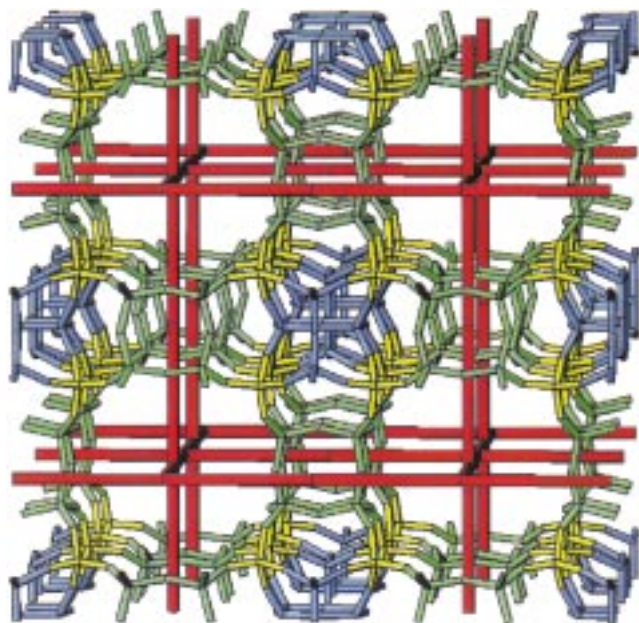


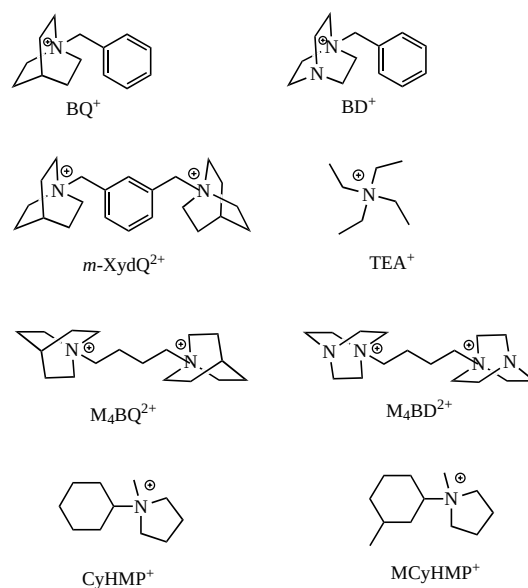
Figure 3. A [001] perspective view of the crystal structure of the calcined polymorph C of zeolite Beta showing the three-dimensional pore system formed by linear channels of nearly circular 12-membered rings intersecting at different heights as indicated by the bars. The pore diameter of the channels calculated from the crystallographic data ranges from 6.3 to 6.6 Å, which is very close to the experimental value of 6.9 Å calculated from the Ar adsorption isotherm by using the Horvath–Kawazoe formalism.

Due to the high contrast in scattering power between Si and Ge, one simple way to determine the distribution of Ge among the different T sites consists on the least-squares refinement of the effective number of electrons at each site. This refinement yields for site T1 a Ge occupancy of 46 % while for the two remaining sites T2 and T3 the respective occupancies are 28 % and 23 % (Table 1). This Ge distribution is also reflected in the mean T–O distances: $\langle \text{T1–O} \rangle = 1.632$; $\langle \text{T2–O} \rangle = 1.596$; $\langle \text{T3–O} \rangle = 1.615$ Å. As expected, the longest average T–O distance corresponds to site T1, which is preferentially occupied by Ge and is the only one located in D4MR cages.

The preferential occupancy of D4MR cages by Ge is further supported by ^{19}F MAS-NMR spectroscopy and chemical analysis of the noncalcined polymorph C sample. Indeed, the ^{19}F MAS-NMR spectrum of the polymorph C sample with a

Si:Ge ratio of 1.8:1 shows an unique resonance at $\delta = -6.6$ (CCl_3F as reference), which is very close to that observed for the purely Ge-octadecasil material synthesized as reported before^[17] and exactly at the same position and with very similar broadening than the band observed for the ITQ-7^[18] structure with a similar Si:Ge ratio (see Supporting Information). In both materials, octadecasil and ITQ-7, fluoride has been unambiguously located into the D4MR cages.^[18, 19] It is noteworthy that the chemical analysis of polymorph C yielding 1.95F^- per unit cell also closely corresponds to the presence of fluoride anions into the small cavities (2D4MR/u.c.). Consequently, all the experimental results support the assignment of F^- inside the Ge-rich D4MR cavities of polymorph C.

To check the structure-directing effect of Ge, a series of syntheses were carried out using different organic SDAs (Scheme 1). The synthesis procedure was the same as



Scheme 1. Structure-directing agents essayed in this work.

described in the Experimental Section and the gel compositions were $(1-x)\text{SiO}_2 : x\text{GeO}_2 : 0.5\text{SDAOH} : 0.5\text{HF} : w\text{H}_2\text{O}$ and $(1-x)\text{SiO}_2 : x\text{GeO}_2 : 0.25\text{SDA}(\text{OH})_2 : 0.5\text{HF} : w\text{H}_2\text{O}$. The results from Table 3 indicate that all SDAs produce, in absence of germanium, zeolite Beta with a typical intergrowth polymorphs A and B, as well as other zeolite structures. However, if germanium is introduced, all of them give pure polymorph C in a very wide range of Ge contents. The

Table 3. Synthesis conditions and zeolitic structures obtained by using different SDAs with and without germanium in the crystallization gel.

SDA	H_2O [w]	Si/Ge	T [°C]	Time [h]	Ge zeolite	SiO_2 zeolite
BQ ⁺	8	1–10	150	15–120	polymorph C	ITQ-4
BD ⁺	8–24	0.5–30	135–175	15–120	polymorph C	ITQ-4
<i>m</i> -XydQ ²⁺	8	5	150	16–96	polymorph C	Beta
M ₄ BQ ²⁺	7.5–15	2–10	175	24–96	polymorph C	Beta, ZSM-12
M ₄ BD ²⁺	15	2–20	175	24–96	polymorph C	ZSM-12
CyHMP ⁺	7.25	5	135–175	15–96	polymorph C	ZSM-12
MCyHMP ⁺	7.25	5	135–175	15–96	polymorph C	Beta
TEA ⁺	7.5	2	140	96	polymorph C	Beta

structure-directing effect of Ge becomes evident from these results since, in absence of Ge, no polymorph C was obtained despite the fact that F[−] was used in all syntheses. Furthermore, we have found that polymorph C also grows in absence of F[−] (OH[−] media) when Ge is present (see Supporting Information).

Finally, various syntheses have been carried out using BD⁺ as SDA and different Si:Ge ratios in the gel. It has been found that pure polymorph C is obtained for Si:Ge ratios of up to at least 30:1; these samples are highly stable upon calcination in air and after exposure to moisture.

A sample of polymorph C with a Si:Ge = 5:1 was calcined in air and a micropore volume of 0.21 cm³ g^{−1} was calculated from the N₂ adsorption isotherm using the t-plot method. This value corresponds very well with the value predicted by the structural parameters given in this work (0.23 cm³ g^{−1}).

In conclusion, we have shown that the pure polymorph C of zeolite Beta can be synthesized using germanium for stabilizing the structure. Germanium has a greater tendency to occupy the positions at the double four-member ring cages which can be responsible for stabilizing this structure. We have found that this is a general effect, since germanium also facilitates the formation of all the high-silica zeolites reported up to now having D4MR cages in their structures (ITQ-7^[18] and octadecasil^[19]). In both materials, a selectivity for the occupancy of D4MR by germanium has been observed (see Supporting Information).

Experimental Section

Synthesis: A Ge-containing polymorph C was synthesized by using the hydroxide form of benzyl-DABCO (BD⁺) as SDA. A series of synthesis gels were prepared with the following molar compositions:

0.666 SiO₂ : 0.333 GeO₂ : 0.5 BDOH : 0.5 HF : 8 H₂O **1**

0.833 SiO₂ : 0.166 GeO₂ : 0.5 BDOH : 0.5 HF : 8 H₂O **2**

0.937 SiO₂ : 0.062 GeO₂ : 0.5 BDOH : 0.5 HF : 8 H₂O **3**

The gels were autoclaved at 150 °C for 15 h in Teflon-lined stainless steel autoclaves under static conditions. The three synthesizing gels resulted in pure polymorph C, with final Si:Ge atomic ratios of 1.8:1, 5.0:1, and 11.6:1, respectively.

XRD: The sample was calcined at 400 °C in air for 1 h. The air was purged at this temperature by several cycles of pumping and filling the high-temperature chamber with N₂. Subsequently, the sample was cooled under the inert atmosphere. The pattern was measured at room temperature in N₂ within the high-temperature chamber attached to an diffractometer (Philips X'Pert) with Bragg–Brentano geometry using a Pt sample holder and graphite secondary monochromator. Intensity data obtained with variable divergence slit. Cu_{Kα1,2} radiation (λ = 1.5406, 1.5444 Å). Tube voltage and intensity: 45 kV and 40 mA. Step scan size and time: 0.02° 2θ and 10 s.

Rietveld refinement:^[20] The Rietveld refinement with LSP7 was performed using a 2θ range from 5.00 to 65.00° with two excluded regions, 39.04°–40.53° and 45.45°–46.77°, due to the appearance in these regions of the (111) and (200) Pt diffraction peaks of the sample holder. The transmission coefficient at the Pt(111) Bragg position is 0.20, which was used for correcting the finite thickness of the sample. Number of contributing reflections: 247. Number of geometric restraints of type d(T–O) = 1.62(3) Å: 12. Number of structural parameters: 24. Number of profile parameters: 8, including unit cell parameters and zero shift (−0.095° 2θ),

with visually estimated background. Profile function used was Pearson-VII. Refined overall thermal coefficient: B = 2.4 Å². The residuals of the refinement were: R_{wp} = 0.081; R_{exp} = 0.032; R_p = 0.062; R_i = 0.117 (see Supporting Information).

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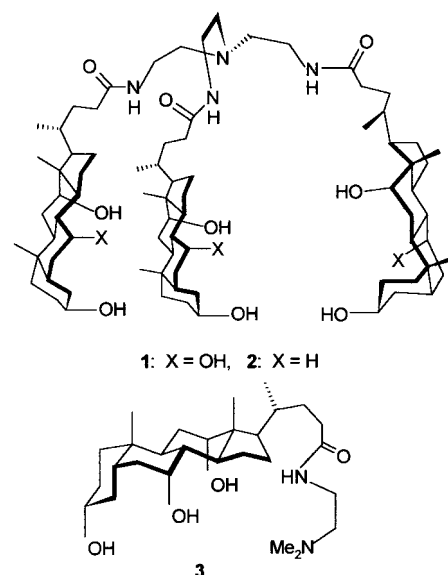
Hydrophobic Pockets in a Nonpolymeric Aqueous Gel: Observation of such a Gelation Process by Color Change**

Uday Maitra,* Samrat Mukhopadhyay, Arnab Sarkar, Photon Rao, and S. S. Indi

Dedicated to Professor Ronald Breslow on the occasion of his 70th birthday

Studies on aqueous and organogels derived from low molecular mass species have been of considerable interest in recent years because of the many potential applications envisaged.^[1] While gel formation in aqueous and nonaqueous media by polymers and biopolymers is a well-documented phenomenon,^[2] detailed study of low molecular mass gelators has been embarked upon only during the past decade. Recently published examples of small molecule organogelators include steroids,^[3] carbohydrates,^[4] anthryl derivatives,^[5] and urea.^[6] We recently reported the first example of the gelation of organic fluids that was promoted by a donor–acceptor interaction.^[7] Although there is a resurgence in the study of low molecular mass organogelators, there is little activity in the investigation of analogous hydrogelators.^[8] Herein we report that a novel tripodal^[9] cholic acid derivative **1** forms gels in aqueous media with remarkable efficiency, and that the gelation process creates highly hydrophobic pockets in a predominantly aqueous environment. We have also demonstrated for the first time the sol to gel transition for a nonpolymeric gel by a color change.

Our interests in bile acid based receptors^[10] for small organic molecules led us to the design of tripodal hosts derived from bile acids (**1** and **2**). These molecules are characterized by an anion-binding site^[11] on the “top” and multiple hydroxyl groups on the bile acid segment. Compounds **1–3** were synthesized from readily available bile acids using standard procedures.^[12] We serendipitously discovered that compound **1** is a highly efficient gelator of aqueous acids,^[13] and leads to the formation of gels in many acidic solutions at remarkably low concentrations (0.04 % w/v, 0.30 mM and above, that is, with one gelator molecule immobilizing more than 10⁵ water molecules!). Gels prepared with acetic acid/water were strong^[14] and transparent. The hydrochloride salt (**1**·HCl) was prepared to determine if protonation of the tertiary nitrogen atom was important for



gelation. This salt was found to form a weak^[14] and slightly turbid gel in water. However, the addition of small amounts (8 to 10 % v/v) of an organic cosolvent (such as acetone, ethanol, methanol, or DMSO) led to the formation of strong and transparent gels. It appears that such mixed aqueous–organic media provide the correct hydrophobic–hydrophilic balance for optimum gelling conditions for **1**·HCl. Gel to sol transition temperatures (T_{gel}) were measured as a function of the concentrations of the gelator and acetic acid to get an estimate of the thermal stability of the gels (Figure 1). The value of T_{gel} decreased at higher acetic acid concentrations, possibly as a result of the solubilizing effect of acetic acid.

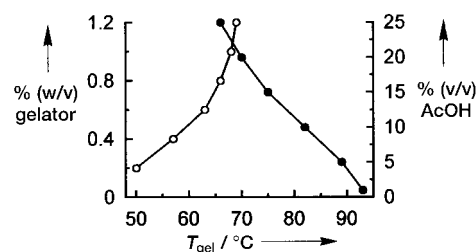


Figure 1. Variation of T_{gel} as a function of the concentration of **1** in 20 % AcOH/H₂O (○) and of AcOH (●) at a constant (7.5 mM) concentration of **1**.

The morphology of the gel was examined by transmission electron microscopy (TEM; OsO₄ staining) which showed a network structure composed of fibers with submicron dimensions (Figure 2). Electrostatic, hydrophobic as well as hydrogen-bonding interactions may be responsible for the aggregation, but how these fibers are constructed from the individual molecules is not understood at this stage. Closely related compound **2** and nontripodal structure **3** did not gel aqueous acids under identical conditions.

Since aggregation processes in aqueous media are predominantly driven by the hydrophobic effect, we thought it would be interesting to probe the gelation process using a hydrophobic fluorescent probe such as ANS.^[15] For this purpose a

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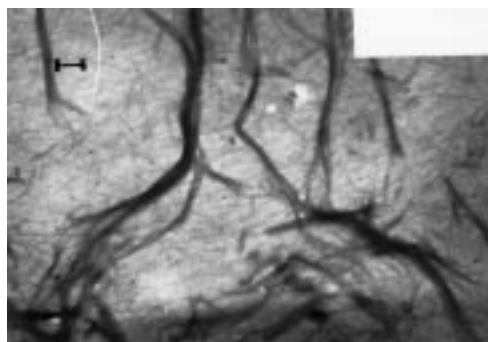


Figure 2. Transmission electron micrograph of a dried gel derived from **1** (1% w/v in 20% AcOH/H₂O) showing a fibrous network (scale bar: 1 μm).

solution of **1** in acetic acid was mixed with an aqueous ANS solution (final concentrations of AcOH, **1**, and ANS were 20% v/v, 5.25 mM, and 10 μM, respectively) and the evolution of ANS fluorescence with time was monitored (λ_{ex} 365 nm, λ_{em} 475 nm) at 26 °C. In the first few minutes (Figure 3) the

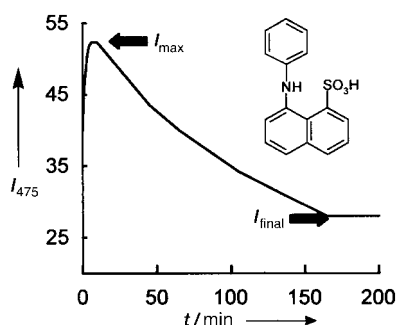


Figure 3. Time dependence of the ANS fluorescence during gelation of **1** in 20% AcOH/H₂O at 26 °C. The final concentrations of **1** and ANS were 5.25 mM and 10 μM, respectively. I_{475} = emission intensity at 475 nm relative to that of 10 μM of ANS alone in 20% AcOH/H₂O. The structure of ANS is shown.

fluorescence rapidly increased to reach a maximum (I_{max} , “intermediate state”), then it decreased at a slower rate. Practically no change in the emission intensity (I_{final} , “gel state”) was observed after 3 h, which suggested completion of the gelation process.^[16, 17] From the time course of the ANS fluorescence during gelation it seems likely that the gelation process proceeds via an intermediate state of aggregation, where ANS has a higher binding affinity than the final gel state.

The mere presence of **1** in solution in neat AcOH or EtOH, or below the critical gelling concentration (<0.10% w/v in 20% AcOH/H₂O) did not enhance the fluorescence of ANS relative to the values for ANS measured in the corresponding solvents in the absence of **1**. The enhancement of fluorescence intensity for 5.25 mM of gelator **1** in 20% AcOH/H₂O was 50 fold at the intermediate state and 30 fold at the final gel state (both measured relative to the fluorescence of ANS in 20% AcOH/H₂O, Figure 3). We feel that the unusual enhancement of hydrophobicity is the result of the formation of networks having highly hydrophobic cavities and/or clefts in which ANS is accommodated. The hydrophobicity in these

pockets of the gel network is clearly much higher than the interior of β-cyclodextrin.^[18]

These studies suggested that it should be possible to visualize the sol to gel transition using a suitable dye whose pK_a value is close to the bulk pH value of the gel (ca. 4), and in which the two forms of the indicator bind differentially to the hydrophobic pockets. We found that on addition of the sodium salt of bromophenol blue (BPB) to a solution of **1** in AcOH/H₂O (final concentrations of **1**, BPB, and acetic acid were 7.50 mM, 0.37 mM, and 25% v/v, respectively) the color of the mixture changed from yellow in the sol phase to green upon gelation. The absorption spectrum of the sol showed a peak at 620 nm which intensified on gelation while the intensity of the peak at 430 nm decreased (Figure 4). The

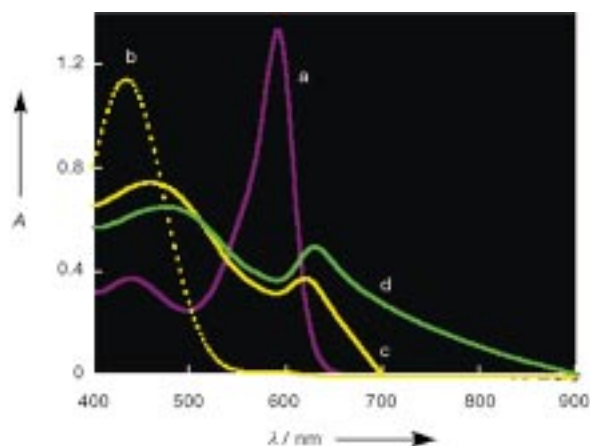
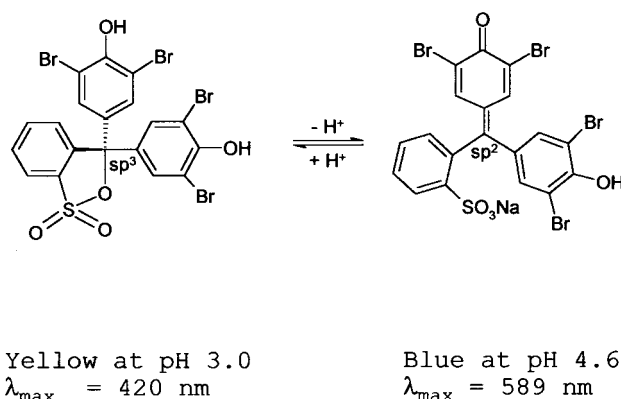


Figure 4. Absorption spectra (26 °C) of the sodium salt of bromophenol blue (0.37 mM): a) in neutral water, b) in 25% AcOH/H₂O, c) in the presence of **1** (5.25 mM) in 25% AcOH/H₂O (before forming a gel) and d) after forming a gel. The sample colors closely resemble the colors used in the plots. A = absorbance.

intensity ratio I_{620}/I_{430} changed from 0.5 in the sol to 0.8 in the gel which indicated a perturbation of the equilibrium between the neutral and the ionized forms of the indicator. We believe that the conversion of the sp^3 center in the neutral form of BPB to an sp^2 center in the ionized form makes the species more planar, and this form is more easily accommodated in the hydrophobic pocket (Scheme 1). This hypothesis is supported by the fact that induced circular dichroism (CD)



Scheme 1. Proton-transfer equilibrium of bromophenol blue.

of BPB is observed for the peak at 620 nm (in the gel state), but not for the peak at 430 nm (Figure 5). This CD band around 620 nm is substantially reduced in intensity on gel to sol transition which implies that these pockets created in the gel network have chiral influence on the bound achiral species in the gel state.

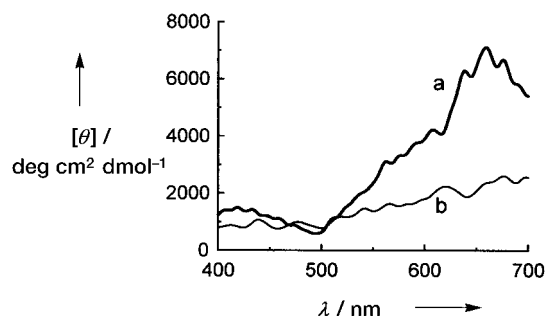


Figure 5. Induced circular dichroism of bromophenol blue in the a) gel state at 20 °C and b) sol state at 70 °C. Concentrations of bromophenol blue and the gelator **1** are 0.37 mM and 7.50 mM, respectively. $[\theta]$ = Molar ellipticity.

In conclusion, we have discovered a novel and highly efficient tripodal cholic acid derived gelator showing unusual aggregation properties that lead to the gelation of aqueous fluids. Structural details of hydrophobic pockets formed in the gel remain to be elucidated, but it is likely that lipophilic β -faces of the cholic acid backbone associate to form the hydrophobic pockets. Detailed structure–property relationship on this new class of molecules, and further studies on gels from this novel molecule are currently in progress. We are also examining the possibility of utilizing the chiral hydrophobic pockets formed in the gel for carrying out selective chemical transformations.

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- [13] In a typical gelation experiment **1** (5 mg) was dissolved in acetic acid (100 μ L). Water (400 μ L) was added slowly and then the mixture was allowed to stand. After a few minutes a colorless and transparent gel was obtained. At lower percentages of acetic acid the gels were somewhat translucent.
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Two Isomers of $C_{60}F_{48}$: An Indented Fullerene**

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Olga V. Boltalina,* Ilya N. Ioffe, Lev N. Sidorov, and
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$C_{60}F_{48}$ has the highest known fluorine content per fullerene molecule, and thus possesses many unique properties, such as high reduction potential^[1] and high electron affinity;^[2] it is able to accept up to two electrons in solution^[1] and even in the gas phase.^[3] Bulk preparation of $C_{60}F_{48}$ by direct fluorination as reported recently now makes it possible to explore useful properties of this remarkable compound.^[4]

On the basis of ^{19}F NMR spectroscopy, $C_{60}F_{48}$ was assigned a structure with D_3 symmetry.^[5] The chiral D_3 isomer, which can exist in R,R and S,S forms, also has an R,S *meso* form with S_6 symmetry; both D_3 and S_6 molecules consist of two equivalent hemispheres related by C_2 rotation or inversion, respectively (Figure 1). These isomers were found to be isoenergetic and indistinguishable by simple NMR spectroscopy, and it has been suggested that infrared (IR) spectroscopy could assist with the assignment of the isomeric composition of $C_{60}F_{48}$.^[6] A more definitive result could come from a single-crystal structure determination as was recently performed for $C_{60}F_{18}$ and its oxygenated and trifluoromethylated derivatives.^[7] Hitherto, attempts to determine the precise structure of highly fluorinated fullerenes ($C_{60}F_x$, $x \geq 36$) by X-ray methods have been unsuccessful

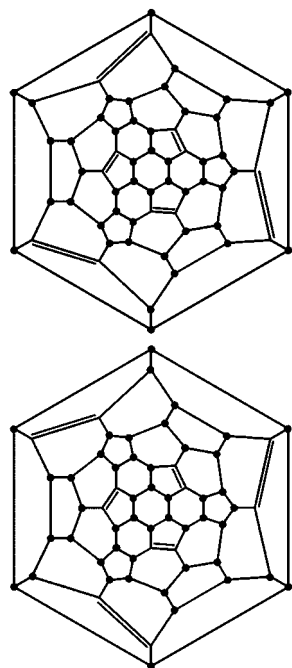


Figure 1. The Schlegel diagrams for the D_3 (top) and S_6 (bottom) isomers of $C_{60}F_{48}$.

because of the rotational disorder of the molecules and the unavailability of specific fluorofullerenes in pure form.^[8]

Herein, the first single-crystal X-ray structure of $C_{60}F_{48}$ is reported. Single crystals of molecular complexes of $C_{60}F_{48}$ with *o*-, *m*-xylenes, toluene, and mesitylene were studied, but only with the latter were we able to succeed in determining the structure by X-ray analysis. The crystal structure determination is complicated by the presence of both D_3 and S_6 isomeric $C_{60}F_{48}$ molecules, which are each statistically disordered over two positions. After careful analysis we managed to separate the contribution of the R and S configurations on both hemispheres of the $C_{60}F_{48}$ molecule.

Both structures have crystallographic three-fold symmetry and contain six isolated double bonds, three on each hemisphere (Figure 2). In the carbon cage, the C–C bonds can be divided into three groups according to the hybridization type of the C atoms:^[9] $C(sp^2)$ – $C(sp^3)$ (A–D), $C(sp^3)$ – $C(sp^3)$ (E–H),

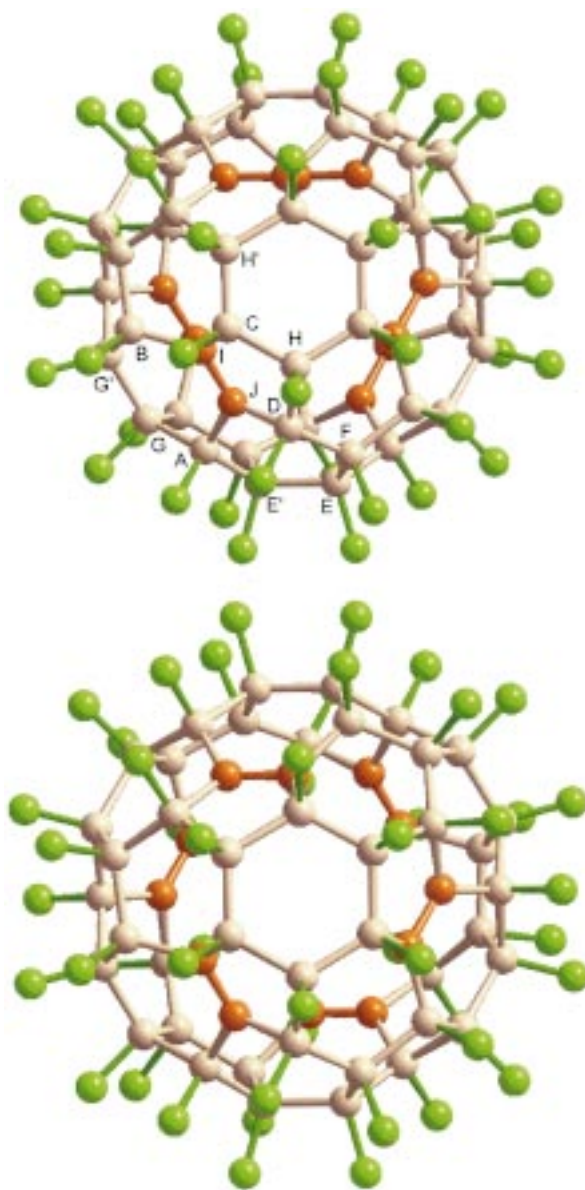


Figure 2. The structures of the D_3 (top) and S_6 (bottom) isomers of $C_{60}F_{48}$ as determined by X-ray crystallography. Double bonds and sp^2 carbons are indicated by orange color.

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C(sp²)–C(sp²) (**I**, **J**) with average C–C bond lengths, 1.49–1.53 Å, 1.54–1.63 Å, and 1.30 Å, respectively (Table 1). The C–F bond lengths fall in the range 1.36–1.40 Å. The C–C double bonds are much shorter than the 6,6 bonds in C₆₀

Table 1. C–C and C–F bond lengths [Å] in C₆₀F₄₈ (*D*₃ isomer) determined from the X-ray data and DFT calculations.

C–C	X-ray	Calcd	C–C	X-ray	Calcd	C–F	X-ray	Calcd
A–J	1.493(3)	1.488	C–H	1.566(3)	1.582	a	1.385(3)	1.392
B–I	1.513(4)	1.494	C–H'	1.544(3)	1.553	b	1.358(3)	1.390
C–I	1.534(4)	1.503	D–F	1.544(4)	1.570	c	1.362(3)	1.392
D–J	1.530(4)	1.510	D–H	1.606(4)	1.611	d	1.376(4)	1.387
A–E	1.562(3)	1.583	E–F	1.604(3)	1.633	e	1.370(3)	1.368
A–G	1.576(3)	1.574	E–E'	1.627(3)	1.636	f	1.395(3)	1.369
B–F	1.559(3)	1.578	G–G'	1.610(3)	1.610	g	1.366(3)	1.374
B–G	1.558(3)	1.560	I–J	1.301(4)	1.338	h	1.377(3)	1.368

(1.40 Å) and close to the value for a localized double bond (1.33–1.34 Å). The longest C–C bonds (1.60–1.63 Å) are situated near the equator of the molecule. For comparison, C₆₀F₁₈ has even longer C(sp³)–C(sp³) bonds (up to 1.67 Å).^[7]

Mutual repulsion of the F atoms results in a considerable shift of four F atoms bonded to carbons **A–D** towards the area over the double bond. Distortions of the cage in such areas are so significant that prominent concavities are formed (Figure 3). This allows us to add an “indented” fullerene

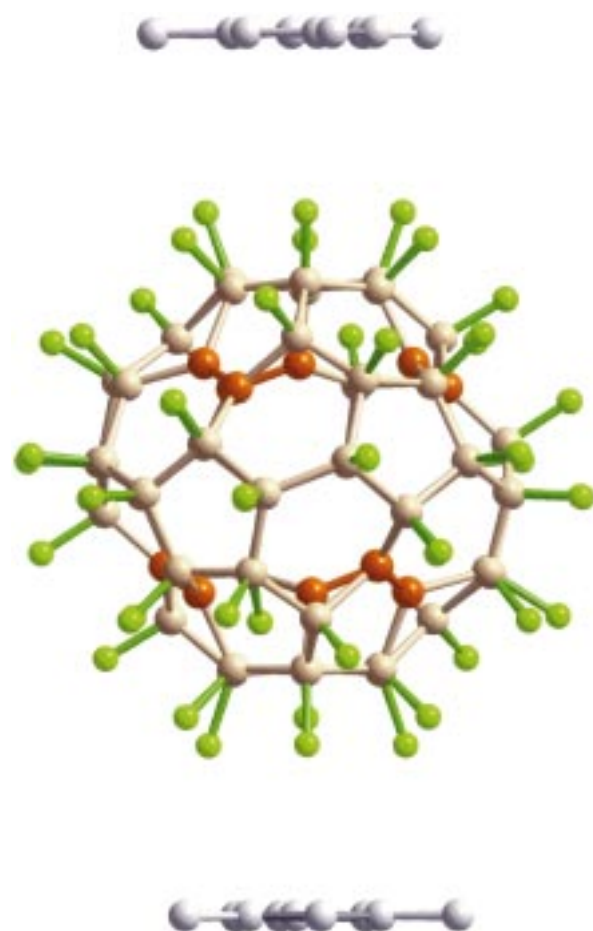


Figure 3. View of the *D*₃ isomer of C₆₀F₄₈ along the noncrystallographic twofold axis. Two mesitylene molecules are also shown.

molecule C₆₀F₄₈ to the previously reported series of distorted cages of fluorofullerenes: C₆₀F₁₈—a flattened cage^[7] and C₆₀F₂₀—a squashed fullerene.^[10]

The difference between 360° and the sum of three C–C–C angles gives the measure of convexity at a given C atom, it falls in the range 15–30° for all the “normal” sp³ carbon atoms, whereas the C atoms in the concave regions have values of 3–5°. This results in a considerable difference in the distances of the C atoms from the center of the C₆₀F₄₈ carbon cage compared with that of the parent C₆₀ (3.56 Å):^[11] there is a dramatic shortening of the distance between the sp² carbons and the cage center (3.05 Å, **I**, **J**) and an increase in the distance between the cage center and the two types of sp³ carbons (3.79 Å, **A–D**; 3.94 Å, **E–H**). For the same reason, there are two sets of cage-center to F atom distances with average values of 5.05 Å (**a–d**) and 5.31 Å (**e–h**). These values can be compared with the single-crystal data for rotating molecules in a sample with an average composition C₆₀F₄₆,^[8] where the distance distribution was approximated by three spherical shells with radii of 3.13 Å (**I**, **J**), 3.83 Å (**A–H**), and 5.12 Å (fluorine shell).

One of the most important consequences of the distribution of fluorine atoms over the cage is the effective shielding of the double bonds, the F⋯F distances between the **a** and **c**, and the **b** and **d** atoms being only 4.2 Å (Figure 4). Thus, one might expect lower reactivity of C₆₀F₄₈ compared with that of C₆₀F_x (*x* < 48). Indeed, C₆₀F₄₈ was found to be the final product of direct fluorination.^[4] Furthermore, attempts to achieve perfluorination of C₆₀ by applying more harsh experimental conditions resulted in cage disruption but not in the preparation of C₆₀F₆₀.^[12]

The packing of C₆₀F₄₈ in the crystal of the mesitylene solvate can be approximated as a simple cubic arrangement with an average center–center separation of 11.6 Å. For comparison, the separation between rotating molecules in the solid C₆₀F₄₆ was found to be 12.2 Å.^[8] Mesitylene molecules of two types are situated in parallel orientation above and below the fluorinated hexagons on the top and the bottom of C₆₀F₄₈ (Figure 3). The alternation of C₆₀F₄₈ and two types of mesitylene molecules along a threefold axis can be given as C₆₀F₄₈–mesitylene1–mesitylene1–C₆₀F₄₈–mesitylene2–mesitylene2–C₆₀F₄₈⋯. The shortest C⋯F separations (3.25–3.60 Å) between a mesitylene molecule and a C₆₀F₄₈ molecule on the same three-fold axis as well as to two other neighboring C₆₀F₄₈ molecules are apparently responsible for hindering rotational motion of fluorofullerenes in the crystal.

Experimental Section

C₆₀F₄₈ was prepared by direct fluorination of C₆₀ (>99.9%, TERMUSA) at 350 °C as described previously^[4] and used for crystal growth without further purification. The purity, estimated by chemical analysis, solid state ¹⁹F NMR spectroscopy, and mass spectrometry, was around 95%. Dark violet

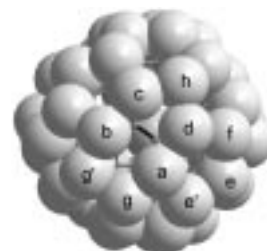


Figure 4. A drawing of the C₆₀F₄₈ molecule (*D*₃), which illustrates shielding of the C–C double bond (shown as a black line) by the adjacent fluorine atoms **a–d**.

cubic crystals of $\text{C}_{60}\text{F}_{48} \cdot 2\text{C}_6\text{H}_3\text{Me}_3$ of X-ray quality were grown from the mesitylene solution. A crystal with dimensions $0.3 \times 0.3 \times 0.2$ mm was investigated on an image-plate diffractometer (IPDS, Stoe) at 180 K (graphite monochromatized MoK_α radiation, $\lambda = 0.71073$ Å, $2\theta(\text{max}) = 53.5^\circ$). A primitive cubic unit-cell parameter was refined with 1267 reflections to $a = 23.229(3)$ Å, $V = 12534(3)$ Å³, $Z = 8$. The intensities of 99277 measured reflections were corrected for Lorentz and polarization factors and averaged, yielding 4526 unique reflections. Absorption correction was not applied ($\mu = 2.16$ cm⁻¹). Space group $Pa\bar{3}$ was established on the basis of systematic absences. The structure was solved by direct methods (SHELXS-97) resulting in a raw model with a $\text{C}_{60}\text{F}_{48}$ molecule on a three-fold axis. However, a high R_1 value (20%) and splitting of some atoms were indicative of disorder. It was found that the duplicate positions of some atoms correspond to an overlap of the R and S configurations of two hemispheres. The different R/S ratios for hemisphere I (83/17) and hemisphere II (56/44) can be interpreted as overlap of $\text{C}_{60}\text{F}_{48}$ molecules with a noncrystallographic D_3 (R, R' and S, S') and S_6 (R, S' and S, R') point symmetry. In the mixture of two isomers in the single crystals, the estimated content of D_3 is in the range of 39–73%. The final refinement on F^2 with 4331 reflections and 474 parameters was carried out anisotropically for all non-hydrogen atoms (except for the 17% component on hemisphere I and H atoms of mesitylene in calculated positions), and converged to $wR_2 = 0.1589$ and $R_1 = 0.0508$ (SHELXL-97).^[13] As a result of a different degree of disorder, the positions of C and F atoms belonging to the main component on hemisphere I were determined with better precision (standard deviations 0.003–0.004 Å for C–C and C–F bonds), than for hemisphere II (standard deviations 0.003–0.007 Å). The more reliable values for C–C and C–F bond lengths on hemisphere I were used for comparison with the results of theoretical calculations (Table 1).

The geometry optimization was performed by using density functional theory (DFT) calculations with the PRIRODA program, which employs an economic calculating approach with insignificant loss of accuracy.^[14] The PBE exchange-correlation functional^[15] and a Gaussian-type basis set of TZ2P quality^[14] was used. The validity of our approximations was tested on $\text{C}_{60}\text{F}_{18}$ and some other fluorocarbons, revealing good accuracy with only slight bond length overestimations (0.01 Å on average).

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Bi₄Te₄⁴⁺—A Cube-Shaped, Polycationic Main Group Element Cluster**

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Electron-rich main group elements are able to form polycationic clusters. Such ligand-free clusters are known for the halogens chlorine to iodine, for all chalcogens, for bismuth, for cadmium, and for mercury.^[1] There are several methods for their synthesis, all of which involve electrophilic and acidic media such as H_2SO_4 , HSO_3F , anhydrous HF, molten salts such as $\text{Na}[\text{AlCl}_4]$, or liquid SO_2 . The respective elements are oxidized and converted to the polycationic clusters by suitable oxidants such as AsF_5 , SbF_5 , WCl_6 , or MoOCl_4 , or by an element halide in the presence of a strong halide-ion acceptor such as AlCl_3 or ZrCl_4 . The number of known structure types increases with the atomic mass of the elements. Only three homonuclear cations of sulfur are known and have been structurally characterized, S_4^{2+} ,^[2] S_8^{2+} ,^[3] and S_{19}^{2+} .^[4] In contrast, for tellurium more than a dozen ring- or chain-shaped species have been described. The situation is similar for the elements belonging to Group 15. Sb_5^{3+} ^[5] is poorly characterized; for bismuth, however, a family of cluster ions exists, such as Bi_5^{3+} ,^[6] Bi_8^{2+} ,^[7] Bi_9^{5+} ,^[8] which were isolated as the corresponding chloroaluminates, hexachlorozirconates, and -hafnates, and Bi_5^{+} and Bi_6^{2+} , which were discovered in the structure of the subbromide $\text{Bi}_{34}\text{Ir}_3\text{Br}_{37}$.^[9]

Like no other element tellurium is able to form heteronuclear polycations besides homonuclear molecules. A number of mixed clusters are known containing the lighter chalcogens sulfur and selenium, for example $\text{Te}_4\text{Se}_3^{2+}$ ^[10] and $\text{Te}_3\text{S}_3^{2+}$.^[11] So far no other mixed polycations apart from Te/Se

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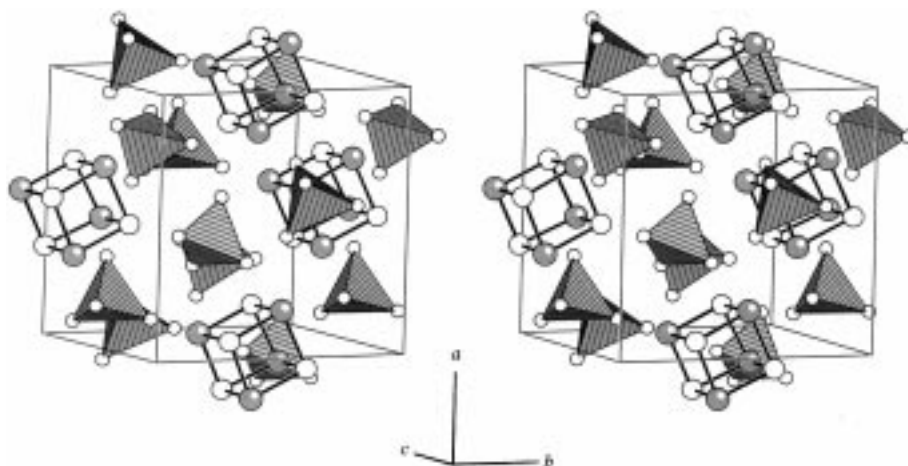


Figure 1. The unit cell of $\text{Bi}_4\text{Te}_4[\text{AlCl}_4]_4$ (**1**) (stereoview). $[\text{AlCl}_4]^-$ ions are depicted as tetrahedra.

and Te/S element combinations have been reported. Since Bi- and Te-containing polycations can be obtained from $\text{Na}[\text{AlCl}_4]/\text{AlCl}_3$ melts we have tried to synthesize mixed polycationic Bi/Te clusters.

Black crystals of $\text{Bi}_4\text{Te}_4[\text{AlCl}_4]_4$ (**1**) were formed from elemental Te and Bi, as well as TeCl_4 and BiCl_3 in a $\text{Na}[\text{AlCl}_4]/\text{AlCl}_3$ melt. The crystal structure analysis shows that **1** is built of $\text{Bi}_4\text{Te}_4^{4+}$ and tetrachloroaluminate ions (Figure 1). The cations exhibit crystallographic S_4 symmetry, and have the

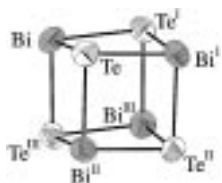


Figure 2. The $\text{Bi}_4\text{Te}_4^{4+}$ ion in the structure of **1**. The displacement ellipsoids represent a probability of 90%. The uppercase roman numerals denote the following symmetry operations: I = $-x, -y+1, z$; II = $y-1/2, -x+1/2, -z+1/2$; III = $-y+1/2, x+1/2, -z+1/2$.

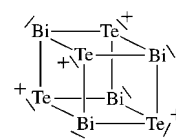
shape of a slightly distorted cube whose corners are occupied alternately by Bi and Te atoms (Figure 2). The two slightly different Bi–Te bond lengths of 294.9(1) and 301.7(1) pm are shorter than the Bi–Bi bonds in homonuclear polybismuth cations (307–328 pm), but they are in agreement with the Te–Te bonds in tellurium polycations. For instance, in the structurally related ion Te_8^{4+} ,^[12] Te–Te bonds are present with lengths between 274 and 301 pm. The angles in the cation of **1** are between 87.70(2) and 92.25(1)° and underline the only slightly distorted cubic shape of the

ion. The tetrachloroaluminate ions have a moderately distorted tetrahedral structure in which the Al–Cl bond lengths range between 210.4(4) and 216.0(3) and the Cl–Al–Cl angles between 103.5(1) and 114.3(2)°.

Strong cation–anion interactions are a typical feature of structures with naked charged clusters. Such interactions are present in the structure of **1**. The Bi and Te atoms of the cation are coordinated by five and six Cl atoms of the neighboring $[\text{AlCl}_4]^-$ ions, respectively, within an arbitrary cutoff of 400 pm. The Bi–Cl distances start at 305 pm and are thus significantly shorter than the Te–Cl distances which start at 367 pm. This is consistent with the higher electronegativity and therefore reduced positive charge on the Te atoms.

A straightforward Lewis valence formula can be set up for the $\text{Bi}_4\text{Te}_4^{4+}$ ion (Scheme 1). Each edge of the cube represents

a covalent bond, and in addition each atom carries a nonbonding lone pair of electrons. The Zintl–Klemm concept can be used to explain



Scheme 1. Lewis valence formula for the $\text{Bi}_4\text{Te}_4^{4+}$ ion.

the formal charges. Each atom exhibits three bonds, which is consistent with neutrality for Bi as a Group 15 element. With three bonds Te as an element of Group 16 behaves as a pseudoelement of Group 15 with a positive charge. Thus $\text{Bi}_4\text{Te}_4^{4+}$ belongs to the electron-precise clusters.

A striking feature of the cubic shape

of $\text{Bi}_4\text{Te}_4^{4+}$ is the structural difference compared to the homonuclear Bi polycations Bi_5^+ (square pyramidal), Bi_5^{3+} (trigonal bipyramidal), Bi_6^{2+} (octahedral), Bi_8^{2+} (square antiprismatic), and Bi_9^{5+} (tricapped trigonal prismatic). The pronounced tendency for deltahedral structures, all of which can be interpreted with the help of the Wades rules, is not continued with $\text{Bi}_4\text{Te}_4^{4+}$ since here the polyhedron exhibits only quadrangular faces.

To obtain an explanation we have carried out quantum-chemical ab initio calculations based on second-order Møller–Plesset perturbation theory (MP2), gradient-corrected density functional theory (DFT), relativistic, energy-consistent ab initio pseudo potentials (PP), and core polarization potentials (CPP) with the programs TURBOMOLE^[13] and MOLPRO.^[14] The optimization of the molecular structure led to the higher T_d symmetry for $\text{Bi}_4\text{Te}_4^{4+}$. The PP/CPP/MP2 calculations resulted in Bi–Te bond lengths of 297.8 pm and in angles Bi–Te–Bi of 86.13° and Te–Bi–Te of 93.71°. The corresponding PP/DFT calculations under exclusion of the core polarization yielded bond lengths of 304.1 pm, and angles of 87.8° for Bi–Te–Bi and 92.2° for Te–Bi–Te, respectively. The distortion of the cation resulting in the lower S_4 symmetry is caused by the cation–anion interactions in the structure of **1**. The molecular orbital schemes based on the 32 s and p valence orbitals for $\text{Bi}_4\text{Te}_4^{4+}$ and Bi_8^{2+} are shown in Figure 3.

$\text{Bi}_4\text{Te}_4^{4+}$ has $4 \times 5 + 4 \times 6 - 4 = 40$ valence electrons, whereas Bi_8^{2+} has only $8 \times 5 - 2 = 38$. A square-antiprismatic cluster with 38 valence electrons like Bi_8^{2+} has a stable closed-shell ground state with a large HOMO–LUMO gap. The addition of two electrons would result in a hypothetical uncharged Bi_8 cluster with D_{4d} symmetry, which would be isoelectronic to $\text{Bi}_4\text{Te}_4^{4+}$ with an occupation of the nearly degenerate LUMOs with b and e symmetry. This would lead to a Jahn–Teller distortion of first or second order. In contrast, a neutral Bi_8 cluster with 40 valence electrons and a cube-shaped structure with O_h symmetry would have a closed-shell ground state with a large HOMO–LUMO gap. Removing two electrons from the triply degenerate HOMO would again lead to a Jahn–Teller distortion. Thus, in a cube-shaped 38-electron cluster and in a square-antiprismatic 40-electron cluster the HOMO–LUMO gap and the stability would be diminished.

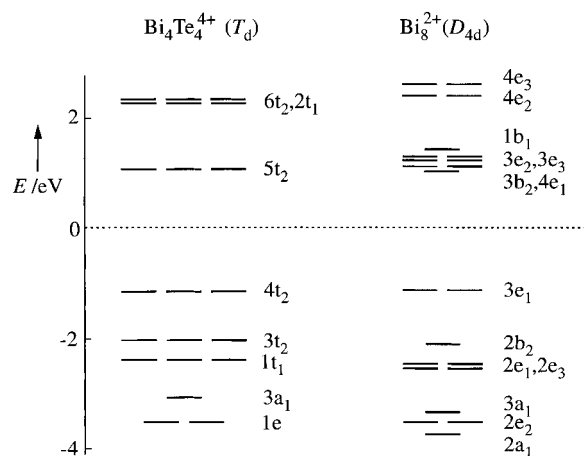


Figure 3. MO schemes for the clusters $\text{Bi}_4\text{Te}_4^{4+}$ (T_d symmetry) and Bi_8^{2+} (D_{4d} symmetry). All MOs below the Fermi energy (dashed line) are fully occupied, all others are empty. a and b denote nondegenerate, e and t doubly and triply degenerate orbitals, respectively. The lowest energy MOs are each derived from the eight s^2 orbitals; depicted are only those MOs which are derived from the p-valence orbitals. The zero level of the energy scale was defined as the Fermi energy in the middle of the HOMO–LUMO gap, since only in this case the relative orbital energies (E) of the two differently charged clusters become comparable.

This general principle of the structure-determining effect of the number of valence electrons is supported by the recently discovered Zintl anion Sn_8^{6-} , which has 38 valence electrons, a square-antiprismatic structure and is isoelectronic to Bi_8^{2+} .^[15] The partial charges in $\text{Bi}_4\text{Te}_4^{4+}$ can be calculated by different methods. A Mulliken population analysis of the Kohn–Sham wave function yields partial charges of +0.74 for Bi and +0.26 for Te. An alternative analysis according to Roby and Davidson yields similar values of +0.68 for Bi and +0.32 for Te. The analysis of orbital localization according to Foster and Boys shows that both Bi and Te carry a lone pair of electrons. The single bond between both kinds of atoms is slightly polarized towards Te in a ratio 3:2. The formal oxidation numbers are therefore +0.6 for Bi and +0.4 for Te. The observed alternating arrangement of the atoms on the corners of the cube in $\text{Bi}_4\text{Te}_4^{4+}$ permits a maximal number of interactions between atoms of different electronegativity and leads to an increased, stabilizing ionic contribution in the covalent Bi–Te bonds. The hypothetical P_8 , a product of dimerization of P_4 molecules, also represents a 40 valence electron cluster. For several years the structure of P_8 was the subject of theoretical work with sometimes contradictory results. The cubic structure and the cuneane-analogous structure, however, were always calculated to be the most stable modifications.^[16] These results find an impressive confirmation with the structure of the presented cube-shaped 40 valence electron cluster.

Experimental Section

BiCl_3 , TeCl_4 , and AlCl_3 were purified by sublimation; elemental Bi and Te were used as purchased, NaCl was dried in vacuo at 140 °C. A glass ampoule was filled with Bi (100.4 mg, 0.48 mmol), Te (91.8 mg, 0.72 mmol), BiCl_3 (75.6 mg, 0.24 mmol), AlCl_3 (246 mg, 1.98 mmol), and NaCl (10.5 mg, 0.18 mmol). The ampoule was evacuated, sealed, and placed in a horizontal tube furnace for six days at 130 °C, and then cooled to room temperature

with 20 K h^{−1}. An in principle difficulty of reactions in chloroaluminate melts is the crystallization of the melt below about 80 °C, which causes the inclusion of the crystals in a hard solid mass. To overcome this problem, the ampoule was opened under argon and the content of the ampoule was heated to a maximum of 150 °C using an electrically heated sand bath in an argon-filled glove box. At this temperature, the solidified $\text{Na}[\text{AlCl}_4]/\text{AlCl}_3$ mixture became liquid again, and the crystals could be separated mechanically. Crystals of **1** are black and commonly occur grown together with rectangular and hexagonal faces. Compound **1** was obtained in a yield of about 10 %. The composition was determined by energy-dispersive X-ray fluorescence. Crystals of **1** are sensitive towards hydrolysis in moist air. For the crystal structure analysis, crystals were sealed under Ar in glass capillaries.

Crystal structure analysis of **1**: Crystal dimensions $0.18 \times 0.14 \times 0.15 \text{ mm}^3$, crystal system tetragonal, space group $I4$ (no. 82), four-circle diffractometer Nonius KappaCCD, $\text{MoK}\alpha$ radiation ($\lambda = 71.073 \text{ pm}$), room temperature 293(2) K, lattice constants $a = 1227.26(6) \text{ pm}$, $c = 1145.35(7) \text{ pm}$, unit cell volume $1725.1(2) \times 10^6 \text{ pm}^3$, calculated density $\rho = 3.892 \text{ g cm}^{-3}$, measurement range $6.64^\circ < 2\theta < 54.94^\circ$, intensities of 46386 reflections measured, 1981 independent reflections, $R_{\text{int}} = 0.091$, structure solution by direct methods (SHELXS-97^[17]), refinement with anisotropic displacement factors for all atoms, 64 parameters, absorption coefficient 250 cm^{-1} , numerical absorption correction (HABITUS^[18]), $R(|F|) = 0.027$, $R(F^2) = 0.067$ (SHELXL-97^[19]), Flack parameter $x = 0.025(5)$, max./min. residual electron density $1.60 \times 10^{-6} / -2.00 \times 10^{-6} \text{ pm}^{-3}$. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-411714.

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Hybrid Molecular Materials Based on Covalently Linked Inorganic Polyoxometalates and Organic Conjugated Systems**

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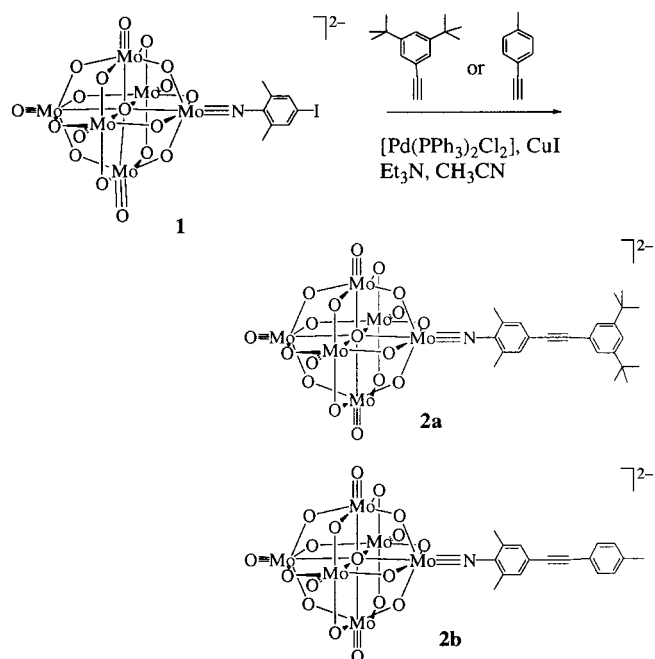
Polyoxometalate (POM) chemistry has advanced dramatically during the past two decades, and numerous new structural types with fascinating topological beauty and important electronic, optical, and catalytic properties have been developed.^[1–4] Parallel to the rapid progress made on these inorganic metal–oxygen cluster anions, studies on organic and polymeric conjugated materials have also exploded and flourished.^[5–8] The fact that the Nobel Prize in chemistry for 2000 went to three preeminent scientists working on conjugated polymers is the ultimate testimony to the important developments in organic conjugated systems.^[9]

Although they are vastly different in molecular structures, POMs and organic conjugated molecules/polymers are both electrically active materials with similar electrical and optical properties such as photochromism, electrochromism, and conductivity. The underlying mechanisms of these properties are, however, different for the two types of materials, with $d\pi$ electrons responsible for the inorganic clusters, and delocalized π electrons responsible for the organic counterpart. While both areas have been enjoying considerable success, there has been little success in bringing these two types of materials together through covalent bonds.^[10, 11] Not only will such hybrid materials combine the advantages of organic materials, such as ease in processing and structural fine tuning, with those of inorganic clusters, but the close interaction of

organic delocalized π electrons with the cluster d electrons may bring exciting synergistic effects. Such materials with their unique structures are extremely interesting not only to synthetic chemists and materials scientists, but also to theoretical and experimental physicists.

Herein, we report the synthesis of such hybrid materials through Pd-catalyzed coupling reactions and demonstrate, for the first time, that iodo-functionalized hexamolybdates can undergo Pd-catalyzed coupling reactions with ethynylarenes. These reactions open an exciting research arena where a variety of hybrid materials containing covalently bonded POM clusters and organic conjugated segments can be prepared in a controllable and rational way.

Scheme 1 shows the structures and synthesis of the hybrid materials. Compound $[\text{Bu}_4\text{N}]_2\text{-1}$ was synthesized by using an approach developed in our laboratory.^[12] The coupling of



Scheme 1. Pd-catalyzed coupling of the iodo-functionalized hexamolybdate anion **1** with alkynes.

$[\text{Bu}_4\text{N}]_2\text{-1}$ with 1-ethynyl-3,5-di(*tert*-butyl)benzene or 1-ethynyl-4-methylbenzene was carried out in acetonitrile at room temperature under the protection of nitrogen.^[13] The reaction is unusually fast and is completed in a few minutes as monitored by thin-layer chromatography. The cluster not only survived under the reaction conditions, it apparently activates the coupling reaction. The enhanced reactivity of the iodo function in **1** is presumably due to the electron-withdrawing nature of the Mo–N triple bond. Prolonged reaction time is found to be detrimental, as the coupling product slowly decomposes to its parent $\{\text{Mo}_6\text{O}_{19}\}$ cluster under the reaction conditions. Nevertheless, pure products $[\text{Bu}_4\text{N}]_2\text{-2a}$ and $[\text{Bu}_4\text{N}]_2\text{-2b}$ can be synthesized in excellent yields.

Both $[\text{Bu}_4\text{N}]_2\text{-2a}$ and $[\text{Bu}_4\text{N}]_2\text{-2b}$ exhibit excellent solubility in common organic solvents such as dichloromethane, chloroform, acetone, acetonitrile, THF, and DMF. They also show remarkable stability against O_2 and moisture. No obvious

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decomposition is observed after their solutions stand in air for nearly one month. The structures of the products were confirmed by elemental analysis, spectroscopic measurements, and X-ray single-crystal structure analysis. Figure 1 shows the ^1H NMR spectra of $[\text{Bu}_4\text{N}]_2\text{-1}$, $[\text{Bu}_4\text{N}]_2\text{-2a}$, and $[\text{Bu}_4\text{N}]_2\text{-2b}$ in $[\text{D}_6]\text{acetone}$. All spectra show clearly resolved signals, all of which can be unambiguously assigned. In each case the integration matches well with the desired structure.

Single crystals of $[\text{Bu}_4\text{N}]_2\text{-2b}$ were grown by diffusion of diethyl ether into a solution of the compound in acetonitrile. The crystals are very thin plates which generate rather weak X-ray diffraction signals. Nevertheless, the X-ray diffraction measurement does confirm the targeted structure.^[14] Figure 2 shows the ORTEP drawing of the crystal structure of the anion **2b**. Compound $[\text{Bu}_4\text{N}]_2\text{-2b}$ crystallizes in space group $C2/c$ with two crystallographically independent anions in the asymmetric unit. One axis is significantly longer (ca. 60 Å) than the other two (22 and 19 Å). Similar to its precursor **1** and other arylimido

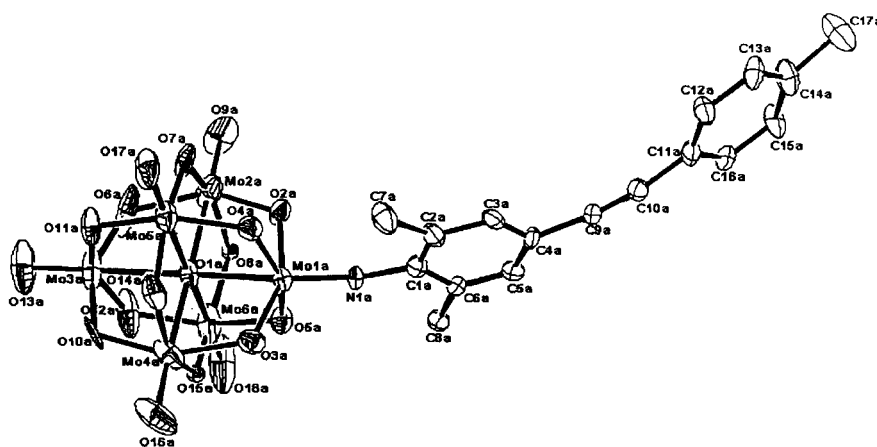


Figure 2. Structure of one of the two crystallographically independent anions of **2b** (ORTEP diagram). Selected bond lengths [Å] and angles [°]: Mo1a-N1a 1.739(19), Mo2a-O9a 1.67(2), Mo3a-O13a 1.68(2), Mo4a-O16a 1.71(3), Mo5a-O17a 1.74(2), Mo6a-O18a 1.69(3), O1a-Mo1a 2.193(14), O1a-Mo6a 2.293(16), O1a-Mo5a 2.317(16), O1a-Mo4a 2.335(18), O1a-Mo3a 2.334(14), O1a-Mo2a 2.367(18), N1a-C1a 1.41(3), C1a-C6a 1.36(3), C1a-C2a 1.43(3), C2a-C3a 1.41(3), C2a-C7a 1.56(4), C3a-C4a 1.37(3), C4a-C5a 1.38(3), C4a-C9a 1.48(3), C5a-C6a 1.35(3), C6a-C8a 1.52(3), C9a-C10a 1.17(3), C10a-C11a 1.44(3), C11a-C12a 1.41(3), C12a-C13a 1.37(3), C13a-C14a 1.41(3), C14a-C15a 1.36(3), C14a-C17a 1.55(4), C15a-C16a 1.39(3), C1a-N1a-Mo1a 171.4(18), C10a-C9a-C4a 172(3), C9a-C10a-C11a 173(3).

derivatives of hexamolybdates, the Mo-N bond in **2b** shows triple-bond character, as evidenced by the short bond length (1.74 Å) and nearly linear Mo-N-C angle (171.4°). It is rather unusual that the oligo(phenylene acetylene) unit is not linear, instead showing some curvature.

The electronic properties of functionalized hexamolybdates were studied by UV/Vis absorption and static fluorescence measurements. As shown in Figure 3, the lowest energy

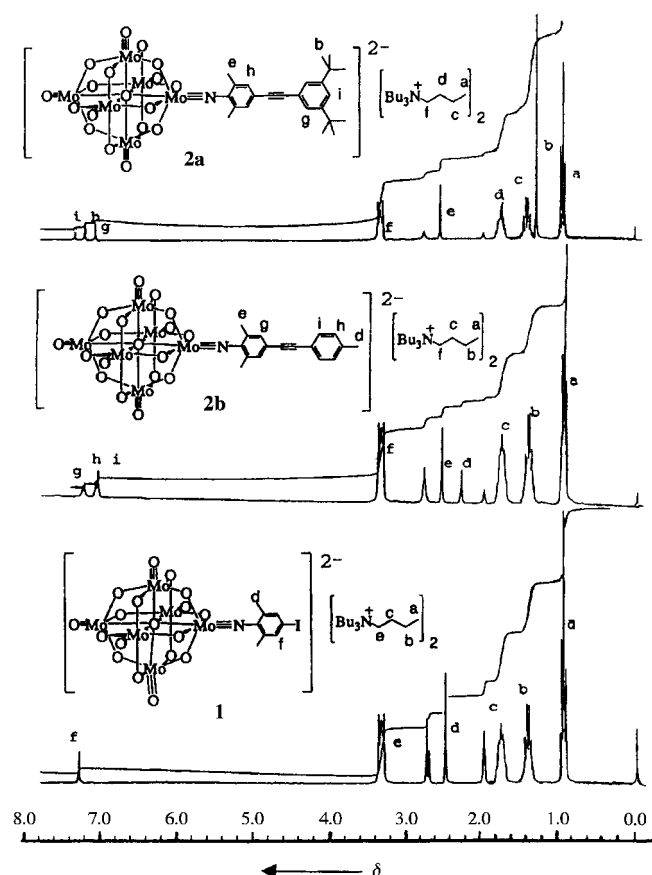


Figure 1. ^1H NMR spectra of $[\text{Bu}_4\text{N}]_2\text{-1}$, $[\text{Bu}_4\text{N}]_2\text{-2a}$, and $[\text{Bu}_4\text{N}]_2\text{-2b}$ in $[\text{D}_6]\text{acetone}$. The two unlabeled peaks are solvent signals (acetone and water).

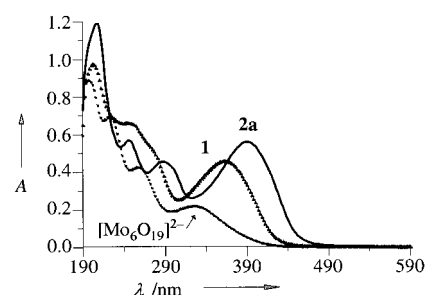


Figure 3. UV/Vis absorption spectra of $[\text{Mo}_6\text{O}_{19}]^{2-}$, **1**, and **2a**.

electronic absorptions are significantly red-shifted from parent $[\text{Mo}_6\text{O}_{19}]^{2-}$ to mono-arylimido hexamolybdate **1**, and to the coupling product **2a**. If, as commonly believed, the lowest energy absorption is due to the charge-transfer transition originated in a state dominated by Mo-N π -bonding,^[15] the bathochromic shifts observed may imply that the Mo-N π bond is delocalized with the organic conjugated π electrons. In other words, there is a strong electronic interaction between the metal-oxygen cluster and the organic segment. Fluorescence studies show that **2a** and **2b** show no fluorescence under excitation from 200 nm to 500 nm. Considering the fact that oligo(phenylene ethynylene)s are highly fluorescent molecules,^[16] the hexamolybdate

cluster evidently acts as a fluorescence quencher, presumably by accepting the excited electrons.

In conclusion, the reported Pd-catalyzed C–C coupling of iodo-functionalized hexamolybdate building blocks and alkynes thus offers a route to hybrid materials in which POM clusters are covalently bonded with organic conjugated segments.

Experimental Section

A mixture containing $[\text{Bu}_4\text{N}]_2[\text{Mo}_6\text{O}_{18}\equiv\text{NC}_6\text{H}_2(\text{CH}_3)_2\text{I}]$ ($[\text{Bu}_4\text{N}]_2\text{-1}$), (2.00 g, 1.26 mmol), 1-ethynyl-3,5-di(*tert*-butyl)benzene or 1-ethynyl-4-methylbenzene (1.90 mmol, 1.5 equiv), $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$ (0.026 g, 0.03 equiv), CuI (0.014 g, 0.06 equiv), and triethylamine (1 g) was stirred in acetonitrile (40 mL) at room temperature for 20 min, which led to a shiny red solution. Dichloromethane (100 mL) was then added. The resulting solution was washed twice with H_2O and brine water, and then concentrated to about 10 mL. After the addition of hexane (200 mL) to the above concentrated solution, it was left standing for 2 h. The top yellowish clear solution was discarded. The oily dark red residue was dried under vacuum to yield the products as dark red solids ($[\text{Bu}_4\text{N}]_2\text{-2a}$, 85% yield; $[\text{Bu}_4\text{N}]_2\text{-2b}$, 72% yield).

$[\text{Bu}_4\text{N}]_2\text{-2a}$: Elemental analysis (%) for $\text{C}_{56}\text{H}_{101}\text{N}_3\text{O}_{18}\text{Mo}_6$: calcd: C 40.04, H 6.06, N 2.51; found: C 40.99, H 6.07, N 2.55; ^1H NMR (250 MHz, $[\text{D}_6]$ acetone, 25 °C, TMS): δ = 0.97 (t, J = 7.25 Hz, 24H; CH_3), 1.34 (s, 18H; $\text{C}(\text{CH}_3)_3$), 1.47 (sextet, J = 7.30 Hz, 16H; CH_2), 1.83 (quintet, J = 7.94 Hz, 16H; CH_2), 2.64 (s, 6H; ArH), 3.45 (t, J = 8.50 Hz, 16H; NCH_2), 7.25 (s, 2H; ArH), 7.39 (s, 2H; ArH), 7.52 (s, 2H; ArH).

$[\text{Bu}_4\text{N}]_2\text{-2b}$: Elemental analysis (%) for $\text{C}_{49}\text{H}_{87}\text{N}_3\text{O}_{18}\text{Mo}_6$: calcd: C 37.21, H 5.54, N 2.66; found: C 36.83, H 5.32, N 2.61; ^1H NMR (250 MHz, $[\text{D}_6]$ acetone, 25 °C, TMS): δ = 0.99 (t, J = 7.38 Hz, 24H; CH_3), 1.46 (sextet, J = 7.3 Hz, 16H; CH_2), 1.83 (quintet, J = 7.94 Hz, 16H; CH_2), 2.37 (s, 3H; ArH), 2.64 (s, 6H; ArH), 3.47 (t, J = 8.5 Hz, 16H; NCH_2), 7.23 (s, 2H; ArH), 7.25 (d, J = 8.5 Hz, 2H; ArH), 7.42 (d, J = 7.25 Hz, 2H; ArH).

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0.71073 Å. A total of 56870 reflections (18191 independent, R_{int} = 0.0899) were collected on a Bruker SMART system ($2\theta_{\text{max}}$ = 46.50). The structure was solved by direct methods (SHELXS, 1997) and refined by full-matrix least-squares (on F^2) and difference Fourier cycles (SHELXL, 1997). A semiempirical absorption correction (SADABS, G. M. Sheldrick, 1996) was applied (T_{max} = 0.86, T_{min} = 0.62). All non-hydrogen atoms were refined anisotropically and no attempts were done for H atoms. Final residuals ($I > 2\sigma(I)$ = 10777) were R_1 = 0.0933, and wR_2 = 0.2680. Largest difference peak and hole = 3.258 and -2.752 e Å^{−3}. GOF (F^2) = 1.046. Drawings were generated using ORTEP-III (Burnett & Johnson, 1996). 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-154486. 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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Chemoenzymatic-Chemical Synthesis of a (2-3)-Sialyl T Threonine Building Block and Its Application to the Synthesis of the N-Terminal Sequence of Leukemia-Associated Leukosialin (CD 43)**

Nicole Bézay, Gregor Dudziak, Andreas Liese, and Horst Kunz*

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

Enzymatic reactions are valuable tools in syntheses of polyfunctional natural products and drugs. This holds true, in particular, for syntheses of oligosaccharides and their glycoconjugates, since numerous protecting-group manipulations can be avoided and glycosidic linkages can be formed regio- and stereoselectively by using glycosyltransferases^[1] and glycosidases.^[2] Successful enzymatic chain extensions of saccharides have been reported, in particular, for the formation of oligosaccharides and glycopeptides that contain sialic acid, in the course of which the enzymatic reactions constitute the final steps of the whole synthesis.^[3] If, however, enzymatically prepared sialyl glycoconjugates are to be used in continuing chemical syntheses (e.g. of glycopeptides), their numerous functional groups must be blocked by selectively removable protecting groups.

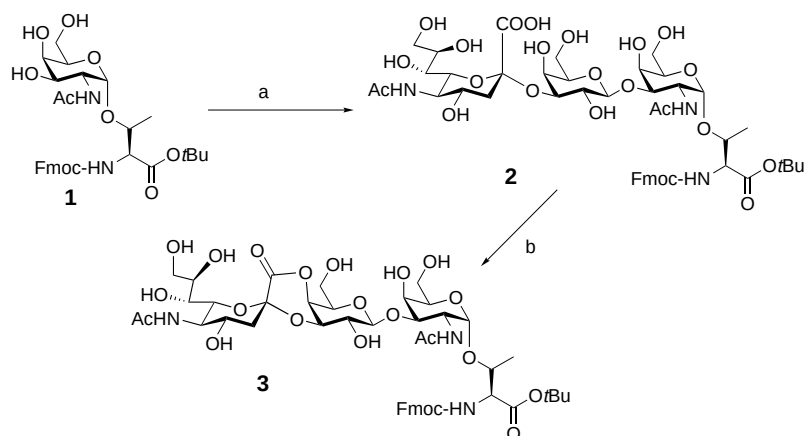
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We describe herein a solution to this problem in the synthesis of the N-terminal glycopeptide sequence of leukosialin (CD 43) with a (2-3)-sialyl T antigen saccharide side chain. Leukosialin^[4] with the tumor-associated sialyl T antigen (Neu5A($\alpha 2 \rightarrow 3$)-Gal-($\beta 1 \rightarrow 3$)-GalNAc($\alpha 1 \rightarrow O$)-Ser/Thr) is found on leukocytes of patients suffering from acute myeloid leukemia,^[5] and with other aberrant carbohydrates on colon carcinoma cells.^[6] In addition, the (2-3)-sialyl T antigen has been detected on breast cancer cells.^[7] Therefore, glycopeptides with the (2-3)-sialyl T structure as well as the regioisomeric (2-6)-sialyl T antigen analogues^[8] and the sialyl T_N antigen glycopeptides^[9] are considered candidates for the development of antitumor vaccines.

The chemical synthesis of sialyl T antigen threonine conjugates^[10] requires numerous protecting-group manipulations and three stereoselective glycosylation reactions of which the sialylation is particularly demanding. The chemoenzymatic synthesis of sialyl T threonine esters can start with *N*-Fmoc-(*O*-*N*-acetylgalactosaminyl)threonine *tert*-butyl ester (**1**), which is readily available in preparative amounts.^[11] The sialyl T threonine derivative **2** was obtained in a one-pot reaction cascade consisting of a regio- and stereoselective galactose transfer from lactose, catalyzed by a galactosidase from bovine testes, and a subsequent enzymatic sialylation^[12] (Scheme 1). At first, the low solubility of **1** in water appeared to be an insuperable problem, but was overcome by the insertion of the hydrophobic Fmoc moiety into a β -cyclodextrin dimethyl ether (twofold excess relative to **1**), and **2** was obtained in an overall yield of 50% (100 mg). Because of the reduced stability of the sialyltransferase in weak acids, the reactions were carried out at pH 6.5. To prevent inhibition by the cytidine phosphate, alkaline phosphatase was added.

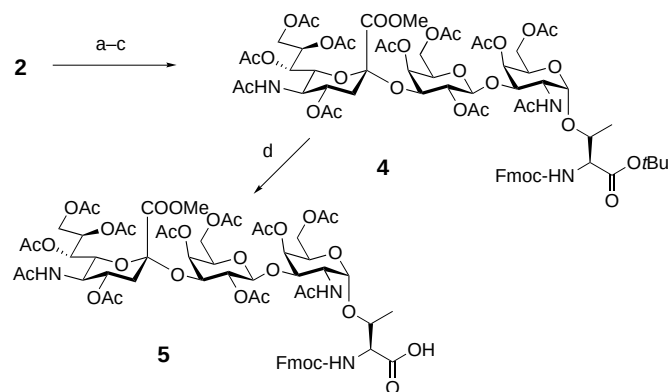
Prior to the use of **2** as a building block in glycopeptide synthesis, the numerous functional groups in its carbohydrate portion must be blocked by protecting groups. The protection of the sialic acid carboxy group is of particular importance. This protection must be of orthogonal stability to the protecting groups within the peptide portion. Treatment of **2** with acidic ion-exchange resin in dry methanol did not give the methyl ester, but the 4-lactone **3** and, presumably, the



Scheme 1. a) Lactose, β -galactosidase (bovine testes) and CMP-Neu5Ac, sialyltransferase and calf intestine alkaline phosphatase in the presence of bovine serum albumin, 2,6-di-*O*-methyl- β -cyclodextrin in water, pH 6.5, yield 50%;^[12] b) Dowex 50W (H⁺-form) in methanol. Fmoc = 9-fluorenylmethoxycarbonyl.

corresponding 2-lactone (MALDI-TOF-MS in α -cyano-cinnamic acid (cca) matrix m/z 1076.8, $[M+Na]^+$, calcd 1077.1).

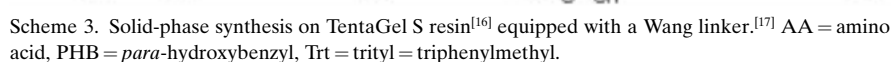
In contrast to the lactones of the chemically synthesized, fully protected sialyl T threonine derivatives^[10, 13, 14] and to the 4-lactones of sialyl Lewis^x glycopeptides,^[15] the lactone **3** and its isomer are unstable during subsequent reactions. Therefore, an alternative protection of the carbohydrate functional groups of **2** was developed. Treatment of **2** with acetic anhydride/pyridine (1:3) for 20 h at room temperature and subsequent codistillation with toluene (three times) resulted in complete *O*-acetylation and formation of a mixed anhydride. The latter was solvolyzed by the addition Hünig's base in methanol (*N*-ethyl-diisopropylamine, DIPEA, 0.1%) to yield the methyl ester of the *N*-acetylneuraminic acid. The accompanying de-*O*-acetylation was corrected by a second treatment with acetic anhydride/pyridine. The fully protected sialyl T threonine building block **4** was isolated in 61% yield (Scheme 2).



Scheme 2. a) Ac₂O/pyridine; b) MeOH, *i*Pr₂EtN; c) Ac₂O/pyridine, 61% over three steps, d) trifluoroacetic acid (TFA), 60 min, 84%.

Acidolysis of the *tert*-butyl ester gave the Fmoc-protected (2-3)-sialyl T threonine building block **5**, which was applied to the solid-phase synthesis of the N-terminal glycopeptidopeptide of leukosialin with a sialyl T antigen side chain.

TentaGel S resin^[16] equipped with the acid-labile Wang anchor^[17] was loaded with Fmoc threonine-*O*-*tert*-butyl ether to give **6**. The first seven amino acids were coupled according to Fmoc strategy by using a peptide synthesizer (Scheme 3)^[18]. For removal of the Fmoc group, the resin was treated three times for 2.5 min with piperidine in *N*-methylpyrrolidone (NMP; 20%). The coupling reactions were carried out by using a fivefold excess of each Fmoc amino acid, *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU),^[19] 1-hydroxybenzotriazole (HOBt), and Hünig's base. Unreacted amino groups were acetylated by using Ac₂O/*i*Pr₂EtN/HOBt (4:1:0.12) in NMP. The resin-linked octapeptide was transferred from the



synthesizer into a reaction vessel, and the Fmoc group was cleaved by using morpholine/dimethylformamide (DMF) over 1.5 h. For the coupling of the valuable sialyl T threonine building block **5** (1.1 equiv), 1.2 equivalents each of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU)^[20] and 1-hydroxy-7-azabenzotriazole (HOAt), and 2.4 equivalents of *N*-methylmorpholine (NMM) were applied, and the mixture was vigorously shaken with the resin-linked peptide for four days. The formed polymer-linked glycopeptide was then transferred into the peptide synthesizer. After acetylation with acetic anhydride, the additional eight Fmoc amino acids (40-fold excess) were coupled by activation with HBTU/HOBt/DIPEA. Finally, the Fmoc group was removed by using piperidine/NMP (see above), and the terminal amino group was acetylated.

The completely protected resin-linked sialyl T glycoheptadecapeptide **7** was detached from the polymeric support by using trifluoroacetic acid (TFA)/water/thioanisole/1,2-ethanedithiol (87.5:5:5:2.5). Under these conditions, all *tert*-butyl protecting groups were simultaneously removed from the amino acid residues. The sialyl T glycoheptadecapeptide **8** was isolated after purification by preparative HPLC in an overall yield of 43 % over 35 steps from **6** (27 mg, using 35 mg of **5**; Scheme 3).^[21]

The *O*-acetyl groups were removed from the carbohydrate portion of **8** by using catalytic sodium methanolate in methanol (pH 8.2–8.5), and the methyl ester of the *N*-acetylneuraminic acid was hydrolyzed with aqueous NaOH (5 mM, pH 11–11.5).^[11] This deprotection must be monitored by analytical HPLC. In addition to the target compound **9**, a second component was isolated, which according to ¹H NMR spectroscopic and mass spectrometric analysis still contains an *O*-acetyl group.

The pure glycoheptadecapeptide **9**,^[22] which represents the N-terminus of leukosialin (CD 43) with (2-3)-sialyl T antigen structure typical for acute myeloid leukemia, was isolated by preparative HPLC in 40% yield (10 mg). This synthetic antigen as well as analogous glycopeptides with shorter T_N and T antigen saccharides and the nonglycosylated heptadecapeptide are presently under investigation for immunizations and induction of antibodies.^[9]

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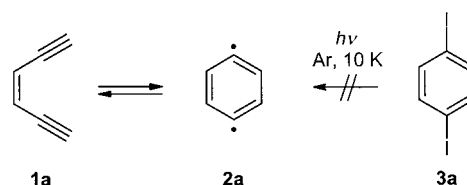
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- [21] **8**: $[a]_D^{25} = -52.9$ ($c = 0.89$, H₂O); $R_t = 34.6$ min (0.1 % TFA in CH₃CN/H₂O, gradient 1:99 (0–5 min), then 50:50 (45 min), and finally 100:0 (50–55 min)); MALDI-TOF-MS (cca matrix, positive-ion mode): m/z (%): 2806.1 (29) [M+K⁺], 2790.2 (100) [M+Na⁺]; ¹H NMR (COSY, 400 MHz, D₂O): $\delta = 5.39$ (s, 3H; H₄, H⁷, H⁸), 4.99–4.84 (m, 2H; H₁, H^{4'}), 4.80–4.70 (m, 1H; H_{1'}), 4.70–4.58 (m, 1H; E^a), 4.58–4.38 (m, 6H; H_{2'}, P^a {4.54}, S^a), 4.38–4.21 (m, 7H; H₂ {4.24}, A^a {4.31}, L^a {4.30}, Q^a {4.38}, 3 × T^b), 4.21–3.98 (m, 5H; H_{3'} {4.05}, V^a {4.04, 4.14}, 2 × T^b), 3.98–3.71 (m, 18H; H₃, H_{5'}, H^{9'a}, H^{9'b}, G^a, S^b, 3 × P^b, CH₃O {3.80}), 3.70–3.59 (m, 1H; 1 × P^b), (4.58–4.38 (m, 2H; 4.38–4.21 (m, 6H), 4.21–3.98 (m, 4H), 3.98–3.71 (m, 1H)) (H_{4'}, H₅, H_{5'}, H₆, H_{6'}, H_{6''}, T^a), 2.58 (d_b, 1H; H_{3'}^{eq}), 2.49–2.38 (m, 2H; E^b), 2.34–1.76 (m, 16H; E^b {2.03, 1.88}, P^b, P^v, Q^b {2.01, 1.90}, Q^v {2.30}, V^b), 2.24, 2.18, 2.10, 2.06, 2.03, 2.00, 1.96, 1.82 (8 × s, 33H; CH₃CO), 1.66–1.46 (m, 4H; H_{3'}^{ax}, L^b, L^v), 1.31 (d, 3H; J_{AA',Aβ} = 6.2 Hz; A^b), 1.26, 1.19 (2 × d, 6H; J_{Tβ,Tγ} = 4.8 Hz; T^v), 1.23–1.08 (m, 12H; T^v), 0.98–0.78 (m, 18H; L^b, V^v); ¹³C NMR (broad-band decoupling, DEPT, 100.6 MHz, D₂O), $\delta = 177.6$, 176.9, 174.5, 174.3, 173.6, 173.3, 172.9, 172.7, 172.1, 171.7, 171.4 (C=O), 100.7 (C_{1'}), 99.2 (C_{2'}), 77.1 (C₃), 73.5 (T^{b*}), 71.5, 71.2, 71.0, 70.2, 69.9, 69.5, 68.1, 67.4, 67.0, 66.8 (C_{2'}, C_{3'}, C₄, C_{4'}, C₅, C_{5'}, C_{6''}, C_{7''}, C_{8''}, T^b), 63.1 (C_{9''}), 62.0, 61.5, 61.3, 60.9 (C₆, C_{6'}, S^b), 60.2, 59.4, 59.1, 59.0, 58.8, 57.9, 57.1, 57.0, 55.5, 55.2, 52.6, 52.4, 50.7, 49.6, 48.5 (C₂, C_{5''}, A^a, E^a, L^a, P^a, Q^a, S^a, T^a, V^a), 53.6 (CH₃O), 48.3, 47.8 (P^b), 42.1 (G^a), 39.5 (L^b), 36.6 (C_{3'}), 30.9 (Q^v), 30.2, 29.9 (V^b), 29.5, 29.4, 29.2 (E^v, P^b), 26.8, 25.5, 24.6, 24.2 (E^b, Q^b, P^v), 24.2, 22.2, 22.0, 21.7, 21.6, 20.8, 20.7, 20.2, 20.1, 19.8, 18.7, 18.6, 18.3, 18.1, 17.7, 17.5 (CH₃CO, L^v, L^b, T^v, V^v), 16.3 (A^b).
- [22] **9**: ESI-MS (positive-ion mode), m/z (%): 1210.3 (15) [(M+2Na⁺)/2], 1207.3 (10) [(M+H⁺+K⁺)/2], 1199.3 (40) [(M+H⁺+Na⁺)/2], 1188.3 (100) [(M+2H⁺)/2]; ¹H NMR (COSY, 400 MHz, D₂O): $\delta = 4.85$ (d, 1H, J_{H-1,H-2} = 3.0 Hz; H₁), 4.66–4.58 (m, 1H; E^a), 4.58–4.53 (m, 1H; 1 × P^a), 4.53–4.47 (m, 2H; 1 × S^a, 1 × T^a), 4.46–4.39 (m, 3H, J_{H-1,H-2} = 7.9 Hz; H_{1'}, 2 × S^a), 4.39–4.09 (m, 12H; H₄, A^a {4.31}, L^a {4.29}, 1 × P^a {4.36}, Q^a {4.36}, 4 × T^a, 3 × T^b {4.26}), 4.18–4.09 (m, 3H; H₂, 1 × T^b, 1 × V^a), 4.09–3.89 (m, 6H; H₃ {4.00}, H_{3'} {4.00}, H_{4'}, H^{9'a}, 1 × T^b {4.05}, 1 × V^a), 3.88–3.71 (m, 10H; G^a, S^b, 2 × P^b), (3.88–3.71 (m, 2H), 3.71–3.49 (m, 12H)) (H_{4'} {3.60}, H₅, H_{5'}, H_{5''}, H_{6a}, H_{6b}, H_{6'a}, H_{6'b}, H_{6''}, H^{7'}, H^{8''}, H^{9'b}, 2 × P^b), 3.49–3.41 (m, 1H; H_{2'}), 2.70 (dd, 1H; J_{H3''eq,H3'ax} = 12.3, J_{H3''eq,H4'} = 3.7 Hz; H_{3''eq}), 2.46–2.38 (m, 2H; E^v), 2.29 (t, 2H, J_{Qβ,Qγ} = 7.5 Hz; Q^v), (2.25–2.12 (m, 1H), 2.08–1.89 (m, 12H)) (E^ba {2.02}, P^b, P^v, Q^b {2.02, 1.90}, V^b), 2.00, 1.96, 1.94 (3 × s, 9H; CH₃CO), 1.89–1.78 (m, 1H; E^bb), 1.71 (t, 1H, J_{H3''eq,H3'ax} = J_{H3''ax,H4'} = 12.0 Hz; H_{3''ax}), 1.64–1.47 (m, 3H; L^b, L^v), 1.31 (d, 3H, J_{AA',Aβ} = 7.0 Hz; A^b), (1.26 (d, 3H, J_{Tβ,Tγ} = 5.9 Hz), 1.20 (d, 3H, J_{Tβ,Tγ} = 6.4 Hz), 1.18–1.08 (m, 9H)) (T^v), 0.88 (m, 12H; V^v), 0.83 (d, 6H, J_{Lγ,Lδ} = 5.9 Hz; L^b); ¹³C NMR (100.6 MHz, D₂O): $\delta = 177.8$, 177.0, 176.6, 174.6, 173.3, 173.2, 172.7, 171.9, 171.7, 171.4, 170.9, 170.8 (C=O), 104.6 (C_{1'}), 99.0 (C_{2'}), 77.4, 75.8, 74.9, 73.0, 71.8, 71.1, 68.9, 68.8, 68.4, 68.3, 67.3, 67.0, 66.9 (C_{2'}, C₃, C_{3'}, C₄, C_{4'}, C_{4''}, C₅, C_{5'}, C_{6''}, C_{7''}, C_{8''}, T^b), 62.8 (C_{9''}), 61.4, 61.2, 61.0 (C₆, C_{6'}, S^b), 60.5, 59.5, 59.3, 59.1, 57.2, 55.7, 55.4, 52.9, 52.6, 51.9, 50.9, 49.8 (C₂, C_{5''}, A^a, E^a, L^a, P^a, Q^a, S^a, T^a, V^a), 48.5, 48.0 (P^b), 42.3 (G^a), 39.7 (L^b), 39.5 (C_{3'}), 31.2 (Q^v), 30.4, 30.2 (V^b), 29.7, 29.4 (E^v, P^b) 27.0, 25.8, 24.7 (E^b, Q^b, P^v), 24.5, 22.2, 21.8, 21.1, 18.9, 18.8, 18.5, 18.2, 17.8, 17.7 (CH₃CO, L^v, L^b, T^v, V^v), 16.6 (A^b); the signal for C₁ could not be assigned.

Matrix Isolation of Perfluorinated *p*-Benzynes**

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David A. Hrovat, and Weston T. Borden

The thermal cyclization of enediynes **1** to produce *p*-benzynes (*p*-didehydrobenzene) and its derivatives **2** (Bergman cyclization)^[1] is the key step for the biological activity of the enediyne antibiotics.^[2] During the past few years this reaction and the proposed intermediates have thus been the target of a large number of synthetic,^[3–11] spectroscopic,^[12–16] and theoretical^[17–21] studies.^[22] The heat of formation of 1,4-didehydrobenzene (**2a**) was determined by Roth et al. to be 138.0 ± 1.0 kcal mol^{−1}, which results in a reaction enthalpy for the cyclization of **1a** → **2a** of 8.5 ± 1.0 kcal mol^{−1}.^[23] The activation barrier for the ring-closure of **1a** was determined to be 28.7 ± 0.5 kcal mol^{−1}. A singlet ground state was predicted for **2a**, and a singlet–triplet splitting ΔE_{ST} of −3.8 ± 0.5 kcal mol^{−1} was measured by Squires et al. using negative-ion photoelectron spectroscopy (NIPES).^[14] Recently the matrix isolation and characterization of **2a** by IR spectroscopy was reported from our laboratory.^[15]



The experimental data available for *p*-didehydrobenzene (**2a**) has contributed to the understanding of the biological activity of calicheamicin-type antitumor drugs. The challenge is now to modify the diradicals **2** in order to control their reactivity.^[24] However, so far all attempts to isolate and characterize derivatives of benzyne **2a** failed.

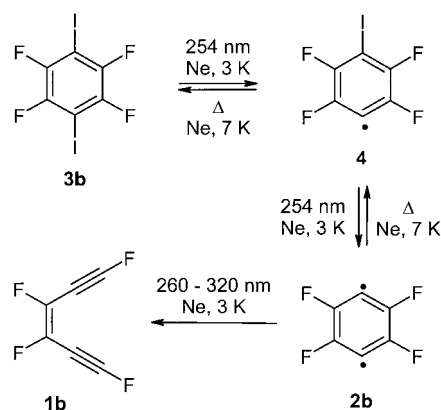
Density functional theory (DFT) and CASSCF calculations indicate that 1,4-didehydro-2,3,5,6-tetrafluorobenzene (**2b**) should be a suitable target for synthesis and isolation in low-temperature matrices. The fluorine substituents at the terminal acetylenic positions result in a large destabilization of 1,3,4,6-tetrafluoro-hex-3-ene-1,5-diyne (**1b**) with respect to *p*-benzyne **2b**, and the cyclization of **1b** is estimated to be exothermic by 7.9 kcal mol^{−1} (UB3LYP/6-311++G(d,p)). The barrier for the ring-opening of **2b** is calculated to be 37.5 kcal mol^{−1}, almost twice that of **2a** (19.8 ± 1 kcal mol^{−1}).^[23]

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A readily available photochemical precursor of **2b** should be 1,4-diiodo-2,3,5,6-tetrafluorobenzene (**3b**). The photolysis of iodobenzenes results in the cleavage of the C–I bond, leading to the formation of phenyl radicals and iodine atoms. However, under the conditions of matrix isolation the radicals generally can not escape the matrix cage; therefore, the yield of radicals is very much limited by rapid in-cage recombinations. Thus, UV irradiation ($\lambda = 254$ nm) of **3b** in argon at temperatures as low as 3 K does not produce the 4-iodo-2,3,5,6-tetrafluorophenyl radical **4** in quantities large enough for IR spectroscopic detection. Only the more sensitive and specific EPR spectroscopy indicates the formation of traces of radicals.



Surprisingly, the irradiation (254 nm) of **3b** in neon at 3 K results in the rapid formation in moderate yields of a new compound with strong IR absorptions at 1471, 1188, 942, 834, and 693 cm^{-1} . By comparison with the IR spectrum calculated at the UB3LYP^[25] level of theory, using the 6-311G(d,p) basis set, this new compound was identified as phenyl radical **4** (Figure 1, Table 1). Apparently, under these conditions the radical pairs are separated by neon atoms.^[16b] Warming the matrix for several minutes to 7.5 K results in the recombina-

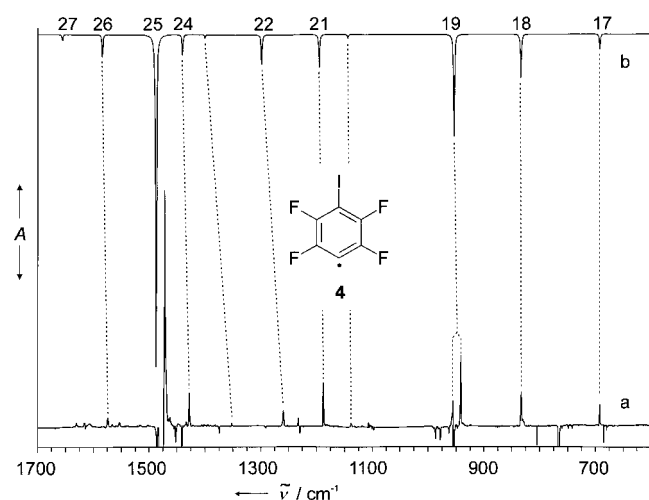


Figure 1. Photochemistry of **3b** in solid neon at 3 K. a) Difference spectrum. Bands pointing upwards arise during 10 min irradiation with 254 nm. b) Calculated spectrum (UB3LYP/6-311G(d,p), unscaled) of radical **4**.

Table 1. IR spectroscopic data of 4-iodo-2,3,5,6-tetrafluorophenyl radical (**4**).

Mode	Symmetry	$\tilde{\nu}_{\text{exp}}^{[a]}$ [cm^{-1}]	$I_{\text{rel,exp}}^{[b]}$	$\tilde{\nu}_{\text{calcd}}^{[c]}$ [cm^{-1}]	$I_{\text{rel,calcd}}$
17	b ₂	692.9	0.09	693.2	0.05
18	a ₁	833.6	0.14	834.1	0.13
19	b ₂	941.9	0.29	954.3	0.31
		956.0	0.11		
20	b ₂	1138.4	0.01	1144.8	0.01
21	a ₁	1188.1	0.18	1195.1	0.10
22	b ₂	1259.4	0.04	1298.1	0.09
23	a ₁	1352.2	0.01	1400.2	0.01
24	a ₁	1428.3	0.13	1440.9	0.06
25	b ₂	1471.7	1.00	1487.2	1.00
26	a ₁	1574.4	0.03	1584.8	0.07

[a] Neon, 3 K. [b] Relative intensities based on the strongest absorption. [c] Calculated at the B3LYP/6-311G(d,p)^[29] level of theory. Band positions are unscaled. The assignment is tentative and is based on band positions and intensities.

tion of **4** and the iodine atom, reforming the starting compound **3b**.

Prolonged 254 nm irradiation of **3b** and **4** at 3 K produces another compound, A, which has its strongest IR absorptions at 1516, 1507, 1117, and 925 cm^{-1} . Warming the matrix to 7.5 K causes all the IR absorptions assigned to radical **4** and to compound A to decrease and results in formation of **3b** (Figure 2). Compound A is photolabile and UV irradiation in

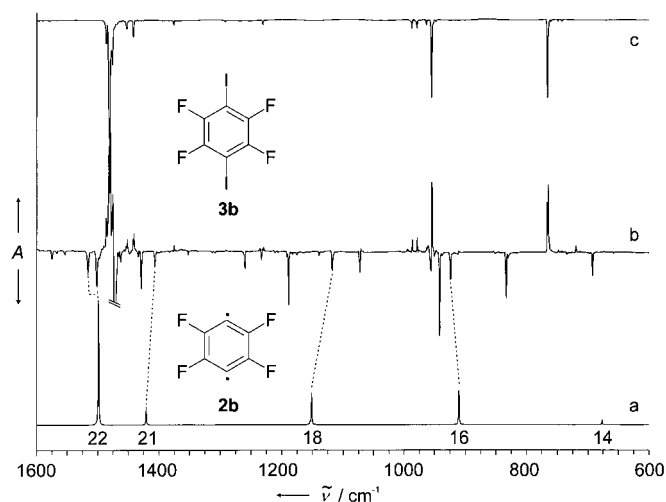


Figure 2. Thermal reactions of the products formed by 254 nm irradiation (3 h) of **3b** in a neon matrix at 3 K. a) Calculated spectrum (CASSCF(8,8)/cc-pVDZ, scaled by 0.91) of singlet **2b**. b) Difference spectrum. Bands pointing upwards appear, bands pointing downwards disappear upon annealing (7.5 K, 10 min). Bands marked with dotted lines are assigned to **2b**, other bands belong to radical **4**. c) IR spectrum of diiodotetrafluorobenzene (**3b**) matrix isolated in solid neon at 3 K.

the range 260–320 nm gives an additional compound, B, which has its strongest IR absorption at 2337 cm^{-1} . Compound B was clearly identified as enediyne **1b** by comparison of the experimental with the DFT calculated IR spectrum (Figure 3, Table 2).

Both the thermal reaction with iodine atoms to reform **3b** and the photochemical formation of **1b** strongly suggest that compound A should be assigned the structure of *p*-benzyne

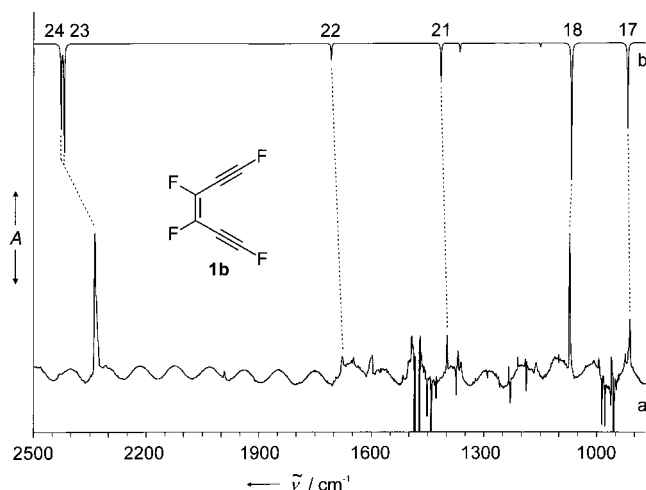


Figure 3. Photochemistry of diradical **2b**. a) Difference spectrum. Bands pointing upwards appear upon broad band irradiation (260–320 nm) of the products formed by 254 nm irradiation (3 h) of **3b** in solid neon at 3 K. Bands marked with dotted lines are assigned to enediyne **1b**. b) Calculated IR spectrum (B3LYP/6-311++G(d,p), unscaled) of **1b**.

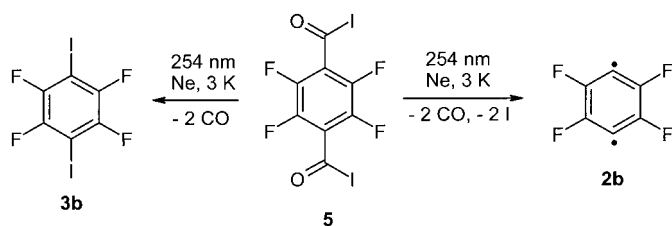
Table 2. IR spectroscopic data of 1,3,4,6-tetrafluorohex-3-ene-1,5-diyne (**1b**).

Mode	Symmetry	$\tilde{\nu}_{\text{exp}}^{[a]}$ [cm ⁻¹]	$I_{\text{rel,exp}}^{[b]}$	$\tilde{\nu}_{\text{calcd}}^{[c]}$ [cm ⁻¹]	$I_{\text{rel,calcd}}$
14	a ₁	—	—	576.3	0.01
15	b ₂	—	—	591.4	0.00
16	a ₂	—	—	680.0	0.00
17	b ₂	912.5	0.32	918.3	0.62
18	a ₁	1072.1	0.98	1067.3	1.00
19	b ₂	—	—	1150.6	0.03
20	a ₁	—	—	1363.0	0.07
21	b ₂	1398.5	0.25	1414.1	0.28
22	a ₁	1678.0	0.09	1707.0	0.13
23	a ₁	2337.3	1.00	2418.6	0.79
24	b ₂	—	—	2426.5	0.61

[a] Neon, 3 K. [b] Relative intensities based on the strongest absorption. [c] Calculated at the B3LYP/6-311++G(d,p)^[29] level of theory. Band positions are unscaled. The assignment is tentative and is based on band positions and intensities.

2b. Thus, our experiments find that the UV irradiation of **3b** in neon at 3 K results in the stepwise loss of two iodine atoms to give **2b**, which at slightly longer wavelength irradiation ring-opens to **1b**.

p-Benzyne **2b** could be independently generated by irradiation (254 nm, neon, 3 K) of 2,3,5,6-tetrafluoroterephthaloyl diiodide (**5**). The photochemistry of the diiodide is quite complex, and it is not clear, whether **2b** is directly formed from **5** or the photodecarbonylation first yields **3b**, which in subsequent photochemical steps loses iodine atoms to give **4** and **2b**.



The assignment of **2b** was confirmed by (8/8)CASSCF calculations, which nicely reproduce the experimental IR spectrum (Figure 2, Table 3). The only major deviation is the splitting of the very strong b_{2u} symmetrical v(C–F) stretching vibration into two components at 1516 and 1502 cm⁻¹ in the experimental spectrum.

Table 3. IR spectroscopic data of singlet 1,4-didehydro-2,3,5,6-tetrafluorobenzene (**2b**).

Mode	Symmetry	$\tilde{\nu}_{\text{exp}}^{[a]}$ [cm ⁻¹]	$I_{\text{rel,exp}}^{[b]}$	$\tilde{\nu}_{\text{calcd}}^{[c]}$ [cm ⁻¹]	$I_{\text{rel,calcd}}$
14	b _{1u}	—	—	677	0.04
15	a _g	—	—	690	0.00
16	b _{2u}	924.6	0.59	911	0.28
17	b _{3g}	—	—	1148	0.00
18	b _{1u}	1117.3	0.44	1151	0.26
19	b _{2u}	—	—	1154	0.03
20	a _g	—	—	1360	0.00
21	b _{1u}	1406.6	0.37	1421	0.15
22	b _{2u}	1501.7	0.5	1499	1.00
		1516.1	0.5		
23	a _g	—	—	1560	0.00
24	b _{3g}	—	—	1610	0.00

[a] Neon, 3 K. [b] Relative intensities based on the sum of the components of the strongest absorption (mode 22). [c] Calculated at the CASSCF(8,8)/cc-pVDZ level of theory. Band positions are scaled by a factor of 0.91. The assignment is tentative and is based on band positions and intensities.

UB3LYP/6-311++G(d,p) DFT calculations predict a near degeneracy of the lowest lying triplet and singlet states of **2b**, as do (8/8)CASSCF and CASPT2/cc-pVDZ ab initio calculations. The singlet is computed to be the ground state with $\Delta E_{\text{ST}} = -0.1$, -1.5 , and -0.5 kcal mol⁻¹, respectively, at these levels of theory. The singlet ground state found for unsubstituted *p*-benzyne (**2a**)^[14] results from the through-bond stabilization of the molecular orbital (MO), formed from the antisymmetrical combination of the nonbonding atomic orbitals (AOs), relative to the MO formed from the symmetrical combination.^[26] However, the fluorine substituents in **2b** stabilize the MO formed from the symmetrical combination of the nonbonding AOs more than the MO formed from the antisymmetrical combination. Consequently, these two nonbonding MOs are much closer to being degenerate in fluorocarbon **2b** than in hydrocarbon **2a**, and this results in the magnitude of ΔE_{ST} being predicted to be considerably smaller in **2b** than in **2a**.

Since the calculated IR spectra for the singlet and triplet states of **2b** are virtually identical at both the UB3LYP and CASSCF levels of theory, we are not able to determine the ground state multiplicity from the IR data. Experimental identification of the ground state of **2b** will have to await our developing the capability to obtain EPR spectra at 3 K in neon matrices.

Experimental Section

Matrix isolation experiments were performed by standard techniques with a Sumitomo Heavy Industries RDK-408D closed-cycle refrigerator. Matrices were produced by co-deposition of a large excess of neon (Messer-Griesheim, 99.9999%) and the trapped species on a cold CsI window. Argon matrices for EPR spectroscopy were deposited on a sapphire rod at 15 K. Infrared spectra were recorded with a Bruker Equinox 55 FTIR spectrometer with a standard resolution of 0.5 cm⁻¹ in the range of 400–4000 cm⁻¹. EPR spectra were measured with a Bruker Elexsys E500 spectrometer. Irradiations were carried out with a Grätzel

low-pressure mercury lamp (254 nm) and an Osram HBO 500 W/2 high-pressure mercury arc lamp in an Oriel housing with quartz optics and a dichroic mirror (260–320 nm). 1,4-Diiodotetrafluorobenzene was purchased from Aldrich and used as supplied. DFT and CASSCF calculations were performed with the Gaussian98 suite of programs.^[27] CASPT2 calculations were carried out with MOLCAS.^[28]

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Terminal Borylene Complexes as a Source for the Borylene B–N(SiMe₃)₂: Alternative Synthesis and Structure of [(OC)₅Cr=B=N(SiMe₃)₂]**

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The generation of hypovalent borylenes B–R—the boron analogues to carbenes CR₂—usually requires drastic conditions: the classical method involves the reduction of boron trihalides at temperatures above 2000 °C,^[1] and alternatively, the silylborylene B–SiPh₃ can be obtained photochemically at –196 °C from RB(SiPh₃)₂ (R = Me, 2,4,6-Me₃C₆H₂ (Mes)) in hydrocarbon matrices.^[2] The reductive^[3] or photochemical^[4] generation of species B–R in condensed phase might be assumed from the nature of the corresponding trapping products. There is, however, no direct proof for the intermediacy of borylenes—in particular, the MeBBr₂/2C₈K system as a source for B–Me appears questionable.^[5]

Already in 1973 borylene complexes were recognised to be a potentially useful source for borylenes in cases where gaseous species cannot be used.^[1b] Since 1995 we have reported on both bridged^[6] and terminal^[7] borylene complexes of the type [L_xM–B(R)–ML_x] and [L_xM=BR], respectively, thus demonstrating the possibility of stabilizing borylenes B–R in the coordination sphere of a transition metal. Related species, however, showing boron in higher coordination number were also reported recently.^[8] As the synthesis of borylene complexes is mainly restricted to salt elimination reactions,^[6, 7, 8b] we began to investigate compounds of the type [L_xM=BR] as possible sources for B–R with borylene transfer reactions between different metal centers to provide an alternative synthetic route for this novel class of compounds.

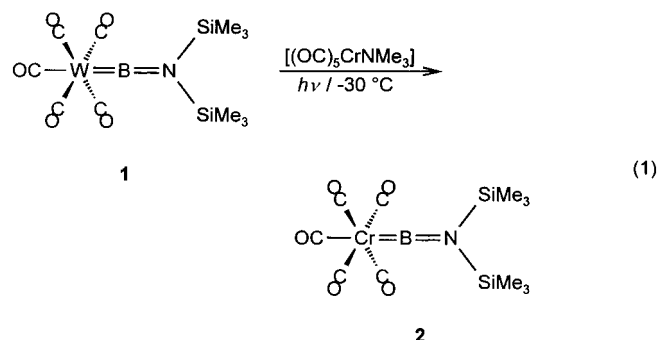
In an initial experiment the photochemically induced transfer of the aminoborylene BN(SiMe₃)₂ from [(OC)₅W=B=N(SiMe₃)₂] (**1**)^[7] to [Cr(CO)₆] was investigated, since the expected chromium–borylene complex [(OC)₅Cr=B=N(SiMe₃)₂] (**2**) was already obtained by a different method and known to be stable under the chosen conditions.^[7] Compound **1** was irradiated at –30 °C in toluene in the presence of three equivalents of [Cr(CO)₆]. After 12 h

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the ^{11}B NMR spectrum of the reaction mixture showed two signals at $\delta = 86.6$ (**1**) and 92.3 (**2**) in a 1:1 ratio, thus indicating the formation of **2** in 50 % yield. Longer irradiation times gave no significant change in the ^{11}B NMR spectrum—a more complete transfer was evidently hampered by the poor solubility of $[\text{Cr}(\text{CO})_6]$ in toluene at -30°C . NMR-spectroscopic studies on corresponding reactions in THF indicated no intermetallic borylene transfer, which may be attributed to insertion of the borylene into the C–O bond of THF.^[2] Photolysis of **1** with a 1.5-fold excess of the more soluble $(\text{OC})_5\text{CrNMe}_3$ in toluene at -30°C for 12 h, however, afforded **2** almost quantitatively according to Equation (1) (>95 % according to the ^{11}B NMR spectrum).



The structure of **2** in solution was confirmed by IR and NMR spectroscopic data, which matched those of an independently prepared sample.^[7] Because there are no structural data for boryl- or borylene complexes of chromium, an X-ray structure analysis of **2** was carried out (Figure 1).^[9] The

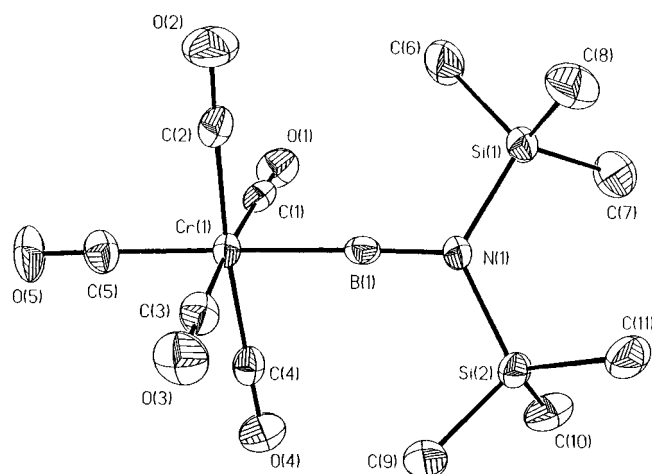
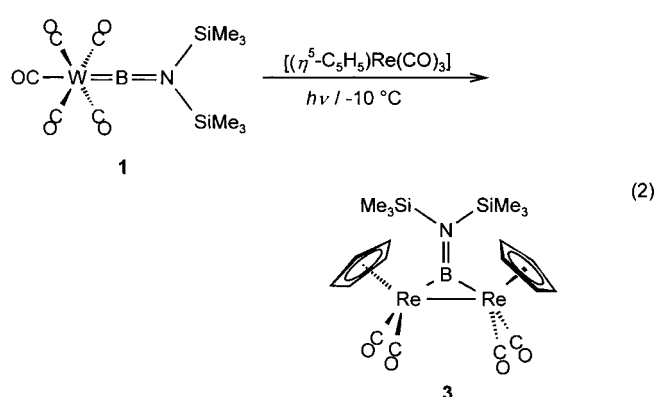


Figure 1. Structure of **2** in the crystal. Selected distances [Å] and angle [°]: Cr–B 1.996(6), B–N 1.353(6); Cr–B–N 177.4(4).

compound crystallizes in the space group $P\bar{1}$, and the molecule adopts C_1 symmetry in the crystal. Similar to the W–B–N moiety of the tungsten analogue **1**, the central Cr–B–N moiety is arranged almost linearly (Cr–B–N 177.4(4)°), the Si1–Si2–B plane is twisted by 38° with respect to the C4–C5–C2 plane, and the B–N distance of 135.3(6) pm is in the expected range for a B–N double bond between a three-coordinate

nitrogen and a two-coordinate boron atom.^[7, 10] The Cr–B distance of 199.6(6) pm is thus 15.5 pm shorter than the corresponding W–B distance in **1**. The close resemblance of the spectroscopic and structural data of **1** and **2** corroborate the description of the Cr–B double bond in terms of a strong boron-to-metal σ -donation and weaker π -backbonding^[7]—a bonding situation which was predicted on the basis of ab initio calculations of the parent complex $[(\text{OC})_5\text{Cr}=\text{B}=\text{NH}_2]$.^[11] Very recent theoretical studies on terminal borylene complexes, though, pointed out that the sum of the covalent metal–boron interactions only gives a bond order of less than one and that the nature of the M–BR bond is mainly ionic.^[12]

To exploit further the intermetallic borylene transfer we treated **1** with $[(\eta^5\text{-C}_5\text{H}_5)\text{Re}(\text{CO})_3]$ under similar conditions. Although manganese complexes of the type $[(\mu\text{-BNR}_2)-\{(\eta^5\text{-C}_5\text{H}_5)\text{Mn}(\text{CO})_2\}_2]$ (R = Me and various other substituents) were afforded by salt elimination reactions,^[6a, b, f] the corresponding rhenium complexes were not obtained.^[13] After irradiation of **1** with $[(\eta^5\text{-C}_5\text{H}_5)\text{Re}(\text{CO})_3]$ for four days at -10°C in toluene, the ^{11}B NMR spectrum showed two signals in a 3:2 ratio at $\delta = 86.6$ and 100.4, respectively, the latter indicating the formation of $[(\mu\text{-BN}(\text{SiMe}_3)_2)-\{(\eta^5\text{-C}_5\text{H}_5)\text{Re}(\text{CO})_2\}_2]$ (**3**) according to Equation (2). Although photolysis for another 24 h did not significantly



change the ratio of **1** and **3** in the ^{11}B NMR spectrum, it was possible to isolate the new rhenium borylene complex as yellow crystals in approximately 20 % yield together with some amount of the unreacted starting material **1**. The constitution of **3**, the first rhenium–borylene complex, was unambiguously deduced from multinuclear NMR spectroscopy and mass spectrometry.

So far, all investigations have shown that the photochemical activation of the borylene complex initiates the observed borylene transfer. Various compounds of the type $[(\text{OC})_5\text{CrL}]$ (L = NMe₃, THF) underwent no reaction with **1** at ambient temperature without irradiation. Further attempts have also been made to thermally induce the borylene transfer between **1** and $(\text{OC})_5\text{CrNMe}_3$ by heating both compounds in toluene to 60 °C. ^{11}B NMR spectra of this mixture after one day indicated the formation of **2**, however, only in small amounts together with further boron-containing species.

Experimental Section

2: A solution of $[(OC)_5CrNMe_3]^{[14]}$ (0.90 g, 3.60 mmol) and **1** (1.19 g, 2.40 mmol) in toluene (100 mL) was irradiated with a high-pressure Hg lamp (Hereaus TQ 150) at $-30^\circ C$ for 12 h. The reaction mixture was warmed to ambient temperature, and all volatile materials were removed under high vacuum (0.001 Torr). The brown residue was treated with hexane (50 mL) and the resulting slurry was filtered. The small amount of the remaining dark brown residue was washed with hexane (10 mL). The combined filtrates were concentrated under vacuum to 20 mL and stored at $-80^\circ C$. After 48 h, **2** (0.31 g, 0.85 mmol, 35.5%) was obtained as light brown crystals. All NMR spectra were recorded in $[D_6]benzene$ at $25^\circ C$. ^1H NMR (500 MHz, TMS): $\delta = 0.14$ (s; $SiMe_3$); ^{11}B NMR (160 MHz, $Et_2O \cdot BF_3$): $\delta = 92.3$; ^{13}C NMR (126 MHz, TMS): $\delta = 2.6$ ($SiMe_3$), 217.6 (CO_{eq}), 218.0 (CO_{ax}); IR (toluene): $\tilde{\nu} = 2064$ (w), 1981 (m), 1942 (vs) cm^{-1} (CO); elemental analysis (%) calcd for $C_{11}H_{18}CrNBO_5Si_2$: C 36.37, H 5.00, N 3.86; found: C 35.47, H 5.10, N 3.72.

3: A solution of $[(\eta^5-C_5H_5)Re(CO)_3]$ (0.68 g, 2.02 mmol) and **1** (0.50 g, 1.01 mmol) in hexane (100 mL) was irradiated at $-10^\circ C$ for five days. The reaction mixture was warmed to ambient temperature and all volatile materials were removed under high vacuum (0.001 Torr). The remaining unconverted $[(\eta^5-C_5H_5)Re(CO)_3]$ was removed by sublimation ($50^\circ C$, 0.001 Torr). The brown residue was treated with hexane (40 mL), filtered, and concentrated under vacuum to 15 mL. After storage at $-80^\circ C$ for 48 h, a mixture of **3** and the unconverted starting material **1** was obtained. This crystalline material was redissolved in hexane (10 mL) and stored at $-80^\circ C$ for another 48 h. Pure **3** (0.15 g, 0.19 mmol, 18.9%) was obtained as light yellow crystals. All NMR spectra were recorded in $[D_6]benzene$ at $25^\circ C$. ^1H NMR (500 MHz, TMS): $\delta = 0.35$ (s, 18H; $SiMe_3$), 4.88 (s, 10H; C_5H_5); ^{11}B NMR (160 MHz, $Et_2O \cdot BF_3$): $\delta = 100.4$; ^{13}C NMR (126 MHz, TMS): $\delta = 3.7$ ($SiMe_3$), 86.7 (C_5H_5), 203.5 (CO); MS (eV): m/z (%): 785 (22.7) [M^+], 729 (2.9) [$M^+ - 2CO$], 73 (43.3) [$SiMe_3$].

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The $[(\eta-C_6H_5Me)NbSn_6Nb(\eta-C_6H_5Me)]^{2-}$ Ion: A Complex Containing a Metal-Stabilized Sn_6^{12-} Cyclohexane-Like Zintl Ion**

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Homoatomic tin Zintl ions isolated from solution include the *nido*- Sn_6^{4-} ion,^[1,2] the *nido/closo*- Sn_9^{3-} ion,^[3] and the *closo*- Sn_5^{2-} ion.^[4] Metal-stabilized Zintl ions include the *closo*- Sn_6^{2-} ion^[5] in $[Sn_6\{Cr(CO)_5\}_6]^{2-}$ and *closo*- $Li_2Sn_8^{4-}$.^[6] These structures are characterized by electron-deficient boron hydride like cluster bonding described by Wades rules.^[7] Related Ge and Pb Zintl ions also adopt *closo*- and *nido*-structures that are occasionally linked to form dimers or polymers.^[8,9] Although the *intercluster* connections in the linked polyhedra are frequently two-center, two-electron bonds ($2c-2e$), the *intracluster* bonding is always electron deficient.

In contrast, the Group 15 polypnictide Zintl ions are characterized by $2c-2e$ bonds in which structures are directly related to cyclic hydrocarbons.^[10,11] For the polypnictides, conversion of hydrocarbon-like structures into electron-deficient boron hydride like structures can be accomplished by adding vertexes to the clusters that do not contribute electrons to cluster bonding. One such transformation involves the conversion of the nortricyclane-like Sb_7^{3-} cluster into the *nido*- $[Sb_7Ni_3(CO)_3]^{3-}$ complex through the addition of $Ni(CO)$ fragments.^[12] By comparison, conversion of the boron hydride like Group 14 Zintl ions into cyclic hydro-

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carbon type structures could, in theory, be achieved by adding extra electrons to the clusters. However, reductions of these anionic clusters are not experimentally feasible because of the unrealistically high charges necessary to reach the correct electron count. Alternatively, coordination of a metal fragment that formally donates its valence electrons to intra-cluster bonding could provide the necessary electrons while keeping the charge in a reasonable range. Herein we report the first such transformation in which a polystannide is converted into an unusual metal-stabilized cyclohexane-like Sn_6^{12-} Zintl ion in the complex $[(\eta\text{-C}_6\text{H}_5\text{Me})\text{NbSn}_6\text{Nb}(\eta\text{-C}_6\text{H}_5\text{Me})]^{2-}$.

$\text{Nb}(\eta\text{-C}_6\text{H}_5\text{Me})_2$ ^[13, 14] reacts with ethylenediamine (en) solutions of K_4Sn_9 in the presence of 2,2,2-cryptand to give low but reproducible yields of $[(\eta\text{-C}_6\text{H}_5\text{Me})\text{NbSn}_6\text{Nb}(\eta\text{-C}_6\text{H}_5\text{Me})]^{2-}$ (**1**) as the $[\text{K}(2,2,2\text{-crypt})]^+$ salt. The crystalline solid is dark brown, air sensitive, and sparingly soluble or insoluble in most solvents (en, DMF, THF, DMSO, toluene). The salt has been characterized by single-crystal X-ray diffraction, IR and ^{119}Sn NMR spectroscopy, and elemental analysis.

Crystals of $[\text{K}(2,2,2\text{-crypt})]_2[(\eta\text{-C}_6\text{H}_5\text{Me})\text{NbSn}_6\text{Nb}(\eta\text{-C}_6\text{H}_5\text{Me})] \cdot \text{en}$ are triclinic, space group $P\bar{1}$, with the anion (**1**) located on the inversion center.^[15] The structure of **1** (Figure 1) contains a six-membered ring of tin atoms in a chair

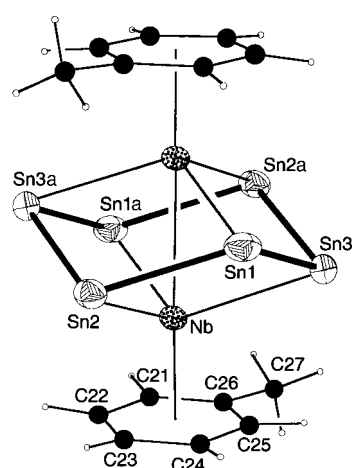


Figure 1. ORTEP plot of **1**. Selected bond lengths [Å] and angles [°]: Sn1–Sn2 2.8355(4), Sn1–Sn3 2.8348(4), Sn2–Sn3a 2.8421(4), Nb–Sn1a 2.8517(4), Nb–Sn2 2.8433(4), Nb–Sn3 2.8484(4), Nb–Nb 3.0049(6), Nb–C 2.399(4)–2.446(4); Sn2–Nb–Sn1a 107.71(1), Sn1a–Nb–Sn3 108.31(1), Sn3–Nb–Sn2 107.71(1), Sn1–Sn2–Sn3a 109.52(1), Sn3–Sn1–Sn2 108.31(1), Sn1–Sn3–Sn2a 108.22(1). The bold lines emphasize the chair cyclohexane structure of the Sn_6 unit and do not imply relative bond strengths.

cyclohexane conformation. The anion has $\bar{1}$ crystallographic symmetry but virtual D_{3d} point symmetry in solution (ignoring the Me groups). The tin–tin contacts in the ring (2.8348(4)–2.8421(4) Å) are significantly shorter than those in other Zintl ions (e.g. Sn_9^{4-} , $d_{\text{Sn–Sn}} = 2.93\text{–}3.31$ Å,^[1, 2] Sn_5^{2-} , $d_{\text{Sn–Sn}} = 2.901, 3.128$ Å)^[4] and metallated Zintl ions (e.g. $[\text{Sn}_9\text{Cr}(\text{CO})_3]^{4-}$, $d_{\text{Sn–Sn}} = 2.97\text{–}3.31$ Å,^[16] $[\text{Sn}_6\{\text{Cr}(\text{CO})_5\}_6]^{2-}$, $d_{\text{Sn–Sn}} = 2.93\text{–}2.96$ Å).^[5] The Sn_6 ring in **1** ligates to two $(\eta\text{-C}_6\text{H}_5\text{Me})\text{Nb}$ groups in an η^3, η^3 fashion. In bonding to the tin centers the

niobium atoms adopt a familiar three-legged piano stool geometry^[17] with Nb–Sn bonds ranging from 2.8433(4)–2.8517(4) Å. These contacts are similar to other Nb–Sn bonds in alkylstannane complexes such as $[\{\text{Nb}(\text{Cp})_2(\text{SnMe}_3)_2(\mu\text{-O})\}]$ where Nb–Sn = 2.8619 Å.^[18] The η^6 toluene ligands are bound in a slightly asymmetric fashion with Nb–C contacts in the range 2.399(4)–2.446(4) Å [2.42(2) Å (av)]. The Nb–C26 bond is 0.02 Å longer than the others but all are statistically longer than the Nb–C bonds in other structurally characterized $(\eta\text{-C}_6\text{H}_5\text{Me})\text{Nb}$ containing compounds. For comparison, the Nb–C bonds in the parent compound $[\text{Nb}(\eta\text{-C}_6\text{H}_5\text{Me})_2]$ average 2.334(5) Å^[13] with other $(\eta\text{-C}_6\text{H}_5\text{Me})\text{Nb}$ compounds having Nb–C bonds in the range 2.305(5)–2.362(5) Å.^[13] In contrast, the C–C bonds in the toluene rings average 1.407(5) Å, which is statistically equivalent to those in other compounds.^[13] Attempts to monitor the degree of charge transfer into the toluene rings through infrared spectroscopic analysis of the C–C and C–H stretching modes was hindered by the strong, characteristic bands of the $[\text{K}(2,2,2\text{-crypt})]^+$ ion.

The $[\text{Nb}_2\text{Sn}_6]$ core of the structure can also be described as a distorted cube with the two Nb atoms at opposite corners. The cube is compressed along the Nb–Nb diagonal giving rise to a short niobium–niobium distance of 3.0049(6) Å compared with the long tin–tin diagonal of 5.38–5.45 Å. The Nb–Nb separation is consistent with a metal–metal single bond, which allows each Nb center to achieve an 18-electron configuration (see below).

For electron counting purposes, the structure can be viewed as an Sn_6^{12-} Zintl ion which requires fully oxidized Nb^{5+} centers. This formalism is similar to that used for the ME_8^{n-} ions where $\text{M} = \text{Nb}, \text{Mo}$; $\text{E} = \text{Sb}, \text{As}$; $n = 2, 3$.^[19–21] Experimentally, the ME_8^{n-} ions are prepared by insertion of zero-valent $\text{M}(\text{arene})_2$ precursors into polypnictide clusters. For electron counting, however, the structures are conveniently viewed as having fully oxidized metal centers (i.e. $\text{Nb}^{5+}, \text{Mo}^{6+}$) with E_8^{8-} rings. While these formalisms do not accurately represent true electronic distributions in the clusters,^[22] the S_8 crown-like structures of the E_8 rings are well described by this electron-transfer model. For **1**, the formalism is equally incorrect in describing the actual oxidation states, however, it accurately describes the bonding within the Sn_6 ring. The formal -12 charge is consistent with the cyclohexane-like structure and the short 2c–2e tin–tin bonds. For comparison, the *closo*- Sn_6^{2-} unit in $[\text{Sn}_6\{\text{Cr}(\text{CO})_5\}_6]^{2-}$ has significantly longer Sn–Sn bonds (2.93–2.96 Å)^[5] associated with 3c–2e bonding common to deltahedral clusters. The bond lengths of **1** ($d_{\text{Sn–Sn}} = 2.8348(4)\text{–}2.8421(4)$ Å) are more akin to those in the cyclic polystannanes^[23] with 2c–2e bonds ($d_{\text{Sn–Sn}} = 2.77\text{–}2.91$ Å) than those of the polyhedral Zintl ion clusters ($d_{\text{Sn–Sn}} = 2.90\text{–}3.31$ Å). Using the neutral atom formalism, the Nb ions in **1** can be viewed as 18-electron centers, whereby the Sn atoms are two-electron donors and the metal–metal bond is taken into consideration.

The ^{119}Sn NMR spectrum of **1** shows a single resonance signal at $\delta = -149$ with $^1J_{^{119}\text{Sn},^{117}\text{Sn}} = 1975$ Hz and $^{2,3}J_{^{119}\text{Sn},^{117}\text{Sn}} \approx 630$ Hz. Although the signal is of low resolution, a result of the very limited solubility of the ion, the chemical shift and, more importantly, the $^1J_{^{119}\text{Sn},^{117}\text{Sn}}$ coupling constants are also consistent with 2c–2e Sn–Sn interactions.^[23] For comparison, the

cyclohexastannanes, $(R_2Sn)_6$, show $^1J_{119Sn,117Sn}$ coupling in the range 462–1339 Hz,^[23] whereas the electron deficient borane-like Zintl ions display much smaller couplings (e.g. $nido-Sn_9^{4-}$, $^1J_{119Sn,117Sn} = 254$ Hz, $[L_2PtSn_9]^{4-}$, $^1J_{119Sn,117Sn} = 79$ Hz).

In the solid state, the stannides show a rich chemistry that spans valence compounds containing discrete Zintl ions, to intermetallic phases characterized by delocalized bonding and metallic behavior.^[24] Six-membered rings are found in several of these materials, including Li_3NaSn_4 (puckered 6-rings, chair conformation),^[25] $BaSn_5$ (planar 6-rings),^[26] and in α -tin itself. Each of these is derived from diamond or graphite related extended structures and does not contain isolated Zintl anions. Other compounds do contain isolated Zintl ions, such as the Sn_2^{6-} ion in $BaMg_2Sn_2$ with an ethane (or dihalogen) like structure and a short Sn–Sn bond of 2.87 Å.^[27] The number of tin Zintl ions isolated from solution methods is low and the prospects of preparing new ones are limited by the apparent stability of the $E_9^{3/4-}$ clusters and their derivatives. However, through the use of appropriate transition metal precursors, other metal-stabilized Zintl ions may be accessible through cluster degradation reactions and internal electron transfer.

Experimental Section

Preparation of $[K(2,2,2-crypt)]_2[(\eta-C_6H_5Me)NbSn_6Nb(\eta-C_6H_5Me)] \cdot en$. All reactions were performed in a nitrogen atmosphere dry box (Vacuum Atmospheres Company). In vial 1, K_4Sn_9 (50.0 mg, 0.041 mmol) and 2,2,2-crypt (46 mg, 0.12 mmol) were dissolved in en (ca. 3 mL). In vial 2, $Nb(\eta-C_6H_5Me)_2$ (11.3 mg, 0.041 mmol) was dissolved in toluene (ca. 1 mL) producing a red solution. The content of vial 2 was added to the vial 1 yielding a green-brown solution. The reaction mixture was stirred for 12 h and filtered through tightly packed glass wool in a pipette. Dark brown crystals formed in the reaction vessel after one week. Yield: 12 mg (15%); NMR analysis of the reaction mixtures showed free toluene (^1H and ^{13}C NMR) as the only by-product of the reaction; ^{119}Sn NMR (186.5 MHz (en/toluene), 25 °C): $\delta = -149$; elemental analysis calcd (%) for $C_{52}H_{36}K_2N_6Nb_2Sn_6O_{12}$: C 31.64, H 4.87, N 4.26%; found: C 30.53, H 5.00, N 4.33.

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Inversion of Enantioselectivity during the Platinum-Catalyzed Hydrogenation of an Activated Ketone**

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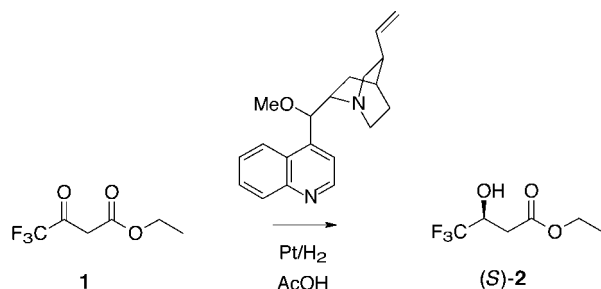
In the past few years there has been a remarkable progress in the enantioselective hydrogenation of α -functionalized (activated) ketones over chirally modified Pt catalysts. This development is reflected by the growing number of reactions in which enantiomeric excesses (*ee*) of 90% or higher have been achieved. Even more promising is the shift from the early “trial-and-error” strategy to a more rational basis for designing new modifiers and discovering new applications through mechanistic investigations.^[1–6] Several mechanistic

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models have been suggested for rationalizing the observed enantiodifferentiation.^[4–9] In one point all these models conform: the chiral modifier interacts on the Pt surface with the carbonyl group of the reactant. Other equilibrated species such as the enol form,^[10] or the hemiketal in alcoholic solvents,^[11] are considered as spectator species. Herein we show the first striking evidence against the general applicability of this assumption.

We have recently reported the facile hydrogenation of ethyl 4,4,4-trifluoroacetoacetate **1** in AcOH and in the presence of *O*-methylcinchonidine (MeOCD) as chiral modifier to afford β -hydroxyester **2** in 90% *ee* (Scheme 1).^[12] Analysis of the



Scheme 1. Hydrogenation of ethyl 4,4,4-trifluoroacetoacetate (**1**).

influence of reaction conditions revealed a significant variation of *ee* value with conversion in the presence of even trace amounts of water. This variation was enlarged by catalytic amounts of a strong acid. The hydrogenation of **1** in THF containing small amounts of water (0.8 vol%) and trifluoroacetic acid (TFA; molar ratio: TFA/MeOCD = 8:1) is a typical example (Figure 1). The *ee* value decreased gradually

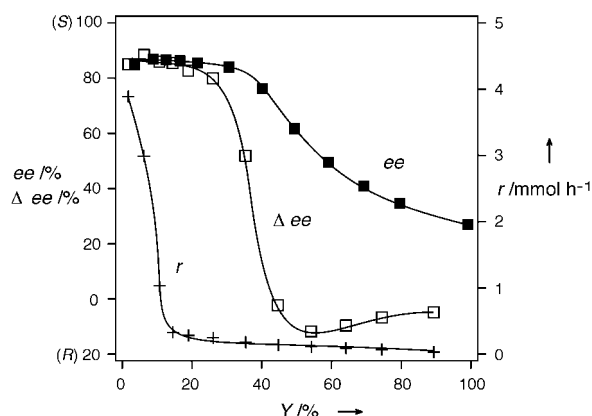
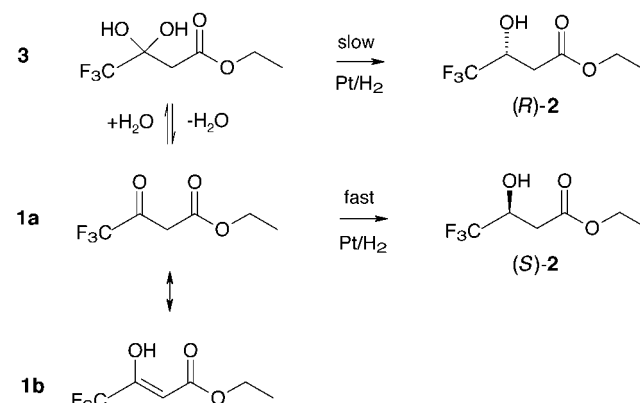


Figure 1. Changes in enantioselectivity and rate *r* during the course of the reaction (Y: yield). Standard reaction conditions (see Experimental Section) with preequilibration overnight; addition of TFA (10 μ L) directly before initiating hydrogenation.

after an initial constant period (87% (*S*)) and dropped at full conversion to only 27% (*S*). The calculated actual or incremental *ee* (Δee) value shows that the sense of enantio-differentiation inverted at around 50% yield (*Y*) and (*R*)-**2** became the dominant product. The highest Δee value in favor of (*R*)-**2** was 12%. To our knowledge, such an inversion has never been observed in the hydrogenation of any activated

ketone over chirally modified Pt. No racemization of the product could be detected under the described reaction conditions. Note also the dramatic decrease in reaction rate (by a factor of >100) with conversion. With increasing water content in the system the product distribution shifted towards the dominance of (*R*)-**2**. With double amount of water (1.6 vol%) the final, cumulative *ee* value shifted from 27% (*S*) to 4% (*R*).

Evidently, at least two reacting species, dominating at different stages of the reaction and providing excess to the opposite enantiomers, are needed to explain the conversion-dependent changes in rate *r* and *ee*. NMR spectroscopic analysis revealed the equilibration of **1** as keto (**1a**), enol (**1b**), and hydrate (**3**, at $\delta = -87.3$ in the ^{19}F spectrum) species (Scheme 2). In the $[\text{D}_8]\text{THF}$ used, only minor amounts of **3**



Scheme 2. Reaction scheme during hydrogenation of **1** in THF, in the presence of water.

(<5%) were detected, while the equilibrium was shifted towards **3** by addition of water. Rate of formation and equilibrium concentration of **3** under reaction conditions (0.8 vol% water) are shown in Figure 2. Though only

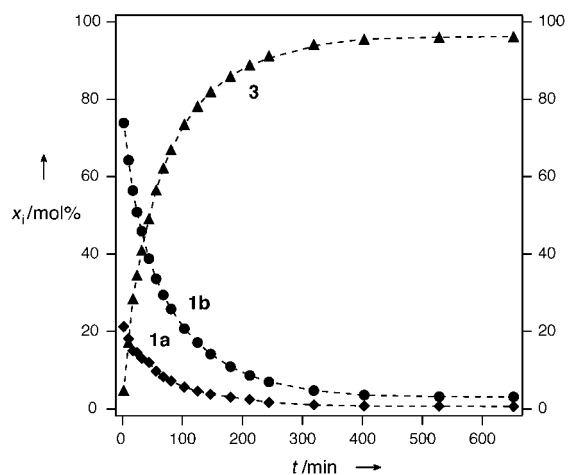


Figure 2. Hydrate (**3**) formation from **1** in THF; the equilibrium concentration x_i of component *i* in the mixture was determined by NMR spectroscopy. Concentrations according to general reaction conditions; the addition of 0.8 vol% water occurred at time $t = 0$ (water/**1** = 1.2).

1.2 molar equivalents of water was present, in equilibrium the fraction of **3** was 95% and only 0.5% **1a** remained. Equilibration was three times slower in the absence of MeOCD and 20 times faster in AcOH (acid–base catalysis). The ratio of **1a/1b** remained constant, indicating that the keto–enol equilibration was much faster than hydrate formation.

On the basis of the catalytic and NMR data the inversion of enantioselectivity may be explained as follows. Hydrogenation of **1a** is fast and affords up to 87% *ee* (*S*). To judge the reactivity of **1a**, we have to point out that this is a minor species compared to **1b** and **3**, still, its hydrogenation determines the enantioselectivity at low conversions. This assumption is in accordance with all mechanistic models suggested for the enantioselective hydrogenation of activated ketones on a cinchona-alkaloid-modified Pt surface.^[4–9] The high reactivity of the carbonyl group is partly due to the rate increase resulting from interaction with the chiral modifier MeOCD.^[12]

Despite the relatively high concentration of **1b** in solution, it is likely a spectator species. In AcOH, in which hydration is much faster than in THF, a small drop in the **1a/1b** ratio at the beginning of equilibration (monitored by NMR spectroscopy) indicates that the rate of interconversion between **1a** and **1b** is in the same range as the initial rate of hydration (>30 mmol h^{−1}) under these conditions. Because this rate is considerably higher than even the initial rate of hydrogenation of **1** (*r* = 4.3 mmol h^{−1}, Figure 1), we can deduce that the **1a/1b** ratio remains constant during hydrogenation, and the observed changes in *ee* values with conversion cannot be attributed to a shift from the hydrogenation of **1a** to **1b**.

We suggest that hydrogenolysis of **3** leading to (*R*)-**2** is responsible for the inversion of *ee* at higher conversions. There has been no evidence yet available in the literature on the hydrogenation of a geminal diol, but it is well established that hydrogenolysis of a C–OH bond is much slower than hydrogenation of a ketone, and the rate of hydrogenolysis is dramatically enhanced by acids.^[13] Our observations in Figure 1 may well be explained on this basis. In the early stage of the reaction the fraction of **1a** is high and hydrogenation of this reactive species governs the enantioselectivity. With increasing time and yield the ratio of **3/1a** strongly increases due to conversion of **1a** and to the proceeding equilibration to form **3** as the dominant species. At medium conversion, the hydrogenation of **3** affording (*R*)-**2** can compete with the hydrogenation of **1a** leading to (*S*)-**2**, and the product distribution is gradually shifted to the dominance of (*R*)-**2**.

The critical role of equilibration is demonstrated in Figure 3. When the hydrogenation is started without preequilibration (that is about 6 min after addition of water) the *ee* is high and almost constant in the initial period. In this region the hydrate concentration is low and hydrogenation of **1a** is almost exclusive. With increasing hydrate concentration the *ee* value gradually decreases. When the same reaction mixture is preequilibrated overnight, the initial *ee* value is lower (already significant hydrate concentration, hydrogenation of **1a** is dominant but not exclusive) and decreases from the beginning of the reaction.

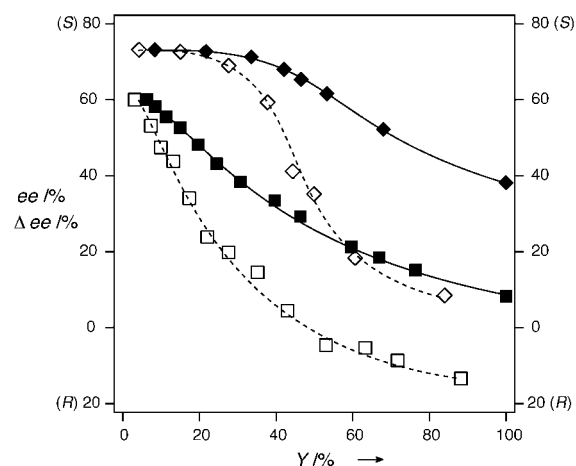
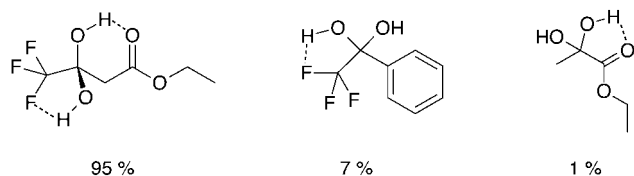


Figure 3. Influence of hydrate (**3**) formation on the conversion dependence of enantioselectivity, with (diamonds) and without preequilibration overnight (squares). Standard reaction conditions without TFA. Full symbols: cumulative (measured) *ee* values; open symbols: incremental (calcd) *ee* values.

To obtain unambiguous evidence for the hydrogenolysis of **3** over Pt, the experiment in Figure 3 (with preequilibration) has been repeated with a tenfold amount of water (8 vol %). In this mixture the molar ratio **3/1a** was 1975:1 as determined by NMR spectroscopy, and the initial (cumulative) *ee* value was 7% in favor of (*R*)-**2**. Evidently, hydrogenolysis of **3** over cinchona-alkaloid-modified Pt affords a small but significant *ee* value in favor of (*R*)-**2**, though the *ee* is diminished by the inevitable competition by the hydrogenation of **1a**. Interestingly, hydrogenation of all known activated ketones over Pt modified by cinchonidine or MeOCD afford the *R* enantiomer in excess.^[5] The only exception is the hydrogenation of **1**, where the *S* enantiomer forms in excess, indicating a substantially different reactant–modifier interaction in this reaction. Understanding the formation of the *R* enantiomer from the hydrate **3** may help in developing a feasible model for the enantiodifferentiation in the hydrogenation of **1**.

The role of TFA is rather complex. It protonates the chiral modifier leading to higher initial *ee* values (compare Figure 1 and 3). Furthermore, TFA accelerates the equilibration of **1a** and **3**, and the hydrogenolysis of **3** to (*R*)-**2**. To sum up, TFA enhances the striking effect of water in the reaction mixture but its presence is not a necessary requirement for achieving an inversion of enantioselectivity during hydrogenation of **1**.

The crucial requirement is the high stability, and thus the high actual concentration, of the hydrate relative to the keto form in order to compensate the much higher reactivity of the latter. NMR spectroscopic analysis indicated that under identical conditions (in the presence of 1.2 molar equivalents of water), the molar fraction of hydrate was 0.95, 0.07, and 0.01 in case of **1**, trifluoroacetophenone, and ethyl pyruvate, respectively (Scheme 3). Considerable hydration of **1** is attributed to the extra stabilization by a hydrogen bond involving one of the F atoms.^[14] We conclude that such a dramatic inversion of enantioselectivity as observed in the hydrogenation of **1** cannot be expected in general in the hydrogenation of activated ketones over cinchona-alkaloid-



Scheme 3. Possible structures and the equilibrium fractions of the hydrates formed from different activated ketones. Values were measured by NMR spectroscopy in $[D_8]THF$ containing 0.8 vol % water (water/reactant = 1.2:1).

modified Pt. Nevertheless, the frequently observed significant loss of *ee* with conversion of ethyl pyruvate in the best solvent AcOH (e.g. ref. [15]) may partly be attributed to the competing hydrogenolysis of the hydrate form, as this solvent generally has not been dried before use.

Experimental Section

Ethyl 4,4,4-trifluoroacetoacetate (**1**; Fluka, purum) was distilled before use, THF was dried over Na, and TFA was used as received. MeOCD was synthesized as described.^[16] The 5 wt % Pt/ Al_2O_3 catalyst (Engelhard 4759) was reduced in flowing hydrogen for 90 min at 400 °C before use.

The reactions were carried out at room temperature in an autoclave equipped with a 50 mL glass inlet and a PTFE cover. Prerduced catalyst (110 ± 3 mg) was added to a mixture of MeOCD (5.3 mg, 17.2 μ mol) and reactant (0.34 g, 1.85 mmol) in 5 mL solvent. Water (40 μ L; 0.8 vol %) was added either directly (6 min) or 15 h before the start of the reaction (preequilibration). Yields (*Y*) and *ee* values were determined by direct gas chromatographic analysis of the reaction mixture using diglyme as an internal standard. The incremental *ee* was calculated as $\Delta ee = (ee_1 Y_1 - ee_2 Y_2)/(Y_2 - Y_1)$, where *Y* indicates yield to **2**, and index 2 refers to a sample taken subsequent to sample 1. Compounds **1a**, **1b**, and **3** were identified by ^1H , ^{13}C , and ^{19}F NMR spectroscopy.^[17] Relative amounts of the different compounds were calculated by integration of the peak areas in the ^{19}F NMR spectra.

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The Mechanism of the $[Cp_2TiMe_2]$ -Catalyzed Intermolecular Hydroamination of Alkynes**

Frauke Pohlki and Sven Doye*

The addition of ammonia or primary and secondary amines to nonactivated alkenes and alkynes is a direct and efficient approach towards the synthesis of higher substituted nitrogen-containing products. Although this hydroamination reaction is extremely interesting for industrial applications, efforts to develop related processes have met with only limited success.^[1]

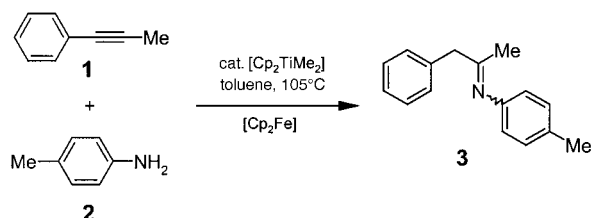
Inspired by the work of Bergman et al.^[2a,b] and Livinghouse et al.,^[2c–f] we recently reported that $[Cp_2TiMe_2]$ ^[3] is a very efficient catalyst for the intermolecular hydroamination of alkynes.^[4] By using $[Cp_2TiMe_2]$ as the catalyst, primary arylamines as well as sterically hindered *tert*-alkyl- and *sec*-alkylamines can be coupled to alkynes in high yields. However, hydroamination reactions employing sterically less hindered amines such as benzylamine or *n*-hexylamine are very slow and the corresponding products could only be isolated in poor yields. To explain the mentioned differences in the behavior of different amines and to understand the mechanistic details of the reaction a kinetic investigation was carried out.

Initial studies showed that the reaction between 1-phenylpropyne (**1**) and 4-methylaniline (**2**) is suitable for kinetic experiments (Scheme 1). In the presence of ferrocene as internal standard, the changes in the concentrations of **1**, **2**, and **3** (two isomers) could be determined by ^1H NMR spectroscopy.^[5] Representative plots of $c(\mathbf{1})c_0(\mathbf{1})^{-1}$ versus time *t* for different concentrations of $[Cp_2TiMe_2]$ are shown in Figure 1.

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Scheme 1. Kinetically investigated reaction of 1-phenylpropyne (**1**) and 4-methylaniline (**2**).

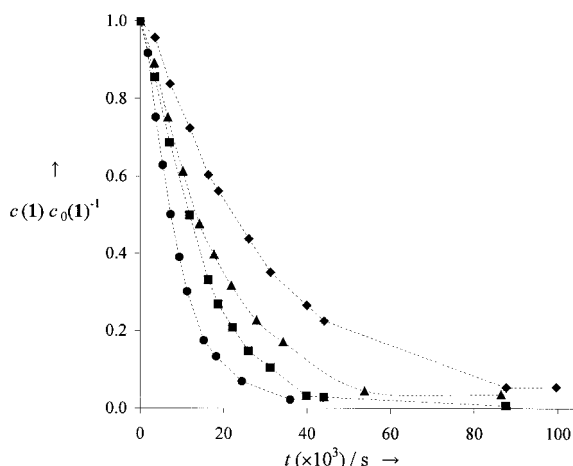


Figure 1. Representative plots of $c(\mathbf{1})c_0(\mathbf{1})^{-1}$ versus t for $[\text{Cp}_2\text{TiMe}_2]$ concentrations of 22.4 (●), 9.5 (■), 7.1 (▲), and 3.3 mol % (◆).

After a short induction period in which $[\text{Cp}_2\text{TiMe}_2]$ is probably converted into the catalytically active species, all obtained plots showed a first-order disappearance of alkyne **1**. Plots of $-\ln[c(\mathbf{1})c_0(\mathbf{1})^{-1}]$ versus t gave straight lines for all employed catalyst concentrations indicating that the rate law in Equation (1) (v = reaction rate) describes the reaction in a correct manner.

$$v = -\frac{dc(\mathbf{1})}{dt} = k_{\text{obs}} c(\mathbf{1}) \quad (1)$$

The obtained data for k_{obs} for different concentrations of $[\text{Cp}_2\text{TiMe}_2]$ are summarized in Table 1 (entries 1–14). A plot of k_{obs} versus $c([\text{Cp}_2\text{TiMe}_2])$ (Figure 2) shows that the reaction is not first order in $[\text{Cp}_2\text{TiMe}_2]$.

In addition, the dependence of the amine concentration on the rate of the reaction was investigated by determining k_{obs} for different concentrations of amine **2**, while the $[\text{Cp}_2\text{TiMe}_2]$ concentration remained constant. The obtained data (Table 1, entries 7, 15–17) are presented graphically in Figure 3, which clearly shows k_{obs} is not independent from the concentration of amine **2**.^[6]

All mentioned observations can be explained by the complex mathematical relationship between k_{obs} , $c([\text{Cp}_2\text{TiMe}_2])$ and $c(\mathbf{2})$ shown in Equation (2)^[7] which is consistent with the catalytic cycle outlined in Scheme 2. Interestingly, this catalytic cycle includes a reversible dimerization of the catalytically active imido complex **4**^[8] and a reversible addition of **2** to **4**. The hydroamination of **1** takes place by a reversible [2+2] cycloaddition between **1** and **4**, a

Table 1. Determined rate constants k_{obs} at $105 \pm 0.1^\circ\text{C}$.

Entry	Catalyst	$x(\text{cat.})$ [mol %]	$c(\text{cat.})$ [mol L ⁻¹]	$c_0(\mathbf{1})$ [mol L ⁻¹]	$c(\mathbf{2})$ [mol L ⁻¹]	k_{obs} [s ⁻¹]
1	$[\text{Cp}_2\text{TiMe}_2]$	1.4	3.77×10^{-3}	0.278	2.54	8.14×10^{-6}
2	$[\text{Cp}_2\text{TiMe}_2]$	1.4	3.81×10^{-3}	0.270	2.50	1.50×10^{-5}
3	$[\text{Cp}_2\text{TiMe}_2]$	1.8	5.10×10^{-3}	0.278	2.48	9.65×10^{-6}
4	$[\text{Cp}_2\text{TiMe}_2]$	2.7	7.43×10^{-3}	0.272	2.53	3.23×10^{-5}
5	$[\text{Cp}_2\text{TiMe}_2]$	3.3	9.01×10^{-3}	0.272	2.56	3.44×10^{-5}
6	$[\text{Cp}_2\text{TiMe}_2]$	3.7	9.80×10^{-3}	0.267	2.57	4.46×10^{-5}
7	$[\text{Cp}_2\text{TiMe}_2]$	4.5	1.23×10^{-2}	0.276	2.66	5.21×10^{-5}
8	$[\text{Cp}_2\text{TiMe}_2]$	7.1	1.90×10^{-2}	0.269	2.50	5.84×10^{-5}
9	$[\text{Cp}_2\text{TiMe}_2]$	8.0	2.15×10^{-2}	0.270	2.50	6.91×10^{-5}
10	$[\text{Cp}_2\text{TiMe}_2]$	9.5	2.49×10^{-2}	0.263	2.58	8.73×10^{-5}
11	$[\text{Cp}_2\text{TiMe}_2]$	10.2	2.66×10^{-2}	0.261	2.53	8.68×10^{-5}
12	$[\text{Cp}_2\text{TiMe}_2]$	11.9	3.25×10^{-2}	0.257	2.55	8.72×10^{-5}
13	$[\text{Cp}_2\text{TiMe}_2]$	16.4	4.19×10^{-2}	0.256	2.54	9.49×10^{-5}
14	$[\text{Cp}_2\text{TiMe}_2]$	22.4	5.79×10^{-2}	0.259	2.72	1.18×10^{-4}
15	$[\text{Cp}_2\text{TiMe}_2]$	5.7	1.34×10^{-2}	0.237	1.28	4.32×10^{-5}
16	$[\text{Cp}_2\text{TiMe}_2]$	4.6	1.24×10^{-2}	0.270	3.22	5.73×10^{-5}
17	$[\text{Cp}_2\text{TiMe}_2]$	4.3	1.18×10^{-2}	0.272	3.87	5.71×10^{-5}
18	10	5.8	1.63×10^{-2}	0.279	2.51	3.93×10^{-5}
19	11	6.2	1.71×10^{-2}	0.275	2.52	6.70×10^{-5}

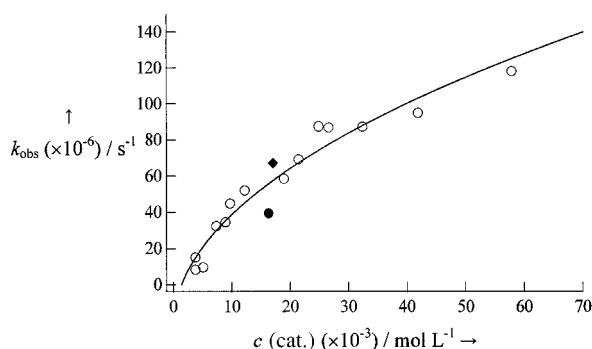


Figure 2. Plot of k_{obs} versus the $[\text{Cp}_2\text{TiMe}_2]$ concentration (○) with an additional fit-curve corresponding to Equation (3), as well as the k_{obs} data determined for **10** (●) and **11** (◆).

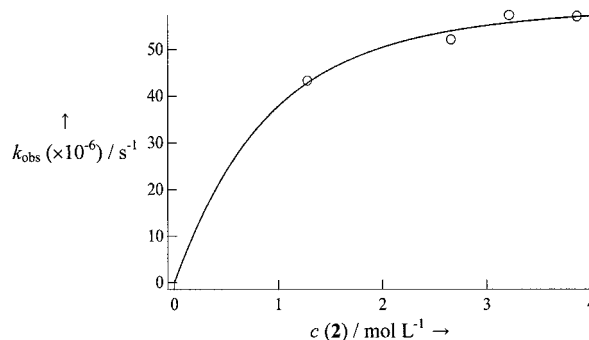
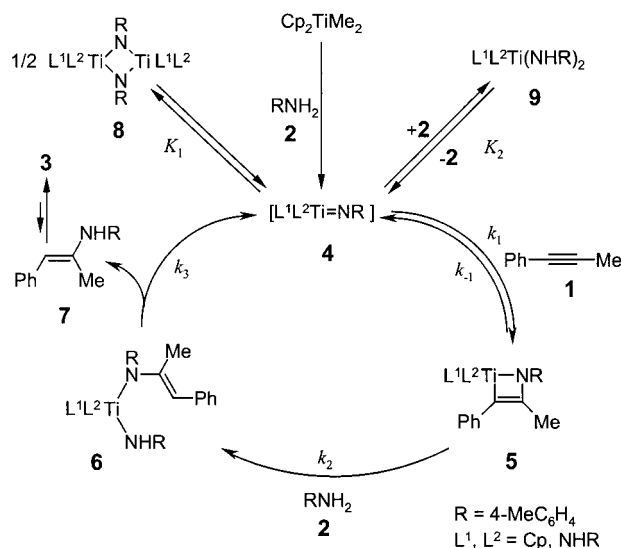


Figure 3. Plot of k_{obs} versus the concentration of amine **2** with an additional fit-curve corresponding to Equation (4).

protonation of the formed azametallacyclobutene **5**, and a final α -elimination of the product which regenerates **4**.

$$k_{\text{obs}} = -\frac{k_1 k_2 c(\mathbf{2}) [K_2 c(\mathbf{2}) + 1]}{4 K_1 [k_{-1} + k_2 c(\mathbf{2})]} + \sqrt{\left(\frac{k_1 k_2 c(\mathbf{2}) [K_2 c(\mathbf{2}) + 1]}{4 K_1 [k_{-1} + k_2 c(\mathbf{2})]} \right)^2 + \frac{k_1^2 k_2^2 c(\mathbf{2})^2}{2 K_1 [k_{-1} + k_2 c(\mathbf{2})]^2} c([\text{Cp}_2\text{TiMe}_2])} \quad (2)$$

with $K_1 = \frac{c(\mathbf{8})}{c(\mathbf{4})^2}$ and $K_2 = \frac{c(\mathbf{9})}{c(\mathbf{2})c(\mathbf{4})}$



Scheme 2. Mechanism of the $[\text{Cp}_2\text{TiMe}_2]$ -catalyzed hydroamination of 1-phenylpropyne (**1**) with 4-methylaniline (**2**).

First of all, Equation (2) predicts that large values for the equilibrium constants K_1 and K_2 result in small values for k_{obs} and therefore decreased reaction rates. Since K_1 and K_2 probably increase if sterically less demanding amines are used Equation (2) easily explains the poor reactivity of benzylamine and *n*-hexylamine observed in the past.^[4a]

Since the concentration of the amine **2** was kept constant during the investigation of the relationship between k_{obs} and $c([\text{Cp}_2\text{TiMe}_2])$, Equation (2) can be simplified to Equation (3). The additional parameter p_3 was introduced to consider a possible decomposition of the catalyst caused by trace amounts of water on the glassware.

$$k_{\text{obs}} = -p_1 + \sqrt{p_1^2 + p_2 c([\text{Cp}_2\text{TiMe}_2]) + p_3} \quad (3)$$

A fit-curve corresponding to Equation (3), which was calculated and plotted (program Igor-Pro (Version 4)) for the obtained data, demonstrates that this equation explains the relationship between k_{obs} and $c([\text{Cp}_2\text{TiMe}_2])$ in a correct way (Figure 2).^[9] In addition, for a constant concentration of $[\text{Cp}_2\text{TiMe}_2]$ Equation (2) can be simplified to Equation (4) if it is assumed that $K_2 c(\mathbf{2}) \gg 1$ and $k_{-1} \gg k_2 c(\mathbf{2})$; thus, Equation (4) describes the relationship between k_{obs} and $c(\mathbf{2})$.

$$k_{\text{obs}} = -p_4 c(\mathbf{2})^2 + \sqrt{p_4^2 c(\mathbf{2})^4 + p_5 c(\mathbf{2})^2} \quad (4)$$

In Figure 3 a fit-curve corresponding to Equation (4) is plotted for the obtained data for k_{obs} .^[10] It clearly shows that Equation (4) describes the relationship between k_{obs} and $c(\mathbf{2})$ in a correct way. The assumptions $K_2 c(\mathbf{2}) \gg 1$ and $k_{-1} \gg k_2 c(\mathbf{2})$, which were necessary to simplify Equation (2) to Equation (4), indicate that the equilibrium between the imido complex **4** and the bisamide **9** strongly favors the bisamide **9** and that the protonation of the azametallacyclobutene **5** is slow compared to the cycloreversion of **5**.

For a comparison of the catalytic activities of $[\text{Cp}_2\text{TiMe}_2]$ and the recently identified hydroamination catalysts

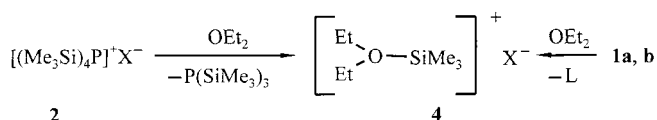
$[\text{Cp}^*\text{TiMe}_3]$ ^[11] (**10**) ($\text{Cp}^* = \text{C}_5\text{Me}_5$) and $[\text{CpTi}=\text{N}t\text{Bu}(\text{Cl})\text{Py}]$ (**11**),^[12] k_{obs} values were determined for these complexes (Table 1, entries 18, 19).^[13] It was found that at 105 °C **10** is slightly less active than $[\text{Cp}_2\text{TiMe}_2]$, while the catalytic activities of **11** and $[\text{Cp}_2\text{TiMe}_2]$ are almost the same (Figure 2). This similar catalytic activity suggests that under the reaction conditions the same catalytically active species is formed from $[\text{Cp}_2\text{TiMe}_2]$ and **11**.^[8] Since no induction period was observed for reactions employing **11** as the catalyst, this conversion seems to be faster for **11**.^[14] However, the obtained results for **10** and **11** undoubtedly show that other easily accessible titanium complexes also catalyze the hydroamination of alkynes.^[13]

In conclusion, the obtained kinetic data suggest that the mechanism of the $[\text{Cp}_2\text{TiMe}_2]$ -catalyzed intermolecular hydroamination of alkynes is correctly described by Scheme 2. It is important that a reversible equilibrium exists between the catalytically active species **4** and the dimer **8**. This equilibrium is responsible for the fact that no linear relationship between the catalyst concentration and the observed rate of the reaction exists. Furthermore, the kinetic data are consistent with the assumption that the protonation of the azatitanacyclobutene **5** is slow compared to the cycloreversion of **5**. These relationships are thus opposite to those established by Bergman et al. for the hydroamination of allenes.^[8b] In addition, the mechanism shown in Scheme 2 explains the fact that sterically demanding amines are better substrates for the $[\text{Cp}_2\text{TiMe}_2]$ -catalyzed hydroamination of alkynes than sterically less hindered amines because the equilibria between imido complex, imido complex dimer, and bisamide for sterically hindered amines favor a fast reaction. Furthermore, it was shown that mono-Cp- and Cp*-titanium complexes are also active hydroamination catalysts.

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- [6] In addition, experiments were carried out with a tenfold excess of alkyne **1**, and the concentration of amine **2** was monitored as a

spectrum ($I=3/2$, 100 %) from **3** in CD_2Cl_2 could also be obtained: the singlet at $\delta = -325.4$ (standard: KAsF_6) indicates a deshielding of the As atom by more than 500 ppm, which is unusually large for an arsonium ion. In contrast, the $\delta(^{75}\text{As})$ values of AsR_4^+ ions with $\text{R} = \text{alkyl}$ and phenyl are in the relatively narrow range from +206 to +258.^[7] As expected **2** shows a doublet at $\delta = 12.70$ in the ^{29}Si NMR spectrum, but with an unusually small coupling constant of $^1J(^{29}\text{Si}, ^{31}\text{P}) = 1.4$ Hz ($\text{P}(\text{SiMe}_3)_3$: $^1J(\text{Si}, \text{P}) = 27.5$ Hz). That there is no dissociation of SiMe_3^+ in CH_2Cl_2 was further demonstrated by the addition of $\text{P}(\text{SiMe}_3)_3$ and $\text{As}(\text{SiMe}_3)_3$ to solutions of **2** and **3**, respectively. The multinuclear NMR spectra of the resulting mixtures show the unchanged signals of $\text{E}(\text{SiMe}_3)_3$ and $\text{E}(\text{SiMe}_3)_4^+$ ($\text{E} = \text{P}, \text{As}$). In contrast, with the $\text{P}(\text{SnMe}_3)_4$ salts, a ready SnMe_3^+ exchange occurs in spite of the presence of triflate and $\text{B}(\text{C}_6\text{H}_5)_4$ ions as slightly and noncoordinating counterions, respectively;^[3] presumably this can be attributed to the weak $\text{Sn}-\text{P}$ bond and Me_3Sn^+ ions having a lower Lewis acidity than Me_3Si^+ ions. In agreement with this premise **2** and **3** react on addition of Et_2O readily to give the silyloxonium salt **4** and free $\text{E}(\text{SiMe}_3)_3$ ($\text{E} = \text{P}, \text{As}$). Whereas up to now the $\text{Et}_2(\text{Me}_3\text{Si})\text{O}^+$ ion could only be



identified in solution by means of ^{29}Si NMR spectroscopy at -30°C ,^[8] we could successfully isolate its room-temperature stable salt **4**, which is obtained in crystalline form through the equimolar reaction of **2** or **3** with Et_2O . However, compound **4** can be prepared more easily, and in crystalline form (87 %), from the direct solvation of **1a** with a mixture of Et_2O and C_6H_6 .

The crystal structure analyses of **2** and **3** show almost perfect tetrahedral coordination of the P and As centers to the Me_3Si groups (Figure 1).^[9] The average $\text{Si}-\text{P}$ bond length in **2**

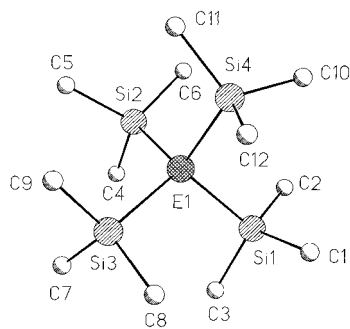


Figure 1. Molecular structure of the $[\text{E}(\text{SiMe}_3)_4]^+$ ions in the $[\text{B}(\text{C}_6\text{F}_5)_4]$ salts **2** ($\text{E} = \text{P}$) and **3** ($\text{E} = \text{As}$). Selected distances [$\text{\AA}$] and angles [$^\circ$] for $[\text{P}(\text{SiMe}_3)_4]^+$: P1-Si1 2.310(2), P1-Si2 2.290(2), P1-Si3 2.307(2), P1-Si4 2.294(2), Si1-C1 1.855(5), Si1-C2 1.851(5), Si1-C3 1.845(5); Si2-P1-Si3 109.65(8), Si2-P1-Si4 109.41(7), Si4-P1-Si3 111.06(7), Si2-P1-Si1 110.74(7), Si4-P1-Si1 108.65(7), Si3-P1-Si1 107.30(7). Selected distances [$\text{\AA}$] and angles [$^\circ$] for $[\text{As}(\text{SiMe}_3)_4]^+$: As1-Si1 2.379(3), As1-Si4 2.380(3), As1-Si3 2.388(3), As1-Si2 2.397(3); Si1-As1-Si4 108.8(1), Si1-As1-Si3 109.6(1), Si4-As1-Si3 109.4(1), Si1-As1-Si2 109.9(1), Si4-As1-Si2 110.0(1), Si3-As1-Si2 109.1(1).

(2.300(2) $\text{\AA}$) is only about 2 % longer than in $\text{P}(\text{SiMe}_3)_3$.^[10] The corresponding average $\text{Si}-\text{As}$ bond in **3** is 2.386(3) $\text{\AA}$ and is thus hardly longer than those in other silylarsanes.^[11] This result is in agreement with density functional calculations, that also predict a relatively small increase in the natural bond orbital (NBO) partial charges for the $\text{Si}-\text{E}$ bonds in persilylated onium complexes of phosphorous and arsenic.^[3, 12]

The crystal structure of **4**^[9] shows that the C_1 symmetric silyloxonium ion has a trigonal planar geometry (Figure 2) and the geometric parameters are in good agreement with the

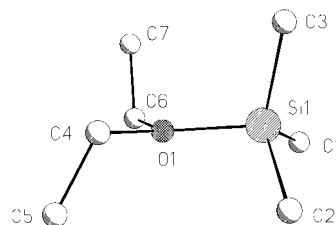
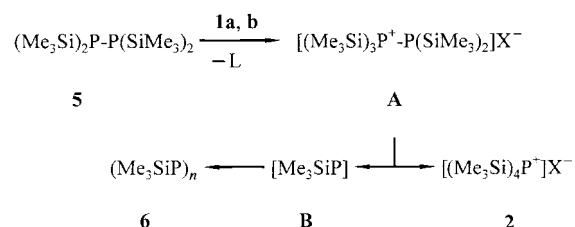


Figure 2. Molecular structure of the $[\text{Et}_2(\text{Me}_3\text{Si})\text{O}]^+$ ion in **4**. Selected distances [$\text{\AA}$] and angles [$^\circ$]: Si1-O1 1.777(3), Si1-C1 1.829(4), Si1-C2 1.836(4), Si1-C3 1.842(5), C4-O1 1.485(5), C6-O1 1.495(4); Si1-O1-C6 123.3(2), Si1-O1-C4 121.1(2), C4-O1-C6 114.2(3).

calculated values.^[13] The $\text{Si}-\text{O}$ bond (1.777(3) $\text{\AA}$) is about 9 % longer than that in $(\text{Me}_3\text{Si})_2\text{O}$ (1.63 $\text{\AA}$) and in silylalkyl ethers,^[14] but almost identical to the $\text{Si}-\text{O}$ bond in the $t\text{Bu}_3\text{SiOH}_2^+$ ion.^[15] The $\text{C}-\text{O}$ bonds (1.495(4) and 1.485(5) $\text{\AA}$) are indistinguishable from those in trialkyloxonium ions,^[16] and the $\text{C}-\text{O}-\text{C}$ angle at $114.2(3)^\circ$ is, as expected, smaller than the $\text{C}-\text{O}-\text{Si}$ angles (121.1(2) and 123.3(2) $^\circ$).

With unexpected ease the $\text{P}(\text{SiMe}_3)_4^+$ ion can also be obtained from the reaction of the diphosphane $\text{P}_2(\text{SiMe}_3)_4$ (**5**) with **1a, b** (Scheme 1). This reaction also produces the



Scheme 1.

insoluble yellow polymer **6**, which has a composition corresponding to $(\text{PSiMe}_3)_n$ but, as yet, could not be structurally characterized. Presumably the reaction proceeds via the intermediate **A**, from which the salt **2** and the carbene-like silylphosphandiyl **B** are formed through $\text{P}-\text{P}$ bond cleavage and a simultaneous silyl migration; **B** then polymerizes to **6**. Whether stable salts of the still unknown tetrasilylonium ions $\text{E}(\text{SiMe}_3)_4^+$ ($\text{E} = \text{N}, \text{Sb}, \text{Bi}$) can be obtained through analogous reactions with the homologous $\text{E}_2(\text{SiMe}_3)_4$ compounds of nitrogen, antimony, and bismuth remains to be seen.

Experimental Section

2: **1a** was formed in situ by dissolving the required equimolar amount of $[\text{Me}_3\text{Si}]^+[\text{B}(\text{C}_6\text{F}_5)_4]^-$ ^[6] in warm benzene (50 mL); $\text{P}(\text{SiMe}_3)_3$ (0.50 g, 2.00 mmol) was added at room temperature to such a solution of **1a**

(2.00 mmol), immediately a colorless solid precipitated, the solid was redissolved by addition of CH_2Cl_2 (2 mL) at around 40 °C. Colorless cubes were obtained by slowly cooling the solution to room temperature, yield: 1.74 g (1.74 mmol, 87 %). Alternatively **2** can be prepared by the reaction of **5** (0.16 g, 0.45 mmol) in toluene (10 mL) with **1a** (0.40 mmol) in toluene (50 mL) at 0 °C. The resulting yellow suspension was treated with CH_2Cl_2 (ca. 2 mL) heated to about 40 °C and the insoluble residues removed by filtration. At room temperature cubic crystals of **2** formed from the colorless filtrate, yield: 0.31 g (0.31 mmol, 67 %); ^1H NMR (CD_2Cl_2 , 250 MHz): δ = 0.64 (d, 36 H, $^3J(\text{H},\text{P})$ = 6.3 Hz, SiMe_3); ^{31}P NMR: δ = –200.1 (s); ^{29}Si NMR: δ = 12.70 (d, $^1J(^{29}\text{Si}, ^{31}\text{P})$ = 1.4 Hz); correct elemental analysis.

3: Analogous to the preparation of **2** a solution of **1a** (0.43 mmol) was treated with $\text{As}(\text{SiMe}_3)_3$ (0.13 g, 0.43 mmol) at room temperature. Immediately a colorless, amorphous precipitate was formed, which can be redissolved by the addition of CH_2Cl_2 (5 mL) at about 40 °C. Slowly cooling the solution to room temperature gave colorless needles of the product, yield: 0.35 g (0.33 mmol, 78 %); ^1H NMR (CD_2Cl_2 , 250 MHz): δ = 0.58 (s, SiMe_3); ^{29}Si NMR: δ = 12.79 (s); ^{75}As NMR (CD_2Cl_2 , KAsF_6 standard): δ = –325.4 (s); correct C,H analysis.

4: Analogous to the preparation of **2** a 1/9 mixture of diethyl ether/benzene (0.35 g) was added to a solution of **1a** (0.38 mmol). The resulting solid was recrystallized from CH_2Cl_2 (ca. 2 mL), yield 0.27 g (0.32 mmol, 83 %); ^{29}Si NMR (CD_2Cl_2): δ = 66.3 (s); correct C,H analysis.

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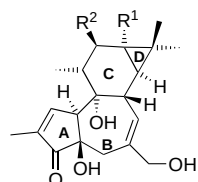
Diastereocontrol in the Synthesis of Models of Rings C and D of Phorbol: Directing Effect of an Ether Substituent on Lithium Carbenoid Mediated Cyclopropanation**

Michael G. B. Drew, Laurence M. Harwood,*
Antonio J. Macías-Sánchez, Richard Scott,
R. M. Thomas, and Daniel Uguen

Phorbol esters is a term used collectively to describe a family of structurally related, biologically active tetracyclic diterpenes.^[1] Phorbol (**1**), the parent compound of this class of diterpenes, was first isolated in 1934 by Bohm et al.^[2] as a hydrolysis product of *Croton tiglium* oil. Its core structure was elucidated by X-ray crystallography by Hecker and co-workers in 1967.^[3] Probably the most important physiological property of the phorbol esters is their capacity to act as tumor promoters;^[4] for example, tetradecanoyl phorbol acetate (TPA; **2**) is the most potent tumor promoter known to man, being active at levels of 0.02 μmol .^[5] The origin of such activity was identified in 1982 when Castagna et al.^[6] showed TPA (**2**) bound to the ubiquitous enzyme protein kinase C.

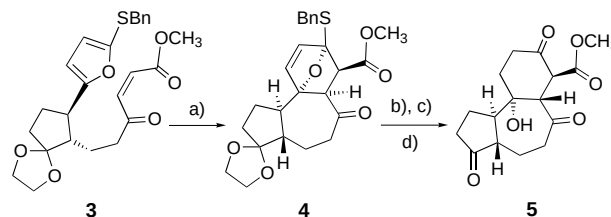
The complex polycyclic structure of phorbol, together with an intense interest in structure–activity relationship studies to map the basis of the tumor-promotion activity have fueled extensive efforts towards establishing efficient synthetic routes to phorbol (**1**) and its derivatives.^[7]

The approach adopted by our group has involved the intramolecular Diels–Alder reaction of **3**, which bears a furan system and a suitable dienophile fragment. In one step, we obtained the ABC tricyclic core **4**, which possessed strategically situated functionality for further elaboration.^[8] Additional transformations of the cycloadduct led to a β -ketoester functionality on ring C (compound **5**),^[9] which allows us to tackle the construction of the bicyclo[4.1.0]heptane moiety of rings C and D in phorbol (**1**; Scheme 1).



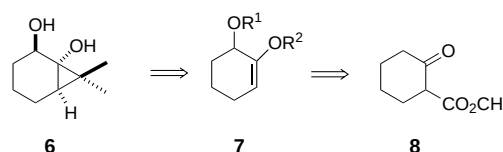
- 1** $R^1 = R^2 = \text{OH}$
2 $R^1 = \text{OCO}(\text{CH}_2)_{12}\text{CH}_3$
 $R^2 = \text{OAc}$

Herein we report the synthesis of 1*S*(*R*),2*R*(*S*)-dihydroxy-7,7-dimethyl-(6*R*(*S*))-bicyclo[4.1.0]heptane (**6**), as a model of rings C and D of phorbol (**1**), by means of a stereoselective cyclopropanation of an intermediate enol ether **7**, which in



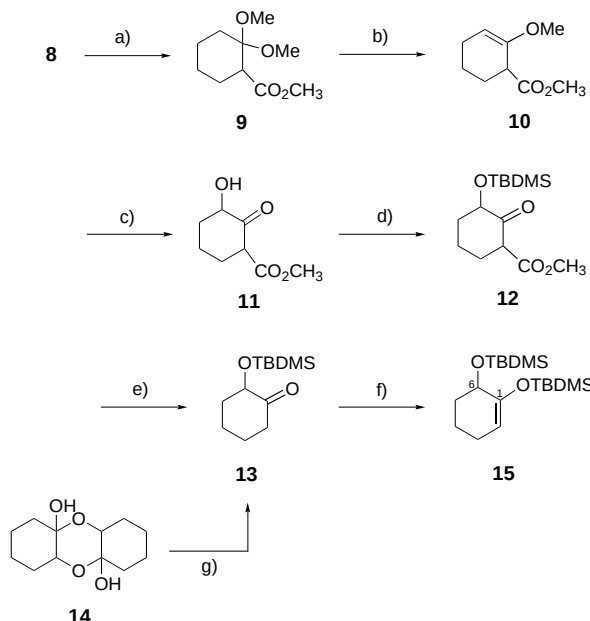
Scheme 1. Reagents and conditions: a) 1900 MPa, CH_2Cl_2 , 15 h, 65%; b) H_2 (1.5 MPa), EtOAc , Pd/BaSO_4 , 83%; c) NaOMe cat., MeOH , room temperature, 84%; d) HgCl_2 , aq. CH_3CN , 50 $^\circ\text{C}$, 8 days, 58%.

turn would be obtained from methyl 2-oxocyclohexanecarboxylate (**8**) (Scheme 2).



Scheme 2. Retrosynthetic analysis of the synthesis of model compound **6** from methyl 2-oxocyclohexanecarboxylate (**8**).

In the initial part of the study, β -ketoester **8** was treated with trimethyl orthoformate and 10-camphorsulfonic acid (10-CSA) in MeOH , and heated at reflux for 16 h to furnish the dimethyl acetal **9**. This compound was transformed into the methyl enol ether **10** under kinetic conditions by treatment of compound **9** with two equivalents of lithium diisopropylamide (LDA) in THF at $-40\text{ }^\circ\text{C}$ (Scheme 3).



Scheme 3. Synthesis of enol ether **15** from either β -ketoester **8** or adipoin (**14**). Reagents and conditions: a) $\text{HC}(\text{OMe})_3$, 10-CSA, MeOH , reflux, 16 h, 99%; b) LDA (2 equiv), THF, $-40\text{ }^\circ\text{C}$, 1 h, 92%; c) 1. DMDO (0.1M solution in acetone), CH_2Cl_2 , 10 min; 2. 10-CSA, acetone, 30 min, 70%; d) TBDMSCl, imidazole, DMAP (cat.), CH_2Cl_2 , room temperature, 2 h, 91%; e) dimethyl sulfoxide, H_2O , NaCl , 130 $^\circ\text{C}$, 30 min, quant.; f) TBDMSOTf, Et_3N , CH_2Cl_2 , room temperature, 3 h, 83%; g) TBDMSOTf, imidazole, DMAP (cat.), CH_2Cl_2 , room temperature, 2 h, quant.

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To accomplish the incorporation of the secondary hydroxy group, a consecutive two-step sequence was conceived in which an epoxidation of the enol ether **10** with dimethyldioxirane (DMDO)^[10] was followed by an acidic workup to allow the formation of the α -hydroxyketone **11**. Subsequently, the secondary hydroxy group was protected by treatment with *tert*-butyldimethylsilyl chloride (TBDMSCl), imidazole, and a catalytic amount of 4-dimethylaminopyridine (DMAP), to yield compound **12** (Scheme 3).

The β -ketoester function in **12** was decarboxylated by the application of a variation of the procedure of Krapcho,^[11] to give compound **13**. An alternative and convenient short route to **13** was subsequently employed from this point. Treatment of the commercially available 2-hydroxycyclohexanone dimer (adipoin; **14**) with TBDMSCl, imidazole, and a catalytic amount of DMAP in CH_2Cl_2 at room temperature, provided the protected hydroxyketone **13** in a quantitative yield. To proceed to the critical cyclopropanation step, compound **13** was transformed into the TBDMS enol ether **15** by treatment with TBDMSOTf (OTf = trifluoromethanesulfonate) and triethylamine at room temperature in dichloromethane for three hours (Scheme 3).^[12]

Initially, the construction of the dimethylcyclopropane moiety was addressed by reaction of compound **15** with dibromocarbene^[13] and further transformation of the resulting dibromocompound with a homocuprate,^[14] to yield the dimethylated compounds **18** and **19**. Thus, when one equivalent of bromoform was added dropwise for one hour to a stirred slurry of compound **15** and potassium *tert*-butoxide in anhydrous pentane at -10°C , dibromo compounds **16** and **17** were obtained (Scheme 4). Both compounds showed analogous patterns in their ^1H and ^{13}C NMR spectra, but the signals

at $\delta = 4.07$ (dd, $J = 4.3$ Hz, 11.5 Hz, 1H; *CHOTBDMS*) in compound **16** and at $\delta = 4.13$ (t, $J = 9.1$ Hz, 1H; *CHOTBDMS*) in compound **17** suggested that they were epimers at C2. Compound **16** proved to be thermally unstable and after one week at room temperature was completely degraded. Nevertheless, compound **17** was stable under the same conditions. This permitted a pure sample of compound **17** to be obtained, a difficult task by chromatography. Compound **17** furnished crystals suitable for X-ray crystallographic analysis,^[15] which established the structure of compound **17** as 7,7-dibromo-1*S*(*R*),2*S*(*R*)-di-*tert*-butyldimethylsilyloxy-(6*R*(*S*))-bicyclo[4.1.0]heptane. Therefore, the major compound **16** was concluded to be the epimeric 7,7-dibromo-1*S*(*R*),2*R*(*S*)-di-*tert*-butyldimethylsilyloxy-(6*R*(*S*))-bicyclo[4.1.0]heptane.

Treatment of a mixture of **16** and **17** with four equivalents of lithium dimethylcuprate at -23°C , and then with MeI at -63°C , yielded the corresponding *gem*-dimethyl compounds **18** and **19** (Scheme 4). The stereochemistry in compound **18** was established by NOE analysis, which in turn served to confirm the stereochemistry of the major dibromo adduct **16**.

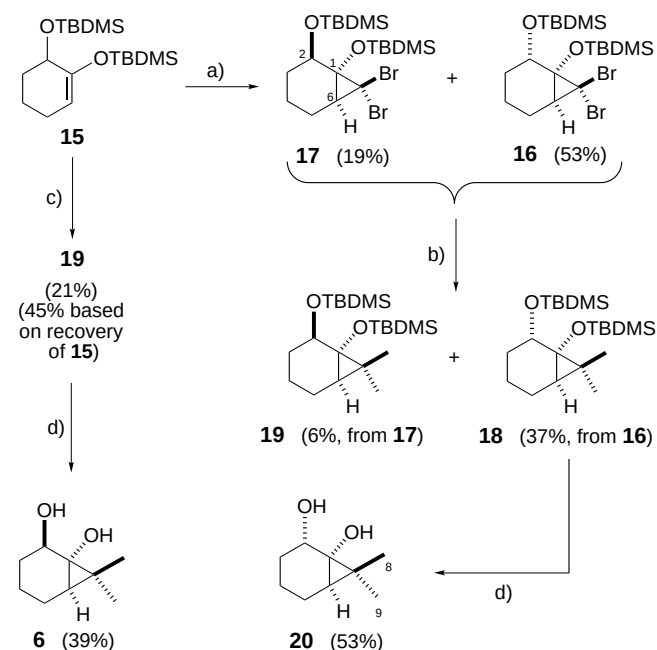
An alternative and direct route to compound **19** was found when the enol ether **15** was treated with the lithium carbenoid generated from *n*BuLi and 2,2-dibromopropane^[16] in pentane at -78°C .^[17] Compound **19** was furnished as the sole adduct. The separate treatment of **19** and **18** with tetra-*n*-butyl ammonium fluoride in THF yielded the epimeric diols **6** and **20** in yields of 39% and 53%, respectively.

The behavior of the dibromocarbene and that of the lithium carbenoid derived from 2,2-dibromopropane are different. For dibromocarbene, steric hindrance seems to play a major role in determining the course of the approach of the reagent to the double bond, to yield **16**, with a cyclopropane ring *trans* to the secondary silyl ether group, as the major product. On the other hand, the reaction with the lithium carbenoid only yields a single product, compound **19**, whose cyclopropane ring is *cis* to the secondary silyl ether group. This suggests a directing effect from the oxygen in the ether functionality on the cyclopropanation reaction. This kind of effect has been reported previously in Simmons–Smith type reactions,^[18] but, to our knowledge, has not been described previously for lithium carbenoids.

In summary, we have converted a β -ketoester into a hydroxydimethylcyclopropane derivative with diastereocontrol, by means of a protocol that may be applied in our synthetic strategy towards phorbol derivatives. We have also shown an interesting diastereocomplementarity of halocarbenes and alkylcarbenes in this process.

Experimental Section

Selected spectroscopic data: **20**: ^1H NMR (250 MHz, CDCl_3 , 25°C , TMS): $\delta = 3.89$ (m, 1H; *CHOTBDMS*), 2.90–2.70 (2H; -OH) 1.98–1.83 (1H; 5-H), 1.69–1.42 (4H; 3-H, 3'-H, 4-H, 4'-H), 1.39–1.05 (m, 1H; 5'-H), 1.21 (s, 3H; CH_3), 1.00 (s, 3H; CH_3), 0.81 (dd, $J = 2.5$, 9.5 Hz, 1H; CH); ^{13}C NMR (62.5 MHz, CDCl_3 , 25°C , TMS): $\delta = 65.20$, 60.65, 31.22, 27.78, 23.38, 22.75, 19.14, 18.64, 16.04. **6**: ^1H NMR (250 MHz, CDCl_3 , 25°C , TMS): $\delta = 4.38$ (dd, $J = 7.9$, 10.6 Hz, 1H; *CHOTBDMS*), 2.18–1.89 (2H; 3-H, 5-H) 1.55 (m, 1H; 4-H), 1.28–1.13 (3H; 3'-H, 4'-H, 5'-H), 1.23 (s, 3H; CH_3), 1.17 (s, 3H; CH_3), 0.98 (dd, $J = 3.3$, 10.0 Hz, 1H; CH); ^{13}C NMR



Scheme 4. Synthesis of the epimeric diols **6** and **20** from the enol ether **15**. Reagents and conditions: a) CHBr_3 (1 equiv, dropwise over 1 h), *t*BuOK, pentane, -10°C →room temperature, 3 h; b) Me_2CuLi (4 equiv), Et_2O , -23°C , 3 h, then MeI, -63°C , 1 h; c) $(\text{CH}_3)_2\text{CBr}_2$, *n*BuLi, pentane, -78°C (3 h), -78°C →room temperature (14 h); d) *n*Bu₄NF, THF, reflux, 2 h.

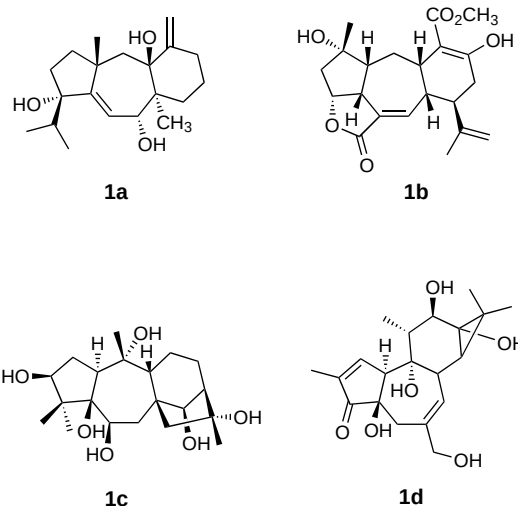
(62.5 MHz, CDCl₃, 25 °C, TMS): δ = 76.31, 62.70, 31.84, 31.58, 25.65, 24.17, 22.71, 19.04, 16.37.

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Constructing Tricyclic Compounds Containing a Seven-Membered Ring by Ruthenium-Catalyzed Intramolecular [5+2] Cycloaddition**

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Polycyclic natural products that contain an embedded polyhydroazulene subunit, for example, dilatrilol^[1a] (**1a**), rameswaralide^[1b] (**1b**), grayanotoxin^[1c] (**1c**), and phorbol^[1d] (**1d**), possess a diversity of biological activities. As such, they



represent interesting yet demanding synthetic challenges and stimulate the development of new methodologies. The ability to increase molecular complexity rapidly by cycloaddition reactions should prove to be particularly interesting in offering short, atom-economical routes to such targets. Among these reactions, Rh^[2] and Ru-catalyzed^[3] [5+2] cycloaddition reactions that involve cyclopropyl enynes have been discovered by the Wender group and by our group, respectively. We have shown that the Ru^{II} catalyst **2** can catalyze this process under very mild conditions^[3] (room temperature in acetone within a few hours). This fact encouraged us to examine the applicability of this strategy to complex targets represented by **1a–d**, which raises a number of reactivity and selectivity issues that are addressed herein.

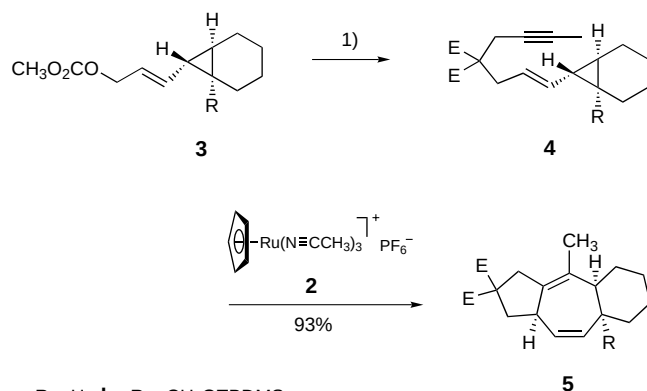
The sensitivity of the Ru-catalyzed reactions to steric hindrance immediately led us to test the ability of 1,2,3-trisubstituted cyclopropanes to participate in these reactions.

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We chose to investigate the norcarane derivative **4a**, which was prepared in 70 % yield by a Pd⁰-catalyzed allylic alkylation^[4] (Scheme 1; Ph₃P, (C₂H₅)₃N, CH₂Cl₂, room temperature). The substrate **3a** for the alkylation is easily

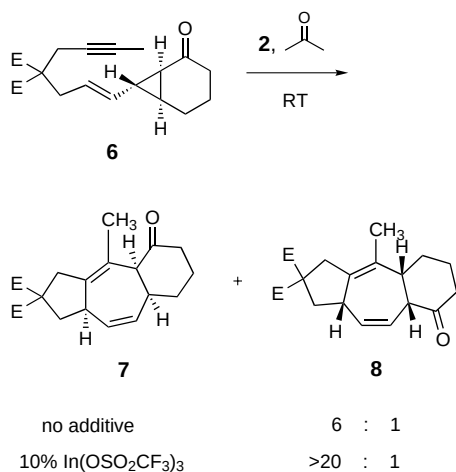


a: R = H, **b**: R = CH₂OTBDMS
E = CO₂CH₃

Scheme 1. Preparation and Ru-catalyzed intramolecular cycloaddition of cyclopropyl enyne **4**. Reagents and conditions: 1) Ph₃P, [Pd₂(dba)₃]·CHCl₃, Et₃N; dba = *trans,trans*-dibenzylideneacetone.

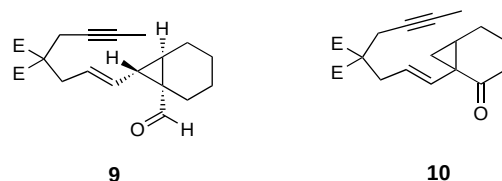
accessed from cyclohexene by typical cyclopropanation^[5] and chain-extension protocols. An acetone solution of enyne **4a** was exposed to complex **2** (10 mol %) at ambient temperature for 6 h to ensure complete conversion, since the spots for the product and the starting material overlap on the TLC plate. Tricycle **5a** was isolated as a single stereoisomer in 93 % yield. The *syn,syn* stereochemistry was assigned by NOE studies. A further increase in the steric congestion by employing a tetrasubstituted cyclopropyl substrate **4b**, derived in a similar manner from **3b**, also raises the question of the regioselectivity of the ring opening. Interestingly, the reaction proceeded within 3 h at room temperature, to give tricycle **5b** as a single stereoisomer in 85 % yield (Scheme 1).

A most interesting regioselectivity question arises with the ketone **6**. Previous work showed that an acetyl substituent in a 1,2-disubstituted cyclopropane produced nearly equal amounts of the two regioisomers.^[3b] On the other hand, in the case of **6** [Eq. (1)], both cyclopropyl bonds are disub-

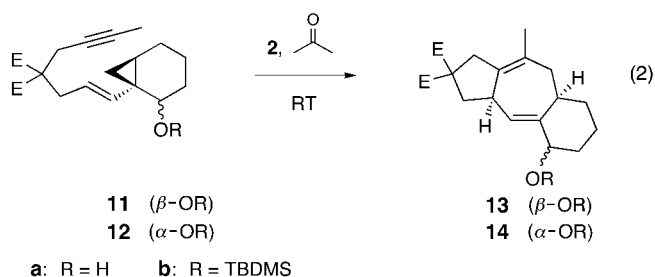


stituted. In contrast to our earlier study, a selectivity in favor of **7** was observed, but still a small amount of **8** was formed (74 % yield, **7/8** 6:1). This fact indicates that electronic factors can dominate when steric effects are equivalent, but the electronic effects are not overwhelming. Interestingly, the addition of indium triflate as a cocatalyst increased the selectivity to favor **7** (83 % yield) such that none of isomer **8** was detected. Apparently, Lewis acid complexation of the carbonyl group activates the adjacent cyclopropyl bond towards cleavage.

In contrast to the facile cycloisomerization of Equation (1), which was complete within 4 h, aldehyde **9** and ketone **10** failed to react. Since previous work^[3b] clearly establishes that

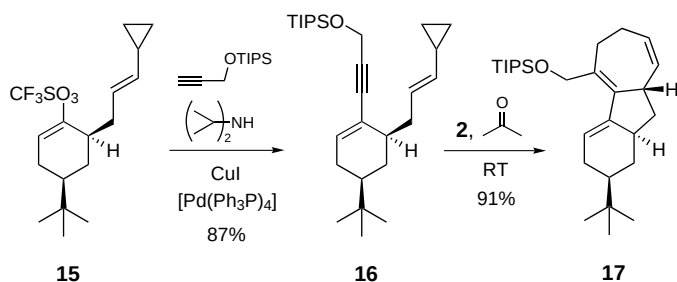


the functionality is not responsible for this lack of reactivity, we examined the reduced forms of ketone **10**, that is, **11a,b** and **12a,b** [Eq. (2)].



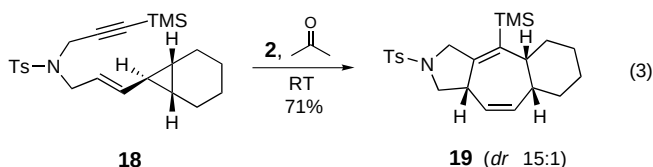
Gratifyingly, both epimers of both alcohols **11a** and **12a** reacted normally to give the tricycles **13a** (70 % yield) and **14a** (80 % yield) in 4–5 h. The sterically bulkier silyl ethers **11b** and **12b** also reacted within 2–3 h to form the desired cycloisomers **13b** (81 % yield) and **14b** (69 % yield). In every case, excellent diastereoselectivity was observed. In light of these results, the failure of the carbonyl substrates **9** and **10** but not in **6** accounts for these differences in reactivity.

Varying the placement of the cyclohexyl ring provides an entry to alternative tricycles. For example, dienyne **16** was readily available by means of a Sonogashira coupling^[6] of vinyl triflate **15** and the triisopropylsilyl (TIPS) ether of propargyl alcohol. The former was derived from 4-*tert*-butylcyclohexanone by straightforward methodology.^[7] Dienen-yne **16** was exposed to complex **2** (10 mol %) at room temperature in acetone to give a 91 % yield of the triene **17** (*dr* 10:1) in 4 h (Scheme 2). The use of a conjugated enyne for the acetylene segment provides an entry to 1,3-dienes and thus sets the stage for further elaboration by means of Diels–Alder reactions.

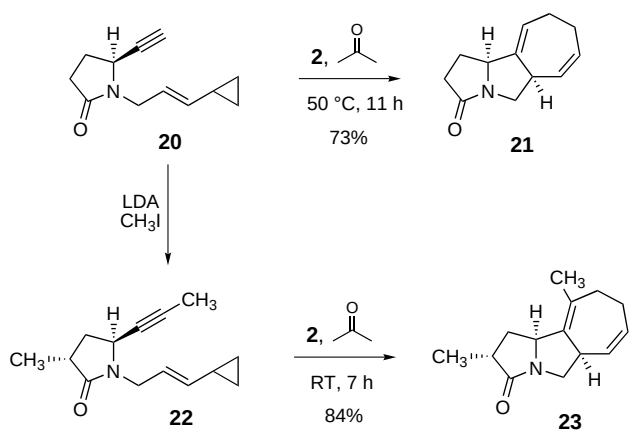


Scheme 2. Formation of alternative tricycles from cyclopropyl enyne **16**.

The incorporation of nonbasic nitrogen in the tether provides an entry to azapolyhydroazulenes. For example, alkyl carbonate **3a** can be converted into sulfonamide **18** by Pd⁰-catalyzed alkylation.^[4] Intramolecular cycloaddition proceeded under standard conditions in 8 h to produce azatri-cycle **19** with excellent diastereoselectivity [Eq. (3)]. A lactam



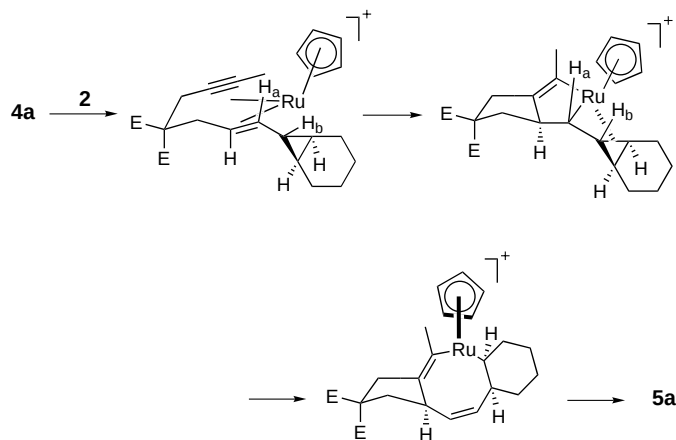
is also a suitable substrate. Thus, ketoglutaric acid was readily converted into enyne **20**. The [5+2] cycloaddition proceeded under standard conditions albeit somewhat more slowly (11 h at 50 °C) but still in excellent yield to give **21** with excellent diastereo- and enantioselectivity (Scheme 3). It



Scheme 3. Effect of terminal versus substituted alkynes on cycloaddition rate. LDA = lithium diisopropylamide

appears that terminal alkynes react more slowly in general in these reactions, presumably because there is a reversible side reaction that involves insertion into the C–H bond by ruthenium.^[8] To test this speculation, the terminal alkyne was methylated, a process that was accompanied by simultaneous methylation α to the carbonyl group, to form enyne **22**.^[9] The [5+2] cycloaddition reaction to form **23** proceeded at room temperature within 7 h, considerably shorter and milder than required for **21** (Scheme 3).

The diastereoselectivity of all the reactions is outstanding. A mechanism that involves a ruthenacyclopentene^[3, 10] accounts nicely for the observed stereochemistry (Scheme 4). Coordination of the double bond results in a dihedral angle of



Scheme 4. Mechanistic rationale for observed diastereoselectivity.

0° between H_a and H_b, since a double bond is formed between the corresponding carbon atoms. This requirement accounts for the propagation of the stereochemistry in a 1,4-manner. It is particularly significant that trisubstituted substrates such as **4** and **6** can be employed, invoking secondary carbon–ruthenium bonds. This type of substitution provides a simple entry to targets represented by **1a–c**. Furthermore, it appears that this methodology extends to these much more complicated substrates with no apparent ill effects—a feature that bodes well for the applicability of this method to complex natural product synthesis.

Experimental Section

General procedure: Distilled acetone (0.5 mL) and then **2** (4 mg, 0.009 mmol) was added to a 5-mL round-bottomed flask containing malonate ester **4a** (30 mg, 0.094 mmol) under argon at room temperature. The resulting brown solution was stirred for an additional 6 h. Without further work-up, flash chromatography of the reaction mixture, eluted with diethyl ether/petroleum ether (5% to 10%), afforded **5a** as yellow oil (28 mg, 0.088 mmol, 93 %).

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Correlating Electron Transport and Molecular Structure in Organic Thin Films**

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Understanding how electrons travel through organic matter is important in designing materials for organic microelectronics^[1] and understanding biological electron-transport processes.^[2,3] Herein we describe a simple experimental procedure to measure rates of electron transport across organic thin films having a range of structures, compare the data for several types of films, and outline a theory appropriate for analyzing these rates. We use a junction that is particularly easy to assemble: M-SAM(1)SAM(2)-M' (Figure 1, "SAM" is a self-assembled monolayer).^[4,5] We have

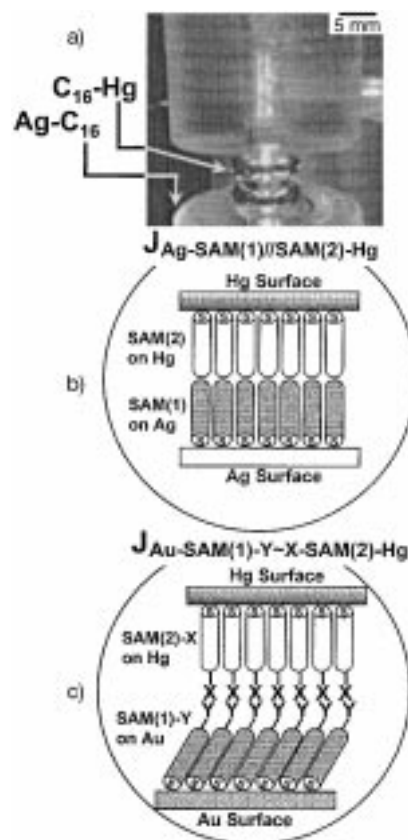


Figure 1. Schematic illustrations of junctions with structures $J_{\text{Ag-SAM}(1)/\text{SAM}(2)\text{-Hg}}$ and $J_{\text{Au-SAM}(1)\text{-X-Y-SAM}(2)\text{-Hg}}$ (see text for the nomenclature). The photographic image (a) is that of a $J_{\text{Ag-C}_{16}/\text{C}_{16}\text{-Hg}}$ junction; the scale bar represents ~ 0.5 mm. To assemble $J_{\text{Ag-SAM}(1)/\text{SAM}(2)\text{-Hg}}$ junctions (b), a SAM was formed on the surface of a thin evaporated film of silver; we normally used $M = \text{Ag}$, since silver gives highly ordered SAMs.^[5] This electrode was covered with a solution of hexadecane containing 1 mM thiol. A small drop of Hg (5 μL) was expressed into a solution of hexadecanethiol (HDT) from a capillary connected to a mercury reservoir, and a SAM of HDT allowed to form on it.^[5] The HDT-covered mercury drop ($\text{C}_{16}\text{-Hg}$) was then brought into contact with the solid electrode using a micromanipulator. The area of interfacial contact was estimated by using a microscope. With each electrode connected to an electrometer (in two-electrode mode), we applied a potential and recorded the response, and then increased the potential in steps over a range of voltages to generate I - V curves. Junctions of structure $J_{\text{Au-SAM}(1)\text{-X-Y-SAM}(2)\text{-Hg}}$ (c) were made as described for $J_{\text{Ag-SAM}(1)/\text{SAM}(2)\text{-Hg}}$ except that one electrode was a thin film of gold, and the thiols used had terminal groups that could react and form covalent bonds ($X = \text{carboxylic anhydride}$, $Y = \text{H}_2\text{N}$),^[15] or interact strongly but noncovalently ($X = \text{CO}_2\text{H}$ and $Y = \text{HO}_2\text{C}$, or $X = \text{CO}_2\text{H}$ and $Y = \text{H}_2\text{N}$) through hydrogen or ionic bonds.

examined two sets of junctions: 1) one in which SAM(1) was formed on Ag from aliphatic or aromatic thiols, and SAM(2) was formed on Hg from hexadecanethiol, and 2) a second in which SAM(1) and SAM(2) have terminal functional groups. In the first, the SAMs contact through van der Waals interactions; in the second, through covalent, hydrogen, or ionic bonds. The current measured across these junctions obeyed the relation $I = I_0 e^{-\beta d}$ (where d is the distance between the electrodes, and β is the structure-dependent attenuation factor for the molecules in SAM(1)); the values of β compare well with those obtained by other experimental methods. The experimental current versus voltage (I - V) curves have been fitted using two theoretical models for electron transport: one

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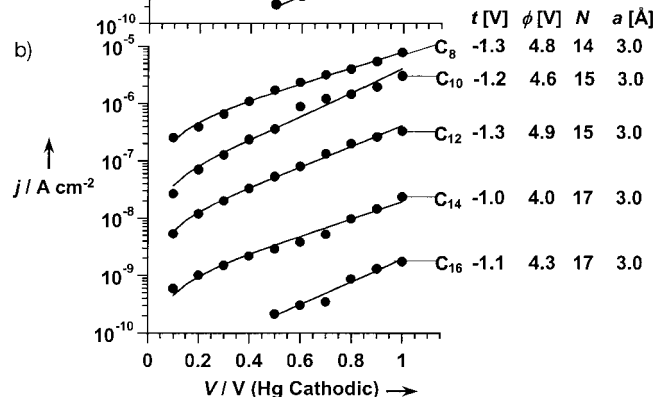
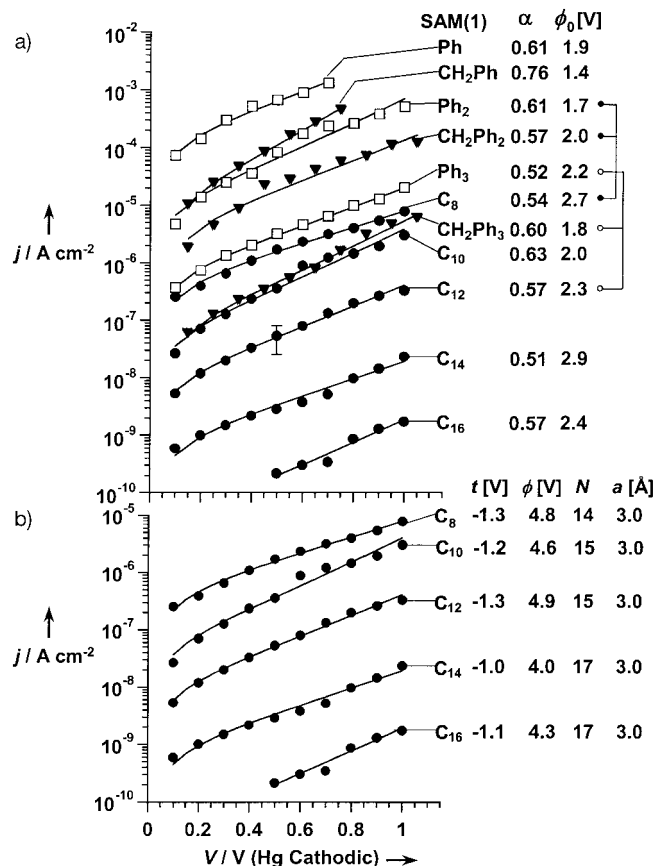
based on tunneling through an unstructured barrier with a parabolic profile, and the second based on “superexchange” tunneling through molecules. These models generate values of β and potential barrier that are internally consistent and comparable with relevant information in the literature. Measurements of current across these junctions as a function of the structure of the SAMs provide information fundamental to understanding electron transport in organic matter.

We describe the two types of junctions we have studied (Figure 1) by using a nomenclature in which J indicates a junction: for the first, $J_{\text{M-SAM}(1)/\text{SAM}(2)\text{-Hg}}$, // represents van der Waals interactions at the interface between methyl-terminated SAMs; for the second, $J_{\text{M-SAM}(1)\text{-X}\sim\text{Y-SAM}(2)\text{-Hg}}$, $\sim$ represents covalent, hydrogen, or ionic bonds that bridge the interfaces through functional groups X and Y. We use — for covalent bonds, and $\cdots$ for hydrogen or ionic bonds. The procedure used to assemble the junctions was straightforward (Figure 1, caption). Current was measured in response to a fixed applied potential across the junction.^[5] Most junctions were stable for applied potentials over the range 0–1 V; ^[5] 1 V corresponds to a potential gradient of approximately 10^8 V m^{-1} , well below the breakdown voltage of the system.^[5]

Junction 1: Figure 2a shows the current density across junctions with the structure $J_{\text{Ag-SAM}(1)/\text{SAM}(2)\text{-Hg}}$ as a function of

applied voltage for SAMs of alkanethiols, $\text{HS}(\text{CH}_2)_{n-1}\text{CH}_3$ ($n=8,10,12,14,16$), oligophenylene thiols, $\text{HS}(\text{Ph})_k\text{H}$ ($k=1,2,3$), and benzylic homologues of the oligophenylene thiols $\text{HSCH}_2(\text{Ph})_m\text{H}$ ($m=1,2,3$). Comparison of these I – V curves, and of their fits to theoretical models (described below) indicate that: a) the *shape* of the I – V curves is the same for C_n , Ph_kH , and $\text{CH}_2\text{Ph}_m\text{H}$; b) the magnitude of the current density decreases in the order $\text{Ph}_k\text{H} > \text{CH}_2\text{Ph}_m\text{H} > \text{C}_n$ for films of the same thickness; c) the magnitude of the current density depends on the thickness of the monolayers. The decrease in current density with increasing distance separating the electrodes ($d_{\text{Ag,Hg}}$) obeyed the relation $I = I_0 e^{-\beta d_{\text{Ag,Hg}}}$, as expected for tunneling (Figure 2b). For alkanethiols forming SAM(1) on Ag, β is $0.87 \pm 0.1 \text{ \AA}^{-1}$; for oligophenylene thiols, β is $0.61 \pm 0.1 \text{ \AA}^{-1}$; and for the benzylic derivatives of oligophenylene thiols, β is $0.67 \pm 0.1 \text{ \AA}^{-1}$.

The value of β is approximately independent of V (over the range 0.1–1 V). This observation suggests that the molecular bridge states, which determine the effective pathway of transport, are weakly sensitive to voltage changes in the range considered. We assumed that any scattering of electrons at the interface between the SAMs was the same for aliphatic and aromatic SAMs. These values of β are in good agreement with corresponding values obtained by photoinduced electron transfer in molecular systems comprising electron donor and



certain. The error bar in a) is $\pm$ the standard deviation of the data, s ; each datum is the average of six measurements on six independent junctions. b) Plot of current density j as a function of the bias voltage V (solid circles) for junctions with composition for $J_{\text{Ag-C}_n/\text{C}_{16}\text{-Hg}}$ ($n=8, 10, 12, 14, 16$). The solid lines represent the best nonlinear, least-squares fits of the data for each junction to Equation (3); all points were weighted equally. Each line in this figure is a fit to Equation (3) using four floating parameters. c) Plot correlating values of current density and distance between electrodes for $J_{\text{Ag-SAM}(1)/\text{C}_{16}\text{-Hg}}$ at $V=0.5 \text{ V}$. The lines are linear least-squares fits to the equation $\ln(I) = -\beta d + \ln(I_0)$.

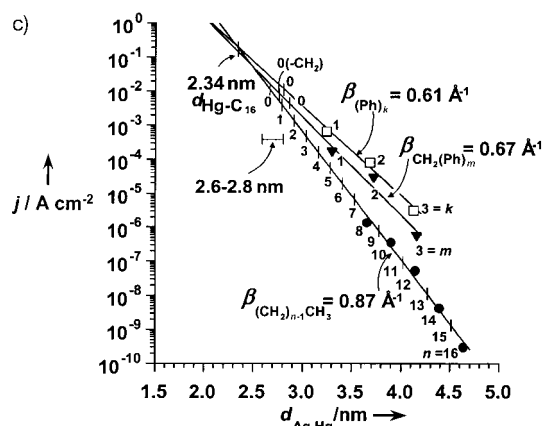


Figure 2. a) Plots of current density j as a function of the bias voltage V between the mercury and silver electrodes for $J_{\text{Ag-SAM}(1)/\text{C}_{16}\text{-Hg}}$. The symbols used to represent different classes of compounds are: $\bullet$, $\text{HS}(\text{CH}_2)_{n-1}\text{CH}_3$; $\square$, $\text{HS}(\text{Ph})_k\text{H}$ (all substitution of benzene rings is 1,4); $\blacktriangledown$, $\text{HSCH}_2(\text{Ph})_m\text{H}$. The solid lines represent the best nonlinear, least-squares fits of the data for each junction to Equation (1); all points were weighted equally, and the equation had two floating parameters, ϕ_0 and α . The correlation coefficient (R^2) for each was >0.95 . We list the value of ϕ_0 and α obtained by these fittings. The lines connecting triads of data adjacent to values of ϕ_0 and α are for SAMs on Ag having the same thickness. To test the statistical significance of our inference that the magnitude of the current density decreases in the order $\text{Ph}_k > \text{CH}_2\text{Ph}_m > \text{C}_n$ for films of the same thickness, we examined the curves for Ph_2 and CH_2Ph_2 . Application of the Student's t -test indicated that, for uncertainties of the size shown, $I(\text{Ph}_2) > I(\text{CH}_2\text{Ph}_2)$ ($V=0.1$ – 1) at $>95\%$ confidence level. Other comparisons are even more

acceptor linked by a bridge^[6, 7] and by electron transfer between a solid electrode and redox-active species in solution.^[8] In these systems, values of β for saturated hydrocarbons range from 0.8–1.0 Å⁻¹,^[6, 8] and values of β for oligophenylenes range from 0.4–0.6 Å⁻¹.^[7, 9] In directly comparable work, Majda and co-workers found $\beta = 0.8 \pm 0.1$ Å⁻¹ for alkanethiols in J_{Hg-SAM/SAM-Hg}.^[10] The agreement among the values of β suggests that the mechanism of charge transport in these solid-state junctions is closely related to that in molecular systems in solution, and that across SAMs on solid electrodes to molecules in solution in electrochemical experiments.

Figure 2c summarizes an analysis that establishes the internal consistency of the data for the three sets of junctions, J_{Ag-S(CH₂)_{n-1}CH₃/C₁₆-Hg}, J_{Ag-(Ph)_k/C₁₆-Hg}, and J_{Ag-CH₂(Ph)_m/C₁₆-Hg}. We extrapolated plots of current density against $d_{\text{Ag,Hg}}$ for each of the three junctions to their intersection points (where, in principle, there is no contribution to the junctions from an organic monolayer on silver). The thickness calculated for the hypothetical junction J_{Ag/C₁₆-Hg} is $d_{\text{Ag,Hg}} = 2.34$ nm; that for a junction in which the organic groups on silver had been removed, and only the Ag–S bond and the van der Waals radius of the terminal methyl group or hydrogen atom remain is $d_{\text{Ag,Hg}} = 2.6$ –2.8 nm. The difference between 2.34 nm and 2.6–2.8 nm—0.3–0.5 nm—is a reasonable value for an aggregate contribution to the thickness from the Ag–S bond, the S–C bond, and the van der Waals radii of the terminal groups. The consistency of our data for the three sets of organic compounds suggests that they are directly comparable.

Junction 2: Comparisons of rates of electron transfer through different types of covalent bonds and through nonbonding interactions have been challenging^[11] and only a few have been reported.^[12–14] Assembling a junction by bringing together two metal surfaces coated with SAMs that terminate in different functional groups (X and Y) makes it straightforward to incorporate a variety of interactions into the junction J_{Au-SAM(1)-X~Y-SAM(2)-Hg}; we have compared van der Waals interactions and hydrogen or hydrogen/ionic bonds (Figure 3). It was also possible to bridge two SAMs covalently by reaction of a SAM terminated with anhydride groups on gold with a second SAM terminated in amine groups on

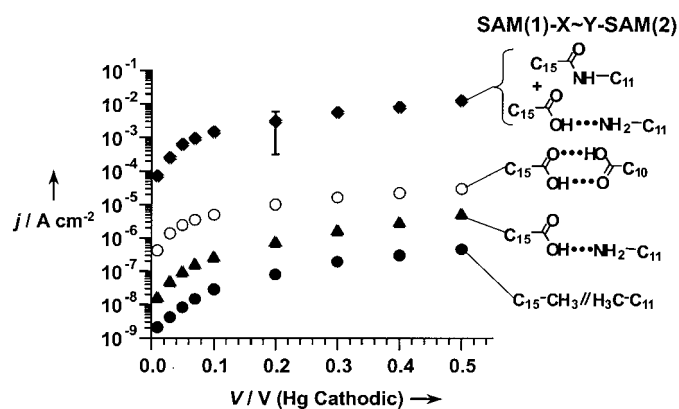


Figure 3. Plots of current density as a function of the bias voltage between the mercury and gold electrodes for J_{Au-SAM(1)-X~Y-SAM(2)-Hg}. The error bar is $\pm$ the standard deviation of the data, s .

mercury.^[15] This reaction generates a 1:1 mixture of two kinds of bridging groups: covalent amide C(O)–NH groups and hydrogen-bonded CO₂H...NH₂ pairs.

The current density measured at a particular value of applied voltage depended significantly on the structure of the interface. Using the junction having only van der Waals interactions at the interface as the reference, $I_{(-\text{CO}_2\text{H}\cdots\text{NH}_2)}/I_{(-\text{CH}_3/\text{H}_3\text{C})} \simeq 9$; $I_{(-\text{CO}_2\text{H}\cdots\text{HO}_2\text{C})}/I_{(-\text{CH}_3/\text{H}_3\text{C})} \simeq 40$; and $I_{(-\text{C}(\text{O})\text{NH}\cdots\text{CO}_2\text{H}\cdots\text{NH}_2)}/I_{(\text{CH}_3/\text{H}_3\text{C})} \simeq 10^4$ (this ratio becomes $\sim 10^3$ after correcting for small differences in the thicknesses of the organic films). We estimate that an interface having only van der Waals interactions is equivalent in its ability to pass current to a chain of approximately six transoid sigma bonds: that is –CH₃/H₃C– is equivalent in its ability to pass current to a –(CH₂)₆– unit. The smaller differences in the rates of electron transport across –CO₂H...NH₂– and –CO₂H...HO₂C– bridges that we observe are similar to those reported by Nocera et al.^[13] Beratan, Onuchic, and Betts^[17] developed theoretical models that fit experimentally determined rates of electron transfer in proteins to details of their structures, and inferred these orders of rates of tunneling: covalent > noncovalent bonds, and hydrogen bonds > van der Waals contacts. The agreement of our results with these limited experimental^[12–14] and theoretical data^[16, 17] suggests that the junction described here will be useful in quantifying these rates.

Theory: To fit the I – V curves, we have used two different theoretical models: the first assumes tunneling through a metal-insulator-metal junction; and the second assumes superexchange tunneling through a molecular bridge. The first approach is based on the Wentzel–Kramers–Brillouin (WKB) approximation for tunneling through an unstructured barrier, and gives a current density expressed by Equation (1), where ϕ_0 (in J) is the barrier height, V (in Volts) is the applied potential, m is the mass of an electron (in kg), $\hbar$ is Planck's constant (in J s⁻¹) divided by 2π , e is the charge of an electron (in Coulombs) and d is the tunneling distance (in m).^[18]

$$I = \frac{e}{4\pi^2 \hbar d^2} \left\{ \left(e\phi_0 - \frac{eV}{2} \right) \exp \left[-\frac{2(2m)^{1/2}}{\hbar} \alpha \left(e\phi_0 - \frac{eV}{2} \right)^{1/2} d \right] - \left(e\phi_0 + \frac{eV}{2} \right) \exp \left[-\frac{2(2m)^{1/2}}{\hbar} \alpha \left(e\phi_0 + \frac{eV}{2} \right)^{1/2} d \right] \right\} \quad (1)$$

This model has been used successfully in the pioneering work of Mann and Kuhn.^[30] It is possible to extend the model for a rectangular potential barrier^[18] to barriers of parabolic shape^[19] by introducing an adjustable parameter, α , which is related to the shape of the barrier.^[19, 20] In this treatment, Equation (2) gives β . Fitting the I – V curves (Figure 2a) to Equation (1) for junctions in which SAM(1) consists of n -alkanethiols gave an average value of $\alpha = 0.6$ and $\phi_0 = 2.5$ eV. Introducing these values into Equation (2) gave a value of $\beta = 0.9$ Å⁻¹ at zero voltage, and a stronger voltage dependence than that observed experimentally over the range of 0.1 to 1 V.

$$\beta = -\frac{2(2m)^{1/2}}{\hbar} \alpha \left(e\phi_0 - \frac{eV}{2} \right)^{1/2} \quad (2)$$

The second theoretical model incorporates molecular structure into the tunneling barrier.^[21] This model considers

off-resonance tunneling of electrons across a single molecule in a metal-molecule-metal junction in response to the applied voltage. The model assumes a) that the molecules in the monolayer act independently, that is, the total current density is the product of the molecular current times the molecular density, and b) that the electrostatic potential profile is determined self-consistently through the combined solution of Poisson and Schrödinger equations.^[22] This model leads to an approximately constant electrostatic potential in the molecular bridge region, while the voltage drop occurs at the electrode–molecule interface. This approach gives Equation (3), where n is the number of molecules per unit area, N is the number of sites that compose a homogeneous molecular bridge, t is the transfer integral between sites, Δ_0 is the spectral density of either of the two electrodes at zero bias, and ϕ is the difference between the Fermi level of the electrode and the energy of each site. A “site” in this model is an atom or a group of atoms, whose orbital overlap provides the best superexchange pathway for electron transfer within a one-dimensional model.^[23] Equation (3) predicts 1) a power law dependence of the current on the applied potential; 2) an exponential dependence of the current on the length of the molecule L , where $I \propto e^{-\beta L}$ (β , derived from Equation (3), is given by Equation (4), for positive bias and $\phi < eV/2$); and 3) a much weaker dependence of β on V [Eq. (4)] compared to that from Equation (2).

$$I(V) = \frac{2e}{\pi\hbar} \frac{\Delta_0^2}{(1-2N)t} n \left\{ \left(\frac{e\phi + (eV/2)}{t} \right)^{1-2N} - \left(\frac{e\phi - (eV/2)}{t} \right)^{1-2N} \right\} \quad (3)$$

$$\beta = \frac{2}{a} \ln \left(\frac{e\phi - (eV/2)}{|t|} \right) \quad (4)$$

The fit of Equation (3) to the experimental I – V curve for $J_{\text{Ag-C}_{10}/\text{C}_{16}\text{-Hg}}$ ($d_{\text{Ag,Hg}} = 39 \text{ \AA}$), using ϕ , a , N , and t as adjustable parameters, gave physically reasonable values^[24, 25] for alkanes: $\phi = 4.8 \text{ V}$ and $t = -1.2 \text{ eV}$, for $N = 15$ and $a = 3 \text{ \AA}$. By using these values, Equation (4) gives a value of $\beta = 0.9 \text{ \AA}^{-1}$ that is approximately constant over the range 0–1 V. These characteristics of the calculated β value agree closely with our experimental observations. The value of a is larger than the average values of carbon–carbon distances in *trans*-extended alkyl chains, and the value of N is smaller than that expected if each site is defined as a carbon atom. One interpretation of these results is that each site corresponds to a methylene unit ($-\text{CH}_2-$) but that the dominant electron-transfer pathway is one that corresponds to “skipping” connecting CH_2 units.^[23] This interpretation amounts to mapping the zigzag geometry of a *trans*-extended alkyl chain onto a one-dimensional tight-binding (Hückel-type^[25] or ladder-type^[26]) chain. The calculated product of N and a is very close to the interelectrode separation.

As a whole, the experimental data fit Equation (3) quite well, particularly given the assumption that the total current is simply the product of the current/molecule by the number of molecules per cm^2 (5×10^{14}).^[27] The molecular structure of the tunneling barrier and the electrostatic potential enter naturally in this model, which does not require the parameter a invoked in the Simmons model.^[19] Furthermore, the barrier

value deduced from Equation (1) is too low compared with the experimental expectation.^[24]

Junctions $J_{\text{Ag-SAM}(1)/\text{SAM}(2)\text{-Hg}}$ have both advantages and disadvantages relative to other experimental systems as the basis for measurements of the influence of organic structure on rates of electron transport. Their advantages are that they: 1) are very easy to assemble and use; 2) are mechanically stable; 3) support a range of organic structures; 4) allow one electrode to be changed readily; 5) allow the direct correlation of electron transport and molecular structure. Their disadvantages are that they: 1) do not have the molecular-level resolution that makes measurements using scanning tunneling microscopy (STM)^[28] and break junctions^[29] so informative; 2) probably cannot be developed into practically useful microelectronic components; 3) are not compatible with measurements over a range of temperatures.

We believe that the combination of these junctions and the associated theory provide an experimentally straightforward and theoretically tractable system with which to explore the ability of thin films of organic molecules to support electron transport. This combination is a new tool for use in the development of organic microelectronics.

Experimental Section

Materials: Alkanethiols ($\text{HS}(\text{CH}_2)_{n-1}\text{CH}_3$ ($n = 8, 10, 12, 14, 16$)), thiophenol ($\text{HS}(\text{Ph})\text{H}$), and benzylthiol ($\text{HSCH}_2(\text{Ph})\text{H}$) were purchased from Aldrich or TCI and were used without further purification. Preparation of 4-biphenylthiol ($\text{HS}(\text{Ph})_2\text{H}$), 4-methylene-biphenylthiol ($\text{HSCH}_2(\text{Ph})_2\text{H}$), 4-triphenylthiol ($\text{HS}(\text{Ph})_3\text{H}$), and 4-methylene-triphenylthiol ($\text{HSCH}_2(\text{Ph})_3\text{H}$) was described previously.^[31–33] Hexadecane was purchased from Aldrich. Electronic grade mercury (99.9998 %) was purchased from Alpha. **Caution:** Mercury is highly toxic.

SAMs on silver were prepared by immersing a freshly evaporated thin film of silver ($\text{Ag}(111)$; $2000 \text{ \AA}$) on a Si/SiO_2 wafer in a solution of the appropriate thiol (10 mm) in anhydrous ethanol (alkanethiols, thiophenol, and benzylthiol; the oligophenylene thiols) or THF (oligophenylene thiols) for 24 h. SAMs on mercury were formed by extruding a drop of liquid mercury from a capillary ($\sim 5 \text{ \mu L}$) and exposing it to a solution of thiol (10 mm) in ethanol or hexadecane for ~ 10 min. The junctions were assembled as described previously.^[34] I – V curves were measured with the electrodes attached to an electrometer (Keithley 617 programmable electrometer) in two-electrode mode. During the measurement, the potential was increased in steps over the range of 0 to 1 V, or to the break-down voltage).

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Quantitative Studies of Binding between Synthetic Galactosyl Ceramide Analogues and HIV-1 Gp120 at Planar Membrane Surfaces**

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The primary cellular receptor for the HIV-1 virus is CD4, a protein abundantly expressed on T cells. The HIV-1 viral envelope glycoproteins, gp120 (120 kD) and gp41 (41 kD) mediate the recognition and infection of CD4+ cells.^[1–3] However, in the early 1990s, it was discovered that HIV-1 can also infect CD4– cell lines, such as neural cells and epithelial cells.^[4, 5] Galactosyl ceramide (GalCer), a glycosphingolipid (GSL) that is highly expressed in neural and intestinal tissues, is thought to be the alternate receptor to which gp120 binds to initiate the infection of CD4– cells.

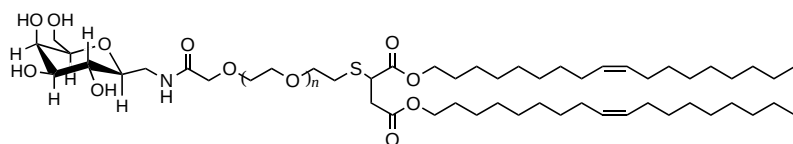
Although the interaction between CD4 and gp120 has been extensively studied, relatively limited information has been obtained about the interaction between GSLs and gp120.^[6–14] In an effort to elucidate the relationship between gp120 binding activity and GSL structure, we previously investigated recombinant gp120 (rgp120) binding to several naturally occurring GSLs reconstituted into planar supported lipid bilayers by using total internal reflection fluorescence microscopy (TIRF).^[13] The presence of a carbohydrate on ceramide was shown to be required for rgp120 binding. Among the GSLs studied, galactosyl ceramide (GalCer) was the preferred receptor with respect to binding affinity, although rgp120 also recognized lactosyl ceramide (LacCer) and glucosyl ceramide (GlcCer). No attempt was made to investigate whether structural variations in the noncarbohydrate portion of the GSL (i.e. the ceramide) affected rgp120 binding.

Previous studies of protein binding to water-soluble receptors tethered to planar membranes have established that the structure of the nonreceptor portion of lipid is an important variable.^[15] For example, the efficiency of streptavidin binding to a biotin-conjugated lipid at a planar membrane surface is strongly influenced by the length of the spacer arm linking the biotin moiety to the lipid.^[16, 17]

Herein we have assessed the influence of steric accessibility in rgp120–galactosyl recognition at a membrane surface. GalCer analogues with a water-soluble spacer arm of variable length between the galactosyl receptor and the lipophilic portion of the molecule were designed and synthesized. The analogues Gal-3, Gal-4, and Gal-5 were prepared by using tri(ethylene glycol), tetra(ethylene glycol), and penta(ethylene glycol) linkers, respectively. Each ethylene glycol unit adds approximately 3 Å to the length of the spacer arm. The lipophilic portion of each molecule is dioleoyl maleate. The

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Gal-3, 4, 5 $n = 1, 2, 3$

presence of unsaturated linkages ensured that the analogues would not undergo phase segregation when incorporated into a fluid bilayer membrane.^[18]

To study the interaction of rgp120 with these analogues at a membrane-mimetic surface, they were incorporated into planar lipid bilayers deposited on fused silica substrates.^[13, 19] The outer leaflet of the bilayer was composed of Gal-3, Gal-4, or Gal-5 mixed with 1,2-dioleoylphosphatidylcholine (DOPC; 5 mol %). TIRF microscopy^[20] was used to quantitatively measure the binding of fluorescein-tagged rgp120 to each type of membrane.

In Figure 1 are shown representative TIRF isotherms for rgp120 binding to membranes doped with Gal-3, Gal-4, and Gal-5, and to a pure DOPC membrane, which served as a control.^[21] Attempts to fit the binding data to a conventional

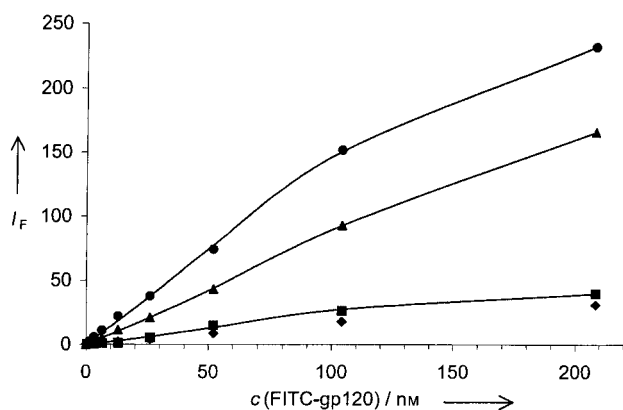


Figure 1. TIRF isotherms of FITC-rgp120 adsorption to DOPC membranes, either pure ($\diamond$) or doped with 5% (mol mol⁻¹) of Gal-3 ($\blacksquare$), Gal-4 ($\bullet$), or Gal-5 ($\blacktriangle$). Experimental fluorescence intensities were normalized to the respective rgp120 surface coverages (Table 1). The solid lines through the data represent fits obtained with a cooperative binding model in the form of $\omega(F/F_{\max})K_a[\text{rgp120}] = F/(F_{\max} - F)$, where K_a is the binding constant, ω is a coefficient that accounts for cooperativity in the binding process ($\omega > 1$ for cooperative binding, $\omega = 1$ for noncooperative (Langmuir-type) binding, and $\omega < 1$ for negative cooperativity), and $F_{\max}$ is the fluorescence intensity in the plateau region of the isotherm (presumably where all the receptors are occupied by protein molecules).^[22, 23]

Langmuir model, for which the binding sites are assumed to be equivalent, produced unsatisfactory results. Satisfactory results were obtained by fitting the data sets to a cooperative model in which rgp120 binding promotes adsorption of additional protein molecules.^[22, 23] The association constants (K_a) obtained for Gal-3, Gal-4, and Gal-5 as well as the respective cooperativity coefficients (ω) are listed in Table 1. The K_a values are in the range of 2×10^6 to 6×10^6 for all three compounds and are statistically indistinguishable. Cooperativity coefficients of approximately 1.5 suggest that a moder-

ate increase in rgp120 affinity occurs over the concentration range studied.

Comparable K_a and ω values were measured previously for cooperative rgp120 binding to 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) membranes that bear glucosyl, galactosyl, and lactosyl receptors.^[13] In that study, isolates of naturally occurring GSLs were used,

Table 1. Summary of rgp120 binding behavior to planar DOPC membranes, either pure or doped with Gal-3, -4, or -5 (5 mol %) in the outer leaflet.^[a]

	DOPC	Gal-3	Gal-4	Gal-5
$K_a \times 10^6$	–	5.4 ± 1.8	3.8 ± 0.57	2.5 ± 0.57
cooperativity coefficient (ω)	–	$1.44 \pm .20$	1.50 ± 0.28	1.59 ± 0.11
surface coverage [$\times 10^{-14}$ mol cm ⁻²] ^[b]	3.1 ± 0.49	5.9 ± 2.1	18.5 ± 0.92	13.2 ± 0.71

[a] All values listed are the mean and standard deviation of two experimental trials. [b] Surface coverages were determined at a dissolved rgp120 concentration of 208 nM, by using a modification of the method described by Hlady et al.^[26]

in which the lipophilic chains on most of the molecules are saturated. Upon mixing these GSLs with a fluid-phase lipid such as POPC, phase segregation may occur, producing GSL-rich domains.^[24] It was not clear from the earlier study whether the cooperative binding observed could be due to the laterally heterogeneous distribution of GSL receptors in the membrane. The results obtained here show that the rgp120–GSL interaction is also cooperative when the receptors appear to be uniformly distributed in the membrane (at optical resolution, when examined by epifluorescence microscopy).^[18a] Thus the cooperative nature of rgp120–GSL binding cannot necessarily be attributed to the formation of GSL domains.^[18b, 25]

The K_a and ω values listed in Table 1 do not provide any information on the amount of protein bound at membranes that bear Gal-3, -4, and -5. To address this question, an in situ calibration method^[26] was used to determine the surface coverage of rgp120 bound to these membranes, as well as the amount of protein nonspecifically adsorbed on a pure DOPC membrane (Table 1). The rgp120 surface coverage obtained on Gal-3 was only twice the value measured on a pure DOPC membrane. However, when the spacer was extended to four ethylene glycol units (versus three units in Gal-3), the protein surface coverage increased threefold to approximately 18×10^{-14} mol cm⁻². A further increase in the linker length to five ethylene glycol units in Gal-5 resulted in a moderate decrease in rgp120 surface coverage (to 13×10^{-14} mol cm⁻²).

These results show that a spacer arm of three ethylene glycol units is inadequate for highly efficient rgp120 recognition of a galactosyl receptor present on the surface of a DOPC membrane. A significant fraction (ca. 50%) of the protein binding observed at a Gal-3-bearing membrane is nonspecific in nature. The sharp increase observed with Gal-4 indicates that a spacer arm of four ethylene glycol units is necessary to allow the galactosyl receptor to access the carbohydrate binding region on rgp120. The cause of the lower surface coverage observed with Gal-5 is not yet clear, but it is possible that: 1) the longer spacer arm may have a

higher probability of adopting conformation(s) unfavorable for rgp120 recognition; or 2) the degree of nonspecific rgp120 adsorption on a Gal-5-bearing membrane may be less than that on a Gal-4-bearing membrane.

In summary, we have prepared synthetic GalCer analogues that bind to rgp120 cooperatively when incorporated uniformly into a planar fluid membrane at 5 mol %. A critical spacer arm length necessary to promote efficient binding has been identified. These results should aid efforts to design anti-HIV-1 agents based on membrane-tethered, carbohydrate-based receptors for rgp120.

Experimental Section

DOPC was purchased from Avanti Polar Lipids and used as received. Rgp120 expressed in baculovirus, labeled with fluorescein isothiocyanate (FITC; FITC/rgp120 4:1, molar), was purchased from Intracel Corporation and used without further purification. Dextran (10000 M_w) labeled with FITC (1:2.9, molar) was obtained from Molecular Probes.

A convergent approach was used to synthesize the galactosyl lipids.^[27] Each component, the galactosyl moiety, the hydrophilic spacer, and the hydrophobic maleic ester, were synthesized and then linked together. The galactose methyl amine was obtained by reaction of the peracetylated galactose with TMS cyanide, followed by reduction to the amino-substituted C-galactose. Each spacer group was prepared from readily available oligo(ethylene glycol) chains. Each diol was differentiated and modified to yield a thiol and a carboxylic acid at opposite ends of the spacer molecule. The lipid portion was obtained by reaction of maleic anhydride with oleoyl alcohol. A Michael addition of the nucleophilic thiol of the spacer to the maleic ester then gave an intermediate lipid with an available carboxylic acid. This acid was coupled with the galactose methyl amine to form the final amide link in compounds **3**, **4**, and **5**.

The procedures used to measure rgp120 binding isotherms were similar to those described previously.^[13] Briefly, Gal-**3**, Gal-**4**, or Gal-**5** was incorporated into the upper leaflet of a supported planar DOPC bilayer at a concentration of 5 mol %. The asymmetric bilayer was deposited at 35 mN m⁻¹ on a fused silica substrate by using the Langmuir–Blodgett–Schaefer technique.^[19] A series of FITC–rgp120 standard solutions was prepared in phosphate buffer (10 mM, pH 7.2, containing 150 mM NaCl). To measure TIRF isotherms the solutions were injected sequentially from lowest to highest concentration into a ca. 50- μ L TIRF flow cell. After each injection, the solution was equilibrated in the cell for 30 min before the fluorescence intensity was measured.

An in situ calibration procedure was performed to determine the amount of rgp120 protein adsorbed from the most concentrated protein solution (208 nM) on each type of membrane. After protein adsorption was allowed to proceed for 30 min, aqueous surfactant solution (PCC-54, Pierce; 2%, v/v) was injected into the flow cell to dissolve the lipid bilayer and associated protein. After 20 min, the cell was flushed with phosphate buffer to re-establish the optical baseline. A series of four FITC–dextran standard solutions (range of 5–25 μ g mL⁻¹, prepared in phosphate buffer) was injected, sequentially from lowest to highest concentration, into the flow cell. Fluorescence intensities were measured by TIRF to generate a calibration curve. Protein surface coverages were calculated according to Equation (8) in Hlady et al.,^[26] using 173 nm as the penetration depth of the evanescent wave and assuming equivalent quantum yields for FITC–rgp120 and FITC–dextran.

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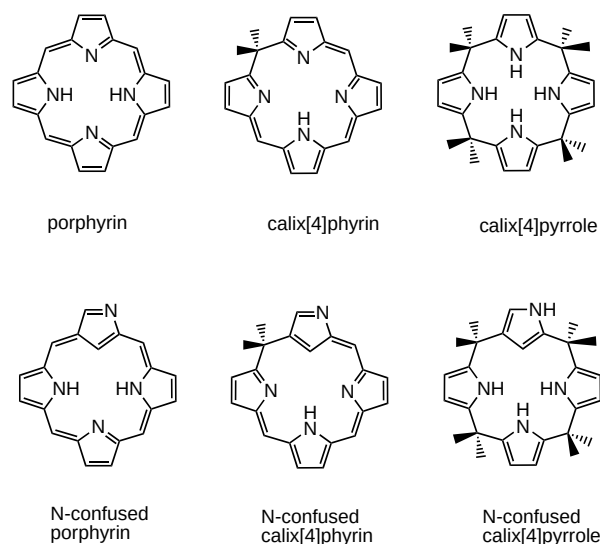
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Metal Complexes of an N-Confused Calix[4]phyrin Derivative—The First X-ray Structure of an Organometallic Compound of Divalent Copper

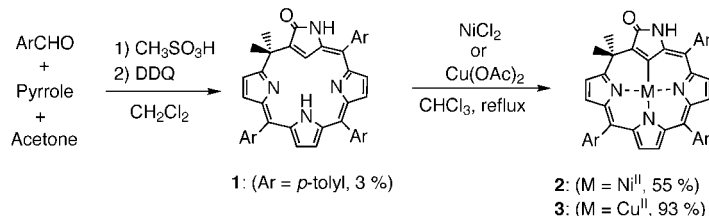
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The preparation and properties of new porphyrin analogues have recently received a great deal of attention in the literature.^[1] Among them, the so called N-confused porphyrins (NCPs), in which α - α' (normal) and α - β' (confused) linkages of pyrrole rings exist in the porphyrin framework, have shown unique coordination chemistry.^[2, 3] In particular, as a consequence of the inward-pointing carbon atom in the core, NCPs can complex with metal ions through formation of a metal–carbon bond to afford organometallic compounds. Thus, it is of interest to prepare a variety of confused analogues to examine the scope and limitation, if any, of coordination in confused systems. The two important questions are: Is the π -conjugated system necessary to stabilize the organometallic compounds? Are the properties of the organometallic compounds maintained with the nonconjugated macrocycles? To answer these questions we have chosen calix[4]phyrin, an intermediate between calix[4]pyrrole and porphyrin, as a confused target, because the conjugation is disconnected only at an sp^3 *meso* carbon atom while the structural rigidity seems relatively preserved.^[4, 5] Herein we report the synthesis and X-ray structures of Ni^{II} and Cu^{II} complexes of N-confused calix[4]phyrin. Both Cu^I and Cu^{III} complexes are known in organocopper chemistry, but a stable Cu^{II} complex is seldom reported.^[6] To the best of our knowledge complex **3** is the first example of an organocopper(II) complex to be characterized by X-ray crystallography.^[7]

The title compound was prepared by a modified NCP synthesis,^[8] namely, a methanesulfonic acid catalyzed cyclization of a mixture of pyrrole, *p*-tolualdehyde, and acetone (4:3:1), followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). This synthesis afforded N-confused tetratolylporphyrin (NCTTP: 19%) and N-confused calix[4]phyrin **1** containing an sp^3 *meso* carbon atom and an



amide group in the confused pyrrole ring in a yield of approximately 3%.^[9] Interestingly, the acetone moiety was introduced as a *gem*-dimethyl unit selectively between the α - and β' -position of the pyrrolic rings; the formation of other confused isomers of **1** was not observed. As the reactivity of acetone is lower than *p*-tolualdehyde, it is highly probable that the ring confusion occurs at the final step of the cyclization. The Ni and Cu complexes were synthesized in a refluxing solution of **1** in $CHCl_3$ in the presence of $NiCl_2$ and $Cu(OAc)_2$, respectively (Scheme 1). The optical absorption spectra of free ligand **1** and the metal complexes (Ni : **2** and Cu : **3**) are shown in Figure 1.^[10]



Scheme 1. Synthesis of N-confused calix[4]phyrin **1** and the metal complexes **2** and **3**.

Explicit evidence for the existence of metal–carbon bonds in the complexes was obtained from single-crystal X-ray analyses (Figure 2).^[11] The Ni atom of **2** was located in the middle of the core and the molecule showed a ruffled structure: the pyrrole rings were tilted 20.55, 11.37, 14.63, and 0.00°, and the mean deviation was 0.2981 Å to the mean plane consisting of 25 atoms (including the Ni atom). The $Ni(1)–C(2)$ bond length is 1.905(4) Å, which is slightly shorter than that in Ni^{II} -NCTTP (1.963(3) Å).^[2a] The Cu complex **3**, however, showed a more planar structure: the tilting angles of the pyrrole rings were 6.69, 4.25, 2.91, and 4.70° and the mean deviation from the plane was 0.1028 Å. The $Cu(1)–C(2)$ bond length (2.007(4) Å) was intermediate between that of the $Cu^I–C$ bond (2.014 Å) of $[Cu(CN)_4]^{3-}$ ^[12] and that of the $Cu^{III}–C$ bond (1.93–4 Å) in the doubly N-confused porphyrin.^[3c] Both the Ni and Cu complexes formed dimeric structures through hydrogen bonding between the peripheral amide groups.^[13]

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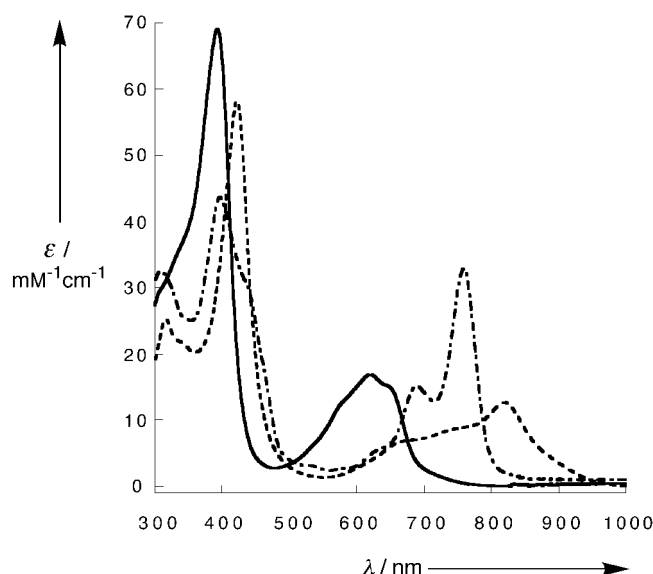


Figure 1. Absorption spectra of N-confused calix[4]pyrin **1** (—), the Ni^{II} complex **2** (---), and the Cu^{II} complex **3** (-·-) in CH₂Cl₂.

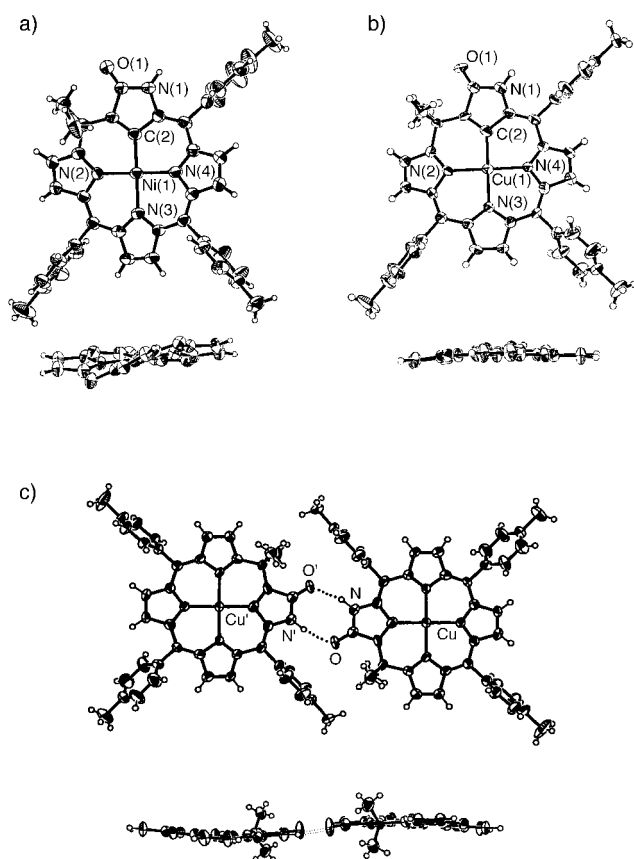


Figure 2. ORTEP structures of a) Ni complex **2**, b) Cu complex **3**, and c) the dimeric structure of **3**. The *meso*-tolyl groups are omitted for clarity in the side views. Selective bond lengths [Å]: a) Ni(1)–C(2) 1.905(4), Ni(1)–N(2) 1.956(3), Ni(1)–N(3) 1.967(3), Ni(1)–N(4) 1.935(3); b) Cu(1)–C(2) 2.007(4), Cu(1)–N(2) 2.076(4), Cu(1)–N(3) 2.010(3), Cu(1)–N(4) 2.056(4); c) N–O⁺ 2.949.

The ¹H NMR spectrum of the Ni complex **2** displayed distinct signals in the normal diamagnetic region, which indicates a square-planar Ni^{II}(d⁸) coordination geometry. On

the other hand, a CDCl₃ solution of Cu complex **3** showed broad ¹H NMR signals, which suggests the presence of the paramagnetic Cu^{II} ion. We have carried out magnetic susceptibility measurements for the powder sample of **3** by using a SQUID to estimate the percentage of Cu ions present in the paramagnetic d⁹ form. The effective magnetic moments (μ_{eff}) at 300 K and 77 K were calculated to be 1.75 and 1.67 μ_{B} , respectively, which indicates that all the Cu ions exist in the *S* = 1/2 state, namely, in the divalent d⁹ form. In addition, the nearest organometallic Cu^{II} ions, separated by 9.005 Å in the single crystal of **3**, were only slightly magnetically coupled, as evidenced by the susceptibility obeying the Curie law.^[14]

Although the crystal of **3** shows a planar structure, the sp³ *meso* carbon atom present in the skeleton seems to us to be a potential trigger for the loss of planarity, especially in solution. Figure 3 compares the ESR spectra of a powder

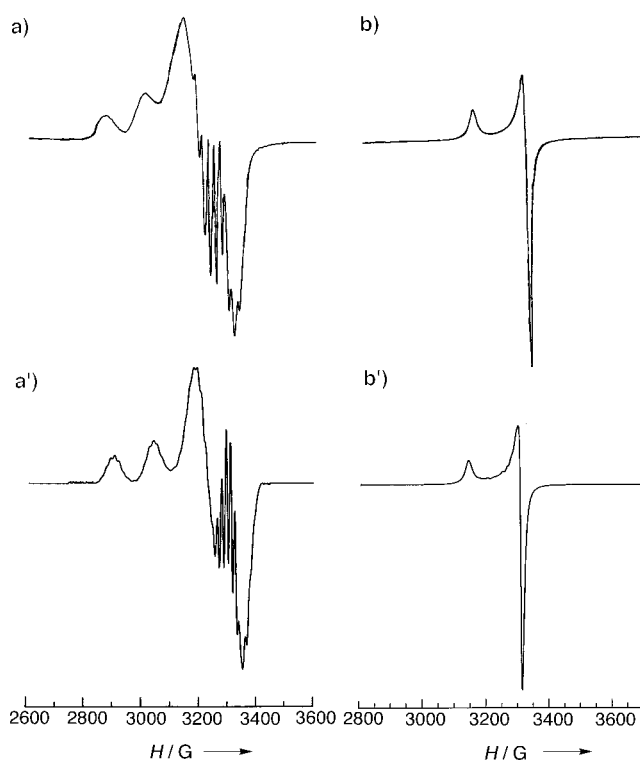


Figure 3. Observed (top) and simulated (bottom) ESR spectra of the Cu complex **3** as a powder at 298 K (a, a') and in DMF at 77 K (b, b'). a), a') $g_x = g_y = 2.031$, $g_z = 2.139$, $LW_x = LW_y = 9.5$, $LW_z = 15 \times 10^{-4} \text{ cm}^{-1}$ (LW = line width), line shape: Lorentzian, frequency, 9405 MHz, mod. $6.3 \times 10^{-4} \text{ cm}^{-1}$, 5 mW; b), b') $g_x = 2.01$, $g_y = 2.06$, $g_z = 2.13$, $A_x^{\text{Cu}} = 14$, $A_y^{\text{Cu}} = 17$, $A_z^{\text{Cu}} = 135$, $A_x^{\text{N}} = A_y^{\text{N}} = A_z^{\text{N}} = 10$, $LW_x = 7.5$, $LW_y = 13$, $LW_z = 12.5 \times 10^{-4} \text{ cm}^{-1}$, 9190 MHz, mod. $12.5 \times 10^{-4} \text{ cm}^{-1}$, 3 mW.

sample and a DMF solution of **3**. The ESR spectrum of the powder consists only of $g_x = g_y = 2.031$ and $g_z = 2.139$ peaks, which are indicative of the square-planar geometry in accordance with the X-ray structure. The rhombic structure ($g_x \neq g_y \neq g_z$) must be taken into account, however, to simulate the observed solution spectrum. The ESR parameters determined are $g_x = 2.01$, $g_y = 2.06$, $g_z = 2.13$ and $A_z^{\text{Cu}} = 135 (\times 10^{-4} \text{ cm}^{-1})$, which suggests a distortion from the square-planar form (Figure 3).^[15] A hydrogen-bonding interaction with the DMF molecule through the peripheral amide

moiety may also induce the conformational change; the ESR spectra of **3** in toluene showed the superposition of both planar and distorted signals. This conformationally greater flexibility than present in the ordinary porphyrin could provide additional advantages for the molecular design of metal complexes.

The oxidative potential values ($E_{1/2}$) for the $\text{Ni}^{\text{II}}/\text{Ni}^{\text{III}}$ and $\text{Cu}^{\text{II}}/\text{Cu}^{\text{III}}$ couples of **2** and **3** in CH_2Cl_2 were determined by cyclic voltammetry as +398 and +160 mV (versus the ferrocene/ferrocenium couple (Fc/Fc^+)), respectively. The reductive potentials, however, could not be clearly measured as a consequence of the irreversible reduction of the ligand itself. The observed $E_{1/2}$ values were more anodic-shifted than those of N-confused tetraphenylporphyrin complexes,^[2b,c] thus reflecting the poorer electron-donating nature of **1**. This feature might be the cause of the remarkable stability of the Cu^{II} complex **3**.^[16]

In conclusion, we have shown here that the N-confused calix[4]pyrrole **1** could serve as a carbon ligand to stabilize rare organometallic complexes, such as a Cu^{II} complex. Complete π conjugation was not a prerequisite for the formation of the metal–carbon bond. The facile synthesis of the ligands and the large structural flexibility of the metal complexes would make this type of ligand attractive for the wide study of organometallic reagents.

Experimental Section

1: *p*-Tolualdehyde (691.0 mg, 5.75 mmol), pyrrole (525.1 mg, 7.83 mmol), and acetone (110.3 mg, 1.90 mmol) were dissolved in CH_2Cl_2 (750 mL). Methanesulfonic acid (0.35 mL, 5.4 mmol) was then added and the reaction mixture stirred for 30 min at room temperature. After the addition of DDO (1.48 g, 6.52 mmol), the solvent was removed and the residues were separated by column chromatography on alumina and, subsequently, on silica gel using $\text{CH}_2\text{Cl}_2/\text{MeOH}$ as the eluent. The blue-colored fraction was evaporated and the residue was recrystallized from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to give **1** as a violet powder; 41.2 mg (3.4%).

2: A solution (1 mL) of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (15.4 mg, 0.0648 mmol) in MeOH was added to a solution of **1** (17.8 mg, 0.0285 mmol) in CHCl_3 (25 mL). After refluxing the mixture for 1 h, the solvent was removed and the residue was separated by column chromatography on silica gel with CH_2Cl_2 as the eluent. The first eluted, green-colored fraction was evaporated and the residue was recrystallized from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to afford **2** as greenish crystals; 10.7 mg (55%).

3: The Cu complex was obtained by a similar procedure as above but using **1** (20.4 mg, 0.0327 mmol) and $\text{Cu}(\text{OAc})_2$ (6.87 mg, 0.0378 mmol). Complex **3** was isolated as greenish crystals; 20.9 mg (93%).

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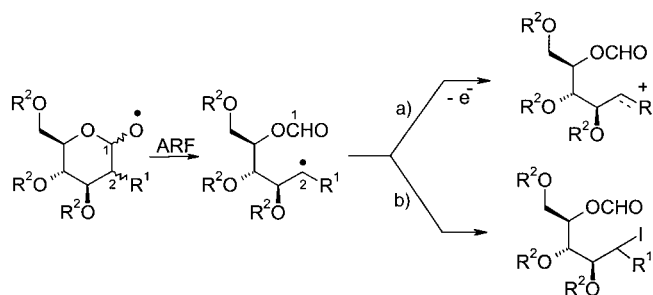
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Fragmentation of Carbohydrate Anomeric Alkoxy Radicals: A New Synthesis of Chiral 1-Halo-1-iodo Compounds**

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1,1-Dihaloalkanes, and specifically the highly reactive 1,1-diiodoalkanes, are versatile compounds in organic synthesis.^[1] Several methods for the synthesis of these compounds have been developed.^[2] Among them are the iodolysis of 1,1-bis(diisobutylaluminio)alkanes,^[2a] the alkylation of diiodomethylthium or diiodomethylsodium with reactive electrophiles,^[2b] and the reaction of 1,1-bis(trifluoromethyl)sulfonyloxy-alkanes with magnesium iodide.^[2c] None of these approaches can be easily applied to the preparation of complex or sensitive molecules. Consequently, in the majority of cases the 1,1-diiodoalkanes obtained are derivatives of relatively simple hydrocarbons.^[3] A similar situation is found for the synthesis of mixed halo-iodo species, for example 1-fluoro-1-iodo,^[4] 1-chloro-1-iodo,^[5] and 1-bromo-1-iodo compounds.^[6] Moreover, there are sufficient drawbacks to most of these procedures to justify the need for a general and practical method of generating these types of compounds under mild conditions.

Earlier research from our laboratory^[7] has shown the facile formation of glycopyran-1-*O*-yl and glycofuran-1-*O*-yl radicals by reaction of carbohydrate anomeric alcohols with hypervalent iodine reagents in the presence of iodine. The reactions presumably proceeds through an alkyl hypiodite intermediate.^[8] Subsequently the alkoxy radical undergoes fragmentation of the C1–C2 bond and gives rise to a C2 radical (Scheme 1). The substituent at C2 may have a strong influence on the ultimate fate of the radical. When the substituent is an ether group the radical is rapidly oxidized by an excess of the hypervalent iodine reagent to give an oxycarbenium ion (path a). Inter- or intramolecular trapping by nucleophiles leads to a variety of modified carbohydrate derivatives with one carbon atom less.^[7] The presence of a stronger electron-withdrawing group at C2 (e.g., an ester group, path b) decreases the electron density at this position and oxidation of the radical should be more difficult. This opens the possibility of competitive trapping of the intermediate radical by atoms of iodine from the reaction medium.



Scheme 1. The mechanism of alkoxy radical fragmentation (ARF). a) R¹ = O-alkyl; R² = protecting group. b) R¹ = OC(O)-alkyl, halogen; R² = protecting group. See text for details.

The α -iodoalkyl esters thus formed may be interesting chiral synthons.^[7f]

With the above results in mind, we decided to introduce a halogen atom at C2 in order to develop an advantageous methodology for preparing 1-halo-1-iodo compounds. We carried out the synthesis of 1,2-halohydrins of carbohydrates in pyranose and furanose form as outlined in Table 1. 1,2-Chlorohydrins, 1,2-bromohydrins, and 1,2-iodohydrins were prepared from the corresponding 2-deoxy-hex-1-enitol by reaction with *N*-chlorosuccinimide,^[9] *N*-bromoacetamide,^[10]

Table 1. Synthesis of 1-halo-1-iodo compounds.^[a]

Entry	Substrate	<i>t</i> [h]	Product	Yield [%] (<i>dr</i>)
1	1 R = F	1	5 R = F	96 (1:1)
2	2 R = Cl	3	6 R = Cl	95 (1:1)
3	3 R = Br	1.5	7 R = Br	99 (1:1)
4	4 R = I	0.75	8 R = I	92
5	9 R = Cl	1.5	12 R = Cl	96 (1:1)
6	10 R = Br	2	13 R = Br	98 (1:1)
7	11 R = I	0.5	14 R = I	84
8	15 R = Cl	1	18 R = Cl (<i>R</i> and <i>S</i>)	92 (3:2)
9	16 R = Br	1.5	19 R = Br (<i>R</i> and <i>S</i>)	93 (3:2)
10	17 R = I	1	20 R = I	90
11	21 R = Cl	0.5	24 R = Cl	83 (3:2)
12	22 R = Br	0.5	25 R = Br	92 (3:2)
13	23 R = I	0.5	26 R = I	69

[a] Halohydrin (1 mmol) in CH₂Cl₂ (50 mL) containing DIB (1.5 mmol) and iodine (1.5 mmol) was irradiated with two 80-W tungsten filament lamps at reflux temperature.

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

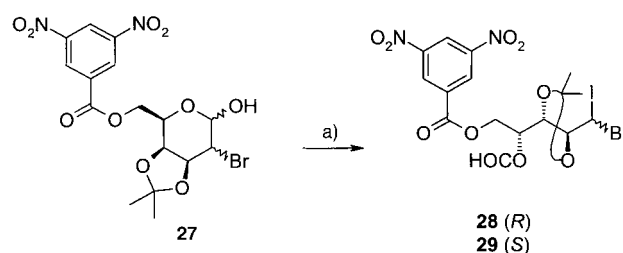
and *N*-iodosuccinimide,^[11] respectively, in THF/water. The fluorohydrin **1** was synthesized by reaction of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-*D*-arabino-hex-1-enitol with xenon difluoride,^[12] followed by acid hydrolysis of the anomeric fluoride, peracetylation, and selective anomeric *O*-deacetylation with hydrazine acetate.^[13] As detected spectroscopically, the halohydrins were diastereoisomeric mixtures in most cases.^[10] Chromatographically homogeneous products which gave correct elemental analyses were used in the fragmentation reaction.

The alkoxy radical fragmentation (ARF) reactions were performed under the conditions stated in Table 1, with (diacetoxyiodo)benzene and iodine in CH₂Cl₂ at reflux temperature and irradiation with two 80-W tungsten filament lamps. Complete consumption of the starting material was observed in all cases. In entries 1–4 of Table 1 we compare the reaction of several halohydrins of the 2-deoxy-2-haloglucopyranose type. The reaction proceeded smoothly in excellent yield to give 1-halo-1-iodo-arabinitol derivatives **5**–**8**, without affecting the stereogenic integrity of the adjacent center. As expected, diastereoselection was very low for the mixed halogen compounds, which were obtained as a chromatographically inseparable mixture of isomers. These compounds seem to be stable for long periods of time and were handled without any special precautions apart from avoiding overexposure to light or heat. The *galacto* halohydrins **9**–**11** provided a new series of 5-halo-5-iodo-arabinitol derivatives **12**–**14**, also in excellent yields and without any diastereoselectivity (entries 5–7).

Several differently protected galactopyranose halohydrins, **15**–**17**, were prepared in order to study the influence of the protecting groups on the selectivity of the fragmentation reaction (entries 8–10). A modest increment in the diastereoselectivity is observed as the steric demand of the starting halohydrin increases (compare entries 5 vs. 8 and 6 vs. 9). The mixed 1-chloro-1-iodo and 1-bromo-1-iodo diastereoisomers **18** and **19** can now be separated by chromatotron chromatography. The configuration at C1 was tentatively assigned on the basis of the significant deshielding of the C3 resonance ($\delta_S - \delta_R = 1.8$ – 2.8) observed in the ¹³C NMR spectra of the *S* series (see below).

To further extend the scope of the described method, we investigated the feasibility of applying it to the five-membered glucofuranose halohydrins **21**–**23** (entries 11–13). In all cases the reaction proceeded analogously to give a new set of halo-iodo-arabino derivatives **24**–**26** with a very different protection pattern.

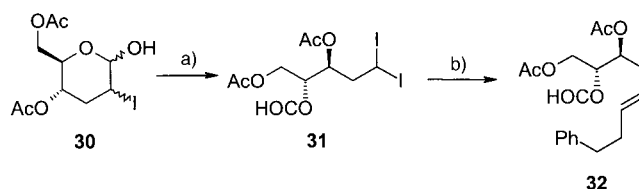
Since neither of the diastereoisomers of **18** or **19** could be crystallized, we prepared 3,5-dinitrobenzoate **27** (Scheme 2) in order to establish the absolute configuration at C1 by X-ray diffraction experiments. The diastereoisomeric mixture obtained (dr 2:1) after the ARF reaction was separated by chromatography to provide the 5-bromo-5-iodo-arabinitol derivatives **28** and **29**. Crystallization of **28** from EtOAc/*n*-hexane yielded colorless crystals suitable for X-ray studies, which confirmed the *R* configuration at C1.^[14] The observed deshielding of the C3 signal in the ¹³C NMR spectrum of **29**, possibly due to restricted rotation around the C1–C2 bond, allowed us to tentatively assign the



Scheme 2. Alkoxy radical fragmentation of halohydrin **27**. a) DIB (1.5 equiv), iodine (1.5 equiv), CH₂Cl₂, *hν*, reflux, 1 h, 93%. DIB = (diacetoxyiodo)benzene.

configuration at C1 for the mixed 1-halo-1-iodo compounds prepared previously.

Preliminary attempts to use these compounds in a Takai (*E*)-olefination^[15] of aldehydes were unsuccessful. For example, when compounds **8** and **20** were treated with hydrocinnamaldehyde with the complex chromium(II) chloride–DMF as reagent, only a mixture of the corresponding (*Z*)- and (*E*)-1-iodoalkenes was obtained by β elimination. Nevertheless, when pentitol **31**^[16] was submitted to the above conditions the expected (*E*)-olefin **32** was obtained in good yield (Scheme 3). It is worth noting the stability of the highly



Scheme 3. Alkoxy radical fragmentation of halohydrin **30**. a) DIB (1.5 equiv), iodine (1.5 equiv), CH₂Cl₂, *hν*, reflux, 30 min, 94%; b) CrCl₂ (4 equiv), hydrocinnamaldehyde (Ph(CH₂)₂CHO; 2 equiv), DMF (4 equiv), THF, RT, 30 min, 70%.

sensitive formyl ester under the reaction conditions. In the majority of cases, this reaction has been used in synthetic organic chemistry as an (*E*)-ethylenation of aldehydes with diiodoethane.^[17]

The new ARF reaction presented here offers special advantages for the synthesis of *gem*-dihalo compounds, including high efficiency, procedural simplicity, and mild reaction conditions that are compatible with the protecting groups most frequently used in carbohydrate chemistry.^[18] It is hoped that these 1-halo-1-iodo compounds will be powerful building blocks for organic synthesis since the carbohydrate would potentially be amenable to prior manipulation to provide more specific or complex systems.

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A Schizophrenic Water-Soluble Diblock Copolymer**

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Recently we reported the first example of a water-soluble diblock copolymer capable of existing in three states in aqueous solution, namely, as conventional micelles, reverse micelles, and molecularly dissolved (non-micellar) chains.^[1] This diblock copolymer was based on two tertiary amine methacrylates, 2-(diethylamino)ethyl methacrylate (DEA) and 2-(N-morpholino)ethyl methacrylate (MEMA), and was synthesized using group transfer polymerization,^[2, 3] a type of anionic polymerization which is particularly well suited to the living polymerization of methacrylates at room temperature. Formation of micelles with DEA cores was achieved merely by adjusting the solution pH value, but formation of the reverse micelles with MEMA cores required the addition of a large amount of electrolyte to selectively “salt out” the MEMA chains. To date, this remains the only well-documented example of such a “schizophrenic” block copolymer.^[4]

Since its discovery in 1995,^[5] atom-transfer radical polymerization (ATRP) has proved to be a reliable and versatile method for the synthesis of functional, controlled-structure copolymers.^[6] This free-radical polymerization chemistry is “pseudo-living” and particularly tolerant of monomer functionality; it has been used to polymerize a wide range of hydrophilic monomers with narrow molecular weight distributions and controlled architectures.^[7]

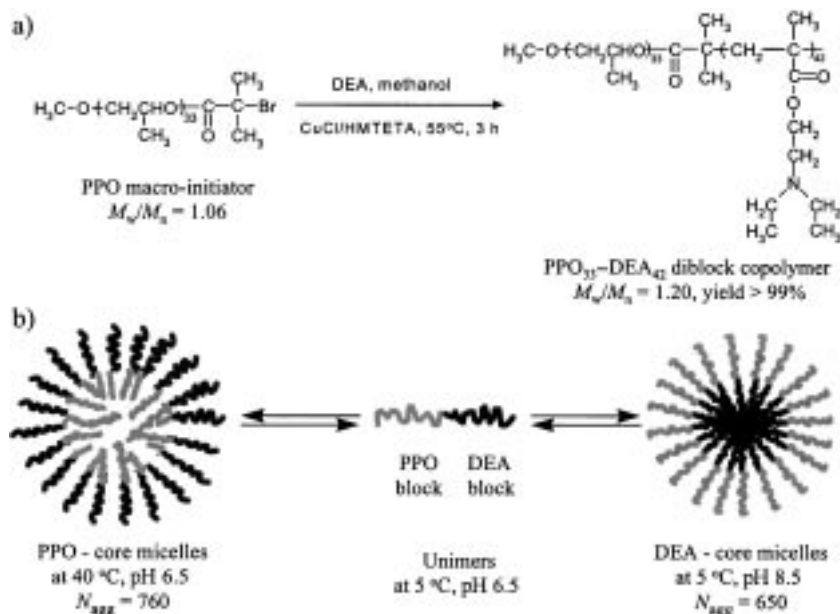
Herein we describe the facile ATRP synthesis of a new diblock copolymer based on poly(propylene oxide) (PPO) and DEA (Scheme 1a). This diblock copolymer dissolves molecularly in cold aqueous solution but undergoes reversible micellar self-assembly to give either PPO-core micelles or DEA-core micelles. Unlike the DEA–MEMA diblock copolymer reported previously, both types of micelles can be formed solely by the judicious selection of solution pH value and solution temperature.

It is well known that PPO with an M_n of around 2000 dissolves in cold, dilute aqueous solution but becomes insoluble at 20 °C; its lower critical solution temperature (LCST) lies between 10 °C and 20 °C, depending on the solution concentration.^[8] Similarly, we have recently shown that DEA homopolymer is soluble in acidic solution as a weak cationic polyelectrolyte (due to protonation of the tertiary amine residues), but precipitates from solution at around neutral pH. We have recently published several papers

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



Scheme 1. a) Synthesis of the poly(propylene oxide-block-2-diethylamino)ethyl methacrylate (PPO-DEA) copolymer by atom-transfer radical polymerization. b) Schematic representation of the formation of micelles and reverse micelles by this diblock copolymer in aqueous solution. HMTETA = 1,1,4,7,10,10-hexamethyltriethylenetetramine.

describing the pH-induced micellization of DEA-based diblock copolymers.^[1, 9]

The aqueous solution behavior of the PPO₃₃-DEA₄₂ diblock copolymer proved to be complex and fascinating, as expected. Thus this copolymer dissolved molecularly in dilute aqueous solution at pH 6.5 and 5 °C (confirmed by both ¹H NMR studies in D₂O and dynamic light scattering measurements on 0.5 w/v % solutions), since both the PPO and DEA blocks are hydrophilic under these conditions. On addition of a small amount of NaOH to this molecular solution at 5 °C, micellization occurred at a solution pH of 8.5 or higher, as indicated by the dramatic increase in hydrodynamic radius (see Figure 1a). On the basis of chemical intuition, the deprotonated DEA chains should form the hydrophobic micelle cores, with the still-solvated PPO chains forming the micelle coronas (see Scheme 1b). The ¹H NMR studies confirmed this to be the case. The NMR spectrum of the PPO₃₃-DEA₄₂ copolymer molecularly dissolved in CDCl₃ is shown in Figure 2a and was used to calculate the block composition. For the spectrum in Figure 2b the copolymer chains are also molecularly dissolved, this time in D₂O at 5 °C and pH 6.5. Comparing Figure 2b and d, it is clear that the signals due to the DEA residues at $\delta = 1.2$ and $\delta = 3.1$ have almost disappeared, indicating much lower mobility and decreased solvation for this block. On the other hand, the signals due to the PPO block at $\delta = 1.0$ and $\delta = 3.4$ are still prominent, indicating that this block forms the solvated micellar corona. Dynamic light scattering (DLS) studies indicated an intensity-averaged hydrodynamic micelle radius $\langle R_h \rangle$ of 40 nm and a polydispersity index (μ_2/I^2) as low as 0.04 by cumulants analysis. Previously we reported that DEA-based diblock copolymers become insoluble above pH 7.1–7.3 at 20 °C.^[9] However, at 5 °C the critical pH for micellization of the DEA-PPO diblock increased to about pH 8.5. Self-

assembly was completely reversible: Addition of acid resulted in instantaneous micellar dissolution, as judged by the disappearance of the characteristic bluish color of the micelles. Static light scattering (SLS) studies of these micellar solutions gave a high-quality Zimm plot (Figure 3a) which yielded an average radius of gyration $\langle R_g \rangle$ of 35 nm and a micelle mass of approximately $7.6 \times 10^6 \text{ g mol}^{-1}$. Taking the M_w of the PPO₃₃-DEA₄₂ diblock copolymer to be 11 700, this indicates a mean micelle aggregation number N_{agg} of approximately 650. The $\langle R_g \rangle / \langle R_h \rangle$ ratio is 0.875, which is only slightly larger than the value of 0.774 predicted for non-draining, uniform spheres. Analysis of transmission electron microscopy (TEM) images of DEA-core micelles (see Figure 5 of the Supporting Information) indicated a mean number-average radius of about 25–30 nm, which, allowing for hydration and probable “flattening” of the surface-adsorbed micelles, as well as polydispersity effects, is in reasonable agreement with the intensity-

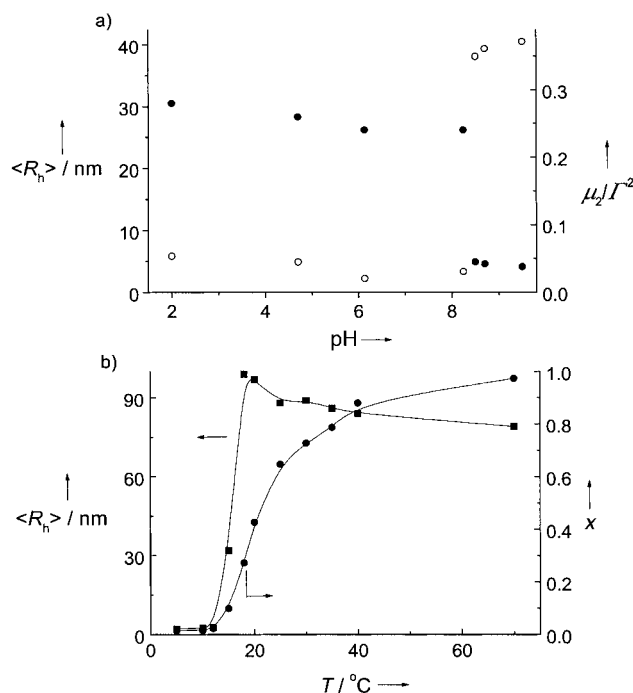


Figure 1. a) Variation of hydrodynamic radius $\langle R_h \rangle$ (○) and polydispersity index μ_2/I^2 (●) as a function of solution pH value for the PPO₃₃-DEA₄₂ diblock copolymer at 0.5 wt % and 5 °C. b) Variation of light scattering intensity X (●) and hydrodynamic radius $\langle R_h \rangle$ (■) as a function of temperature for the PPO₃₃-DEA₄₂ diblock copolymer at 0.5 wt % and pH 6.50.

average radius of 40 nm obtained from DLS studies. The DLS data also supports the formation of spherical micelles since $\langle R_h \rangle$ is almost independent of scattering angle.

Reverse micelles with PPO cores were obtained by heating the same dilute solution of PPO-DEA diblock copolymer

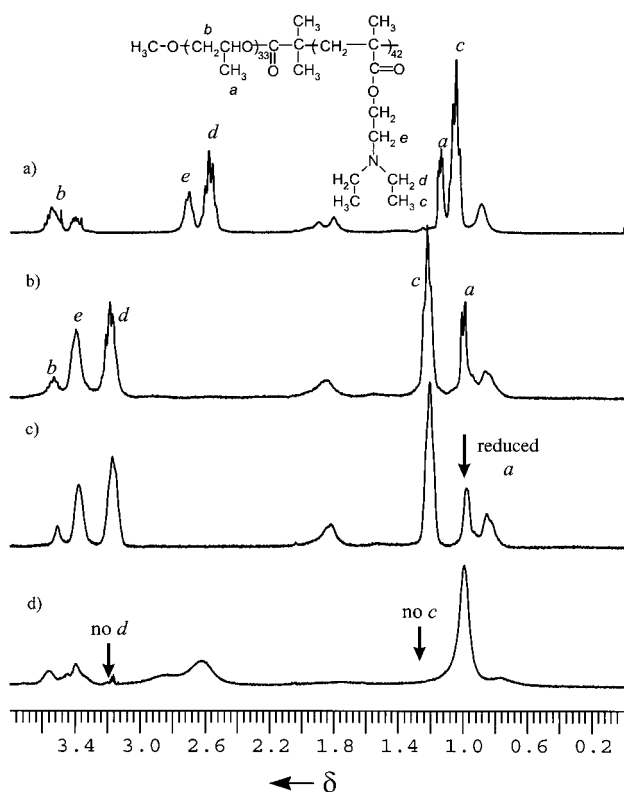


Figure 2. ^1H NMR spectra recorded for the $\text{PPO}_{33}\text{-DEA}_{42}$ diblock copolymer a) in CDCl_3 at 20°C (both blocks solvated), b) in D_2O at pH 6.5 and 5°C (molecularly dissolved copolymer), c) in D_2O at pH 6.5 and 40°C (PPO-core micelles), and d) in D_2O at pH 8.6 and 5°C (DEA-core micelles).

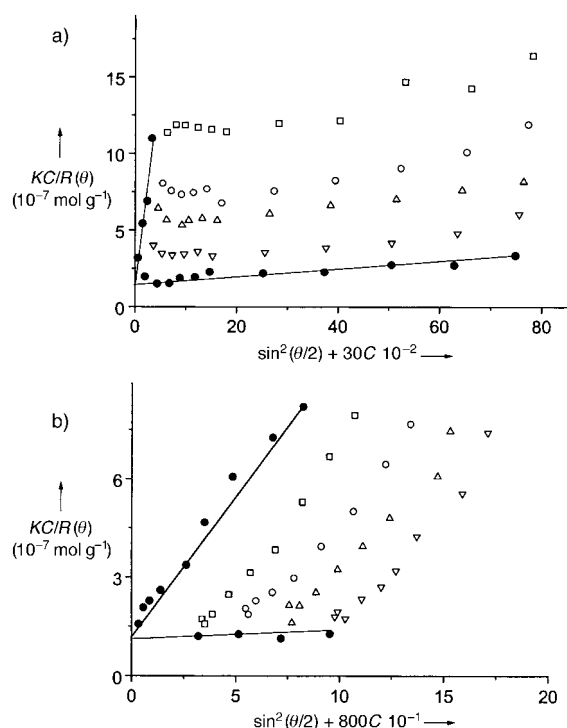


Figure 3. a) Typical Zimm plot of the $\text{PPO}_{33}\text{-b-DEA}_{42}$ micelles in aqueous solution at pH 8.50 and 5°C , where concentration C ranges from 2.074×10^{-4} to $1.109 \times 10^{-3} \text{ g mL}^{-1}$. b) Typical Zimm plot of the $\text{PPO}_{33}\text{-b-DEA}_{42}$ micelles in aqueous solution at pH 6.50 and 40°C , where C ranges from 4.012×10^{-4} to $1.190 \times 10^{-3} \text{ g mL}^{-1}$. K is optical scattering constant, R is Rayleigh ratio at an angle θ .

prepared by dissolution at 5°C and pH 6.5. Figure 1b shows the variation of light scattering intensity and intensity-averaged hydrodynamic radius as a function of solution temperature. The PPO block becomes progressively more insoluble at higher temperatures, leading to large, polydisperse, partially dehydrated aggregates initially being formed at 20°C . At higher temperatures more compact, well-defined micelles are formed with more dehydrated PPO cores, as judged by ^1H NMR spectroscopy (see Figure 2c). The DEA block remained solvated under these conditions (note the prominent signals at $\delta = 1.2$ and $\delta = 3.1$), whereas the relative intensity of the signal due to the PPO block at $\delta = 1.0$ is reduced. However, this PPO signal does not completely disappear even at 70°C (not shown), suggesting that the micelle cores remain partially hydrated. Dynamic light scattering measurements at a scattering angle of 15° indicated hydrodynamic micelle radii of 84 nm (polydispersity index 0.08) and 79 nm (polydispersity index 0.05) at 40°C and 70°C , respectively. Zimm plots yielded molar masses of approximately $8.9 \times 10^6 \text{ g mol}^{-1}$ and $1.2 \times 10^7 \text{ g mol}^{-1}$ (see Figure 3b), and the corresponding micelle aggregation numbers N_{agg} were determined to be 760 and 1020 for micelles formed at 40°C and 70°C , respectively (Table 1). These N_{agg} values are quite

Table 1. Light-scattering characterization of micelles and reverse micelles formed by $\text{PPO}_{33}\text{-b-DEA}_{42}$ diblock copolymer under different conditions.

Conditions	$M_{w,\text{micelles}}$	$\langle R_g \rangle$ [nm]	$\langle R_h \rangle$ [nm]	$\langle R_g \rangle / \langle R_h \rangle$	N_{agg}	$\langle \rho \rangle$ [g cm $^{-3}$]
DEA-core micelles pH 8.5, 5°C	7.6×10^6	35	40	0.875	650	0.047
PPO-core micelles pH 6.5, 40°C	8.9×10^6	86	84	1.02	760	0.0060
PPO-core micelles pH 6.5, 70°C	1.2×10^7	74	79	0.937	1020	0.0096

low given the relatively large micelle radii, but this probably reflects the partially hydrated nature of the PPO micelle cores, suggesting rather loosely packed aggregates. In this context, it is noteworthy that the micelles at 70°C are significantly more compact (i.e., smaller in size but with a higher aggregation number and micelle density) than those formed at 40°C ; the $\langle R_g \rangle / \langle R_h \rangle$ ratio of micelles formed at 70°C is 0.937, which is smaller than the value of 1.02 obtained for the micelles formed at 40°C ; presumably this is due to the increased dehydration of the PPO block, as indicated by the ^1H NMR studies.

For the PPO-core micelles formed, a rather large micelle radius of around 80 nm in water was observed. Even if the DEA units are fully stretched, the block copolymer could not possibly give a spherical micelle with an $\langle R_h \rangle$ of 80 nm. This unusually large micelle size is not consistent with a simple core-shell structure. At this stage, we cannot exclude the possibility that these PPO-core aggregates may be actually compound micelles or vesicles. Regardless of the precise morphology of these aggregates, the temperature-induced self-assembly process is fully reversible: Molecularly dissolved copolymer solutions are obtained on cooling to 5°C .

In summary, we report the second fully verified example of a “schizophrenic” diblock copolymer which can self-assemble to form either micelles or reverse micelles in aqueous solution. This new class of diblock copolymer surfactant is particularly easy to synthesize and its two micellar phase transitions are dictated solely by the solution temperature and the solution pH value. In view of this, we expect that the rich phase behavior of this new diblock copolymer will be of particular interest to theoreticians for testing the validity of the various theories of micellization.^[10]

Experimental Section

Synthesis of the PPO–DEA diblock copolymer: The diblock copolymer was synthesized by ATRP using a macro-initiator approach. A monohydroxy-capped poly(propylene oxide) (PPO–OH; mean degree of polymerization, $D_p = 33$ by ^1H NMR; $M_w/M_n = 1.06$ by gas-phase chromatography (GPC) with THF eluent) was kindly donated by Laporte Performance Chemicals (Hythe, UK). This PPO–OH was converted into an ATRP macro-initiator, PPO–Br, by allowing the terminal hydroxy group to react with 2-bromoisobutryl bromide in the presence of triethylamine in toluene. ^1H NMR spectroscopy confirmed that the degree of chain-end functionalization was 100%. The PPO macro-initiator (1.5 g, 0.75 mmol, 1 equiv), DEA (5.55 g, 30 mmol, 40 equiv), 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA, 172 mg, 0.75 mmol, 1 equiv) and methanol (7 mL) were added to the reaction flask; the solution was degassed by two freeze–thaw cycles. After the solution temperature was increased to 55 °C, CuCl (74 mg, 0.75 mmol, 1 equiv) was introduced as a solid into the reaction flask to start polymerization at this temperature. The reaction solution became dark green and more viscous as polymerization proceeded. After about 3 h the conversion was close to 100% as judged by ^1H NMR spectroscopy; the reaction mixture was diluted with methanol and passed through a silica column to remove residual ATRP catalyst. After solvent evaporation, the products were extracted with ice-cold water (0 °C, pH 9) several times to remove any traces of unchanged PPO macro-initiator and then dried under vacuum at room temperature. The mean D_p of the DEA block was calculated to be 42 using ^1H NMR spectroscopy. The GPC studies (THF eluent, PMMA standards, refractive index detector) of the diblock copolymer indicated a relatively narrow polydispersity (M_w/M_n) of 1.20.

Dynamic light scattering (DLS) studies were conducted with a Brookhaven model BI-200SM and 9000AT correlator using a solid-state laser (50 mW, $\lambda = 532$ nm) at a fixed scattering angle (θ) of 15° with both cumulants and CONTIN software. The dn/dc of the PPO₃₃–DEA₄₂ diblock copolymer was determined to be 0.128 in aqueous solution at pH 6.5 and 20 °C, using an Optokem differential refractometer operating at $\lambda = 632.8$ nm. Static light scattering studies (SLS) were conducted at 5 °C (DEA cores) as well as 40 °C and 70 °C (PPO cores) using the same instrument at scattering angles ranging from 15° to 135°. The M_w and R_g data were obtained using standard Zimm plot analyses, assuming that the effects of temperature and pH on the dn/dc were negligible. Variable-temperature ^1H NMR spectra were recorded on 1.0 w/v % copolymer solutions in D₂O using a Bruker Avance DPX 300-MHz spectrometer. Transmission electron microscopy studies were conducted using a Hitachi 7100 instrument operating at 75 kV and employing OsO₄ as a staining agent.

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σ -Bond Metathesis of Alkanes on a Silica-Supported Tantalum(v) Alkyl Alkylidene Complex: First Evidence for Alkane Cross-Metathesis**

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Here we report on direct evidence for the stoichiometric cross-metathesis of several alkanes (ethane, propane, and butanes) with the hydrocarbyl ligands of the surface complexes $[(\equiv\text{Si}-\text{O})_x\text{Ta}(\text{=CHCMe}_3)(\text{CH}_2\text{CMe}_3)_{(3-x)}]$ (**1**: $x = 1$, **2**: $x = 2$), and the catalytic activity of **1+2** in alkane metathesis.^[1]

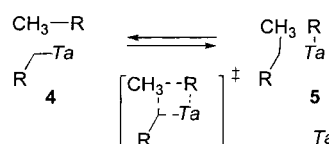
We have shown that the silica-supported tantalum hydride $[(\equiv\text{SiO})_2\text{TaH}]$ (**3**) catalyzes the metathesis of alkanes (Scheme 1).^[2, 3] The key steps proposed for the reaction mechanism are: a) activation of the C–C bond of an incoming alkane on the surface Ta alkyl complex **4** leading to the evolution of an alkane and the formation of a new surface complex **5**; and b) regeneration of **4** in an alkyl-exchange reaction (C–H bond activation).^[4]

The related structures of **1+2** and **4/5**, the two key intermediates of the proposed mechanism for alkane metathesis, is noteworthy. This analogy led us to investigate the relative reactivity towards alkanes of **1+2**, a formal d⁰ 10-e metal center, and **3**, (the precursor of **4/5**) a formal d² 8-e metal center.

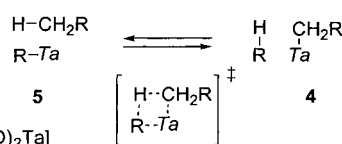
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a) C-C bond activation



b) alkane exchange (C-H bond activation)



Scheme 1. Alkane metathesis by a σ -bond metathesis mechanism.

After reaction of ethane with **1+2** (see Experimental Section), analysis of the gas phase showed the formation of methane, propane, and butanes, that is, the usual metathesis products of ethane. This demonstrates that Ta^V complexes can also act as precursors to the active species in alkane metathesis (Figure 1 and Table 1).^[5] In addition, other products that have so far not been observed in the metathesis of ethane in the presence of **3** were also obtained, namely, neopentane (NpH) and 2,2-dimethylbutane (NpMe), which are presumably derived from the neopentyl groups of **1+2** (Table 1, entry 1). The corresponding reaction of ¹³C-monolabeled ethane with **1+2** gave monolabeled NpMe^[6] and unlabeled neopentane, and thus provided clear evidence for a cross-metathesis process. Since **1+2** contains both neopentyl and neopentylidene ligands, two pathways can be considered (Scheme 2): a) a one-step mechanism involving activation of

the C-C bond by a Ta-C bond (σ -bond metathesis); b) a two-step process involving the Ta=C bond, that is, addition of a C-C bond to a Ta=C bond^[7] followed by an α -H abstraction,^[8] which is overall an apparent σ -bond metathesis process. Both processes can explain the formation of the observed products.

The reaction of **1+2** with ethane also gives neopentane, the formation of which does not

Table 1. Stoichiometric cross-metathesis of alkanes with silica-supported tantalum complexes **1+2**. Selectivity for neopentyl-containing compounds and catalytic activity in alkane metathesis.

Entry	Alkane	NpH	NpMe	NpEt	NpPr	Np/Pr	Total NpR in gas phase ^[a] [%]	TON ^[b]
1	ethane	76	24	< 1 ^[c]	— ^[d]	— ^[d]	37	25 (46)
2	propane	70	26	4	< 1 ^[c]	— ^[d]	48	58 (60)
3	butane	70	15	11	3	— ^[d]	48	55 (55)
4	isobutane	71	29	— ^[d]	— ^[d]	< 1 ^[c]	51	33 (40)

[a] Yield with respect to the amount of neopentyl and neopentylidene groups on the surface before reaction. [b] TON is defined as the number of cycles. Data in parentheses are for **3**. [c] These compounds were detected in amounts of about 0.1 % after concentration of the gas phase. [d] Not detected (< 0.1 % if any).

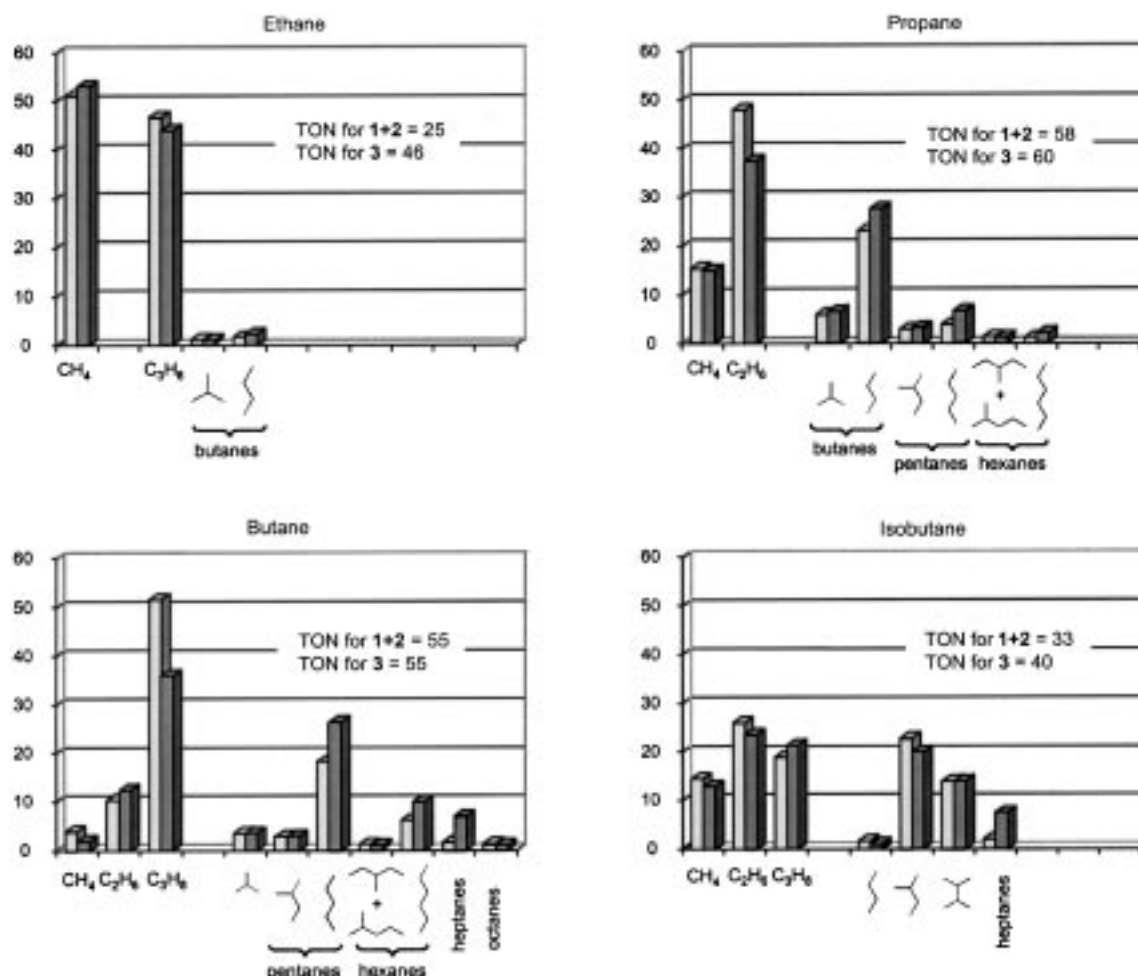


Figure 1. Percentage product distributions and turnover numbers (TONs) for the catalytic metathesis of various alkanes on **1+2** (light gray) and **3** (dark gray). Products of cross-metathesis in the case of **1+2** have been excluded for the sake of clarity; see Table 1 for details.

involve a C–C bond cleavage, but rather the activation of a C–H bond (Scheme 2). Since neopentane is the major product, C–H activation is kinetically favored over C–C activation. A C–H bond is in fact about three times easier to

In conclusion, the reaction of C–C σ bonds with a surface Ta complex containing both neopentyl and neopentylidene groups yields cross-metathesis products that were clearly identified by the *t*Bu “markers” and an active catalyst for σ -bond metathesis of alkanes. The surface complex **1+2** (Ta^{V} d^0 system) gives turnovers and selectivities comparable to those obtained with **3** (Ta^{III} d^2 system). This suggests that both systems probably lead to the same active catalyst. Since σ -bond metathesis has been mainly found for d^0 transition metals, that is, metals in their highest oxidation state, it suggests that the active species could be a Ta^{V} compound in both cases.^[10] However, we do not yet know which of the two oxidation states, if not both, is responsible for this unusual reactivity towards alkanes. Further studies are currently underway to clarify this matter.

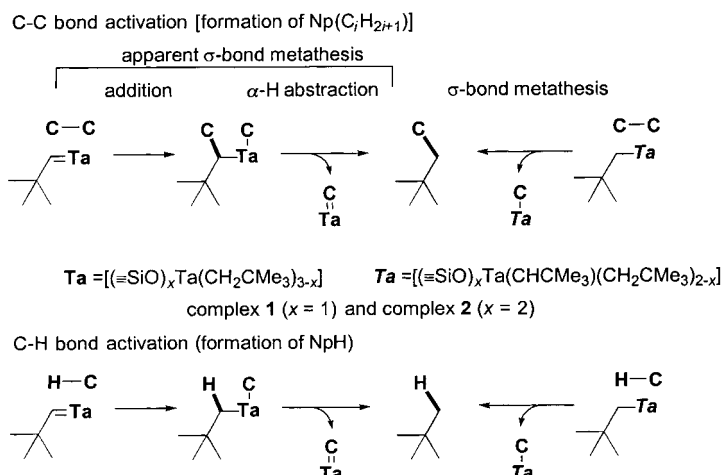
Experimental Section

The reactions were carried out with the same batch of catalyst in the strict absence of oxygen and water. **1+2** (50 mg, 0.013 mmol, 4.8% Ta) was introduced into a Pyrex batch reactor (300 mL) followed by an alkane (500–600 equiv), dried and deoxygenated over freshly regenerated molecular sieves (3 Å) and deoxo. The reaction mixture was then heated at 150 °C. Small-volume aliquots were removed, brought to atmospheric pressure, and analyzed by gas chromatography (HP 5890 apparatus, $\text{Al}_2\text{O}_3/\text{KCl}$ on fused silica column, 50 m $\times$ 0.32 mm) and GC-MS.

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Scheme 2. Carbon–carbon bond activation on **1+2**.

activate than a C–C bond of ethane under these conditions.^[9] Since the neopentyl and neopentylidene ligands were transformed by ethane into NpH and NpMe , the surface Ta complex now bears methyl (or methylidene) and ethyl (ethylidene) ligands;^[5] it is therefore similar to **4/5** or **1+2** and results in the subsequent catalytic metathesis of ethane (Table 1).

The reaction of other alkanes with **1+2** gave similar results, that is, catalytic alkane metathesis and formation of NpH and other neopentyl-containing products NpR (Table 1 and Figure 1). Propane gave NpMe and 2,2-dimethylpentane (NpEt , entry 2). Butane afforded NpMe , NpEt , and 2,2-dimethylhexane (NpPr), in contrast to isobutane, for which NpMe and only traces of 2,2,4-trimethylpentane ($\text{Np}i\text{Pr}$) were detected (entries 3 and 4). This clearly shows that each alkane gives specific products that depend on both its structure and the structure of the surface Ta alkyl complex (in the stoichiometric case: neopentyl). Moreover, the cross-metathesis leading to the transfer of one carbon atom from the incoming alkane to the surface alkyl fragment (NpMe) is favored over that of larger carbon fragments, as previously suggested by the observed selectivities for higher hydrocarbons in the catalytic reaction.^[2] The absence of reverse C–H activation products such as NpR for the reaction of RH on **1+2** is noteworthy. Hence, an order of reactivity can be proposed (Figure 2).

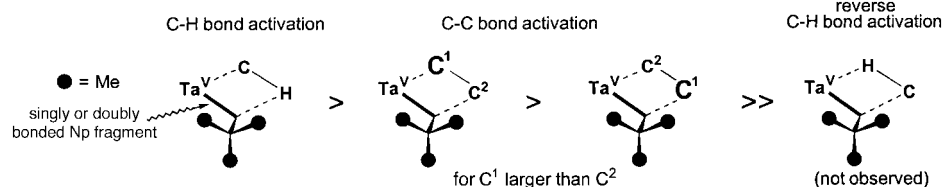


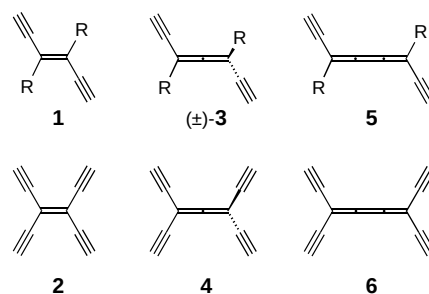
Figure 2. Order of reactivity in the reaction of alkanes with surface Ta hydrocarbyl complexes. C^1 and C^2 represent different alkyl groups.

- ment with the presence of methyldiene tantalum species. Determination of the exact structure of these surface complexes is underway.
- [6] The reaction of ^{13}C -monolabeled ethane on **1+2** gave the partially scrambled metathesis products of ethane along with unlabeled NpH and partially labeled NpMe (35% ^{13}C incorporated). This shows that at least 70% of this compound arises from cross-metathesis. The excess of unlabeled compound probably arises from rearrangement of **1+2**. Heating **1+2** under Ar at 150 °C for 15 h gives 0.25 equiv of NpH and 0.01 equiv of NpMe.
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1,3-Diethynylallenes: New Modules for Three-Dimensional Acetylenic Scaffolding**

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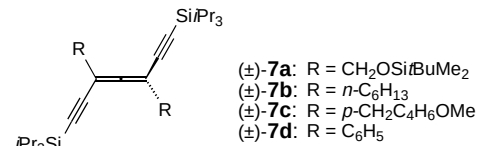
Oxidative coupling^[1] of multiply ethynylated building blocks has facilitated the assembly of well-defined molecular architecture that displays unusual electronic and optical properties.^[2] In particular, derivatives of (*E*)-1,2-diethynylethene (**1**, (*E*)-DEE, (*E*)-hex-3-ene-1,5-diyne) and tetraethynylethene (**2**, TEE, 3,4-diethynylhex-3-ene-1,5-diyne) have provided a unique class of π -conjugated precursors for the modular construction of one- and two-dimensional carbon-rich scaffolds (Scheme 1).^[3] They have provided access to monodisperse, linearly π -conjugated polytriacyetylene (PTA) oligomers that extend up to 18 nm in length,^[4] to perethynylated expanded radialenes that feature all-carbon cores (C_{30} to C_{60}), which undergo facile electrochemical reduction and



Scheme 1. Diethynyl- and tetraethynyl[*n*]cumulenes (*n* = 1–3) as carbon-rich modules for acetylenic scaffolding.

display low-energy electronic absorption bands with remarkably high molar extinction coefficients,^[5] and to photochromic molecules for photochemical switching without competing thermal isomerization pathways.^[6] Expansion of the central olefinic fragment in DEEs and TEEs leads to the di- and tetraethynylated allenes ($\pm$)-**3** and **4**, and butatrienes **5** and **6** (Scheme 1). Whereas silylated derivatives of peralkynylated butatriene **6** have been reported,^[7] 1,3-diethynyl- and tetraethynylallenes have remained elusive, despite intensive efforts aimed at their preparation.^[8] The major problems encountered in previous attempts to synthesize these novel building blocks for three-dimensional acetylenic scaffolding were their high tendency for rearrangement and facile [2+2] cycloaddition, which occurred readily even at room temperature or below.^[9]

Herein we describe the synthesis of the first 1,3-diethynylallenes ($\pm$)-**7a–d**. As a result of the inherent 90° twist of the

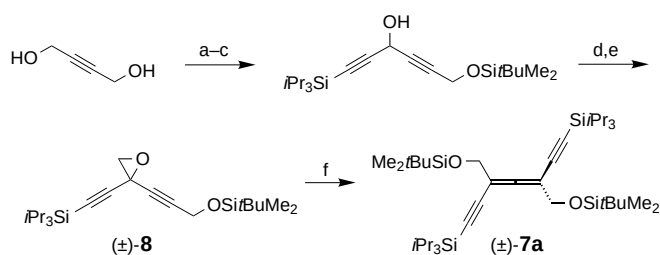


allene moiety, alkyne deprotection and oxidative acetylenic coupling of these compounds in enantiomerically pure form promises access to a fascinating new class of three-dimensional helical oligomers and polymers.^[10] Optically active helical polymers^[11] are attracting increasing interest as materials that exhibit circularly polarized electroluminescence^[12] or as dopants for cholesteric liquid-crystalline phases.^[13]

Palladium-catalyzed cross-coupling reactions have proven valuable in the preparation of alkynylallenes from substrates that bear propargylic leaving groups such as halides, epoxides, acetates, and carbonates.^[14] Given an appropriate regiochemical bias, application of these conditions to bispropargylic precursors should yield the corresponding 1,3-diethynylallenes. Thus, target compound ($\pm$)-**7a** was obtained from bispropargylic epoxide precursor ($\pm$)-**8**^[15] (prepared in five steps from but-2-yne-1,4-diol, Scheme 2) and $i\text{Pr}_3\text{SiCH}\equiv\text{CH}$ under standard palladium-catalyzed cross-coupling conditions ($[\text{Pd}(\text{PPh}_3)_4]$, CuI, HNiPr_2 , CH_2Cl_2). In situ protection of the primary alcohol that results from epoxide ring opening as the Si^tBuMe_2 ether gave 1,3-diethynylallene ($\pm$)-**7a** (Table 1)

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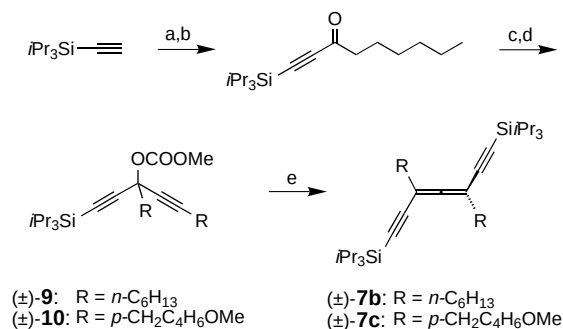
[**] We thank the ETH Research Council and the Fonds der Chemischen Industrie for their support of this work.



Scheme 2. Synthesis of 1,3-diethynylallene (±)-7a by means of epoxide ring opening. Reagents and conditions: a) NaH, *t*BuMe₂SiCl, 0 °C → RT, 65 %; b) MnO₂, Et₂O, RT; c) *n*BuLi, *i*Pr₃SiC≡CH, THF, −78 °C → RT, 34 % (over two steps); d) MnO₂, Et₂O, RT, 77 %; e) MeLi · LiBr, CH₂I₂, THF, −78 °C → RT, 79 %; f) [Pd(PPh₃)₄], CuI, HN*i*Pr₂, CH₂Cl₂, RT; then *t*BuMe₂SiCl, imidazole, DMAP, RT, 52 %. DMAP = 4-(dimethylamino)-pyridine.

as a colorless solid in 52 % yield from (±)-8. Gratifyingly, the difference in steric bulk of the two alkyne substituents (Si*i*Pr₃ vs. CH₂OSi*t*BuMe₂) in (±)-8 had induced the desired regioselectivity in the cross-coupling reaction.^[16]

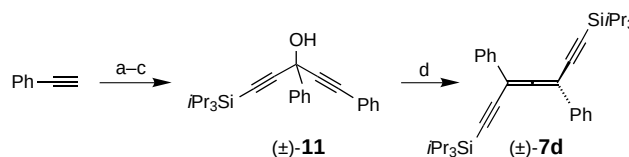
The structural limitations imposed by the epoxide opening were circumvented through the use of carbonate as the propargylic leaving group. Under the same cross-coupling conditions used above, bispropargylic precursor (±)-9 (prepared in four steps from *i*Pr₃SiC≡CH, Scheme 3) provided the



Scheme 3. Synthesis of 1,3-diethynylallenes (±)-7b and (±)-7c from bispropargylic carbonates. Reagents and conditions: a) *n*BuLi, CH₃(CH₂)₅CHO, THF, −78 °C → RT, 79 %; b) (COCl)₂, Me₂SO, Et₃N, CH₂Cl₂, −78 °C, 94 %; c) *n*BuLi, 1-octyne, THF, −78 °C → RT, 66 %; d) *n*BuLi, MeOCOC(OMe), THF, −78 °C → RT, 71 %; e) [Pd(PPh₃)₄], CuI, HN*i*Pr₂, CH₂Cl₂, RT, 94 % ((±)-7b), 57 % ((±)-7c). Carbonate (±)-10 was prepared analogously to (±)-9.

dihexyl-substituted 1,3-diethynylallene (±)-7b (Table 1) in 94 % yield, with complete conversion observed after only 30 min at room temperature. The preparation of the di(4-methoxybenzyl)-substituted allene (±)-7c (Table 1) from (±)-10 proceeded analogously, but the cross-coupling provided the target in only 57 % yield, possibly as a result of the acidity of the benzylic protons. Unlike the more sterically encumbered derivative (±)-7a, compounds (±)-7b and (±)-7c were susceptible to thermal dimerization, presumably through a stepwise radical mechanism.^[17] The half-life of neat (±)-7b was in the order of one day at room temperature, and this process was not entirely suppressed by storage at low temperature, although dilute solutions showed minimal dimerization over the course of several months.

The synthesis of cross-conjugated 1,3-diethynyl-1,3-diphenylallene (±)-7d (Table 1) was hampered by the instability of the desired propargylic carbonate precursor, even in solution at low temperature. Similarly, other acylated derivatives could not be isolated in pure form. Ultimately, access to the desired allene was achieved in a one-pot procedure through the intermediate formation of the benzoate from tertiary alcohol (±)-11, followed by direct application of the cross-coupling conditions (Scheme 4). This allene proved especially susceptible to thermal dimerization, which proceeded within minutes for the neat compound at room temperature, and therefore it could only be handled and characterized in solution.



Scheme 4. Synthesis of cross-conjugated allene (±)-7d via the bispropargylic benzoate, prepared in situ. Reagents and conditions: a) *n*BuLi, PhCHO, THF, −78 °C → RT; b) MnO₂, Et₂O, RT, 99 % (over two steps); c) *n*BuLi, *i*Pr₃SiC≡CH, THF, −78 °C → RT, 96 %; d) *n*BuLi, PhCOCl; then [Pd(PPh₃)₄], CuI, HN*i*Pr₂, THF, reflux, 38 %.

Allene (±)-7a is solid and stable at room temperature, which allowed unambiguous structural determination by X-ray crystallography.^[18] The unit cell contains two molecules each of the *P* and *M* enantiomers. The ORTEP representation (Figure 1A) shows that although there is significant thermal and orientational disorder in the silyl protecting groups, the structure of the diethynylallene backbone is well defined, with all bond lengths and angles within the expected ranges. The view down the allene axis (Figure 1B) clearly shows the orthogonal disposition of the C≡CSi*i*Pr₃ and CH₂OSi*t*BuMe₂ substituents.

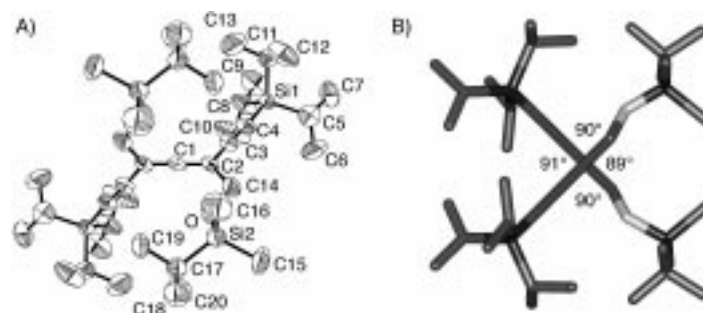


Figure 1. A) ORTEP representation of (±)-7a with vibrational ellipsoids at the 30 % probability level. Bond lengths [Å] and angles [°] for the diethynylallene backbone: C1-C2 1.297(6), C2-C3 1.433(7), C3-C4 1.205(6), C2-C1-C2' 177.7(7), C1-C2-C3 121.7(5), C2-C3-C4 176.6(6), C3-C4-Si1 175.8(5), C1-C2-C14 123.1(4), C3-C2-C14 115.2(5). B) Stick representation of (±)-7a showing the orthogonal orientation of the allene substituents.

Bisalkynylation has a profound effect on the allenic ¹³C NMR resonances. In tetraalkylallenes, the resonance for the central allene carbon atom appears at around δ = 200, whereas in tetraphenylallene the signal is shifted downfield to

$\delta = 208$.^[19] In the 1,3-diethynylallenes, this resonance appears further downfield at $\delta = 215$ –217 in ($\pm$)-**7a–c** and at $\delta = 222.6$ in ($\pm$)-**7d**. The terminal allenic resonance in ($\pm$)-**7a–d** is located between $\delta = 99$ and 102, whereas the acetylenic signals appear between $\delta = 92$ and 97 (Table 1).

Table 1. Selected physical and spectroscopic data of 1,3-diethynylallenes.

($\pm$)- 7a : $R_f(\text{SiO}_2) = 0.45$ (hexane/ CH_2Cl_2 4:1); white solid; m.p. 56–57 °C; IR (film): $\tilde{\nu} = 2944, 2891, 2147, 1944, 1464, 1388, 1361, 1333, 1254, 1111, 994, 878, 833, 779, 667 \text{ cm}^{-1}$; ^1H NMR (300 MHz, CDCl_3): $\delta = 4.20$ (s, 4H), 1.07 (s, 42H), 0.89 (s, 18H), 0.08 (s, 12H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 214.9, 98.7, 95.9, 95.1, 64.1, 25.7, 18.5, 18.1, 11.2, -5.4, -5.5$; EI-MS: m/z : 688.4 [M^+]; elemental analysis calcd for $\text{C}_{39}\text{H}_{76}\text{O}_2\text{Si}_4$ (689.38) (%): C 67.95, H 11.11; found: C 67.85, H 11.13
($\pm$)- 7b : $R_f(\text{SiO}_2) = 0.60$ (hexane); colorless oil; IR (film): $\tilde{\nu} = 2927, 2851, 2133, 1933, 1464, 1380, 1154, 1072, 990, 883, 672 \text{ cm}^{-1}$; ^1H NMR (200 MHz, CDCl_3): $\delta = 2.15$ (t, $J = 7.1 \text{ Hz}$, 4H), 1.58–1.43 (m, 4H), 1.40–1.22 (m, 12H), 1.07 (s, 42H), 0.88 (t, $J = 6.6 \text{ Hz}$, 6H); ^{13}C NMR (50 MHz, CDCl_3): $\delta = 216.2, 101.7, 92.6, 91.8, 34.1, 31.6, 28.2, 27.4, 22.4, 18.5, 14.0, 11.2$; EI-MS: m/z : 568.6 [M^+]; elemental analysis calcd for $\text{C}_{37}\text{H}_{68}\text{Si}_2$ (569.12) (%): C 78.09, H 12.04; found: C 78.22, H 12.08
($\pm$)- 7c : $R_f(\text{SiO}_2) = 0.47$ (hexane/ EtOAc 10:1); colorless oil; IR (film): $\tilde{\nu} = 2943, 2851, 2133, 1939, 1611, 1512, 1464, 1303, 1248, 1174, 1039, 883, 815, 677 \text{ cm}^{-1}$; ^1H NMR (200 MHz, CDCl_3): $\delta = 7.00$ (d, $J = 8.7 \text{ Hz}$, 4H), 6.75 (d, $J = 8.7 \text{ Hz}$, 4H), 3.78 (s, 6H), 3.34 (s, 2H), 3.33 (s, 2H), 1.03 (s, 42H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 216.9, 158.4, 130.2, 130.0, 113.6, 101.0, 93.9, 93.2, 55.1, 39.8, 18.4, 11.1$; EI-MS: m/z : 640.3 [M^+]; HR-EI-MS calcd for $\text{C}_{41}\text{H}_{60}\text{O}_2\text{Si}_2$ [M^+]: 640.4132; found 640.4129
($\pm$)- 7d : $R_f(\text{SiO}_2) = 0.65$ (hexane/ CH_2Cl_2 10:1); yellow oil; IR (film): $\tilde{\nu} = 2944, 2862, 2144, 1944, 1492, 1462, 1062, 990, 882, 759, 676 \text{ cm}^{-1}$; ^1H NMR (300 MHz, CDCl_3): $\delta = 7.65$ –7.61 (m, 2H), 7.40–7.27 (m, 8H), 1.15 (s, 42H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 222.6, 132.7, 128.7, 128.2, 126.8, 98.7, 97.6, 97.3, 18.5, 11.2$. For the [2+2] dimer of ($\pm$)- 7d : EI-MS: m/z : 1104.7 [M^+]; elemental analysis calcd for $\text{C}_{74}\text{H}_{104}\text{Si}_4$ (1106.00) (%): C 80.36, H 9.48; found: C 80.17, H 9.34

These first representative examples show how the overall stability of 1,3-diethynylallenes is affected by the electronic and steric properties of the substituents. The substantial stability of compound ($\pm$)-**7a** clearly demonstrates that bulky side chains prevent the approach of two allene units and are capable of mitigating the undesired thermal [2+2] cycloaddition to an appreciable extent. Since removal of the alkyne-protecting SiPr_3 groups from ($\pm$)-**7b** with Bu_4NF cleanly yields the corresponding bis-terminally deprotected diethynylallene (^1H NMR spectrum (CDCl_3): $\delta_{\text{C}\equiv\text{C}-\text{H}} = 2.94$), oxidative oligomerization of enantiomerically pure 1,3-diethynylallenes is expected to lead to the proposed helical oligomers with unusual chiroptical properties.

Experimental Section

($\pm$)-**7b**: $i\text{Pr}_3\text{SiC}\equiv\text{CH}$ (34 μL , 27 mg, 0.15 mmol) and HNiPr_2 (28 μL , 20 mg, 0.20 mmol) were added to ($\pm$)-**8** (46 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) at room temperature. The solution was purged with Ar for several minutes, and $[\text{Pd}(\text{PPh}_3)_4]$ (5.8 mg, 5.0 μmol) and CuI (1.9 mg, 10 μmol) were added sequentially. After an additional minute of degassing, the solution was allowed to stir at room temperature for 30 min, at which point TLC showed complete conversion. The mixture was diluted with hexanes (5 mL) and filtered through celite. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on SiO_2 (hexane) to give ($\pm$)-**7b** (54 mg, 94 %) as a clear oil.

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- [18] X-ray crystal data of ($\pm$)-**7a** ($\text{C}_{39}\text{H}_{76}\text{O}_2\text{Si}_4$, $M_r = 689.36$): orthorhombic space group *Pbcn*, $Z = 4$, $D_c = 0.963 \text{ g cm}^{-3}$, $a = 14.767(5)$, $b = 11.746(4)$, $c = 27.420(13) \text{ \AA}$, $V = 4756(3) \text{ \AA}^3$, $\text{MoK}\alpha$ radiation, 2229 independent reflections, $2 < \theta < 20^\circ$. Single crystals were grown at 4°C from $\text{CH}_2\text{Cl}_2/\text{MeCN}$. The structure was calculated by direct methods (SHELXS-86) and refined by full-matrix least-squares methods (SHELXL-93). Final $R(F) = 0.0689$, $wR(F^2) = 0.1888$ for 199 variables and 2229 observed reflections with $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) for the structures reported in this paper were deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-157566. 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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Directed Intermolecular Carbomagnesation across Vinylsilanes: 2-PyMe₂Si Group as a Removable Directing Group**

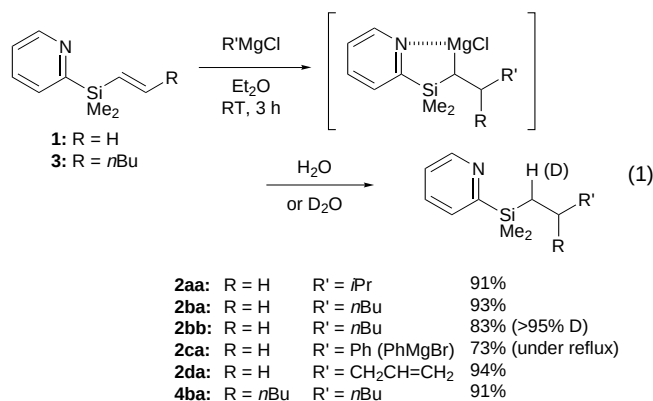
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The addition of organolithium reagents to vinylsilanes is one of the most powerful methods for the generation of synthetically useful α -silyl carbanions.^[1] Although Grignard reagents are viable alternatives for this addition reaction,^[2] serious limitations are associated with the carbomagnesation methodology: 1) Activating groups on silicon (e.g., chloro, alkoxy, and amino groups) are needed for the addition (no reaction with trialkyl(vinyl)silanes); 2) substitutions at the silicon atom are often observed as unavoidable side reactions when these activating groups are used; and 3) primary alkyl Grignard reagents are not applicable in the reaction.^[3, 4] These drawbacks profoundly diminish the synthetic usefulness of this otherwise attractive methodology.

Recently, we initiated a program to develop highly efficient hydro- and carbometalation reactions by utilizing the 2-pyr-

idyldimethylsilyl (2-PyMe₂Si) group as a removable directing group (intramolecular ligand).^[5–8] For example, highly efficient carbopalladation of vinylsilanes can be achieved with 2-PyMe₂Si group as a removable directing group.^[6] In ongoing efforts to exploit the utility of this removable directing group in carbometalation, we investigated directed intermolecular carbomagnesation across pyridyl-substituted vinylsilanes.

2-Pyridyldimethylvinylsilane (**1**) was treated with *i*PrMgCl in Et₂O, and the mixture was stirred for 3 h at room temperature. The reaction gave the corresponding α -silyl organomagnesium compound, and **2aa** was isolated after aqueous workup in 91 % yield [Eq. (1)].^[9] Much milder



reaction conditions and much shorter reaction times compared to the previous reported reactions with vinylsilanes clearly indicate the enhanced reactivity of **1**.^[2] We assume that this carbomagnesation was facilitated by the complex-induced proximity effect (CIPE).^[10] The reaction presumably involves a pre-equilibrium complex of **1** and RMgX, and this makes the subsequent carbomagnesation step intramolecular in nature. The importance of this pre-equilibrium complex was further supported by the observation of dramatic solvent effects: weakly coordinating solvents such as Et₂O favor this reaction, whereas strongly coordinating solvents such as THF disfavor it. These results may be attributed to inhibition of the formation of the pre-equilibrium complex by the coordinating solvent.^[11] In addition to this kinetic preference, we assume that stabilization of the generated α -silyl organomagnesium compound by intramolecular coordination of the pyridyl group is also responsible for the efficiency of this carbomagnesation process.^[8a]

Next we investigated the addition of a primary alkyl Grignard reagent, and found that *n*BuMgCl also adds to **1** at room temperature [Eq. (1)]. To our knowledge, this is the first example of the efficient addition of a primary alkyl Grignard reagent to a vinylsilane. In addition to secondary and primary alkyl Grignard reagents, PhMgBr^[12] and CH₂=CHCH₂MgCl also added across **1** [Eq. (1)]. The addition of CH₂=CHCH₂MgCl was complete within 1 h even at 0°C (90%). Moreover, the addition to β -substituted vinylsilane **3**, which represents a more difficult class of substrate, also took place [Eq. (1)]. Quantitative incorporation of deuterium in the position α to silicon occurred on quenching

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

Table 1. Three-component coupling reaction of vinylsilane, Grignard reagent, and electrophile.^[a]

1: R = H 3: R = <i>n</i>Bu 2: R = H 4: R = <i>n</i>Bu					
Entry	Vinylsilane	Grignard reagent	Electrophile	Product	Yield [%]
1	1	<i>i</i> PrMgCl	CH ₂ =CHCH ₂ Br	 2ac	91
2	1	<i>n</i> BuMgCl	CH ₂ =CHCH ₂ Br	 2bc	93
3	1	CH ₂ =CHCH ₂ MgBr	CH ₂ =CHCH ₂ Br	 2dc	91
4	3	<i>n</i> BuMgCl	CH ₂ =CHCH ₂ Br	 4bc	90
5 ^[b]	1	<i>n</i> BuMgCl	CH ₂ =N ⁺ Me ₂ I ⁻	 2bd	93
6 ^[c]	1	<i>n</i> BuMgCl	PhI (5 % [Pd(PPh ₃) ₄])	 2be	77
7 ^[c]	1	<i>n</i> BuMgCl	PhBr (5 % [Pd(PPh ₃) ₄])	2 be	66
8 ^[c]	1	CH ₂ =CHCH ₂ MgBr	3,5-(CF ₃) ₂ C ₆ H ₃ I (2.5 % [Pd(PPh ₃) ₄])	 2df	82
9 ^[c]	1	CH ₂ =CHCH ₂ MgBr	4-ClC ₆ H ₄ Br (2.5 % [Pd(PPh ₃) ₄])	 2dg	93
10 ^[c]	1	CH ₂ =CHCH ₂ MgBr	3,4-(CH ₃ O) ₂ C ₆ H ₃ Br (5 % [Pd(PPh ₃) ₄])	 2dh	73
11 ^[c]	1	CH ₂ =CHCH ₂ MgBr	3-bromopyridine (5 % [Pd(PPh ₃) ₄])	 2di	72

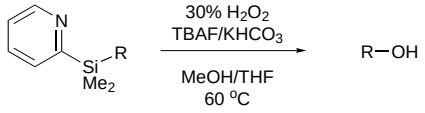
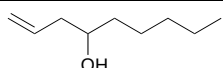
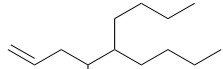
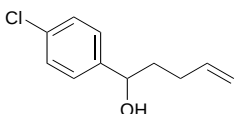
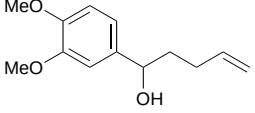
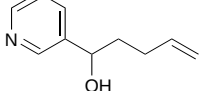
[a] Unless otherwise noted, reactions were carried out as follows: The Grignard reagent (1.1 equiv) was added to the vinylsilane (1.0 equiv) under argon, and the mixture stirred at room temperature for 1–3 h in Et₂O. Then the electrophile (2.4 equiv) was added to the mixture, which was stirred at room temperature for 3–20 h. [b] The electrophile (1.5 equiv) was added at 0 °C, and the mixture stirred for 1 h. [c] After the addition of the Grignard reagent to the vinylsilane was complete, aryl halide, [Pd(PPh₃)₄] (2.5 or 5 mol %), and toluene were added, and the resulting mixture was stirred at 80–90 °C for 24 h.

with D₂O; this indicates the reactivity of the resulting α -silyl organomagnesium compound in subsequent reactions.

Having established that intermolecular carbomagnesation across vinylsilane is efficiently directed by a 2-pyridyl group on silicon, we further investigated the three-component coupling reaction of a Grignard reagent, the vinylsilane, and an electrophile (Table 1). Electrophiles such as allyl bromide (entries 1–4) and an iminium salt (entry 5) can be used for the three-component coupling reaction. Interestingly, aryl and heteroaryl halides were also excellent electrophiles when [Pd(PPh₃)₄] was used as catalyst (entries 6–11).^[13]

Finally, the three-component coupling adducts were converted into the corresponding alcohols by tetrabutylammonium fluoride (TBAF) mediated H₂O₂ oxidation.^[7, 14, 15] Representative results are shown in Table 2. In all cases, oxidation proceeded in good to excellent yields.

Table 2. Oxidation of the coupling products with H₂O₂.^[a]

			
Entry	Coupling adduct	Oxidation product	Yield [%]
1	2bc		89
2	4bc		89
3	2dg		94
4	2dh		91
5	2di		67

[a] All reactions were performed with 30% H₂O₂ (30 equiv), TBAF (6.0 equiv), and KHCO₃ (2.0 equiv) in MeOH/THF (1/1) at 60 °C.

In summary, we have developed a novel strategy for intermolecular carbomagnesation across vinylsilanes by exploiting the 2-PyMe₂Si group as a removable directing group. By using this protocol, facile addition of primary alkyl Grignard reagents to vinylsilanes was realized for the first time. The extension to other carbometalation processes is currently under investigation.

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Pentacoordination of Silicon by Four Covalent Si–S Bonds and One Covalent Si–C Bond**

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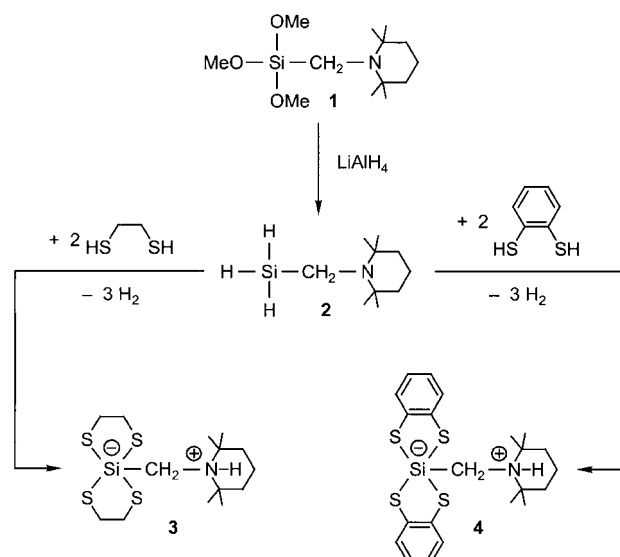
Compared to the well-established silicon–oxygen chemistry, significantly less is known about silicon–sulfur chemistry.^[1, 2] Except for a preliminary report on two pentacoordinate silicates with SiO₂S₂C skeletons,^[3] only tetracoordinate silicon compounds with Si–S bonds have been described. In a series of recent studies, we have realized several hitherto unknown bonding situations of pentacoordinate silicon by

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incorporating the pentacoordinate (formally negatively charged) silicon atom in a molecular framework bearing a tetracoordinate (formally positively charged) nitrogen atom, which leads to formation of zwitterionic species.^[3] By means of this approach, we have now synthesized the first pentacoordinate silicon compounds with SiS₄C frameworks. We report here on the synthesis and structural characterization of the zwitterionic pentacoordinate silicates **3** and **4**.

Compounds **3** and **4** were synthesized from **1**^[4] by two-step procedures (Scheme 1). Treatment of the trimethoxysilane **1** with lithium aluminum hydride in diethyl ether gave the



Scheme 1. Synthesis of the zwitterionic pentacoordinate silicates **3** and **4**.

trihydridosilane **2** (67% yield), which reacted with 1,2-ethanedithiol or 1,2-benzenedithiol in acetonitrile to give the respective zwitterionic pentacoordinate silicates **3** (83% yield) and **4** (74% yield). Both compounds were isolated as crystalline solids, and their identities were established by elemental analyses (C, H, N), crystal structure analyses, NMR spectroscopic studies in solution (¹H, ¹³C, ²⁹Si; only compound **4**), and solid-state ²⁹Si VACP/MAS NMR experiments.^[5, 6]

The zwitterions crystallize in the space groups *P*2₁2₁ (**3**) and *P*2₁/*c* (**4**) with one molecule each in the asymmetric unit. The Si coordination polyhedra of **3** and **4** in the crystal are slightly distorted trigonal bipyramids with sulfur atoms in the two axial positions (Figures 1 and 2). The equatorial Si–S distances (2.16–2.17 Å) are very similar to those observed for a variety of silicon–sulfur compounds with tetracoordinate silicon atoms and fit with the calculated value for a covalent Si–S single bond (2.17 Å).^[1b] The values for the Si–C bonds (1.93–1.94 Å) are in the upper range of the Si–C bond lengths reported so far for zwitterionic pentacoordinate silicates.^[3] The axial Si–S distances (2.29–2.34 Å)^[7] are 6–8% longer than the equatorial ones, but they are still significantly shorter than the sum of the van der Waals radii of silicon and sulfur (3.90 Å). A similar degree of bond lengthening is observed for other axial and equatorial silicon–element bonds (e.g., Si–O and Si–F) of pentacoordinate silicon compounds with a trigonal-bipyramidal structure.^[3] Considering all these struc-

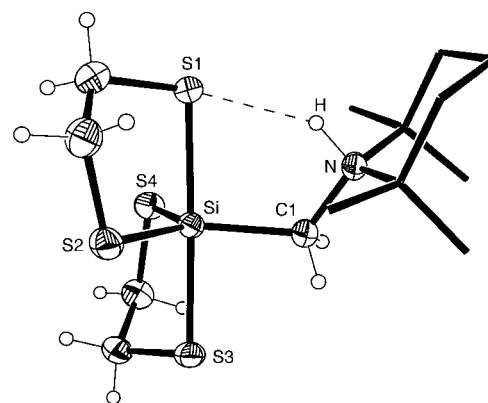


Figure 1. Molecular structure of **3** in the crystal (probability level of displacement ellipsoids 50%; tetramethylpiperidinium moiety represented as stick model for clarity). Selected bond lengths [Å] and angles [°]: Si–S1 2.3366(12), Si–S2 2.1634(14), Si–S3 2.2915(12), Si–S4 2.1675(13), Si–C1 1.939(4); S1–Si–S2 90.99(5), S1–Si–S3 178.47(6), S1–Si–S4 87.43(4), S1–Si–C1 94.45(10), S2–Si–S3 88.03(5), S2–Si–S4 121.50(6), S2–Si–C1 121.81(12), S3–Si–S4 92.08(5), S3–Si–C1 87.07(10), S4–Si–C1 116.60(12); N–H⋯S1 hydrogen bond: N–H 0.98(4), H⋯S1 2.29(4), N⋯S1 3.080(3) Å, N–H⋯S1 137(3)°.

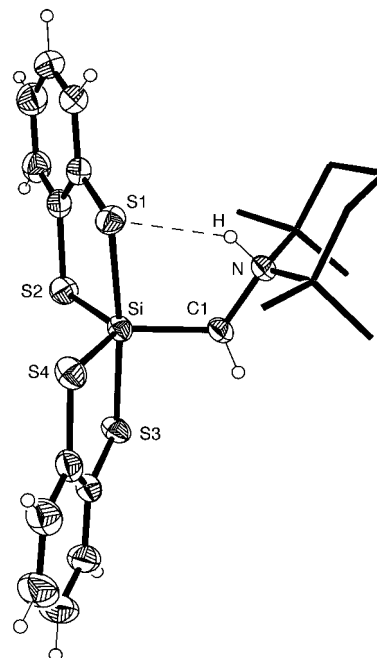


Figure 2. Molecular structure of **4** in the crystal (probability level of displacement ellipsoids 50%; tetramethylpiperidinium moiety represented as stick model for clarity). Selected bond lengths [Å] and angles [°]: Si–S1 2.3280(7), Si–S2 2.1592(9), Si–S3 2.2871(7), Si–S4 2.1588(9), Si–C1 1.929(2); S1–Si–S2 90.84(3), S1–Si–S3 173.89(3), S1–Si–S4 85.36(3), S1–Si–C1 96.54(6), S2–Si–S3 86.19(3), S2–Si–S4 124.92(3), S2–Si–C1 118.48(7), S3–Si–S4 91.96(3), S3–Si–C1 89.58(6), S4–Si–C1 116.54(7); N–H⋯S1 hydrogen bond: N–H 0.93(3), H⋯S1 2.30(3), N⋯S1 3.1017(18) Å, N–H⋯S1 145(2)°.

tural data, it is concluded that the SiS₄C skeletons of **3** and **4** are built up by five covalent bonds and do not involve a bond system in the sense of a [4+1] coordination. This is somewhat surprising in view of the relatively low electronegativity of both carbon and sulfur (Allred–Rochow values: C 2.50, S 2.44). Generally, pentacoordination of silicon is favored by ligand atoms with high electronegativity, such as fluorine, oxygen, and nitrogen atoms.^[3, 8] Hence, a theoretical analysis of the bond systems of **3** and **4** is very challenging.

The ^{29}Si chemical shift of **4** ($\delta = -57.2$) in CDCl_3 is similar to the isotropic chemical shifts determined by solid-state ^{29}Si VACP/MAS NMR experiments on **3** ($\delta = -53.0$) and **4** ($\delta = -61.0$), and this indicates that **4** also exists in solution.^[9] This is further supported by the detection of a signal for the NH group in the ^1H NMR spectrum of **4** ($\delta = 7.8$). At room temperature an A_2X spin system was observed for the $\text{SiC}(\text{H}_A)_2\text{NH}_X$ protons of **4**, which indicates that the Λ and Δ enantiomers are not configurationally stable on the NMR time scale. As shown by variable-temperature ^1H NMR studies (solvent CD_2Cl_2 ; temperature range 23 to -100°C ; 300.1 MHz), the Berry-type Λ/Δ enantiomerization becomes slower on cooling, and coalescence was observed at -95°C . However, the energy barrier for this dynamic process could not be determined, since the expected ABX spin system could not be resolved up to -100°C .

The surprising stability of the covalent Si_4C skeletons of **3** and **4** justifies the speculation that further hitherto unknown spirocyclic pentacoordinate silicate frameworks (e.g., $\text{Si}_2\text{N}_2\text{C}$ and Si_4C) may also be stable. The hydrogen-elimination route used for the synthesis of **3** and **4** offers a promising approach to the preparation of such compounds.

Experimental Section

2: A solution of **1**^[4] (6.00 g, 21.8 mmol) in diethyl ether (20 mL) was added at 0°C over 1 h to a vigorously stirred suspension of lithium aluminum hydride (1.00 g, 26.3 mmol) in diethyl ether (20 mL). The resulting mixture was stirred at 20°C for 18 h and then heated under reflux for another 4 h. After filtration, the solvent of the filtrate was removed under reduced pressure, and the crude product distilled in vacuo. Yield: 2.71 g (14.6 mmol, 67 %); b.p. $55^\circ\text{C}/0.1$ Torr; ^1H NMR (C_6D_6): $\delta = 1.06$ (s, 12 H, CCH_3), 1.42–1.52 (m, 6 H, CCH_2C), 2.12 (q, $^3J(\text{H,H}) = 3.4$, $^2J(\text{Si,H}) = 4.3$ Hz, 2 H, SiCH_2N), 3.94 (t, $^3J(\text{H,H}) = 3.4$, $^1J(\text{Si,H}) = 191.6$ Hz, 3 H, SiH); ^{13}C NMR (C_6D_6): $\delta = 18.1$ (NCCCH_2C), 25.9 (NCCCH_2C), 27.0 (CCH_3), 41.4 (SiCH_2N), 55.2 (NCC_3); ^{29}Si NMR (C_6D_6): $\delta = -54.2$ (tq, $^1J(\text{Si,H}) = 191.6$, $^2J(\text{Si,H}) = 4.3$ Hz); elemental analysis (%) calcd for $\text{C}_{10}\text{H}_{23}\text{NSi}$ ($M_r = 185.4$): C 64.79, H 12.51, N 7.56; found: C 64.4, H 12.4, N 7.7.

3: Compound **2** (504 mg, 2.72 mmol) was added dropwise at 20°C over 5 min to a stirred solution of 1,2-ethanedithiol (514 mg, 5.46 mmol) in acetonitrile (40 mL). The resulting mixture was stirred at 20°C for 2 h, the solvent removed in vacuo, and the solid crude product recrystallized from acetonitrile by cooling a saturated solution from 20 to -20°C to give **3** (834 mg, 83 %) as a colorless crystalline solid. M.p. 116°C (decomp); ^{29}Si VACP/MAS NMR: $\delta = -53.0$; elemental analysis (%) calcd for $\text{C}_{14}\text{H}_{29}\text{NS}_4\text{Si}$ ($M_r = 367.7$): C 45.73, H 7.95, N 3.81; found: C 45.9, H 7.6, N 3.8.

4: The synthesis was carried out analogously to that of **3** (**2**, 935 mg, 5.04 mmol; 1,2-benzenedithiol, 1.44 g, 10.1 mmol; acetonitrile, 20 mL) to give **4** (1.73 g, 74 %) as a colorless crystalline solid. M.p. 173°C (decomp); ^1H NMR (CDCl_3): $\delta = 1.21$ (s, 6 H, CCH_3), 1.28 (s, 6 H, CCH_3), 0.91–1.93 (m, 6 H, CCH_2C), 2.92 (d, $^3J(\text{H,H}) = 3.6$ Hz, 2 H, SiCH_2N), 6.76–6.82 and 7.16–7.18 (m, 8 H, $\text{C}_6\text{H}_4\text{S}_2$), 7.8 (brs) NH; ^{13}C NMR (CDCl_3): $\delta = 15.9$ (NCCCH_2C), 21.4 (CCH_3), 30.0 (CCH_3), 39.1 (NCCCH_2C), 45.6 (SiCH_2N), 64.6 (NCC_3), 124.2 (C_4/C_5 , $\text{C}_6\text{H}_4\text{S}_2$), 126.3 (C_3/C_6 , $\text{C}_6\text{H}_4\text{S}_2$), 139.2 (C_1/C_2 , $\text{C}_6\text{H}_4\text{S}_2$); ^{29}Si NMR (CDCl_3): $\delta = -57.2$; ^{29}Si VACP/MAS NMR: $\delta = -61.0$; elemental analysis (%) calcd for $\text{C}_{22}\text{H}_{29}\text{NS}_4\text{Si}$ ($M_r = 463.8$): C 56.97, H 6.30, N 3.02; found: C 57.1, H 6.4, N 3.1.

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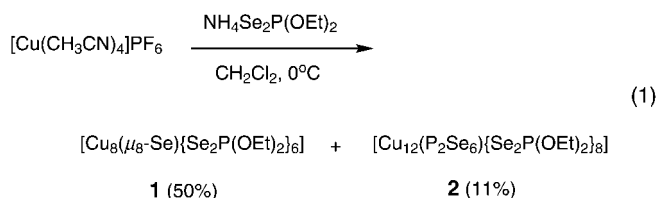
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- [5] Crystal structure analyses of **3** and **4**: Suitable single crystals were mounted in inert oil (perfluoroalkyl ether, ABCR) on a glass fiber and then transferred to the cold nitrogen gas stream of the diffractometer (Stoe IPDS; graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). The structures were solved by direct methods (SHELXS-97) and refined by full-matrix least-squares methods on F^2 for all unique reflections (SHELXL-97). For the CH hydrogen atoms, a riding model was employed. The positions of the NH hydrogen atoms were localized in difference Fourier syntheses and refined freely. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC-154812 (**3**) and CCDC-154813 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Selected data for **3**: single crystal of dimensions $0.4 \times 0.4 \times 0.3$ mm obtained by slow cooling of a solution in acetonitrile from 20 to -20°C , $\text{C}_{14}\text{H}_{29}\text{NS}_4\text{Si}$, $M_r = 367.71$, analysis at 173(2) K, orthorhombic, space group $P2_12_12_1$, $a = 9.787(2)$, $b = 11.999(2)$, $c = 15.482(3)$ Å, $V = 1818.1(6)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.343$ g cm⁻³, $\mu = 0.580$ mm⁻¹, $F(000) = 792$, $2\theta_{\text{max}} = 56.48^\circ$, 10612 collected reflections, 4150 unique reflections ($R_{\text{int}} = 0.0342$), 189 parameters, $R_1 = 0.0457$ ($I > 2\sigma(I)$), wR_2 (all data) = 0.1238, $S = 1.089$, max./min. residual electron density $0.476/-0.525$ e Å⁻³. Selected data for **4**: single crystal of dimensions $0.3 \times 0.3 \times 0.3$ mm³ obtained by slow cooling of a solution in acetonitrile from 20 to -20°C , $\text{C}_{22}\text{H}_{29}\text{NS}_4\text{Si}$, $M_r = 463.79$, analysis at 173(2) K, monoclinic, space group $P2_1/c$, $a = 8.8098(18)$, $b = 13.566(3)$, $c = 19.861(4)$ Å, $\beta = 99.60(3)^\circ$, $V = 2340.5(8)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.316$ g cm⁻³, $\mu = 0.466$ mm⁻¹, $F(000) = 984$, $2\theta_{\text{max}} = 56.28^\circ$, 14812 collected reflections, 5609 unique reflections ($R_{\text{int}} = 0.0400$), 341 parameters, $R_1 = 0.0444$ ($I > 2\sigma(I)$), wR_2 (all data) = 0.1250, $S = 1.052$, max./min. residual electron density $0.398/-0.485$ e Å⁻³.
- [6] NMR studies on **2–4**: The solution ^1H , ^{13}C , and ^{29}Si NMR spectra were recorded at 22°C on a Bruker DRX-300 NMR spectrometer (^1H , 300.1 MHz; ^{13}C , 75.5 MHz; ^{29}Si , 59.6 MHz). CDCl_3 and C_6D_6 were used as solvents. Chemical shifts were determined relative to internal CHCl_3 (^1H , $\delta = 7.24$, CDCl_3), $\text{C}_6\text{D}_5\text{H}$ (^1H , $\delta = 7.28$, C_6D_6), CDCl_3 (^{13}C , $\delta = 77.0$, CDCl_3), C_6D_6 (^{13}C , $\delta = 128.0$, C_6D_6), and external TMS (^{29}Si , $\delta = 0$, CDCl_3 , C_6D_6). Assignment of the ^1H NMR data was supported by ^1H , ^1H COSY experiments; assignment of the ^{13}C NMR data was supported by DEPT 135 experiments. Solid-state ^{29}Si VACP/MAS NMR spectra were recorded at 22°C on a Bruker DSX-400 NMR spectrometer with bottom layer rotors of ZrO_2 (diameter 7 mm) containing 250 mg (**3**) or 50 mg (**4**) of sample (79.5 MHz; external standard TMS, $\delta = 0$; spinning rate 5 kHz; contact time 5 ms; 90° ^1H transmitter pulse length 3.6 μs ; repetition time 4 s; number of transients 82 (**3**) or 181 (**4**)).
- [7] The axial Si–S1 bonds of **3** and **4** are somewhat longer than the respective axial Si–S3 bonds. This bond lengthening can be explained by the presence of intramolecular N–H $\cdots$ S1 hydrogen bonds.
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- [9] Attempts to characterize **3** by solution NMR spectroscopy (solvents: CDCl_3 , CD_2Cl_2 , C_6D_6 , CD_3CN) failed; the NMR data obtained could not be interpreted adequately.

[Cu₁₂(P₂Se₆){Se₂P(OR)₂}]₈: Discrete Copper Clusters Containing an Ethane-Like Hexaselenodiphosphate(IV)**

C. W. Liu,* Hsiu-Chih Chen, Ju-Chung Wang, and Tai-Chiun Keng

Most of the structures containing hexaselenodiphosphate(IV), P₂Se₆⁴⁻, are ternary and quaternary solid-state materials. In addition to the high-temperature reactions of the metals with P and Se, these compounds are usually synthesized by the application of the polychalcophosphate flux method. Notable examples of ternary phases are M₂P₂Se₆ (M = Pb,^[1a] Hg^[1b]) and Ti₄P₂Se₆^[1c] from Brockner et al., M₄(P₂Se₆)₃ (M = Sb, Bi)^[2], and Ag₄P₂Se₆.^[3] The quaternary phases are α,β-KMP₂Se₆ (M = Sb, Bi),^[4a, b] A₂MP₂Se₆ (A = K, Rb, Cs; M = Mn, Fe,^[4c] Pd, Zn, Cd, Hg^[4d]), A₂M₂P₂Se₆ (A = K, Cs; M = Cu, Ag),^[4c] A₂AuP₂Se₆ (A = K, Rb),^[4e] A₂Au₂-P₂Se₆ (A = K, Rb),^[4f] and Cs₈M₄(P₂Se₆)₃ (Sb, Bi)^[4g] from Kanatzidis and co-workers; KReP₂Se₆ (Re = Y, La, Ce, Pr, Gd)^[5] from Dorhout et al.; and CuMP₂Se₆ (M = Cr, In).^[6] A rare quinary selenophosphate, Rb₄Sn₂Ag₄(P₂Se₆)₃, was recently reported by Kanatzidis and Chondroudis.^[7]

The P₂Se₆⁴⁻ moiety has never been observed in discrete molecular structures isolated by the conventional “wet” chemistry method. This may be due to the difficulties arising from the transfer of discrete P₂Se₆⁴⁻ ions into compounds that are soluble in organic solvents; however, PX₄³⁻ (X = S, Se) ions may be isolated from aqueous solution as hydrates.^[8] As a result, very few discrete molecular complexes possessing selenophosphates (PSe₄³⁻) are known.^[9] They are all ionic species. Here we report the serendipitous isolation of [Cu₁₂(P₂Se₆){Se₂P(OEt)₂}]₈ (**2**) during the preparation of the selenide-centered Cu₈ cube **1** [Eq. (1)].^[10] This is the first



example of a discrete, neutral molecule containing an ethane-like P₂Se₆⁴⁻ bridging group. The coexistence of P⁴⁺ and P⁵⁺ centers in one complex is also rare and until now has only been observed in low dimensional compounds with mixed chalcophosphate anions such as K₄In₂(PSe₃)₂(P₂Se₆),

Rb₃Sn(PSe₃)(P₂Se₆),^[11a] K₂MP₂S₇ (M = V, Cr),^[11b] and A₂(RE)P₂Se₇ (A = Rb, Cs; RE = Ce, Gd).^[11c]

The single-crystal X-ray diffraction analysis of **2** establishes the presence of a dodecanuclear copper cluster that is stabilized by eight diselenophosphate (dsep) ligands and a P₂Se₆⁴⁻ ion (Figure 1).^[12] The latter is located in the center

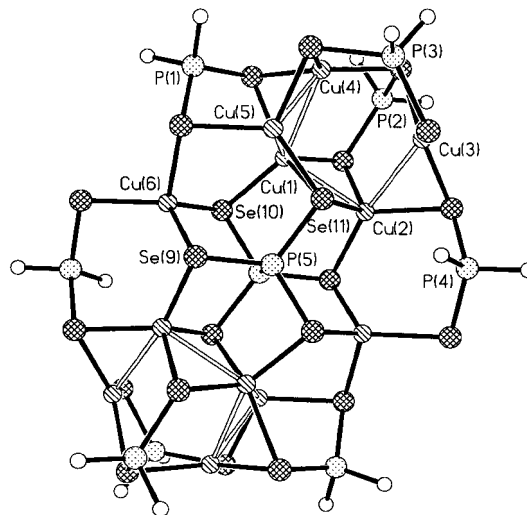
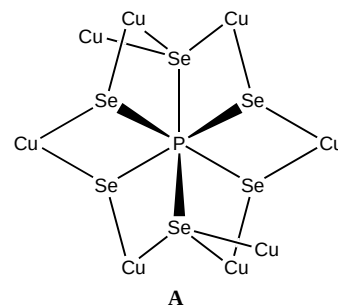


Figure 1. Structure of **2** · 4CH₂Cl₂. Hatched, cross-hatched, dotted, and white spheres represent Cu, Se, P, and O atoms, respectively; the ethyl groups have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Cu(1)–Cu(2) 2.726(2), Cu(1)–Cu(5) 2.774(2), Cu(1)–Cu(4) 2.824(2), Cu(2)–Cu(3) 2.917(2), Cu(4)–Cu(5) 2.610(2), Se(11)–Cu(5) 2.338(2), Se(11)–Cu(2) 2.519(2), Se(11)–Cu(1) 2.657(2), Se(9)–Cu(6) 2.438(2), Se(9)–Cu(2a) 2.445(2), Se(10)–Cu(6) 2.431(2), Se(10)–Cu(1) 2.449(2), P(5)–Se(11) 2.234(3), P(5)–Se(9) 2.185(3), P(5)–Se(10a) 2.177(3), P(5)–P(5a) 2.241(5), P–O 1.564(9)–1.596(9); Se(9)–P(5)–Se(11) 114.8(1), Se(9)–P(5)–Se(10a) 114.2(1), Se(11)–P(5)–Se(10a) 110.3(1).

of the cluster and has an ethane-like geometry in a staggered conformation; the Se–P(5)–Se angle averages 113.1(1)°. With a center of symmetry at the midpoint of the P–P bond, each “PSe₃” moiety of the P₂Se₆⁴⁻ ligand consists of one μ₃-Se atom and two μ₂-Se atoms that bridge seven Cu atoms. The P–P bond length of 2.241(5) Å corresponds to the value expected for a P–P single bond and has been observed in several compounds that contain P₂Se₆⁴⁻ ions.^[1–7] The variation of the bonding modes can be seen in the different P–Se and Cu–Se bond lengths. The P(5)–Se(11) bond at the μ₃-Se atom (2.234(3) Å) is significantly longer than the P(5)–Se(9) and P(5)–Se(10) bonds at the μ₂-Se atom (2.185(3) and 2.177(3) Å, respectively). While the μ₃-Se–Cu bond lengths are in the range of 2.338(2)–2.657(2) Å, the μ₂-Se–Cu bonds within P₂Se₆⁴⁻ are close to 2.440(2) Å.

Overall the hexaselenodiphosphate ligand adopts the unprecedented μ₈:η³:η²:η²:η²:η² coordination mode **A**. The four outer copper atoms are additionally connected to the eight inner copper atoms by eight dsep ligands. Thus three kinds of coordination



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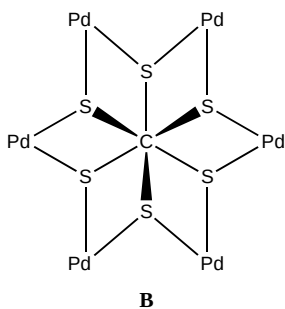
[**] R = Et, iPr. This research was supported by the National Science Council of Taiwan (NSC 89-2113-M-033-017).

environments are observed around the copper atoms. While Cu(3) and Cu(4) and their symmetric counterparts Cu(3a) and Cu(4a) are trigonally coordinated by three selenium atoms from three dsep ligands, Cu(5) and Cu(5a) are coordinated by two Se atoms from two dsep ligands, with a selenium atom of the $P_2Se_6^{4-}$ moiety occupying the third coordination site. On the other hand, Cu(1), Cu(2), and Cu(6) are each tetrahedrally coordinated by two selenium atoms from $P_2Se_6^{4-}$ and two selenium atoms from two dsep ligands. The dsep ligands also exhibit two distinct bridging modes. Four of them (P(3), P(3a), P(4), P(4a)) are trimetallic triconnective (μ_2, μ_1), and the rest (P(1), P(1a), P(2), P(2a)) show tetrametallic tetraconnective (μ_2, μ_2) coordination patterns.^[13]

Several "short" Cu–Cu distances for metal centers connected by dsep ligands are noteworthy: While the bond lengths of Cu(1)–Cu(2), Cu(1)–Cu(5), and Cu(5)–Cu(4) (2.726(2), 2.774(2), and 2.610(2) Å, respectively) are shorter than the sum of the van der Waals radii for copper (2.80 Å),^[14] those of Cu(1)–Cu(4) and Cu(2)–Cu(3) (2.824(2) and 2.917(2) Å) are slightly longer. The short Cu–Cu separations may be rationalized by either the strong d^{10} – d^{10} interactions between the metal centers^[15] or the ligand-imposed cluster geometry.^[16]

The ^{31}P NMR spectrum of **2** exhibits intriguing fluxional behavior in solution. A singlet at $\delta = 134.0$ flanked by two sets of satellites with coupling constants of 173 and 347.8 Hz ($^1J_{P-Se}$) can be reasonably assigned to the P^{4+} center of the $P_2Se_6^{4-}$ moiety; these coupling constants are comparable with those observed in $P_2Se_6^{2-}$,^[9b] $[Fe_2(CO)_4(PSe_5)_2]^{2-}$,^[9b] and $[SeW(PSe_4)(PSe_2)]^{2-}$.^[9a] The satellite with smaller coupling can be assigned to μ_3 -Se (Se(11)), as it displays a slightly longer P–Se bond length (see above). The cluster core, $Cu_8(P_2Se_6)$, remains intact in solution, as reflected by the variable temperature ^{31}P NMR study (Figure 2). On the other hand, the peripheral eight dsep ligands are fluxional in solution. This indicates labile Cu–Se bonding.^[17] The four chemical shifts for P^{5+} in the range of $\delta = 65$ –84 cannot be resolved until $-60^\circ C$ in $CDCl_3$. Each resonance is flanked by two sets of satellites, which indicates slightly different selenium environments in the dsep ligand.

The coordination of $P_2Se_6^{4-}$ observed in **2** is unprecedented and has not even been identified in mixed ligands containing Group 15/16 elements.^[18] Several years ago Kanatzidis and Kim isolated and structurally characterized two hexanuclear palladium clusters containing a hexathioorthoxalate ligand, $C_2S_6^{6-}$, in its center.^[19] The $C_2S_6^{6-}$ ligand, which presumably originated from the methanolothermal reaction



of Na_2S_4 and a liberated methyl group of the starting cation $[(CH_3)_3N(CH_2CH_2)_3N(CH_3)]^{2+}$, also has an ethane-like geometry in a staggered conformation. Each sulfur atom in the cluster bridges two palladium(II) atoms in the $\mu_6:\eta^2:\eta^2:\eta^2:\eta^2:\eta^2$ coordination mode **B**. Although the $C_2S_6^{6-}$ anion is isostructural

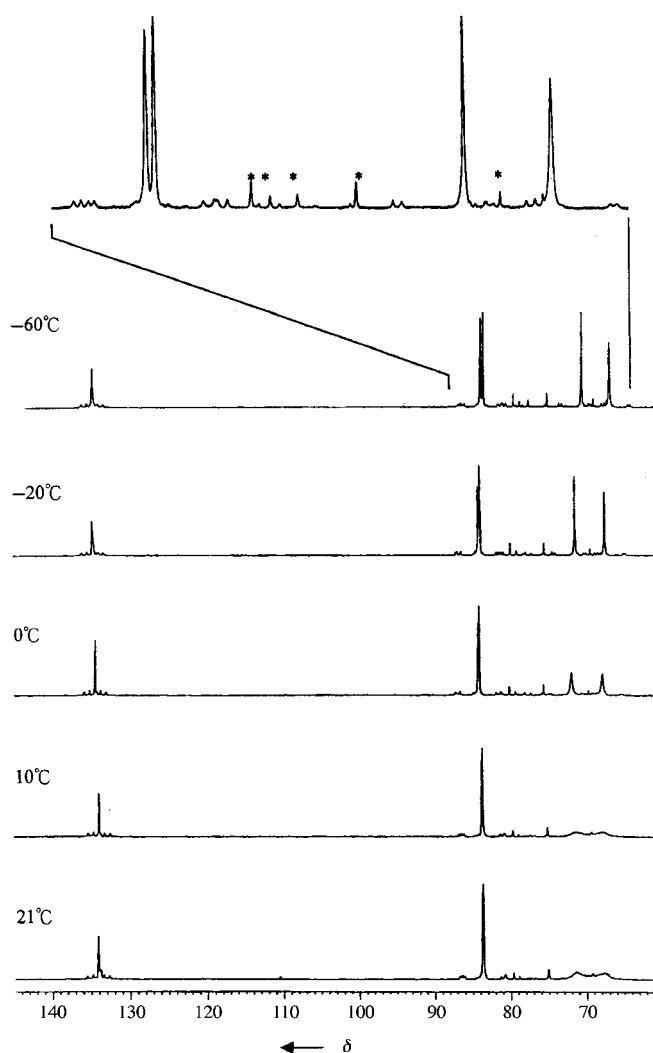


Figure 2. Variable-temperature ^{31}P NMR spectra of cluster **2**. The asterisks indicate impurities.

and isoelectronic to $P_2Se_6^{4-}$, the coordination patterns demonstrated by these two anions are dramatically different.

In conclusion, the first molecular cluster containing the hexaselenodiphosphato ligand has been isolated as the novel dodecanuclear copper species **2**, in which tetravalent and pentavalent phosphorus atoms coexist. The isopropyl derivative **3** has also been structurally characterized.^[12] Although it is still not known how the $P_2Se_6^{4-}$ anion in these clusters is formed, it evidently originates from $Se_2P(OR)_2^-$ during the reaction. Recently Fenske et al. used $SP(SSiMe_3)_3$ as a precursor to $P_2S_6^{4-}$ ligands.^[20] Work toward the development of a rational synthesis of **2** is currently underway.

Experimental Section

All operations were carried out under N_2 atmosphere with standard Schlenk techniques.

1 and 2: $NH_4Se_2P(OEt)_2$ (600 mg, 2.02 mmol) in CH_2Cl_2 (30 mL) at $0^\circ C$ was stirred for 30 min and then $[Cu(CH_3CN)_4]PF_6$ (250 mg, 0.60 mmol) was added; a yellow solution was obtained after 24 h of stirring. The solvent was evaporated under vacuum, and the residue was washed with copious amounts of diethyl ether. Column chromatography of the residue on silica

gel with $\text{CH}_2\text{Cl}_2/n\text{-hexane}$ (1/5) as eluent yielded a yellow band of **1** (85.6 mg, 50%) and an orange band of **2** (20 mg, 11%).

1: Elemental analysis calcd for $\text{C}_{24}\text{H}_{60}\text{Cu}_8\text{O}_{12}\text{P}_6\text{Se}_{13}$: C 12.75, H 2.67; found: C 12.77, H 2.42; $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3): δ = 78.5 ($^1J(\text{Se,P})$ = 674 Hz); ^1H NMR (CDCl_3 , 25 °C): δ = 1.34 (t, $^3J(\text{H,H})$ = 7 Hz, 36H; CH_3), 4.13 (m, 24H; CH_2); positive-ion FAB-MS (nitrobenzyl alcohol): m/z : 2261.4 [M^+].

2: Elemental analysis calcd for $\text{C}_{32}\text{H}_{80}\text{Cu}_{12}\text{O}_{16}\text{P}_{10}\text{Se}_{22}$: C 10.89, H 2.28; found: C 10.99, H 2.35; $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , -60 °C): δ = 134.0 ($^1J(\text{P,Se})$ = 173.0, 347.8 Hz), 65.7 ($^1J(\text{Se,P})$ = 573, 660 Hz), 69.6 ($^1J(\text{Se,P})$ = 660, 729 Hz), 82.8 ($^1J(\text{Se,P})$ = 608, 677 Hz), 83.2 ($^1J(\text{Se,P})$ = 624, 712 Hz); ^1H NMR (CDCl_3 , 25 °C): δ = 1.33 (t, $^3J(\text{H,H})$ = 7 Hz; CH_3), 1.40 (t, $^3J(\text{H,H})$ = 7 Hz; CH_3), 4.09 (m; CH_2), 4.20 (m; CH_2).

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- [12] Crystal data for **2** $\cdot 4\text{CH}_2\text{Cl}_2$ (R = Et; $\text{C}_{36}\text{H}_{88}\text{Cl}_8\text{Cu}_{12}\text{O}_{16}\text{P}_{10}\text{Se}_{22}$): T = 293 K, triclinic, space group $P\bar{1}$, a = 13.1963(7), b = 14.2952(8), c = 15.1684(8) Å, α = 63.016(1), β = 82.315(1), γ = 86.789(1)°, V = 2527.0(2) Å³, Z = 1, ρ_{calcd} = 2.543 g cm⁻³, μ = 10.807 mm⁻¹, $2\theta_{\text{max}}$ = 50.10°, $R1$ = 0.0672 and $wR2$ = 0.1799 for 12 163 data (8440 independent), 469 parameters, max./min. residual electron density 1.557/–1.317 e Å⁻³. Crystal data for **3** $\cdot 2\text{H}_2\text{O}$ (R = *i*Pr; $\text{C}_{48}\text{H}_{116}\text{Cu}_{12}\text{O}_{18}\text{P}_{10}\text{Se}_{22}$): T = 298 K, triclinic, space group $P\bar{1}$, a = 14.5231(8), b = 14.5733(8), c = 14.5958(8) Å, α = 84.055(1), β = 71.493(1), γ = 78.208(1)°, V = 2865.1(3) Å³, Z = 1, ρ_{calcd} = 2.197 g cm⁻³, μ = 9.350 mm⁻¹, $2\theta_{\text{max}}$ = 50.06°, $R1$ = 0.0522 and $wR2$ = 0.1274 for 14 084 data (9588 independent), 446 parameters and 8 restraints, max./min. residual electron density 1.197/–0.875 e Å⁻³. Single crystals were obtained directly from the reaction products. Data were collected on a Siemens SMRT diffractometer using

graphite-monochromated $\text{MoK}\alpha$ radiation (λ = 0.71073 Å) and were corrected for Lorentzian, polarization, and ψ -scan absorption effects. The structures were solved by direct methods and refined against all data using SHELXTL-Plus 5.03. Nine out of 36 carbon atoms were disordered in the crystal of **3** (R = *i*Pr). The bond distances were constrained for disordered atoms and atoms connected to them during the structural refinement (C–C 1.550, O–C 1.450 Å). All but the disordered atoms were refined anisotropically. 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-157620 (**2**, R = Et), and CCDC-157621 (**3**, R = *i*Pr). 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 Superoxovanadium(v) Complex Linking the Peroxide and Dioxygen Chemistry of Vanadium**

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Dedicated to Professor Ernst G. Jäger
on the occasion of his 65th birthday

Within the one-electron redox chemistry of dioxygen species, the superoxide anion links the chemistry of molecular oxygen and peroxide. While peroxovanadium complexes are well established, superoxovanadium complexes are quite rare and have only been observed transiently by ESR spectroscopic methods as short-lived species in the reaction of vanadyl(IV) ions with hydrogen peroxide or in the reaction of metavanadate with mixtures of $\text{Ce}^{4+}/\text{H}_2\text{O}_2$ or $\text{Fe}^{2+}/\text{H}_2\text{O}_2$, using rapid-mixing flow techniques in the cavity of the ESR

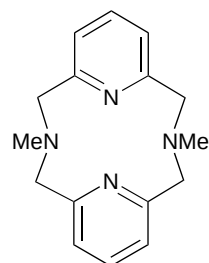
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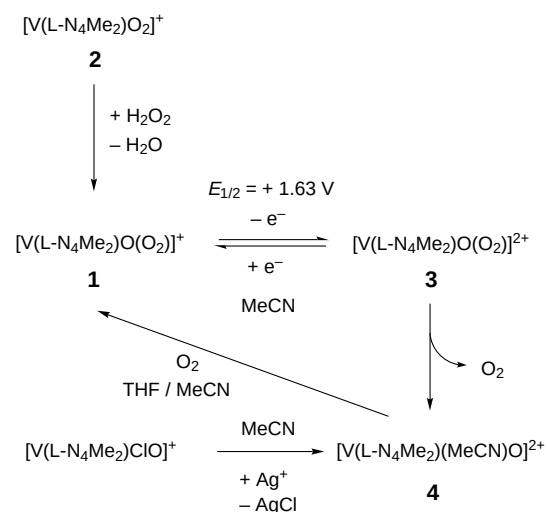
spectrometer.^[1] The possible involvement of an oxosuperoxo-vanadium(v) intermediate has also been proposed, based solely on kinetic evidence, for the reaction of vanadyl(IV) or dioxovanadium(V) ions in hydrogen peroxide in the presence of various oxidizing reagents.^[2] But in all these studies, the precise nature of the compounds involved in the reactions was not resolved. Here we describe for the first time the controlled

preparation of an oxosuperoxo-vanadium(V) complex from a defined and well-characterized precursor complex by electrochemical means. Further, we provide evidence that this oxosuperoxo-vanadium(V) complex represents an important link between the dioxygen and peroxide chemistry of vanadium.

The starting point of our investigation is the red oxoperoxovanadium(V) complex $[V(L-N_4Me_2)O(O_2)]^+$ (**1**), which is obtained in 88% yield from the reaction of the dioxovanadium(V) complex $[V(L-N_4Me_2)O_2]^+$ (**2**)^[3] with 30% aqueous hydrogen peroxide in acetonitrile (Scheme 1). X-ray structure analysis^[4] reveals



$L-N_4Me_2$



Scheme 1. Synthesis and reactions of **1**.

that the overall coordination environment of the vanadium ion in complex **1** (Figure 1) consists of the tetraazamacrocyclic ligand $L-N_4Me_2$, a terminal oxo, and a side-on-bound peroxo group. The O–O bond axis and the $N_{amine}-N_{amine}$ axis are nearly colinear. The O–O bond length of 1.400 Å is consistent with the formulation of the O_2 unit as peroxo group and is at the lower range of the O–O distances commonly found in mononuclear oxoperoxovanadium(V) complexes (1.379–1.451 Å).^[5–7] The coordination of the side-on-bound peroxo group and of the macrocycle $L-N_4Me_2$ is confirmed by ^1H NMR and IR spectroscopy. Thus, the ^1H NMR spectrum of the diamagnetic compound clearly demonstrates that, in solutions of complex **1**, the macrocyclic ligand remains coordinated through all its nitrogen donor atoms. Further, the presence of two AB and two AB₂ splitting patterns for the

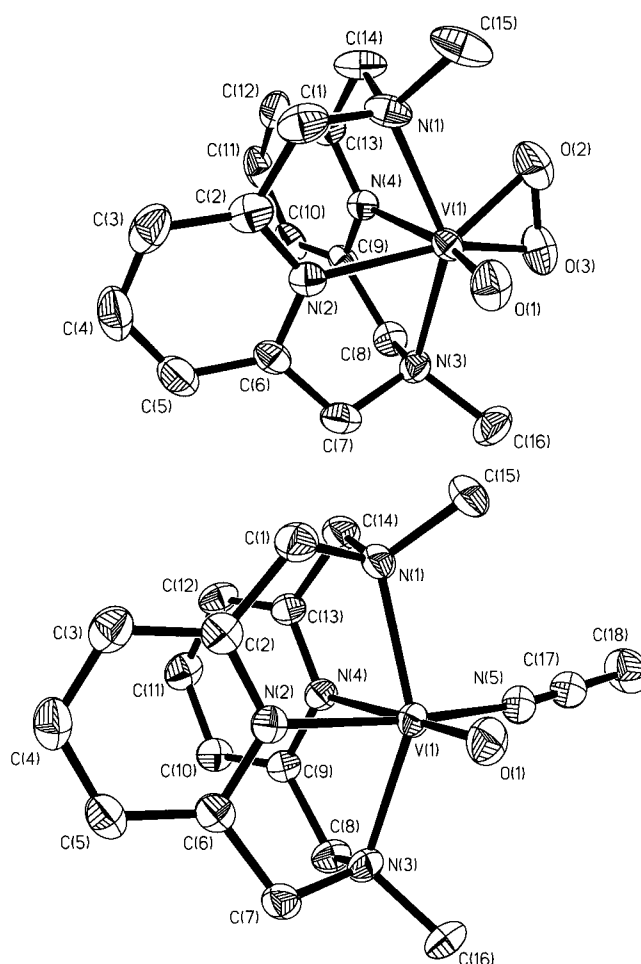


Figure 1. Perspective view of the complex cations $[V(L-N_4Me_2)O(O_2)]^+$ (**1**, top) and $[V(L-N_4Me_2)(MeCN)O]^{2+}$ (**4**, bottom) showing thermal ellipsoids at 50% probability and the atom-numbering schemes. Selected bond lengths [Å] and angles [°]: **1**: V(1)–O(1) 1.613(2), V(1)–O(2) 1.851(3), V(1)–O(3) 1.847(3), V(1)–N(1) 2.204(4), V(1)–N(2) 2.155(3), V(1)–N(3) 2.216(3), V(1)–N(4) 2.159(3), O(2)–O(3) 1.400(5); O(2)–V(1)–O(3) 44.5(1), N(1)–V(1)–N(3) 143.9(1), N(2)–V(1)–N(4) 74.0(1); **4**: V(1)–O(1) 1.602(2), V(1)–N(1) 2.173(2), V(1)–N(2) 2.053(2), V(1)–N(3) 2.177(3), V(1)–N(4) 2.192(2), V(1)–N(5) 2.099(2); N(1)–V(1)–N(3) 148.11(7), N(2)–V(1)–N(4) 78.30(8).

methylene and the pyridine ring protons in **1** are indicative of a C_s symmetry for the complex cation. On the basis of ^{18}O -isotope substitution experiments, the features at 953, 942, 580 and 569 cm^{-1} in the IR spectrum of **1** in acetonitrile are attributed to the V=O, O–O, and the two V– O_2 stretching vibrations, respectively. The visible region of the electronic absorption spectrum of **1** distinguishes itself from that of **2** only in the appearance of an absorption band at 443 nm that is responsible for the red color of the complex. The assignment of this band as a peroxo-to-vanadium ligand-to-metal charge transfer (LMCT) transition,^[6, 8] as well as the previous assignments of the stretching vibrations, were confirmed by resonance Raman spectroscopy.

Probably the most intriguing chemical property of **1** is revealed by its cyclic voltammogram. Thus, complex **1** is oxidized by one electron at 1.63 V versus SCE (1.20 V vs. Fc/Fc^+). At room temperature, the oxidative response approaches electrochemical quasi-reversibility at higher scan rates ($\Delta E = 97$ mV, $|i_{p,c}/i_{p,a}| = 0.89$ at 200 $mV s^{-1}$). Lowering the

scan rates results in a decrease of the current ratio $|i_{p,c}/i_{p,a}|$ to about 0.50 at 10 mV s^{-1} . At -40°C the current ratio is improved, although the separation of the peak potentials ΔE is increased to 167 mV. Quantitative electrolysis of **1** at an applied potential of 1.80 V at -40°C accounts for the transfer of 1.05 e^- per molecule. Upon immediate re-reduction, approximately 79 % of the originally employed **1** is recovered. None of the starting material **1** is regained if the oxidation and the consecutive reduction are carried out at room temperature.

By performing the electrolysis at -30°C in the cavity of an ESR spectrometer, the immediate oxidation product can be investigated. The solution ESR spectrum (Figure 2a) consists

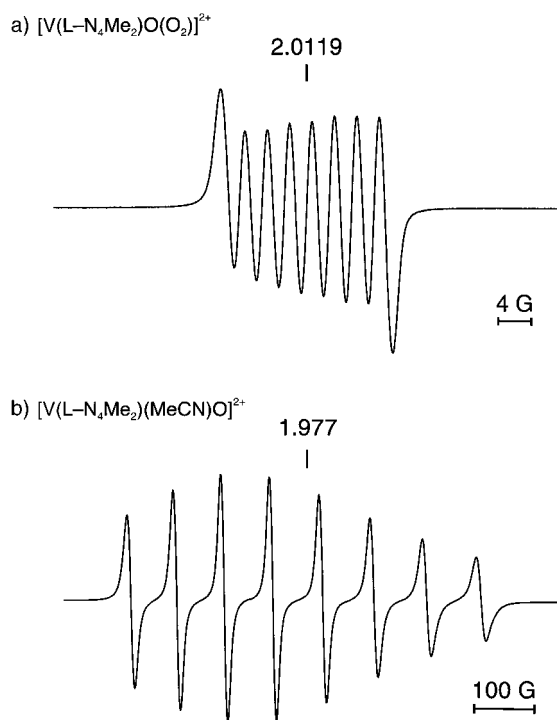


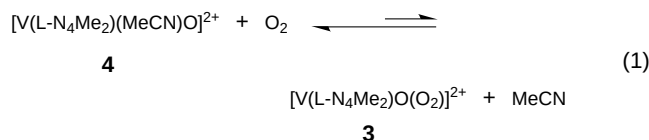
Figure 2. X-Band ESR spectra of a) a solution of $[\text{V}(\text{L-N}_4\text{Me}_2)\text{O}(\text{O}_2)]^{2+}$ ions (**3**) electrochemically generated in MeCN (containing 0.2 M NBu_4ClO_4 as electrolyte) at -30°C in the ESR cavity and b) after raising the temperature to room temperature. (g_{iso} values are indicated).

of a signal at $g_{\text{iso}} = 2.0119$ that is split into eight lines with a hyperfine coupling constant $A_{\text{iso}}^{\text{V}}$ of $2.50 \times 10^{-4} \text{ cm}^{-1}$. The g value larger than 2.0 and the very small hyperfine coupling constant to the vanadium nucleus ($I = 7/2$) suggest the presence of a ligand radical bound to a vanadium ion. This result unambiguously proves that, during oxidation of **1**, the electron is removed from a molecular orbital on the peroxo ligand, resulting in the formation of the oxosuperoxovanadium(v) species (**3**) (Scheme 1). Somewhat similar ESR spectra were observed for the aforementioned short-lived species, using rapid-mixing flow techniques in the cavity of the ESR spectrometer.^[1] However, in most of these investigations,^[1a-c] a hydrogensuperoxide interacting with a vanadium(v) ion was proposed as the originator of the detected ESR spectrum. Considering that the oxidation of **1** is carried

out in dry acetonitrile, the coordinated superoxide in **3** is judged to be deprotonated.

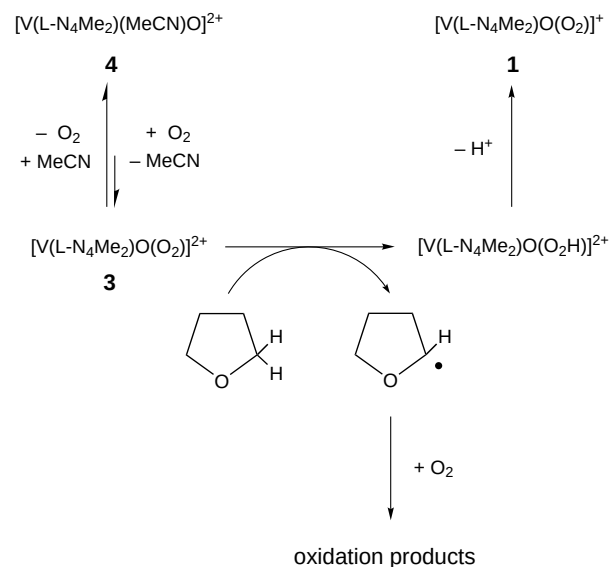
No other ESR signal, except that attributed to complex **3**, is detected at -30°C . If a solution of **3** is exposed to temperatures higher than -30°C for a very short time, then an ESR spectrum corresponding to the vanadyl(IV) complex $[\text{V}(\text{L-N}_4\text{Me}_2)(\text{MeCN})\text{O}](\text{ClO}_4)_2$ (**4**-(ClO_4)₂) can be observed. This complex was independently prepared from the vanadyl(IV) complex $[\text{V}(\text{L-N}_4\text{Me}_2)\text{ClO}](\text{ClO}_4)$ by treatment with $\text{AgClO}_4 \cdot \text{H}_2\text{O}$. The simulation of the solution spectrum of **4** yields an isotropic g value g_{iso} of 1.977 and a hyperfine coupling constant $A_{\text{iso}}^{\text{V}}$ of $92.8 \times 10^{-4} \text{ cm}^{-1}$ (Figure 2b). The ESR spectrum of the frozen solution (not shown) comprises an axial signal with g values $g_{\parallel} = 1.952$ and $g_{\perp} = 1.986$ and anisotropic hyperfine coupling constants $A_{\parallel}^{\text{V}} = 161.3 \times 10^{-4} \text{ cm}^{-1}$ and $A_{\perp}^{\text{V}} = 58.8 \times 10^{-4} \text{ cm}^{-1}$ —all of which are typical for a vanadyl(IV) species.^[3] The vanadyl(IV) species **4** is the direct decomposition product of the thermolabile superoxo complex **3**. The observation that the ESR spectrum of species **3** is not resumed upon cooling of the decomposition product, together with the coulometric results, indicates that the ESR spectrum of the vanadyl(IV) species does not correspond to a valence tautomeric (dioxygen)oxovanadium(IV) complex, but instead that a release of a dioxygen molecule occurs from the oxo(superoxo)vanadium(V) complex through an internal redox reaction yielding complex **4**. A similar decomposition reaction was proposed for the reaction of rather ill-defined vanadyl(IV) ions with hydrogen peroxide where by ESR spectroscopy an oxosuperoxovanadium(V) complex could be detected as the reaction intermediate and an evolution of molecular oxygen was observed.^[1d] Further, it has been suggested that an oxosuperoxovanadium(V) intermediate reacts to give an uncoordinated dioxygen molecule and a vanadyl(IV) complex, solely on the basis of a kinetic study of the reaction of vanadyl(IV) or dioxovanadium(V) ions with hydrogen peroxide in the presence of various oxidizing reagents; also here there exists no spectroscopic characterization of the involved species.^[2]

The question arises whether the oxygen release is reversible. Therefore the vanadyl(IV) complex **4**—a perspective view^[4] of which is shown in Figure 1—was exposed to high pressures of molecular oxygen. No superoxo complex could be detected by ESR spectroscopy, indicating that the reversible equilibrium reaction (1) lies far on the side of the



vanadyl(IV) complex. Therefore efforts were undertaken to trap the formed superoxovanadium(V) species by reducing it immediately to the stable peroxo complex. However, with conventional reducing reagents we were quite limited in raising the concentration of the reducing agents sufficiently in order to compete with the oxygen-release reaction; thus no formation of the peroxo complex was detected. In contrast, by

utilizing an anhydrous acetonitrile–tetrahydrofuran mixture (v:v = 1:1) as solvent, a quantitative conversion of the vanadyl(IV) complex to the oxo(peroxo)vanadium(V) complex could be observed with molecular oxygen (yields of isolated product: 82 %). Using $^{18}\text{O}_2$ results in the quantitative incorporation of ^{18}O atoms into the peroxo group.^[9] We propose that the depicted equilibrium reaction (1) plays an essential role in this process because the very few oxosuperoxovanadium(V) complexes formed in this equilibrium abstract hydrogen atoms from tetrahydrofuran molecules, yielding oxohydroperoxovanadium(V) complexes that are subsequently deprotonated, thus rendering the oxoperoxovanadium(V) product (Scheme 2). Due to the presence of a large excess



Scheme 2. Role of the equilibrium between **3** and **4** in the formation of the oxoperoxovanadium(V) product **1**.

of tetrahydrofuran, the hydrogen atom abstraction reaction can compete with the oxygen release reaction. The tetrahydrofuryl radicals formed in this reaction react further with molecular oxygen in a radical chain reaction yielding three major oxidation products.^[10] Recently, the first example of a direct formation of a vanadium(V) peroxide complex in the reaction of a vanadyl(IV) complex with molecular oxygen was described.^[7, 11] Our results represent the second example of this rare type of reaction.

In summary, we demonstrate for the first time a link between the dioxygen and the peroxide chemistry of vanadium through a superoxide complex for a well-defined system of mononuclear vanadium complexes. On the one hand, the vanadyl(IV) complex **4** can be converted by molecular oxygen in the presence of tetrahydrofuran to the corresponding oxoperoxovanadium(V) complex and, on the other hand, the oxoperoxovanadium(V) complex **1** can react to the vanadyl(IV) complex and molecular oxygen by a one-electron oxidation (Scheme 1). In both reactions an intermediary formed superoxo complex appears to be essential. In addition, we have shown that this relatively stable oxosuperoxovanadium(V) complex can be prepared by controlled synthetic means, thus allowing us the unique opportunity to investigate further the

structural and electronic properties of such generally very unstable and therefore quite elusive species.^[12]

Experimental Section

1-(BPh₄): A solution of $[\text{V}(\text{L-N}_4\text{Me}_2)\text{O}_2](\text{BPh}_4)^{[3]}$ (150 mg, 0.224 mmol) in acetonitrile (6 mL) was treated with 30 % hydrogen peroxide solution (2 mL). The initially yellow solution was stirred for 4 h at 65 °C. After the addition of water (5 mL) to the resulting red solution at room temperature, the volume of the solution was reduced until precipitation of a red solid started to occur. A brief heating of the solution until the entire solid was again redissolved and subsequent storage of the solution at 0 °C for 1 d afforded analytically pure product (136 mg, 88 %) as red crystalline material. Elemental analysis (%) calcd for $\text{C}_{40}\text{H}_{40}\text{BN}_4\text{O}_3\text{V}$: C 69.98, H 5.87, N 8.16; found: C 69.97, H 6.03, N 8.16; UV/Vis (acetonitrile): λ_{max} (ϵ_{M}) = 257 (9610), 263 (10500), 273 (sh, 3970), 443 nm (317); ^1H NMR (200 MHz, CD_3CN): δ = 3.69 (s, 6H; CH_3), 4.37 ($J_{\text{A,B}}$ = 15.9 Hz, 2H; CH_2), 4.68 ($J_{\text{A,B}}$ = 16.6 Hz, 2H; CH_2), 4.86 ($J_{\text{A,B}}$ = 15.9 Hz, 2H; CH_2), 5.23 ($J_{\text{A,B}}$ = 16.6 Hz, 2H; CH_2), 6.75–7.1 (m, 14H; Ph-H and 3,5-py-H), 7.15–7.35 (m, 10H; Ph-H and 3,5-py-H), 7.56 (A-part, $J_{\text{A,B2}}$ = 7.88 Hz, 1H; 4-py-H), 7.77 (A-part, $J_{\text{A,B2}}$ = 7.78 Hz, 1H; 4-py-H); IR (KBr): $\tilde{\nu}$ = 1609, 1581, 1479, 1457, 1445, 1427, 1382, 1029, 939, 881, 792, 735, 712, 704, 606, 566 cm^{-1} (strong bands only).

1-(ClO₄): A solution of $[\text{V}(\text{L-N}_4\text{Me}_2)(\text{MeCN})\text{O}](\text{ClO}_4)_2$ (100 mg, 0.174 mmol) in absolute acetonitrile (5 mL) and absolute tetrahydrofuran (5 mL) was rapidly stirred for 3 d under an atmosphere of pure oxygen. The resulting red solution was evaporated to dryness and the residue was dissolved in acetonitrile (3 mL). Diffusion of diethyl ether into the solution afforded a red crystalline product (67 mg, 83 %), which was filtered off, washed with diethyl ether, and dried in vacuo.

4-(ClO₄)₂: A solution of $[\text{V}(\text{L-N}_4\text{Me}_2)\text{ClO}](\text{ClO}_4)^{[3]}$ (107 mg, 0.228 mmol) and $\text{AgClO}_4 \cdot \text{H}_2\text{O}$ (52 mg, 0.230 mmol) in absolute ethanol (120 mL) was stirred for 3 d in the dark under an atmosphere of nitrogen. After the precipitated silver chloride was removed by filtration through celite, the residual solution was evaporated to dryness. The residue was dissolved in absolute acetonitrile. Diffusion of absolute diethyl ether into the solution rendered pure product as violet blocks, which were filtered off, washed with diethyl ether, and dried in vacuo (102 mg, 78 %). Elemental analysis (%) calcd for $\text{C}_{18}\text{H}_{25}\text{Cl}_2\text{N}_5\text{O}_9\text{V}$: C 37.58, H 4.03, N 12.17; found: C 37.27, H 4.21, N 12.02; UV/Vis (acetonitrile): λ_{max} (ϵ_{M}) = 261 (7930), 266 (9480), 279 (sh, 1770), 541 (27), 652 nm (30); IR (KBr): $\tilde{\nu}$ = 2316, 2288, 1612, 1582, 1483, 1454, 1382, 1169, 1094, 982, 880, 867, 809, 796, 624, 540 cm^{-1} (strong bands only).

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- [4] Crystallographical data of **1**-(BPh₄): orthorhombic space group $Pna2_1$, $a = 23.111(24)$, $b = 15.807(7)$, $c = 9.275(3)$ Å, $V = 3388(4)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.346$ g cm⁻³; $T = 153$ K; 5120 unique reflections (4223 reflections with $F_o > 4\sigma(F_o)$), $\mu(\text{MoK}\alpha) = 3.39$ cm⁻¹; 446 parameters (1 restraint); $R = 0.0427$ ($F_o > 4\sigma(F_o)$). Crystallographical data of **4**-(ClO₄)₂: monoclinic space group $P2_1/n$, $a = 8.545(2)$, $b = 17.267(15)$, $c = 16.757(7)$ Å, $\beta = 94.93(2)^\circ$, $V = 2463(2)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.551$ g cm⁻³; $T = 153$ K; 5675 unique reflections (4393 reflections with $F_o > 4\sigma(F_o)$), $\mu(\text{MoK}\alpha) = 6.77$ cm⁻¹; 323 parameters; $R = 0.0427$ ($F_o > 4\sigma(F_o)$). 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-151355 (**1**-(BPh₄)) and CCDC-151356 (**4**-(ClO₄)₂). Copies of the data can be obtained free of charge on application to

CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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- [10] Of the three major oxidation products, two have been identified as 2-methyl-1,3-dioxane and γ -butyrolactone. The identity of the third product and the reaction mechanism of the oxidation reaction are under current investigation.
- [11] Although not proposed, the reaction could proceed by a similar route via a superoxovanadium(v) intermediate. Here, however, in contrast to the reaction depicted in Scheme 2, the hydroxovanadyl(IV) species itself acts as reducing reagent, therefore rendering bis(oxo)vanadium(v) and oxoperoxovanadium(v) complexes in equimolar amounts.
- [12] Preliminary ESR studies with partially ^{17}O -enriched superoxo complex have shown that at -30°C the superoxide unit is either symmetrically side-on-bound or that an end-on-bound superoxide undergoes a rapid rearrangement reaction, interchanging the bound and the unbound oxygen atoms faster than the ESR time scale.

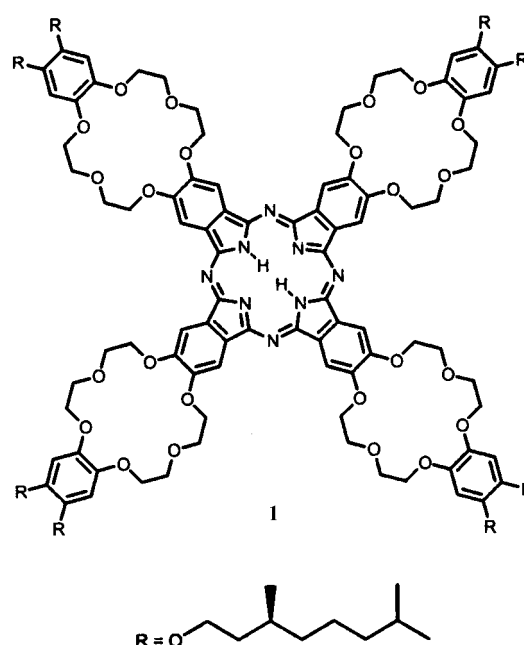
Self-Assembly and Manipulation of Crown Ether Phthalocyanines at the Gel–Graphite Interface**

Paolo Samorì, Hans Engelkamp, Pieter de Witte, Alan E. Rowan, Roeland J. M. Nolte, and Jürgen P. Rabe*

The design, synthesis, and manipulation of supramolecular structures having well-defined geometries are great challenges. Such structures have possible applications in diverse fields such as materials science, molecular electronics, and sensor development.^[1–3] The major source of inspiration for the generation of supramolecular architectures is the biological world.^[4] On the other hand, new synthetic routes need to be developed that allow the construction of molecular systems in such a way that the desired arrangements of components is obtained on the nanometer scale.^[5, 6] Phthalocyanines (Pcs) constitute a widely investigated class of compounds which are

interesting building blocks for the construction of supramolecular architectures.^[7–11] Phthalocyanines have been self-assembled in solution and they can be deposited by using the Langmuir–Blodgett (LB) technique^[9, 11] as well as by sublimation in ultra-high vacuum (UHV).^[8, 12–14] The deposited assemblies have been visualized using scanning force microscopy (SFM)^[11, 12] and scanning tunneling microscopy (STM).^[13, 14]

Herein we report on the self-assembly and manipulation of monomeric Pcs from gels into layers at surfaces, studied by STM imaging. The Pcs (such as **1**) are functionalized with four benzocrown ether rings, which are each disubstituted with enantiomerically pure (*S*)-3,7-dimethyloctyl chains. The



peculiar physicochemical properties of these chiral molecules arise from the fact that 1) they have an extended π -conjugated core which plays a key role in the charge-transfer properties of stacked Pcs; 2) they contain crown ethers which can host alkaline ions, and 3) they possess alkyl side chains which can induce a liquid crystalline behavior. In organic solvents **1** forms a gel in which helical fibers are present. The helicity of these fibers, which are composed of Pc stacks, can be tuned by the addition of alkaline ions, namely K^+ .^[15] The overall diameter of the fibers is equal to the diameter of the Pc discs with extended tails (6 nm), and the distance (d) between two Pc discs is 0.335 nm.

Figure 1 shows sub-molecularly resolved STM images of the monomeric **1** moieties self-assembled at the interface between a gel and highly oriented pyrolytic graphite (HOPG). The molecular arrangement comprises two “face-on” phases (1 and 2 in Figure 1 a), and one “edge-on” lamellar phase (3 and 4 in Figure 1 a).

The “edge-on” lamellae, which are made up of π – π stacked Pcs (Figures 1 b and 2) exhibit widths (w) of (4.7 ± 0.2) nm (Figure 1) and lengths up to hundreds of nanometers (image

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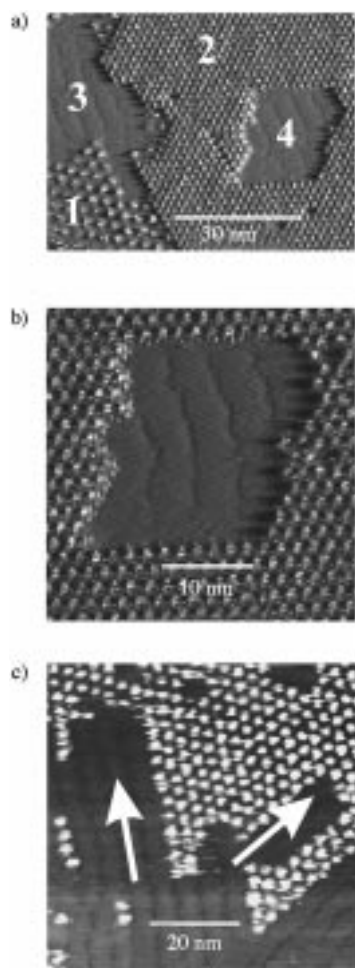


Figure 1. STM images of **1** at the gel–HOPG interface: a) and b) current image ($U_t = 0.58$ V, average $I_t = 53$ pA), c) height image ($U_t = 0.58$ V, average $I_t = 53$ pA). Image a exhibits four main features: a thermodynamically stable, relatively loosely packed hexagonal lattice (1), a metastable, more densely packed hexagonal phase (2), lamellae (3)—which are also visible in the area 4 where this molecular order has been induced by the STM tip. A zoom-in of area 4 revealing the π – π stacked Pcs forming the lamellae is shown in b. In image c the large hexagonal lattice is aligned along the main axes of the lamellae which are marked by the white arrows.

not shown). The distance (d) between two Pc discs is expected to be 0.335 nm in the case of a typical π – π stacking interaction. The intralamellar spacing (s) between neighboring monomeric discs, however, is (0.44 ± 0.03) nm, as determined from the STM profiles on images such as Figure 1 b. This value suggests that the molecules are tilted from the normal by an angle γ , which can be calculated from $d/s = \cos \gamma$ to be 40° . For a molecular structure of the loosely packed hexagonal phase (see below) having an average unit cell vector of $a = (3.5 \pm 0.2)$ nm, the total area occupied by a molecule amounts to $a^2 \sin 60^\circ = (10.6 \pm 1.2)$ nm². Given the lamellar widths (w) of (4.7 ± 0.2) nm, in the approximation of a rectangular shaped molecule packed “edge-on”, the thickness (z) of the lamellae self-assembled on HOPG can be calculated to be $(10.6/4.7)$ nm $= (2.3 \pm 0.4)$ nm. Since the conjugated core has a diameter of about 1 nm, the remaining part of the lamella, which has a thickness of roughly 1.3 nm, consists of aliphatic moieties. It is worth noting that the

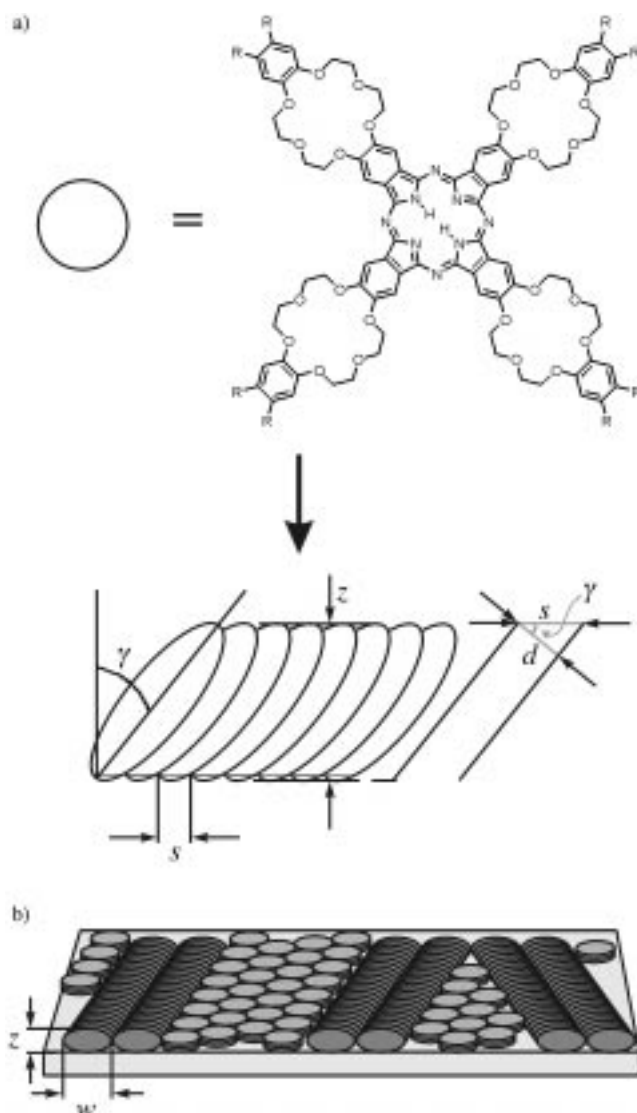


Figure 2. Schematic representation showing the packing of molecules of **1** at the solid–gel interface. a) Single Pcs are stacked forming a lamellar architecture with an intralamellar spacing (s) and a tilt angle with respect to the surface (γ). The thickness (z) of the lamellar layer can be calculated by assuming a typical π – π stacking with distance d between two discs. b) The surface of the HOPG is coated with molecules packed in both “edge-on” (lamellae) and “face-on” structures. The latter packing can also exist in an isolated object at the lamellar boundaries. The lamella width (w) is indicated.

possibility of tunneling electrons through such a 2.3 nm-thick layer of the lamellar phase indicates a remarkable conductivity of the hybrid saturated–unsaturated molecule in the direction parallel to the disc. These lamellar architectures, which have also been observed at the solution–HOPG interface (image not shown), are similar to the tubular nanostructures monitored by SFM in LB films of other Pc derivatives.^[11]

Interestingly, the lamellar phase coexists with two different hexagonal phases (1 and 2 in Figure 1 a): A metastable phase with a cell of $a = (1.83 \pm 0.02)$ nm and $\alpha = 60^\circ$, which disappears after a couple of hours, and a more loosely packed, almost hexagonal structure with $a = (3.4 \pm 0.2)$ nm, $b = (3.7 \pm 0.2)$ nm, and $\beta = (56 \pm 4)^\circ$, which is more stable and lasts for at

least several days. In both these arrangements the conjugated discs are oriented “face-on” on the basal plane of the graphite substrate. These phases are similar to the ones observed recently for a simpler Pc derivative at the HOPG–solution interface.^[16] In our case the dimensions of the crystal lattices indicate that in both “face-on” packings the lateral substituents (crown ethers and aliphatic chains) are not fully extended, and thus adopt a coiled conformation. The main lattice axes of the thermodynamically stable phase are aligned along the main lamella directions (white arrows in Figure 1c and shown schematically in Figure 2), whereas the spacings of the two structures in the *xy* plane are not in registry. By raising the average tunneling current and decreasing the applied voltage one can increase substantially the forces exerted by the STM tip on the organic film. This process allowed us to manipulate the film of **1** at the molecular level. A structural rearrangement from the small hexagonal lattice (“face-on”) to the lamellae (“edge-on”) could be induced. After returning to the standard imaging condition of the adsorbate, the manipulation was visible in area 4 in Figure 1a, which indicated the occurrence of mechanochemical switching. The “face-on” oriented molecules in Figure 2a are present both as packed crystals with sizes of hundreds of square nanometers and as isolated objects embedded where defects in the lamellar structure are located, that is, at lamella boundaries. This unusual type of molecular inclusion in a tightly packed lamellar array, together with the high viscosity of the gel phase, may be the reason for the markedly low mobility of the single Pc molecules, which differs from results obtained in previous studies on Pc films grown and characterized in UHV.^[14]

In STM height imaging (Figure 1c) a feedback loop controls the vertical position of the tip in such a way that a preset tunneling current flowing between the substrate and the tip is maintained constant while the tip scans in a horizontal plane above the sample. Since the conductivity of columnar stacks of Pcs is higher through the stacks than perpendicular to the stacks,^[9c] the thickness of the self-assembled “face-on” phase in the tip–substrate gap is probably larger than the 2.3 nm distance discussed above for the lamellae. This means that the first type of architectures consists of stacks of Pc discs. Unfortunately, however, this type of measurement does not allow a determination of the exact number Pcs in the stacks.

The low mobility of the Pcs at the surface is of particular interest for future scanning tunneling spectroscopy investigations on single Pc molecules or stacks of them. Moreover, STM investigations at the solid–gel interface as presented here have a great advantage over the well-established method of performing studies at the solid–liquid interface,^[17] because of the greater stability of the former gel phase (up to several days). We believe that this approach can be extended to a large variety of low molecular mass molecules which can form gels.

In summary, we have shown that the interplay of intramolecular, intermolecular, and interfacial forces can be used to construct highly organized two- and three-dimensional architectures from phthalocyanine building blocks at the gel–HOPG interface. The switching between different nano-

structures co-existing at the surface can be stimulated with the tip of the STM with a resolution on the molecular scale. These results should be of interest for future applications in areas such as molecular electronics, optoelectronics, and sensor development.

Experimental Section

Scanning tunneling microscopy: The STM investigations were carried out with a home-built beetle-type, low-current STM.^[18] A drop of an almost saturated solution of **1** in a 50:1 mixture of CHCl₃ and 1,2,4-trichlorobenzene (Aldrich) was applied to a freshly cleaved HOPG substrate. Evaporation of the solvent occurred slowly and gave rise to the slow (on a time scale of several hours) formation of a stable gel phase adsorbed on HOPG, which was visible to the naked eye. By varying the tunneling parameters, namely, decreasing the voltage and increasing the average tunneling current, it was possible to visualize the HOPG lattice underneath the gel and therefore to calibrate the piezo in situ. This procedure was also used to induce a structural rearrangement in domain 4 of Figure 1. The tunneling tips were mechanically cut from a 0.25 mm Pt:Ir (80:20) wire. Unit cells and backbone spacings were averaged using several images after their correction for the piezo drift (using a scanning probe image processor (SPIP), Version 1.720, Image Metrology ApS, Lyngby, Denmark).

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[ReH(SH)₂(PMe₃)₄]: A Catalyst for Fundamental Transformations Involving H₂ and H₂S**

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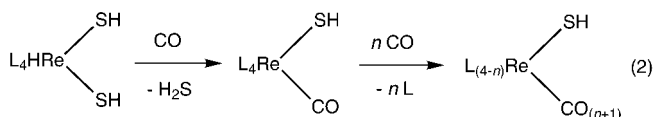
While sulfur is often described as a catalyst poison, many of nature's most remarkable enzymes feature metals embedded in a sulfur-rich coordination sphere. This is especially true for the biological processing of dihydrogen, dinitrogen, and carbon monoxide.^[1–3] In the industrial sector, metal sulfides are used to activate H₂ in the hydrodesulfurization (HDS) process.^[4, 5] Inspired by these precedents, there is much interest in metal sulfides that interact with H₂. Three types of metal complexes are known to do so,^[6, 7] and one, [Cp₂Mo₂S₄] (Cp = cyclopentadienyl), exhibits a range of catalytic properties.^[8] Encouraged by rich organic chemistry of the [ReS₄][–] ion^[9] and [Re₂S₇]^[10] we have probed the activation of dihydrogen by rhenium sulfido complexes.

Initial studies revealed that the reaction of [ReS₄][–] ions with PMe₃ affords diverse compounds because PMe₃ serves as both a desulfurization agent and a trapping ligand. When MeCN solutions of [NEt₄][ReS₄] are allowed to react with excess PMe₃ under an atmosphere of H₂S, we obtained a 75 % isolated yield of beige crystals of [ReH(SH)₂(PMe₃)₄] (**1**). The synthesis is proposed to proceed according to Equation (1).



This unusual synthesis involves a complete revision of the ligand set and metal oxidation state. Preliminary experiments demonstrate that this PMe₃/H₂S reaction can be used to convert other thiometallates into novel M–SH complexes (M = metal center).

As suggested by Equation (1), **1** is a room temperature catalyst for the unusual reaction of H₂S with PMe₃ to give SPMe₃ and H₂.^[11] Because M–SH groups are typically nucleophilic, S-atom transfer from M–SH to PMe₃ is unexpected. S-atom transfer is, however, typical for sulfido complexes. This reasoning suggests that the S-atom transfer may proceed via the reversible formation of a Re=S species. The kinetic lability of **1** is also indicated by its rapid reaction with CO (1 atm, 25 °C) to give *cis*-[ReSH(CO)(PMe₃)₄], [ReSH(CO)₂(PMe₃)₃],^[12] and [ReSH(CO)₃(PMe₃)₂]^[13] [Eq. (2)].



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Crystallographic characterization reveals that **1** has a pentagonal bipyramidal geometry with idealized C_{2v} symmetry (Figure 1). The sulfur-bound H atoms were not observed crystallographically but Re=S bonds are ruled out by the bond length Re–S of 2.52 Å, which is consistent with a single Re–S

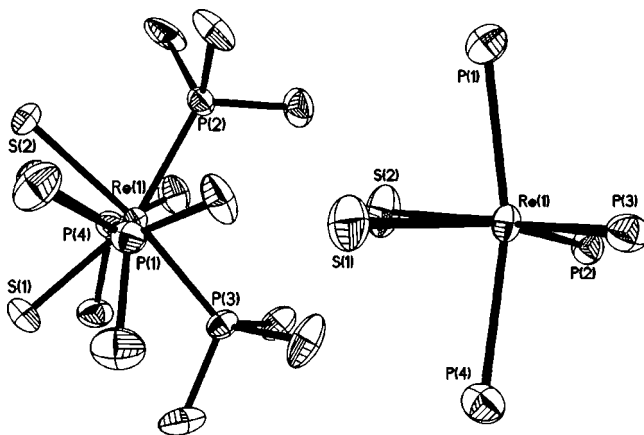


Figure 1. Two views of the molecular structure of **1**, (thermal ellipsoids set at the 50 % probability level). Average selected bond lengths [Å] and angles [°]: Re–S 2.52, Re–P_{eq} 2.37, Re–P_{ax} 2.42; P_{eq}–Re–P_{eq} 110.0, P_{ax}–Re–P_{ax} 163.8, P_{ax}–Re–P_{eq} 95.5, S–Re–S 83.0, P_{ax}–Re–S 85.0, P_{eq}–Re–S 89.15, 77.88.

bond. The position of the hydride ligand between the equatorial phosphane ligands is inferred from the expanded P–Re–P angle (110°) as well as a nuclear Overhauser enhancement effect (NOE) interaction between the Re–H and (PMe₃)_{eq} groups. The ¹H and ³¹P NMR spectra support the crystallographic results, that is, both the SH and ReH protons are coupled to ³¹P nuclei, the former giving rise to a doublet of triplets and the latter a triplet of triplets. At –10 °C ([D₆]-Me₂CO), the ³¹P NMR spectrum of **1** consists of two triplets.

Treatment of **1** with dmpe (Me₂PCH₂CH₂PMe₂) gave [ReH(SH)₂(PMe₃)₂(dmpe)] (**2**), which is characterized by distinctive ³¹P and ¹H NMR spectroscopic signatures (Figure 2). Complex **2** is a rare example of a complex with nonequivalent S–H groups, and magnetization transfer experiments show that exchange between these S-bound H sites is slow (<0.45 s^{–1} = T₁^{–1} for SH). Whereas **1** undergoes complete exchange with P(CD₃)₃ upon mixing (25 °C), **2** exchanges with P(CD₃)₃ only over the course of hours.

Solutions of **1** catalyze the conversion of H₂ and

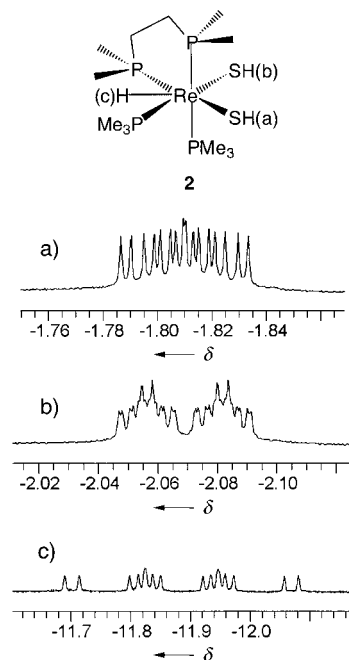


Figure 2. Selected regions of the 500 MHz ¹H NMR spectrum of **2** (C₆D₆ solution).

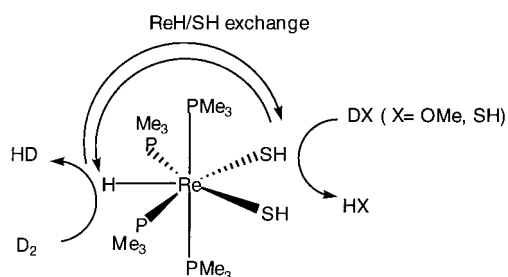
D₂ into HD (monitored by ¹H NMR spectroscopy). Relevant to this process, solutions of **1** react with D₂ to give [ReD(SH)₂(PMe₃)₄] within a few minutes at 25 °C. Under the same conditions, the reaction of D₂ (1 atm) with the dmpe derivative **2** is slow (*t*_{1/2} > 3.5 h). We conclude that H/D exchange proceeds via the intermediate 16e[−] species [ReH(SH)₂(PR₃)₃], which is more difficult to form from **2**. An important observation is that the Re–H sites are deuterated more quickly than the S–H sites, thus the S–H ligands are not directly involved in HD formation, but are spectators.

The S-bound H groups in **1** and **2** exchange with protic reagents: treatment of benzene solutions of **1** and **2** with excess CD₃OD for several minutes, followed by evaporation, resulted in partial deuteration of the S–H sites, as well as significant exchange into the Re–H sites.

Exchange of protons between the M–H and M–SH sites in **1** occurs over the course of several hours at room temperature. This process can be quantitatively analyzed by ¹H NMR spectroscopy by monitoring the conversion of [ReD(SH)₂(PMe₃)₄] into [ReH(SD)(SH)(PMe₃)₄] (*k* = 7.10(8) × 10^{−5} s^{−1} at 20 °C). At equilibrium the deuterium in [D₁]**1** (and in [D₂]**1**) is approximately equally distributed over the three accessible sites (ReH, and two SH sites). The rate of transfer of D from ReD to ReSH sites in **1** and **2** are approximately the same, consistent with an intramolecular process. The intramolecular H-atom exchange in [M(SH)H] complexes, for example, [Ru(SH)(H)(PPh₃)₃], is well established.^[14]

Solutions of **1** catalyze isotopic exchange between D₂ and H₂S to give HD and DHS, as verified by in situ ¹H NMR spectroscopic measurements. This process can be understood by invoking the three aforementioned exchange processes: H/D exchange between ReSH and D₂S, intramolecular H/D exchange between the ReSD and ReH sites, and exchange of the ReD site with H₂.

In contrast to the high reactivity of **1**, the corresponding trihydride [ReH₃(PMe₃)₄] is kinetically inert.^[15] In other words, the usual view that sulfur poisons catalysts is clearly inappropriate in this case: the sulfide ligands are *enabling*. The catalytic properties of **1** result from its bifunctional nature with both protic (SH) and hydridic (ReH) sites that communicate by an intramolecular exchange process (Scheme 1).



Scheme 1.

Complex **1** uniquely undergoes H/D exchange at both SH and ReH with D₂, but by different mechanisms. In [Cp₂⁺Ti(SH)(H)],^[7] both SH and TiH exchange together and dissociatively (by elimination of H₂) whereas in **1**, the ReH exchanges (associatively) with D₂, independent of ReSH

exchange. The importance of our results is that HDS catalysts use H₂, and it is exciting to see that the M–SH group is an electronically important spectator in the H₂ activation process. Compound **1** is a singular example of a L_nM(H)(SH) compound where the hydride site undergoes exchange with D₂ at a faster rate than the SH site.

Experimental Section

1: To (300 mg, 0.67 mmol) of [Et₄N][ReS₄] frozen in MeCN (10 mL) was condensed PMe₃ (0.7 mL, 6.8 mmol) and H₂S (310 mg, 9.1 mmol). The frozen vessel was evacuated, sealed, and warmed to room temperature. After stirring for 7 h, the solution was evaporated. Vacuum sublimation at 50 °C removed (277 mg, 2.56 mmol) of SPMe₃ (³¹P NMR in C₆D₆): δ = 28.3. The residue was extracted with 5 % THF in Et₂O (100 mL). The extracts were evaporated and the crude product was extracted from the remaining solid by washing with 3 % THF in hexanes (100 mL). These extracts were concentrated to ~25 mL and cooled to −78 °C to give 283 mg (75 %) of beige crystals. Field desorption mass spectroscopy (FD-MS): *m/z* = 556.1 [*M*⁺], 482.1 [*M*⁺ − PMe₃]; elemental analysis (%) calcd for C₁₂H₃₉P₄ReS₂: C 25.84, H 7.05, S 11.50; found: C 26.03, H 6.76, S 11.28; IR (KBr): $\tilde{\nu}$ = 2049 (Re–H), 2520 (SH); ¹H NMR (500 MHz, 298 K, C₆D₆): δ = 1.41 (m, 18H), 1.39 (m, 18H), −1.46 (dt, 2H; *T*₁ = 8 s), −11.98 (tt, 1H; *T*₁ = 2.2 s); ³¹P NMR (C₆D₆, 298 K): δ = −47.28 (brs, 2P), −51.81 (brs, 2P); ³¹P NMR ([D₆]Me₂CO, 263 K): δ = −45.5 (t, *J* = 24 Hz), −50.7 (t, *J* = 24 Hz), *T*₁ is the spin–lattice relaxation time. Solutions of **1** are stable in THF and hydrocarbon solvents, less so in MeCN.

2: To (150 mg, 0.27 mmol) of **1** in MeCN (10 mL) was added (0.045 mL, 0.30 mmol) of dmpe. The solution was stirred under a slow stream of N₂ for 45 min to remove free PMe₃. The solution was then concentrated in vacuo to ~3 mL, and then the MeCN solution was extracted with hexanes (2 × 40 mL). Evaporation of the hexane extracts afforded a tan solid, yield: 128 mg (85 %), elemental analysis (%) calcd for C₁₂H₃₇P₄ReS₂: C 25.94, H 6.71; found: C 26.04, H 6.51; IR (KBr): $\tilde{\nu}$ = 2039 (ReH), 2536 (SH). ¹H NMR (500 MHz, 298 K, C₆D₆): δ = 1.71 (d, *J* = 8.43 Hz, 3H), 1.57 (d, 3H, *J* = 8.82 Hz), 1.44 (d, 9H, *J* = 7.75 Hz), 1.36 (d, *J* = 7.55 Hz, 9H), 1.17 (d, *J* = 8.02 Hz, 3H), 1.08 (d, *J* = 7.13 Hz, 3H), −1.81 (m, *J* = 1.89, 4.20, 7.26, 10.10 Hz; ReSH; *T*₁ = 8 s), −2.07 (m, *J* = 0.58, 1.74, 3.32, 3.79, 12.80 Hz; ReSH; *T*₁ = 8 s), −11.88 (m, *J* = 12.2, 54.0, 61.2, 67.0 Hz; ReH; *T*₁ = 2.2 s); ³¹P NMR (C₆D₆, 298 K): δ = 11.04 (s), 3.44 (d, *J* = 257 Hz), −46.0 (s), −49.1 (d, *J* = 257 Hz). The ¹H NMR spectrum was analyzed by computer simulation.

Deuteration of **1** and **2** with CD₃OD: A solution of **1** (50 mg 8.97 × 10^{−5} mol) in THF (5 mL) was treated with CD₃OD (1 g) for 10 min. After removal of the solvent, the residue was dissolved in C₆D₆. ¹H NMR analysis indicated [ReH_{0.75}D_{0.25}(SD_{0.7})₂(SH_{0.3})₂(PMe₃)₄], under identical conditions, **2** gave [ReH_{0.7}D_{0.3}(SD_{0.65})₂(SH_{0.35})₂(PMe₃)₂(dmpe)].

Deuteration of **1** and **2** with D₂: A solution of 50 mg (8.97 × 10^{−5} mol) of **1** in THF (10 mL) was treated with a stream of D₂ for 10 min. After removal of the solvent, the product was redissolved in C₆D₆ and analyzed by ¹H NMR spectroscopy which indicated [ReH_{0.1}D_{0.9}(SH)₂(PMe₃)₄] (no deuteration of SH site), similar treatment of **2** with D₂ but for 90 min gave [ReH_{0.8}D_{0.2}(SD_{0.1})₂(SH_{0.9})₂(PMe₃)₂(dmpe)].

Catalyzed exchange between D₂ and H₂S: A solution of **1** in C₆D₆ (0.7 mL) was treated with H₂S (0.5 atm) and D₂ (0.5 atm) and sealed. The mixture was monitored by ¹H NMR spectroscopy, which indicated conversion into a mixture of HD, H₂, HDS, and H₂S.

Crystal data for **1**: C₁₂H₃₉P₄ReS₂, *M* = 557.63, 193(2) K, monoclinic, space group *P*2₁; *a* = 9.2120(7), *b* = 12.9796(10), *c* = 9.3579(8) Å, β = 90.551(2)°, *V* = 1118.85(15) Å³, *Z* = 2, ρ_{calcd} = 1.655 Mg m^{−3}, *F*(000) = 556, 190 parameters: *R*₁ = 0.0443, *wR*₂ = 0.0897, GOF = 1.102 for all 3474 data (*I* > 2σ(*I*)); max./min. residual electron density: 3.137/−1.359 e[−] Å^{−3}. Crystals of **1**, mounted on glass fibers using Paratone-N (Exxon), were analyzed on a Siemens Platform/CCD automated diffractometer at 193 K. Data was processed with SHELXTL. The structure was solved using direct methods and refined using full-matrix least-squares on *F*² using the program SHELXL-93. Hydrogen atoms were fixed in idealized positions with thermal parameters 1.2 times those of the attached carbon atoms. Data

were corrected for absorption on the basis of integration. 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-150678. 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 Hg₃²⁺ Group as a Framework Unit in a Host–Guest Compound: [Hg₁₁As₄](GaBr₄)₄**

Andrei V. Olenov and Andrei V. Shevelkov*

Various inorganic supramolecular compounds with three-dimensional host structures are known.^[1] Among them is a separate group of phases in which the three-dimensional network is formed by tetrahedrally coordinated pnictogen and linearly coordinated mercury atoms.^[2] In some structures, some or all of the pnictogen atoms are joined into dumbbells

while keeping their tetrahedral arrangement.^[3] Here we report on [Hg₁₁As₄](GaBr₄)₄ (**1**), a novel supramolecular complex in which linear Hg₂²⁺ and Hg₃²⁺ fragments as well as Hg₂²⁺ cations take part in the formation of the three-dimensional host network. This is the first example of a linear Hg₃²⁺ group serving as a part of a three-dimensional framework.

The crystal structure^[4] of **1** consists of a three-dimensional [Hg₁₁As₄]⁴⁺ host network and tetrahedral GaBr₄[−] guest anions, which occupy one-dimensional infinite tunnels of the host framework (Figure 1). Large separations between the

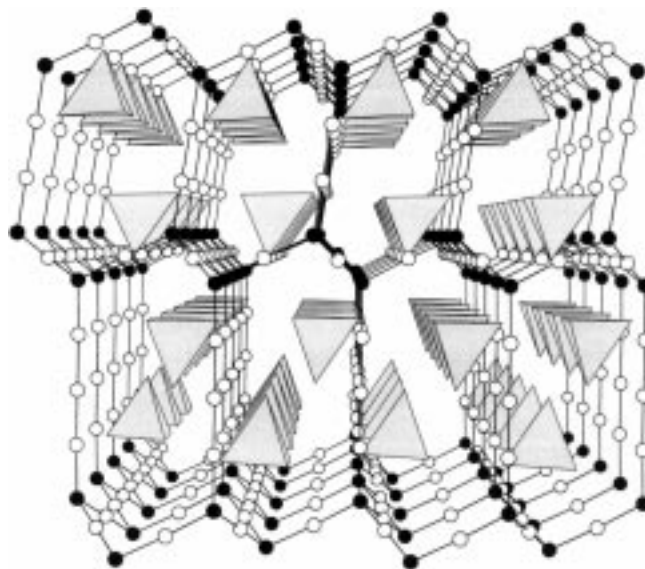


Figure 1. A perspective view of the crystal structure of [Hg₁₁As₄](GaBr₄)₄ (**1**) along the [010] direction of the unit cell. Open circles, mercury; filled circles, arsenic. Polyhedra represent the GaBr₄[−] ions.

bromine atoms of different GaBr₄ tetrahedra (> 3.68 Å), and between the bromine atoms and mercury atoms of the cationic framework (> 3.53 Å) allow the guests to be regarded as almost completely isolated from each other and from the host structure. With such separations, the host–guest interactions between the [Hg₁₁As₄]⁴⁺ framework and the GaBr₄[−] anions are apparently limited to weak electrostatic forces.

All the arsenic atoms in the host framework take part in the formation of corrugated layers, composed of edge-linked six-membered As₆ rings in a chair conformation, in which each edge of a chair is centered by a Hg₂²⁺ cation. These layers are interconnected by linear Hg₂²⁺ and Hg₃²⁺ fragments that alternate along the *c* axis of the unit cell in such a way that tetrahedral coordination of As is achieved. The ordered alternation of the two mercury polycations leads to the formation of two tunnels of different size that extend along the *b* axis of the unit cell (Figure 2). The Hg₂²⁺ and Hg₃²⁺ units serve as boundaries for the smaller and larger tunnels, respectively. The Hg–Hg distances in the Hg₂²⁺ (2.57 Å) dumbbell and in the Hg₃²⁺ group (2.58 Å) are typical of those found in various compounds containing mercury in low oxidation states.^[5] Note that while Hg₂²⁺ dumbbells are quite common in mercury chemistry, only a few compounds containing Hg₃²⁺ are known. In these, such groups are stabilized by AlCl₄[−], AsF₆[−], or (F₅MOSO₂OMF₅)^{2−} (M = Nb,

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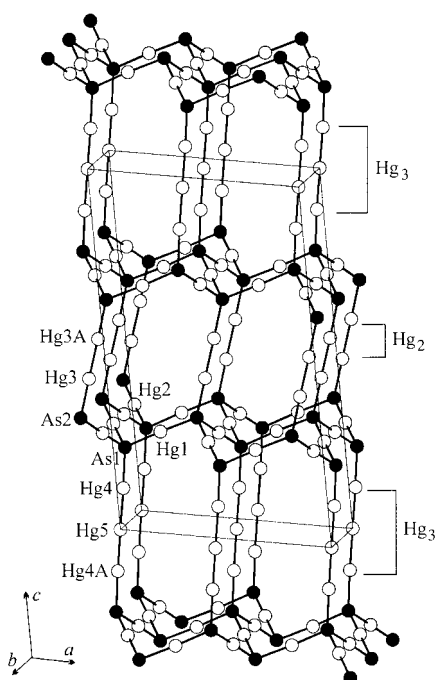


Figure 2. A portion of the $[\text{Hg}_{11}\text{As}_4]^{4+}$ cationic framework. Alternation of the Hg_2^{2+} and Hg_3^{2+} groups is shown. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Hg3–As2 2.520(4), Hg4–As1 2.545(4), Hg3–Hg3A 2.572(3), Hg4–Hg5 2.580(2); Hg3A–Hg3–As2 179.1(1), Hg5–Hg4–As1 178.4(1), Hg4–Hg5–Hg4A 180.

Ta) anions,^[6] that is, derivatives of very strong Lewis acids. Compound **1** is the first example of an architecture in which both Hg_2^{2+} and Hg_3^{2+} ions are present and take part in the formation of a stiff covalent network. The central mercury atom in the Hg_3^{2+} chain has a high thermal vibration amplitude in the plane perpendicular to the direction of the chain. This atom has only two neighboring mercury atoms to which it is covalently bonded and no other neighbors within a distance of 4.37 $\text{\AA}$.

Both types of tunnels in the framework are large enough to each contain two columns of discrete GaBr_4^- anions (Figure 1). This contrasts with phosphorus analogues of the Millon's base salts, the nearest structural analogues of **1**, in which each tunnel always contains only one column of guest anions.^[7] The orientation of the slightly distorted GaBr_4^- anions (Ga–Br 2.28–2.36 $\text{\AA}$, Br–Ga–Br 105.8–113.4 $^\circ$) is the same in each column, but the mutual orientations of the columns inside the larger and smaller tunnels are different (Figure 1).

The crystal structures of two compounds reported earlier,^[3a] namely, $[\text{Hg}_{23}\text{As}_{12}](\text{ZnBr}_4)_6$ and $[\text{Hg}_{13}\text{As}_8](\text{ZnCl}_4)_4$, provide examples for the adaptation of the three-dimensional mer-

cury–pnictogen frameworks to the size of the guest anions by “stitching” the tunnels with As–As bonds. Compound **1** represents another way of modifying the framework: the Hg–Hg groups expand the tunnels.

Experimental Section

Mercury(I) and mercury(II) bromides, gray arsenic, and gallium were mixed in the ratio 3:5:4:4 (1 g total), vacuum sealed in a quartz ampoule, and annealed for 3 d at 400 $^\circ\text{C}$. The product appeared as a dark red air-stable polycrystalline powder. An X-ray pattern of the sample (STADI-P (STOE), $\text{CuK}\alpha_1$ radiation) was identical to that calculated from the crystal data and did not reveal any impurities.

A single crystal for the structure determination was selected from the sample prepared from mercury(I) bromide, arsenic, and gallium, mixed in a 2:2:1 ratio, vacuum sealed, and heated for 4 d at 400 $^\circ\text{C}$.

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- [4] Crystal data for **1**: monoclinic, space group $C2/m$ (no. 12), $a = 13.272(1)$, $b = 7.558(2)$, $c = 22.472(4)$ $\text{\AA}$, $\beta = 98.56(1)^\circ$, $V = 2229.1(7)$ $\text{\AA}^3$, $Z = 2$, $\rho_{\text{calc}} = 6.054$ g cm^{-3} ; 2184 reflections, 2116 of which were independent ($R_{\text{int}} = 0.0251$), $T = 293$ K, $\omega/2\theta$ scans, $\text{MoK}\alpha$ radiation, $\lambda = 0.71069$ $\text{\AA}$, $2\theta_{\text{max}} = 50^\circ$, crystal dimensions $0.3 \times 0.15 \times 0.1$ mm^3 , semiempirical absorption correction (ψ scans of six reflections, min./max. transmission 0.6967/0.9984, $\mu = 55.377$ mm^{-1}). Structure solution: direct methods (SHELXS-97),^[8a] refinement against F^2 , (1017 reflections with $F > 4\sigma(F)$) by full-matrix methods (SHELXL-97)^[8b] with 99 free parameters; $R1 = 0.0642$, $wR2 = 0.1487$; max./min. residual electron density 2.327/–3.493 $\text{e \AA}^{-3}$. Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-411676.
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